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CALIMS

U SARADNJI SA AGENCIJOM ZA LJEKOVE I MEDICINSKA SREDSTVA CRNE GORE

II KONGRES FARMACEUTA CRNE GORE SA MEĐUNARODNIM UČEŠĆEM
II CONGRESS OF PHARMACISTS OF MONTENEGRO WITH THE INTERNATIONAL PARTICIPATION

ZBORNIK SAŽETAKA
ABSTRACT BOOK

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PHARMACY - SCIENCE AND PRACTICE GUIDED BY HUMANITY

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POSTER PREZENTACIJE

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SYSTEMS PHARMACOLOGY - TOWARDS PRECISION TREATMENTS

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[2]President European Federation of Pharmaceutical Sciences

Systems pharmacology is an emerging discipline, which connects systems biology to quantitative pharmacology. A specific feature of systems pharmacology is the focus on biological networks as the basis for drug action. This is important as the network concept explains the well-known plasticity of biological systems with regard to i) drug action (i.e. the often observed lack of efficacy) and ii) disease (i.e. the resilience of disease progression to degeneration). As such systems pharmacology constitutes a novel scientific basis for 1) the identification of novel pathways of disease, 2) the discovery of novel drug targets and 3) the design of novel therapeutic interventions.

Application of systems pharmacology concepts leads to novel therapeutic interventions which are often referred to as “systems therapeutics”. Systems therapeutics interventions are: a) personalized, both with regard to the selection of the drug(s) and the dosing regimen, b) disease modifying rather than symptomatic, with emphasis on pre-emptive and preventive treatments, and c) complex, including the use of multi-target drugs or rational drug combinations, to overcome the plasticity of biological systems.

Systems therapeutics interventions are “precision treatments, which due to their inherent complexity, cannot be designed, nor be applied in clinical practice, by trial and error. A model-based approach is crucial to the successful implementation of systems therapeutic interventions. In recent years important progress has been made in the field of quantitative pharmacology. Novel mechanism-based pharmacokinetic-pharmacodynamics (PKPD) modeling concepts have been proposed for the prediction of in vivo drug effects, including the effects on disease progression. To date, mechanism-based PKPD has focused mainly on the modeling of drug effects through single transduction pathways. However, in theory, these concepts can be extended to the modeling of drug effects through biological networks, by considering the interactions between pathways. They constitute a unique scientific basis for the development and the clinical implementation of “systems therapeutic” interventions.

MAKING BETTER USE OF PHARMACISTS

Howard Duff

Royal Pharmaceutical Society of Great Britain

How the Royal Pharmaceutical Society is campaigning to extend the roles of community pharmacists and promoting the role of pharmacists in hospitals, GP surgeries, public health, care homes and telephone helplines.
•What factors are driving the RPS to examine new roles?
•What are these roles and why should a pharmacist take them on?
•As well as having a compelling case there needs to be mechanisms that can raise the issue to the attention of patients, other health professionals and the government in order to make change happen.

SCIENCE BASED PHARMACEUTICAL SERVICES IN HEALTH CARE DELIVERY SETTINGS

Lilian M. Azzopardi

Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta

A contribution of the pharmacist within healthcare delivery settings is the expertise on medicinal products. Such expertise spans from the pharmacological basis of the use of the product, the pharmaceutical technology employed in the manufacture and the subsequent requirements for the handling of the product, and the pharmaceutical regulatory processes required to ensure safe products.Pharmacists practice in different pharmaceutical healthcare delivery settings including community pharmacies, hospital pharmacies, clinical pharmacy services, long-term care facilities, home services.

Focal contributions of the pharmacists in these healthcare delivery settings are ensuring access to medicinal products, collaboration with other healthcare professionals in disease management to ensure rational, safe and effective use of medications, risk management with pharmacotherapy, and patient advocacy.

Ensuring the integration of science in pharmacy practice driven curricula is essential to achieve the science-focused pharmacist who is equipped to give the specific expertise and contribute to patient safety and patient management. Examples of activities that support the development of skills required in these practice settings are reviewed. The concept of integrating pharmaceutical sciences to the application of pharmaceutical processes in pharmacy education and research is presented. Models of supporting practicing pharmacists within post-graduate education programmes are presented. Such programmes should sustain the development of advanced skills and competences for pharmacists to lead the provision of patient-focused pharmaceutical policies, pharmaceutical regulatory aspects and novel direct patient pharmaceutical services whilst embracing the pharmacoeconomic and innovation challenges are presented.

PREDAVANJA PO POZIVU

INFORMACIONO POVEZIVANJE ALMBIH SA INSTITUCIJAMA SISTEMA I ZDRAVSTVENIM USTANOVAMA OSNOV ZA USPJEŠNO OSTVARIVANJE NADLEŽNOSTI

Nataša Grubiša, Jelena Aničić

Agencija za lijekove i medicinska sredstva BiH

Kao osnov za uspješno ostvarivanje zakonom predviđenih nadležnosti prepoznali smo informaciono povezivanje ALMBIH sa institucijama sistema, zdravstvenim ustanovama i podnosiocima zahtjeva, a sve u cilju zaštite javnog zdravlja. Najznačajniji informacioni projekti ALMBIH u tom pravcu su: primjena aplikacije Ready, IS farmakovigilansa i WEB servis za jedinstvenu identifikaciju lijeka (JIDL).

Primjenom aplikacije Ready uspješno smo prevazišli brojne prepreke uzrokovane prvenstveno fizičkom razdvojenošću i poslovanju na tri lokacije: Banjaluka, Sarajevo i Mostar. Aplikacija je omogućila uvezivanje podataka o svim lijekovima koji imaju dozvolu za stavljanje u promet u BiH i izvještavanje po raznim osnovama, prateći cijeli život jednog lijeka, od podnošenja zahtjeva za registraciju, dobijanja dozvole za stavljanje u promet i kasnije. Na osnovu podataka koji se generišu iz Ready aplikacije, transparentan je i uvijek ažuriran spisak registrovanih lijekova u BiH, objavljen na našoj web stranici, a koji se može pretraživati po različitim osnovama. Jedna od aktivnosti koju uspješno provodimo zahvaljujući mogućnostima Ready aplikacije predstavlja i objavljivanje na našoj web stranici Uputstva za pacijenta i Sažetka karakteristika lijeka za lijekove koji imaju dozvolu za stavljanje u promet u BiH. Kao kruna svega, sa punim pravom možemo se pohvaliti da je naš Registar lijekova za 2015. godinu nastao kao rezultat informatičkih mogućnosti koje pruža Ready softver.

Sredinom 2014. godine počeli smo uvođenje elektronskog podnošenja prijave sumnje na neželjeno dejstvo lijeka u BiH – IS farmakovigilansa. Softver omogućava elektronsku prijavu sumnje na neželjeno dejstvo lijeka od strane zdravstvenog radnika.

Implementacijom WEB servisa jedinstvene identifikacije lijeka (JIDL) želimo da postignemo da kroz softversko generisanje šifre za lijekove u sistemu ALMBIH za svaki lijek posebno imamo identifikaciju (tzv. „ličnu kartu“) lijeka u prometu u veleprodaji i maloprodaji (apotekama), kod proizvođača i kod državnih institucija.

Jednostavno rečeno i umjesto zaključka, možemo konstatovati da novi informacioni sistemi pružaju brojne mogućnosti unapređenja poslovanja unutar naše institucije kao i proširenja funkcionalnosti na stabilnim osnovama, što će se posljedično reflektovati kako na naš dalji razvoj (u smjeru izrade javnog portala, farmakoekonomskih analiza, kvalitetnog praćenja neželjenih dejstava, praćenja prometa lijekova, te reklamiranja i oglašavanja lijekova) ali isto tako i na dalje unapređenje zaštite javnog zdravlja stanovništva BiH.

NOVE PERSPEKTIVE ANTITUMORSKE TERAPIJE - UTIŠAVANJE PROTEINA TOPLINSKOG STRESA POMOĆU SIRNA NANOTERAPIJE

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RNA interferencija (RNAi) jest mehanizam posttranskripcijske regulacije genske ekspresije. Može biti potaknuta endogeno, pomoću mikro RNA (miRNA), prirodnih produkata RNA polimeraze II, ili egzogeno, unosom artificijelnih dvolančanih RNA poput shRNA i siRNA. Egzogeni poticaj RNAi može se iskoristiti u terapijske svrhe.
Cilj istraživanja bio je ispitati a) mogućnost utišavanja ekspresije proteina toplinskog stresa Hsp70, b) mogućnost dostave siRNA za Hsp70 kitozanskim nanočesticama te c) antitumorski učinak smanjene ekspresije Hsp70.
U svrhu utišavanja ekspresije Hsp70 korištena je RNAi egzogeno potaknuta kratkom siRNA za Hsp70 u tumorskim stanicama Jurkat i U251. siRNA za hsp70 mRNA uklopljena je u kitozanske nanočestice postupkom ionotropnog geliranja kitozana natrijevim tripolifosfatom (TPP) uz dodatak siRNA.
U uvjetima in vitro kitozanske nanočestice pokazale su nisku toksičnost, učinkovito uklapanje Hsp70 siRNA te učinkovito utišavanje Hsp70. U staničnim linijama Jurkat i U251N utišavanje Hsp70 prouzročilo je smanjenje vijabilnosti ovih tumorskih staničnih linija u dvo- i tro-dimenzionalnim tumorskim modelima.

Ključne riječi: RNA interferencija (RNAi), protein toplinskog stresa 70 (Hsp70), siRNA, kitozanske nanočestoce

NEW PERSPECTIVES OF ANTITUMOR THERAPY - SILENCING OF HEAT SHOCK PROTEINS BY SIRNA NANODELIVERY

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RNA interference (RNAi) is a mechanism of posttranscriptional regulation of gene expression. It can be triggered endogenously, by microRNA (miRNA), natural products of RNA polymerase II, or exogenously, by an uptake of an artificial double-stranded RNA, such as shRNA and siRNA. RNAi can be used as a potent therapeutic tool.
The aim of this study was to examine a) the possibility of silencing the expression of the heat shock protein 70 (Hsp70), b) the possibility of delivery of siRNA for Hsp70 by chitosan nanoparticles and c) anti-tumor effect of Hsp70 silencing.
RNAi was induced in Jurkat and U251N tumor cell lines by small siRNA for Hsp70 which was entrapped in chitosan nanoparticles.
Chitosan nanoparticles showed low toxicity, efficient entrapping of Hsp70 siRNA and effective silencing of hsp70 gene in vitro. In Jurkat and U251N tumor cell lines silencing of the Hsp70 caused a decrease in viability of these tumor cell lines in two- and three-dimensional tumor models.

Key words: RNA interference (RNAi), Heat shock proteins 70 (Hsp70), siRNA, chitosan nanoparticles

HEMIJSKA ANALIZA ETARSKOG ULJA *SATUREJA CUNEIFOLIA* TEN., LAMIACEAE I MOGUĆNOST NJENE PRIMJENE

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Satureja cuneifolia Ten., Lamiaceae je višegodišnja zeljasta biljka sa stabljikom i listovima obraslim gustim strčećim, oštrim dlakama, cvjetova veličine do 5mm, bjeličaste boje sa purpurno ljubičastim mrljana. Cilj ovog istraživanja je da se izvrši analiza hemijskog sastava izolovanog etarskog ulja iz osušenog nadzemnog dijela biljke (uzorci sakupljeni krajem avgusta 2014. godine na Lovćenu). Etarsko ulje je dobijeno metodom hidrodestilacije u aparaturi po Clevenger-u. Ispitivanje kvalitativnog i kvantitativnog sastava etarskog ulja izvršeno je gasnohromatografskom tehnikom (GC/MS i GC/FID).
Na osnovu gasnohromatografske analize u analiziranim uzorcima identifikovano je oko 80 jedinjenja cineci 98,7 %. GC/MS i GC/FID analizom je utvrđeno da su oksidovani monoterpeni (47,2%) dominantna grupa jedinjenja. Dalje, identifikovani su: monoterpenski ugljovodonici (3,9), seskvi terpenski ugljovodonici (25,8%), oksidovani seskviterpeni (27,3%) i druga jedinjenja (0,8%). Od monoterpenskih jedinenja najzastupljenij su α-pinen (0,7%) i limonen (1,1%), od oksidovanih monoterpenskih jedinjenja najzastupljeniji su linalol (20,3%), borneol (3,6%) i α-terpineol (3,8). Od seskviterpenskih jedinjenja najzastupljeniji su: α-kopaen (4,21%), trans-β-kariofilen (6,1%), germakren D(5,8%). Od oksidovanih seskviterpena najzastupljeniji su: nerolidol (5,2%) i spatulenol (5.0%), kariofilen oksid (3,1%), β-eudezmol (4,5%). Izvršeno je upređivanje identifikovanih jedinjenja sa literaturnim podacima za S. cuneifolia Ten., i S. montana L., Lamiaceae
Upoređivanjem identifikovanih jedinjena konstatovali smo da postoji razlika u kvantitativnom i kvalitativnom sastavu u odnosu na literaturne podatke za biljku koja vodi porijeklo (navesti podatak iz literature koju imas / Grcka. Hrvatska, Juzna Srbija.....). Takođe, razlika u odnosu na literaturne podatke za, u narodu vrlo cijenjenu biljku iz istog roda, S. montana L. je evidentna. S obzirom da pomenute vrste sadrže terpenska jedinjenja, literaturni podaci ukazuju na antimikrobnu aktivnost koja moze naći primjenu u liječenju kao antibakterijski, antinflamatorni, gastropritektivni agensi.Varijabilnost u kvalitativnom i kvantitativnom sastavu najvjerovatnije zavisi od genotipa biljke i uticaja različitih ekoloških faktora. Sastav ispitivanog etarskog ulja je uporedjen sa sastavom etarskog ulja vrijeska koji se upotrebljava u tradicionalnoj medicini, sto je značajno u cilju evaluacije kvaliteta ispitivane biljne sirovine i potencijalne primjene u terapijske svrhe.

Ključne riječi: satureja, etarsko ulje, hemijski sastav.

ESSENTIAL OIL OF *SATUREJA CUNEIFOLIA* TEN., LAMIACEAE – CHEMICAL EVALUATION AND POSSIBLE APPLICATION

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Satureja cuneifolia Ten., Lamiaceae is a perennial herbaceous plant with stems and leaves covered with thick spiky, sharp hairs, flowers up to 5 mm, whitish with purple-violet stain. The aim of this study is to analyze the chemical composition of essential oil isolated from dried aerial parts of plants (samples collected at the end of August 2014, on Lovcen). The essential oil was obtained by the hydrodistillation in Clevenger apparatus. Determination of qualitative and quantitative composition of the essential oil was performed using gas chromatographic technique (GC / MS and GC / FID).

Based on GC / MS and GC / FID analysis of the investigated samples 80 compounds were identified, representing 98.7%. The performed analysis showed that the oxidized monoterpenes (47.2%) were the predominant group of compounds. Sesquiterpene hydrocarbons (25.8%) and oxidized sesquiterpenes (27.3%) were present in a significant amount in the sample, whereas monoterpene hydrocarbones were represented with only 3.9%. The most abundant compound was linalool belonging to the oxidized monoterpenes group and representing 20.4%, Besides linalool, borneol (3.6%) and α-terpineol (3.8%) were present in a relatively high concentration. Within the sesquiterpene compounds α-copaene (4.2%), trans-β-caryophyllene (6.1%), germacrene D (5.8%) were present in a significant quantity, and the constituents belonging to oxidized sesquiterpenes were nerolidol (5.2%) and spathulenol (5.0%), caryophyllene oxide (3.1%), β-eudesmol (4.5%). In the group of monoterpene hydrocarbons, α-pinene (0.7%) and limonene (1.1%) were the main constituents. Besides, the chemical composition of the essential oil of S. cuneifolia and S. montana L. given in literature was compared with our findings.

The comparison of the identified compounds in the investigated samples and the literature data, revealed the significant difference in the qualitative and quantitative composition of two species, S. cuneifolia and winter savory, S. montana. As the polyphenolic compounds within terepenes are the carrier of antioxidant activity, the possible application of the investigated samples might be as an antibacterial, anti-inflammatory and gastroprotective agents. The variability of the qualitative and quantitative composition probably depends on the genotype of the plant and the influence of different environmental factors. The composition of the investigated essential oil was compared to the composition of the essential oil of winter savory used in a traditional medicine, which is important in order to evaluate the quality of the investigated plant material and its possible applications for different therapeutic purposes.

Keywords: satureja, essential oil, chemical composition

COMPETENCIES OF THE "FIRST DAY OF JOB" PHARMACIST

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In the last decades, we are faced with altered approach of educational process on the tertiary level. Competency models are introduced instead of earlier structured type of curricula. Quality assurance was recognized as one of the reason for this, based on the biggest change of higher education area – access to the higher education: 2% of the population in 19th century versus EU stated ambition of 40% of all young people graduating by 2020.
The core mission of higher education remains to enable people to learn. Increased number of students and higher education institution (HEIs), diversification of HEIs landscape on one hand and scarce funding and massive changes in science on the other hand have dramatically changed the context of HEIs. Considering the shorter shelf-life of knowledge it is difficult to know, with what kind of demands will be graduates faced from the working and social surroundings in the next decades. The quality of teaching and learning at HEIs determines how efficiently their graduates will fulfill those demands. Not only knowledge but also development of personal capability should be included into educational process at HEIs to provide competent graduates to the society. Competency, which is a set of defined behaviors that provide a structured guide enabling the identification, evaluation and development of the behaviors in individual employees, are of two types - general and job/program-specific, on five levels: Novice, Experienced Beginner, Practitioner, Knowledgeable practitioner and Expert. The HEIs may provide graduates with competencies as novices – this is called the "first day of job" competencies.
What kind of competencies pharmacists will need in the future? This is the task, treats through European association of faculties of pharmacy (EAFP) and two European projects PHARMacy education IN Europe (Pharmine) and Quality assurance in European pharmacy education and training (Phar QA), both focused on the role for pharmacists and their ability to fulfill future demands of the society. In the XXI century, pharmacists will play an increasingly important role as partners in the efficient use of the health care resources of the EU (community and hospital pharmacists) and be major players in the development of the EU pharmaceutical industry. The bottom line is patient safety. The scope of PHAR-QA is the production of a European Quality Assurance framework, assessing the competences in pharmacy practice and aiming at the development of academic curricula, through which the said mission will be fulfilled. The Delphi method was adopted for the elaboration of the competences: it is a process for structuring communication, allowing a group of individuals, to deal with a complex problem even if the information comes from different countries, sectoral activities and education systems.
The use of competencies eliminates ambiguity and clearly establishes what the student is able to do at the end of the program. Although, the final list of competences is not an absolute guide for curricula modifications, undoubtedly its analysis will promote a productive discussion among the stakeholders.

Key words: Pharmacy education and training, quality assurance, competencies

POLIELEKTROLITNI KOMPLEKSI NA BAZI HITOZANA: KARAKTERISTIKE I PRIMJENA U FORMULACIJI MIKRO- I NANOČESTIČNIH NOSAČA LIJEKOVA

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Hitozani su linearni, binarni heteropolisaharidi dobijeni parcijalnom deacetilacijom hitina. Jedinstvena (poli)katjonska priroda, biokompatibilnost, biodegradabilnost i porijeklo iz obnovljivih izvora čine ove polimere pogodnim za mikro- i nanoinkapsulaciju ćelija, gena, proteina i strukturno različitih ljekovitih supstanci. Strukturna raznovrsnost hitozana, posebno u pogledu molekulske mase i stepena deacetilacije, kao i mogućnost hemijske derivatizacije, pružaju mogućnost da se osobine ovih polimera, odnosno njihovih derivata, prilagode potencijalnoj primjeni.
Hitozani kao (poli)katjoni mogu pod odgovarajućim uslovima (pH vrijednost, koncentracija) da stupaju u elektrostatičku interakciju sa (poli)anjonima, poput alginata, pektina, karagenana, karboksimetilceluloze i karboksivinil polimera, formirajući polielektrolitne komplekse. Polielektrolitni kompleksi su biodegradabilni, a posjeduju fizičko-hemijske karakteristike koje se značajno razlikuju od karakteristika polijona koji ulaze u njihov sastav. Zbog osjetljivosti na biološke stimuluse, a naročito na promjene pH vrijednosti, ovi kompleksi se mogu koristiti kao nosači ljekovitih supstanci samostalno ili za poboljšanje stabilnosti, morfoloških karakteristika, efikasnosti inkapsulacije, sposobnosti bubrenja i profila oslobađanja ljekovite supstance iz mikro- i nanočestičnih nosača na bazi (poli)anjona.
U ovom radu biće predstavljeni osnovni principi polielektrolitnog kompleksiranja, značaj eksperimentalnih uslova (pH vrijednost i jonska jačina reakcionog medijuma, koncentracija i odnos pojedinačnih polimera) i funkcionalnih karakteristika hitozana (molekulska masa, stepen deacetilacije i viskozitet) na ovaj proces, na osnovu dobijenih eksperimentalnih rezultata. Pored toga, biće opisani i formulacioni izazovi, kao i prednosti i mogućnosti primjene čestičnih nosača na bazi hitozanskih polielektrolitnih kompleksa.

Ključne riječi: hitozan, polielektrolitni kompleks, pH-osjetljivost

CHITOSAN-BASED POLYELECTROLYTE COMPLEXES: CHARACTERISTICS AND APPLICATION IN FORMULATION OF MICRO- AND NANOPARTICULATE DRUG CARRIERS

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Chitosans are binary linear heteropolysaccharides derived from chitin by its partial deacetylation. Unique (poly)cationic nature, biocompatibility, biodegradability and origin from renewable sources, make chitosans suitable for micro- and nanoencapsulation of cells, genes, proteins and structurally different drugs. Their chemical versatility, particularly versatility of their molecular weight and deacetylation degree, along with the possibility of chemical derivatisation, make possible to adjust the properties of chitosans to their potential application.
Under suitable conditions (pH value and concentration), chitosans, as (poly)cations, can interact electrostatically with (poly)anions, such as alginate, pectin, carrageenan, carboxymethyl cellulose and carboxyvinyl polymer, creating polyelectrolyte complexes. Polyelectrolyte complexes are non-permanent assemblies, with physicochemical properties that significantly differ from those of the individual polymers. Due to their stimuli-responsive nature, particularly the pH-sensitivity, these complexes can be used as drug carriers independently or to improve stability, morphology, encapsulation efficiency, swelling and drug release properties of (poly) anionic-based micro- and nanoparticulate drug carriers.
This work will summarize basic principles of polyelectrolyte complexation, importance of experimental conditions (pH value and ionic strength of the reaction medium, concentration, and ratio of individual polymers) and chitosans functional properties (molecular weight, degree of deacetylation and viscosity) on this process, based on the obtained experimental results. Additionally, formulation challenges, benefits and possible applications of chitosan-based polyelectrolyte complex particulate drug carriers will be discussed.

Keywords: chitosan, polyelectrolyte complex, pH-sensitivity

DIJETETSKI SUPLEMENTI U PRIMARNOJ I SEKUNDARNOJ PREVENCIJI KARDIOVASKULARNIH BOLESTI

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Poslednjih decenija način ishrane, kao i primena dijetetskih suplemenata bili su predmet brojnih istraživanja sa ciljem sagledavanja njihove uloge u primarnoj i sekundarnoj prevenciji niza bolesti, uključujući i kardiovaskularne bolesti (KVB) za koje je, zbog njihovog visokog morbiditeta i mortaliteta, i dizajniran najveći broj dijetetskih suplemenata. Podaci iz literature sugerišu da prosečno više od jedne trećine kardioloških bolesnika redovno uzima neki od dijetetskih suplemenata, po pravilu zajedno sa konvencionalnim lekovima, a bez znanja svojih lekara, što otvara mnoga pitanja vezana, pre svega, za bezbednost njihove upotrebe.
Imajući u vidu iznesene činjenice cilj ovog rada bio je da se prezentuju relevantni podaci o efikasnosti i bezbednosti primene dijetetskih suplementa u prevenciji KVB.
Analizirani su rezultati kontrolisanih kliničkih studija, meta-analiza i sistematskih pregleda o upotrebi dijetetskih suplemenata u primarnoj i sekundarnoj prevenciji KVB, objavljenih u časopisima koje prate baze PubMed/MEDLINE i Cochrane Database of Systematic Reviews u periodu 1990-2015. Poseban akcent stavljen je na studije o upotrebi pojedinih vitamina (A, B, C, D, E, Q10), minerala i omega-3-nezasićenih masnih kiselina.
Analiza je pokazala da za sada nema dovoljno čvrstih dokaza da se bilo koji od razmatranih dijetetskih suplemenata preporuči kao dokazano efikasno i bezbedno sredstvo za primarnu i sekundarnu prevenciju KVB.
Prezentovani rezultati o efikasnosti i bezbednosti pojedinih dijetetskih suplemenata koji se često koriste u primarnoj i sekundarnoj prevenciji KVB ukazuju na potrebu pažljivog razmatranja preporuka za njihovo korišćenje, ukoliko one nisu zasnovane na kvalitetnim kliničkim studijama, odnosno dobro sprovedenim sistematskim pregledima i meta-analizama tih studija. Dok se ne sakupe dovoljno pouzdani dokazi najbolje je unos analiziranih suplemenata obezbeđivati putem hrane jer se smatra da raznovrsna i uravnotežena ishrana, uglavnom, zadovoljava potrebe organizma za njima.Ovo tim pre, jer je pokazano da ne samo deficit, već i preteran unos pojedinih dijeteskih suplemenata (npr. pojedinih vitamina) može povećati rizik od pojave mnogih bolesti.

Ključne reči: dijetetski suplementi; vitamini; minerali; omega-3-nezasićene masne kiseline; kardiovaskularne bolesti, prevencija.

DIETARY SUPPLEMENTS IN PRIMARY AND SECONDARY PREVENTION OF CARDIOVASCULAR DISEASES

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In recent decades diet as well as the use of dietary supplements have been the subject of numerous studies aiming to estimate their role in primary and secondary prevention of various diseases, including cardiovascular diseases (CVDs), for which, due to their high morbidity and mortality, most of dietary supplements have been designed. Data from the literature suggest that on the average more than 30% of cardiac patients regularly use some dietary supplements, usually together with conventional drugs, but without the knowledge of their physicians, raising several issues related primarily to the safety of their use.
Bearing in mind the above-mentioned facts, the aim of this study was to present relevant data on the efficacy and safety of dietary supplements in the prevention of CVDs.
The results of controlled clinical trials, meta-analyses and systematic reviews on the use of dietary supplements in the primary and secondary prevention of CVDs, published in journals covered by PubMed/ MEDLINE and the Cochrane Database of Systematic Reviews in the period 1990-2015 were analyzed. Special emphasis was placed on the studies on the use of certain vitamins (A, B, C, D, E, Q10), minerals and omega-3 unsaturated fatty acids.
The analysis showed that for now there is not enough confirmed evidence that any of the dietary supplements considered could be recommended as proven effective and safe options for primary and secondary prevention of CVDs.
The presented results on the efficacy and safety of certain dietary supplements that are often used in primary and secondary prevention of CVDs indicate the need for careful consideration of recommendations for their use, if they are not based on well-designed clinical studies or their well-conducted systematic reviews and meta-analyses. While not generating enough reliable evidence it is best to provide the intake of analyzed supplements via food because it is known that different kinds of food and balanced diet mainly meet the needs for them. This is very important because it has been shown that not only the deficit, but excessive intake of certain dietary supplements (eg. some vitamins) may also increase the risk of many diseases.

Keywords: dietary supplements; vitamins; minerals; omega-3-unsaturated fatty acid; cardiovascular disease, prevention.

VANBOLNIČKA POTROŠNJA ANTIBIOTIKA U CRNOJ GORI – NEOPHODNOST EFIKASNIJE INTERVENCIJE FARMACEUTA

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U periodu 2000-2009 vanbolnička potrošnja antibiotika u Crnoj Gori se više nego udvostručila (18,4DDD/1000stanovnika/dan vs. 40,2DDD/1000stanovnika/dan), da bi u prethodnih nekoliko godina došlo do njenog blagog smanjenja. I pored toga smo među evropskim zemljama sa najvišom potrošnjom ovih ljekova, što zabrinjava. Obzirom na činjenicu da se u našoj zemlji antibiotici mogu izdavati samo na ljekarski recept, pogrešno je uvjerenje da je uloga farmaceuta u vanbolničkoj potrošnji ovih ljekova beznačajna, naprotiv.
Farmaceuti, naročito oni zaposleni u javnim apotekama, imaju nezamjenljivu ulogu kada je u pitanju edukacija pacijenata o tome kako prevenirati nastanak infekcija, počev od promovisanja vakcinacije pa do provjetravanja prostorija i pravilnog pranja ruku. Takođe, farmaceuti su u potpunosti kompetentni da u najvećem broju akutnih infekcija gornjeg respiratornog trakta uzrokovanih virusima preporuče odgovarajuću simptomatsku terapiju, čime će dodatno smanjiti pritisak na ljekare-propisivače za propisivanjem antibiotika od strane pacijenata. Veoma važna uloga farmaceuta je i u informisanju pacijenata o tome kako da pravilno upotrebljavaju i čuvaju propisani antibiotik, što je neophodno da bi se očuvala njegova djelotvornost. Nije zanemarljiva ni edukativna uloga farmaceuta na doktore-propisivače, koji su često skloni propisivanju tzv. širokospektralnih i skupih antibiotika i kada to nije neophodno. Suvišno je isticati ulogu farmaceuta u otkriću i razvoju novih antibiotika.
Imajući u vidu prethodno, može se zaključiti da farmaceuti ne smiju biti samo pasivni posmatrači i, zajedno sa ostalim članovima društva, mogući gubitnici bitke za antibiotike koja traje, već odgovorni i kompetentni činioci zdravstvenog sistema koji moraju dati svoj puni doprinos očuvanju postojećih i razvoju novih antibiotika.

Ključne riječi: antibiotici, vanbolnička potrošnja, intervencija farmaceuta

OUTPATIENT ANTIBIOTIC CONSUMPTION IN MONTENEGRO - A NECESSITY OF EFFECTIVE INTERVENTION OF PHARMACISTS

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In the period 2000-2009 outpatient antibiotic consumption in Montenegro has more than doubled (18,4DDD/1000inhabitants/day vs. 40,2DDD/1000inhabitants/day), but in the past few years there has been a slight decrease. Nevertheless, we are among the European countries with the highest consumption of these drugs, which is worrisome. Due to the fact that in our country antibiotics may be issued only on prescription, the wrong belief is that the role of pharmacists in outpatient consumption of these drugs is insignificant, on the contrary.
Pharmacists, especially those employed in public pharmacies, have an indispensable role when it comes to patient education on how to prevent the occurrence of infections, ranging from promoting vaccination to the room ventilation, and proper hand washing. Also, pharmacists are fully competent to recommend appropriate symptomatic treatment for the greatest number of acute upper respiratory tract infections caused by viruses, which will further reduce the pressure on doctors-prescribers to prescribe antibiotics by patients. An important role of the pharmacist is in informing patients about how to properly use and store the prescribed antibiotic, which is necessary in order to preserve its effectiveness. It is significant educational role of pharmacists to doctors-prescribers, who are often prone to prescribe broad-spectrum and expensive antibiotics, and when this is not necessary. Needless to emphasize the role of pharmacists in the discovery and development of new antibiotics.
Bearing in mind the above, it can be concluded that pharmacists should not be just passive observers, along with other members of society, and potential losers battle for antibiotics that lasts, but responsible and competent health system components which must give its full contribution to the preservation of existing and development of new antibiotics.

Keywords: antibiotics, outpatient consumption, pharmacist intervention

SAVREMENI PRISTUP FORMULACIJI PREPARATA SA MODIFIKOVANIM OSLOBAĐANJEM; HRONOTERAPIJSKI SISTEMI

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Cirkadijane varijacije u fiziološkim funkcijama organizma mogu da utiču na tok bolesti i farmakokinetiku lekovitih supstanci. Za simptome bolesti kardiovaskularnog i respiratornog sistema, kancer, artritis, alergijski rinitis, peptički ulkus, itd. pokazano je da prate cirkadijane ritmove. Hronoterapijski sistemi se formulišu tako da oslobađaju lekovitu susptancu u skladu sa cirkadijanim biološkim ritmovima; terapijski nivoi lekovite supstance u krvi obezbeđuju se u tačno određeno vreme čime se optimizuje terapijski ishod.
Različite tehnologije za razvoj hronoterapijskih sistema zasnivaju se na pulsnom, vremenski kontrolisanom, programiranom ili oslobađanju lekovite supstance u prisustvu određenih okidača. Formulisani sistemi mogu biti jedno- ili višečestični, a najčešće se radi o rezervoar sistemima sa membranom. Oslobađanje lekovite supstance iz rezervoara kontrolisano je pucanjem, promenljivom permeabilnošću, bubrenjem ili rastvaranjem membrane. Membrane sadrže polimerne supstance različitih karakteristika. Mehanizam oslobađanja lekovite supstance je rastvaranje ili difuzija. Na vreme odlaganja oslobađanja lekovite supstance (lag time) može se uticati odabirom vrste polimera i debljinom omotača. Plutajući gastroretentivni sistemi su takođe jedan od mogućih pristupa formulaciji hronoterapijskih sistema. Patentirane su brojne tehnologije za razvoj hronoterapijskih sistema koje se zasnivaju na različitim mehanizmima kontrole oslobađanja lekovite supstance: OROS® (mehanizam osmotskog pritiska), CODAS® (višečestični pH zavisni sistem), DIFFUCAPS® (višečestični sistem), PULSINCAP® (sistem sa pucanjem membrane), CONTIN® (matriks tablete), CEFORM® (obložene mikročestice), TIMERx® (hidrogel sistem), itd.
Farmaceutski oblici hronoterapijskih sistema su kapsule, tablete ili implanti. Tablete se formulišu kao višeslojne ili tablete obložene kompresijom. Kapsule se pune višečestičnim hronoterapijskim sistemima ili se radi o posebno obrađenim kapsulama (npr. PULSINCAP® sistem). Napredni hronoterapijski sistemi se zasnivaju na primeni mikročipova ili trodimenzionalnom štampanju.
Na tržištu postoji veći broj registrovanih hronoterapijskih preparata, pre svega za lečenje bolesti kardiovaskularnog sistema, kao i za terapiju astme, peptičkog ulcera, hiperlipidemije, itd.
U ovom radu biće predstavljene aktuelne tehnologije i njihova primena formulaciji hronoterapijskih sistema.

Ključne reči: modifikovano oslobađanje lekovite supstance, hronoterapijski sistemi, mehanizam oslobađanja lekovite supstance, patentirane tehnologije, farmaceutski oblici

MODERN FORMULATION DEVELOPMENT OF MODIFIED RELEASE PRODUCTS; CHRONOPHARMACEUTICS

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Circadian variations in physiological functions of organisms may affect the disease course and drug's pharmacokinetics. Symptoms of diseases of cardiovascular and respiratory systems, cancer, arthritis, allergic rhinitis, peptic ulcer, etc. have been known to follow circadian rhythms. Chronotherapeutic systems are formulated in such a manner to release the drug substance in concordance with circadian biological rhythms, assuring that the therapeutic concentration of the drug substance is provided in specific time frame, optimizing that way the therapeutic outcome.

Various technologies for development of chronopharmaceutics are based on pulsatile, time-controlled, programmed or triggered release of the drug substance. Formulated systems may be single- or multiparticulate, with the membrane surrounded reservoir systems being most frequently used. Drug release from the reservoir may be controlled by the burst effect, variable permeability or by the swelling or dissolution of the membrane. Membranes are made up of the various types of polymers. Mechanism of the drug release is dissolution or diffusion. Lag time of the drug release is affected by selection of the polymer type or the membrane thickness. Floating gastroretentive systems are also potential alternatives for development of chronopharmaceutics. Various technologies based on different mechanisms of drug release have been patented for development of chronopharmaceutics: OROS® (osmotic pressure build-up), CODAS® (multiparticulate pH dependent system), DIFFUCAPS® (multiparticulate system), PULSINCAP® (bursting membrane system), CONTIN® (matrix tablets), CEFORM® (coated microparticles), TIMERx® (hydrogel system).

The final dosage forms of chronopharmaceutics are capsules, tablets or implants. Tablets are formulated as multilayer or compression coated tablets. Capsules are filled with the multiparticulate chronotherapeutic systems, or are specifically processed (such as PULSINCAP® system). Advanced chronopharmaceutics include application of microchips or threedimensional printing.

There are number of marketed chronotherapeutic products, mainly for the treatment of the cardiovascular diseases, asthma, peptic ulcer, hyperlipidemia, etc.

The present study will discuss contemporary technologies and their application in the formulation of chronopharmaceutics.

Keywords: modified drug release, chronopharmaceutics, drug release mechanism, patented technologies, pharmaceutical dosage forms

RACIONALNA PRIMENA ANTIMIKROBNIH LEKOVA U BOLNIČKOJ SREDINI

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Racionalna antimikrobna terapija definisana je kao optimalan izbor, doziranje i trajanje lečenja antibioticima (AB), čiji je rezultat najbolji klinički ishod za lečenje ili sprečavanje zaraze, uz minimalnu toksičnost za pacijenta i minimalan uticaj na kasniju rezistenciju. Uobičajene greške pri AB su propisivanje nepotrebnog ili pogrešnog AB, pogrešan dozni režim i propisivanje leka koji stupa u neželjene interakcije sa drugim lekovima. Neracionalna primena AB ima posledice za pojedinca: neželjena dejstva AB, progresija primarne infekcije, sepsa, smrt, suprainfekcija i nova bolnička infekcija izavana multirezitentnim patogenima (MRP). Sa druge strane, u bolnicama se šire MRP, učestalost i mortalitet od bolničkih infekcija raste, a trškovi produženog bolničkog lečenja su povećani. Empirijska primena AB širokog spektra, nepotrebne kombinacije AB, kašnjenje sa prevodjenjem na peroralnu primenu, dominacija empirijske primene i pogrešna AB profilaksa su glavni uzroci za pojavu MRP. U Univerzitetskom kliničkom centru "Dr Dragiša Mišović Dedinje se od 2006. godine prati prisustvo MRP primenom programa WHO-net. Zabeleženo je prisustvo MRP: Klebsielle pneumoniae, E. coli i Proteus mirabilis, Enterococcusa faecium, Pseudomonas aeruginosa, MRSA i Acinetobacter baumannii. Pri jednomesečnom praćenju navika u propisivanju AB (2012. god.) empirijska primena AB je bila nepotrebno visoka (35-55%), a dominirala je nepotrebna primena AB širokog spektra. Od tada su uvedene sledeće mere: lekari su obaveštavani redovno o lokalnoj mapi rezistencije, o varijacijama MIC za prisutno patogene, organizovane su brojne eukacije o racionalnoj upotrebi AB, obezbedjeno je redovno snadbevanje AB (npr. kolistin), praćena je potrošnja AB i napisam je Vodič za emirijsku i profilaktičku primenu antimikrobnih lekova u bolnica, prema lokalnom izolatu. Sve ovo je smanjilo potrošnju AB, empirijsku primenu AB, broj bolničkih infekcija i prisustvo MRP.

Ključne reči: antimikrobni lekovi, racionalna primena, bolnica

RATIONAL USE OF ANTIBIOTICS IN HOSPITALS

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Common errors in the AB therapy are unnecessary prescribing of AB, wrong choice of AB, incorrect dosage regimen, and prescribing of AB that interacts with other drugs. The implications of un rational AB use for individual patient might be: side effects of antibiotics, progression of primary infection, sepsis, death, suprainfection and intrahospital infection caused by multidrug resistant (MDR) pathogens. The implications for society in whole might be the spread of MDR pathogens in the hospital environment, higer percent of nosocomial infections, higer intrahospital mortality and increased costs of hospital treatment. Empirical use of broad-spectrum AB, unnecessary combinations of AB, delay in translating the parenteral to oral application of AB, the dominance of empiric AB therapy and wrong AB prophylaxis are the main causes for the occurrence of MDR pathogens in hospital. In the University Clinical Center " Dr Dragisa Mišović - Dedinje" the presence of MDR pathogens have been monitoring since 2006. We used the program WHO-net for the analysis of the obtained susceptibility testing. In the last 3-year we recorded the presence of MDR Klebsiella pneumoniae, E. coli, Proteus mirabilis, Enterococcus faecium, Pseudomonas aeruginosa, Acinetobacter baumannii and MRSA. In June 2012, we followed-up the prescribing habits of AB. The empirical application of fluoroquinolones, third generation of cephalosporins and amoxicillin + clavulanic acid was unnecessarily high (35-55%). Because of that, we introduced the following: doctors are informed regularly about the local map of resistance, the educative courses about rational use of AB in hospitals were organized, the regular supply of all necessary AB was provided (eg. colistin), and Guide for empiric and prophylactic use of antimicrobial agents in hospitals (according to the local strain) was published. The use of AB, the empirical therapy of AB and the incidence of nosocomial infections induced by MDR pathogens were reduced.

Key words: antimicrobial agents, rational use, hospital

RAZLOZI I UČESTALOST OFF-LABEL PRIMENE LEKOVA

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Primena leka u skladu sa dozvolom za promet koju je izdao regulatorni organ predstavlja on-label primenu, dok se u praksi često sreće i off-label primena lekova, koja podrazumeva primenu leka mimo odobrenih indikacija, za neodobrenu starosnu grupu, sa drugim režimom doziranja ili drugačijim načinom primene. Lekari specijalisti često propisuju off- label lekove u pedijatriji, neonatologiji, gerijatriji, psihijatriji i onkologiji. Neke zemlje imaju registre upotrebe off-label lekova i vodiče za njihovo propisivanje i primenu.
Cilj rada je bio da se prikažu iskustva iz prakse u off-label primeni lekova.
Izvori podataka su radovi objavljeni u naučnim časopisima i zvaničnim internet stranicama regulatornih tela.
Razlozi zbog kojih se lekari odlučuju za off-label propisivanje lekova su nedostatak lekova za određenu indikaciju ili za određenu starosnu grupu. U praksi, lekari propisuju lekove za off-label primenu na osnovu vlastitog ili iskustva drugih kolega. Mnogo više lekari specijalisti propisuju lekove za off-label primenu nego lekari opšte prakse. Nema jedinstvenog stava o off-label primeni lekova kod nas i u svetu ali sve više udruženja lekara i regulatornih tela odobrava off-label primenu lekova uz poštovanje određenih stručnih i zakonskih uslova.
Primena off-label lekova ima svoje mesto u praksi i široko je prihvaćena među lekarima, te nije u suprotnosti sa zdravstvenim standardima. Off-label primena je zastupljena kod nas i u svetu i neophodno je formirati registre za off-label primenu lekova.

Ključne reči: Off-label primena; Primena lekova, Lekarsko iskustvo, Registri

REASONS FOR AND FREQUENCY OF OFF-LABEL DRUG USE

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The sources of information used are articles published in scientific journals and information from the official websites of regulatory agencies.
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associations and regulatory bodies approve off-label drug use in compliance with certain scientific and legal requirements.
Off-label drug use has its place in practice and it has been widely accepted by the medical community and by itself it is not a violation of the standards of healthcare. Off-label use is common in our country and worldwide, and it is necessary to establish a registry for off-label drug use.

Key words: Off-label use; Drug prescriptions; Physician's practice patterns; Registries

SAVREMENI PRISTUP U RAZVOJU PREPARATA SA MODIFIKOVANIM OSLOBAĐANJEM LEKOVITE SUPSTANCE: GASTRORETENTIVNI TERAPIJSKI SISTEMI

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Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu – Farmaceutski fakultet

Razvoj oralnih farmaceutskih oblika sa modifikovanim oslobađanjem lekovite supstance privlači pažnju formulatora u farmaceutskoj industriji decenijama unazad. Formulacija oralnih preparata sa modifikovanim oslobađanjem lekova, u slučajevima kada za određenu lekovitu supstancu postoje "apsorpcioni prozori", za lekove koji su nestabilni i/ili teško rastvorljivi u nižim delovima GIT-a, bili su nemogući, sve do pojave nove grupe, tzv. Gastroretentivnih terapijskih sistema (GRTS). Koncept na kome se formulacija ovih oblika zasniva je zapravo zadržavanje terapijskog sistema što duže u želucu, tj. sve vreme dok je planirano rastvaranje, oslobađanje i resorpcija leka, što je najčešće period od 6 do 10 časova.
Pristup razvoju gastroretentivnih teraspijskih sistema je izazov za istraživače i do danas je razvijeno nekoliko strategija u njihovoj formulaciji. Ovi sistemi se, pre svega, mogu podeliti prema mehanizmu na koji se postiže gastroretencija u flotirajuće i one koji nisu flotirajući, zasnivajući se na ideji da se terapijski sistem zadrži u želucu što duže na taj način što flotira u želudačnom sadržaju. Ova karakteristika se opet može postići razvojem efervescentnog GRTS (matriks tablete, osmotski kontrolisani sistemi, gas-generišući) ili ne-efervervescentnog flotirajućeg GRTS (hidrodinamički balansirani, mikobaloni, alginatne granule, višeslojne tablete). U GRTS koji ne flotiraju ubrajaju se bioadhezivni, bubreći, sistemi velike gustine i sistemi koji se nakon ingestije „razmotavaju". U radu će biti navedeni lekovi kandidate za razvoj GRTS, biće prikazani pristupi u formulaciji i izradi gastroretentivnih terapijskih sistema kao i proizvodi iz ove grupe koji su registrovani na svetskom tržištu.

Ključne reči: modifikovano oslobađanje, gastroretentivni terapijski sistemi, formulacija

ADVANCED APPROACH IN DEVELOPMENT OF MODIFIED RELEASE DRUG DELIVERY: GASTRORETENTIVE DRUG DELIVERY SYSTEMS

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Development of gastroretentnive drug delivery systems is a challenge for formulators. Up to date, there are several strategies in achieving gastric retention. First of all, GRDDS can be classified into systems which are floating in the stomach and in non-floating systems. Floating drug delivery systems are further divided in effervescent systems (volatile liquid containing systems, matrix tablets or gas generating systems) and non-effervescent systems (hydrodynamically balanced systems, microballoons, alginate beads and layered tablets). Non-floating gastroretentnive drug delivery systems are: bioadhesive systems, swelling systems, high density system and expandable systems. Drug candidates for GRDDS will be presented as well as formulation approaches and products that are present on a world market.

Keywords: modified release, gastroretentive drug delivery systems, drug formulation

FARMACEUTSKA ZDRAVSTVENA ZAŠTITA U SPECIJALNOJ PSIHIJATRIJSKOJ BOLNICI, DOBROTA, KOTOR

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Dok farmaceuti, u razvijenim zemljama, kompetentno: otkrivaju, preveniraju, i riješavaju probleme vezane za ljekove (DRP), optiimizuju terapiju, smanjuju troškove, poboljšavaju ishode liječenja... U manje razmijenim zemljama, ulogu farmaceuta često ograničeva percepcija koja je svodi na obezbjedjivanje i izdavanje ljekova.
Cilj studije je bio evaluacija obezbjedjivanja farmaceutske zdravstvene zaštite hroničnim bolničkim pacijentima sa šizofrenijom.
Ova prospektivna, randomizovana, studija intervencije u zdravstvenoj zaštiti je sprovedena u Specijalnoj psihijatrijskoj bolnici Dobrota. Uključeni su svi pacijenti šizofrenijom, hospitalizivani duže od 6 mjeseci, a pola je randomizovano za intervenciju.
Kliniki farmaceut je: evaluirao farmakoterapiju, identifikovao DRP, definisao plan farmaceutske zdravstvene zaštite i iskomunicirao ga sa ljekarima, koristeći Formular za registraciju DRP (PCNE classification V 6.2). Prihvatanje i ishod predloženih intervencija su procijenjeni nakon feedback-a propisivača.
Kod 49 pacijenata, identifikovan je 71 problem, (1 do 4 po pacijentu), predominantno vezanih za podnošljivost i djelotvornost terapije.
Zabilježeni uzroci (N=184) su najčešće neodgovarajući izbor: lijeka (64%)
ili doze (23.4%). Kod izbora lijeka je bilo sporno: previše ljekova za istu indikaciju (N=33); kost-efektivnost (N=29); neodgovarajuća kombinacija (N=27); ili neodgovarajući lijek (N=23); dok su navedini uzroci u domenu doze bili: izostanka TDM-a(N=14), sub- (N=13) ili supra-terapijske doze (N= 11). Predugo trajanje liječenja je zabilježeno kod 14 problema.
Predložene su 182 intervencije (70% na nivou lijeka): isključivanje lijeka (N=58); promjena doze (N=35), ostale intervencije (najčešće monitoring) (N=35); zamjena lijeka (N=18), izmjena načina primjene (N=9); i/ili uvodjenje novog lijeka (N= 7).
Prihvaćena je 91 intervencija, a 36 odbijeno. Riješeno je 38 DRP (25 potpuno, 12 djelimično), 25 problema nije bilo potrebno ili moguće riješiti, a za 8 DRP ishod je nepoznat.
Broj prihvaćenih intervencija kliničkog farmaceuta u uslovima gdje je koncept farmaceutske zdravstvene zaštite nov, ukazuje na potrebu i značaj koji komplementarno znanje farrmaceuta može pružiti propisivačima i zdravstvenom timu kada je farmakoterapija u pitanju

Ključne riječi: farmaceutska zdravstvena zaštita, intervencija kliničkog farmaceuta, problemi vezani za ljekove, bolnički pacijenti sa šizofrenijom, specijalna bolnica za psihijatriju

PHARMACEUTICAL CARE IN A LONG STAY PSYCHIATRIC HOSPITAL

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In high-income countries, pharmacists, competently, detect, prevent and resolve drug related problems (DRP), improve medications appropriateness; cut expenditures; improve treatment outcomes.... Elsewhere, this might be overlooked by traditional perception of pharmacists as stock-keeper and dispensers of medicines.
The aim of the study was to evaluate provision of pharmaceutical care for long-term hospitalized schizophrenia patients.
This was prospective, healthcare-system interventional study at Specialized psychiatric hospital-Dobrota. Long-term (≥6 months) in-patients with schizophrenia (F20.0-F20.9) were included, and half of them randomly chosen for intervention.
Clinical pharmacist reviewed medication, identified drug related problems (DRP) developed pharmaceutical care plan and communicated it to physicians using DRP Registration Form (PCNE classification V 6.2). After the feedback, acceptance and outcomes of interventions were assessed.
For 49 patients, 71 DRPs were identified, ranging 1 to 4 problems/patient (1,43 (±0,68)), predominantly related to tolerability and treatment effectiveness.
DRPs were caused (N=184) mostly by inappropriate selection of: drug (64%) or dose (23.4%). Drug issues were: too many drugs for indication (N=33); not cost-effective choice (N=29); inappropriate combination (N=27); and inappropriate drug (N=23); Dose inadequacy was due to: lack of TDM (N=14), sub-therapeutic (N=13) or supra-therapeutic dosing (N= 11). Excessive treatment duration was observed for 14 DRP.
Clinical pharmacist proposed 182 interventions (70% at drug level): discontinuation of medication (N=58); dosage change (N=35), other interventions (mostly monitoring) (N=35); drug change (N=18), instructions for use (N=9); and/or introducing new drug (N= 7).
Physicians accepted 91 and refused 36 interventions. Finally, 38 DRP were solved (N=25 completely and N=13partially), for N=25 problems, resolving was not needed or possible and for 8 DRP outcomes of interventions were not known.
Acceptance rate of clinical pharmacist` interventions in pharmaceutical care-naive setting, proves the need and value that pharmacist` complementary expertise might add to healthcare team when making prescribing decision.

Key words: pharmaceutical care, clinical pharmacist` intervention, drug related problems, schizophrenia inpatients, long-stay psychiatric hospital

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Kod 49 pacijenata, identifikovan je 71 problem, (1 do 4 po pacijentu), predominantno vezanih za podnošljivost i djelotvornost terapije.
Zabilježeni uzroci (N=184) su najčešće neodgovarajući izbor: lijeka (64%)
ili doze (23.4%). Kod izbora lijeka je bilo sporno: previše ljekova za istu indikaciju (N=33); kost-efektivnost (N=29); neodgovarajuća kombinacija (N=27); ili neodgovarajući lijek (N=23); dok su navedini uzroci u domenu doze bili: izostanka TDM-a(N=14), sub- (N=13) ili supra-terapijske doze (N= 11). Predugo trajanje liječenja je zabilježeno kod 14 problema.
Predložene su 182 intervencije (70% na nivou lijeka): isključivanje lijeka (N=58); promjena doze (N=35), ostale intervencije (najčešće monitoring) (N=35); zamjena lijeka (N=18), izmjena načina primjene (N=9); i/ili uvodjenje novog lijeka (N= 7).
Prihvaćena je 91 intervencija, a 36 odbijeno. Riješeno je 38 DRP (25 potpuno, 12 djelimično), 25 problema nije bilo potrebno ili moguće riješiti, a za 8 DRP ishod je nepoznat.
Broj prihvaćenih intervencija kliničkog farmaceuta u uslovima gdje je koncept farmaceutske zdravstvene zaštite nov, ukazuje na potrebu i značaj koji komplementarno znanje farrmaceuta može pružiti propisivačima i zdravstvenom timu kada je farmakoterapija u pitanju

Ključne riječi: farmaceutska zdravstvena zaštita, intervencija kliničkog farmaceuta, problemi vezani za ljekove, bolnički pacijenti sa šizofrenijom, specijalna bolnica za psihijatriju

INTERINSTITUCIONALNA SURADNJA U SLUŽBI OČUVANJA SIGURNOSTI PACIJENATA -

PHARMACEUTICAL CARE IN A LONG STAY PSYCHIATRIC HOSPITAL

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In high-income countries, pharmacists, competently, detect, prevent and resolve drug related problems (DRP), improve medications appropriateness; cut expenditures; improve treatment outcomes.... Elsewhere, this might be overlooked by traditional perception of pharmacists as stock-keeper and dispensers of medicines.
The aim of the study was to evaluate provision of pharmaceutical care for long-term hospitalized schizophrenia patients.
This was prospective, healthcare-system interventional study at Specialized psychiatric hospital-Dobrota. Long-term (≥6 months) in-patients with schizophrenia (F20.0-F20.9) were included, and half of them randomly chosen for intervention.
Clinical pharmacist reviewed medication, identified drug related problems (DRP) developed pharmaceutical care plan and communicated it to physicians using DRP Registration Form (PCNE classification V 6.2). After the feedback, acceptance and outcomes of interventions were assessed.
For 49 patients, 71 DRPs were identified, ranging 1 to 4 problems/patient (1,43 (±0,68)), predominantly related to tolerability and treatment effectiveness.
DRPs were caused (N=184) mostly by inappropriate selection of: drug (64%) or dose (23.4%). Drug issues were: too many drugs for indication (N=33); not cost-effective choice (N=29); inappropriate combination (N=27); and inappropriate drug (N=23); Dose inadequacy was due to: lack of TDM (N=14), sub-therapeutic (N=13) or supra-therapeutic dosing (N= 11). Excessive treatment duration was observed for 14 DRP.
Clinical pharmacist proposed 182 interventions (70% at drug level): discontinuation of medication (N=58); dosage change (N=35), other interventions (mostly monitoring) (N=35); drug change (N=18), instructions for use (N=9); and/or introducing new drug (N= 7).
Physicians accepted 91 and refused 36 interventions. Finally, 38 DRP were solved (N=25 completely and N=13partially), for N=25 problems, resolving was not needed or possible and for 8 DRP outcomes of interventions were not known.
Acceptance rate of clinical pharmacist` interventions in pharmaceutical care-naive setting, proves the need and value that pharmacist` complementary expertise might add to healthcare team when making prescribing decision.

Key words: pharmaceutical care, clinical pharmacist` intervention, drug related problems, schizophrenia inpatients, long-stay psychiatric hospital

ISKUSTVO HALMED-A

Darko Krnić

Agencija za lijekove i medicinske proizvode Hrvatske (HALMED)

Agencija za lijekove i medicinske proizvode (HALMED) je regulatorno tijelo nadležno za praćenje sigurnosti primjene lijekova u Republici Hrvatskoj.
Jedan od glavnih ciljeva rada HALMEDa je kontinuirano unaprjeđenja sigurnosti primjene lijekova kako bi se spriječili neželjeni ishodi za bolesnike, ali i za cjelokupni zdravstveni sustav.
Jedan od važnih preduvjeta za osiguravanje što veće koristi primjene lijekova je kvalitetna suradnja s ostalim relevantnim institucijama u RH koje su nadležne za funkcioniranje različitih aspekata zdravstvenog sustava.
HALMED dugi niz godina surađuje s Hrvatskim zavodom za javno zdravstvo na području praćenja sigurnosti primjene cjepiva putem zajedničke radne skupine kako bi ocjene ozbiljnosti i povezanosti Nuspojave s primjenom cjepiva bile ujednačene.
Također, iznimno važna je suradnja HALMEDa s Hrvatskim zavodom za zdravstveno osiguranje koji upravlja Centralnim zdravstvenim informacijskim sustavom Republike Hrvatske (CEZIH). Kroz ovu suradnju omogućeno je ciljano informiranje zdravstvenih djelatnika o važnim sigurnosnim informacijama vezanim uz primjenu lijekova, a nastavak suradnje će omogućiti prikupljanje kvalitetnijih prijava nuspojava te zdravstvenim djelatnicima značajno olakšati prijavljivanje sumnji na nuspojave.
Suradnja s Agencijom za kvalitetu i akreditaciju u zdravstvu omogućit će prepoznavanje stope prijavljivanja iz pojedine zdravstvene ustanove kao dodatnog indikatora kvalitete.

OPTIMIZACIJA PROGRAMSKIH SADRŽINA PREDMETA FARMAKOGNOZIJE I POTREBA OD IZUČAVANJA FITOTERAPIJE U DODIPLOMSKOJ EDUKACIJI FARMACEUTA - MODEL FARMACEUTSKOG FAKULTETA IZ SKOPJA, REPUBLIKA MAKEDONIJA

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Farmakognozija je obavezna disciplina u dodiplomskoj edukaciji farmaceuta, predviđena listom predmeta koje definiše Evropska direktiva 2005/36 EEC. U studiskim programima u Evropi je različito inkorporirana, od izučavanja u nekoliko semestara do slučaja gde čak i nedostaje. Permanentni razvoj farmakognozije dovodi do problema oko definisanja programskih sadržina zbog čega se neki delovi izdvajaju kao posebne celine. Savremeni koncept farmakognozije, pokraj izučavanja biljnih droga, nalaže izučavanje sekundarnih metabolita biljaka, njihovu izolaciju i strukturnu identifikaciju, poznavanje njihovih biosintetskih puteva i mogućnosti proizvodnje primenom metoda biotehnologije. Stoga se sve češće nazivu farmakognozija pridodaje termin fitohemija ili se fitohemija izučava kao poseban predmet, jer predmetna sadržina klasične farmakognozije postaje pretesna za izučavanje sekundarnih metabolita na nivou potrebnom današnjem farmaceutu. Budući da savremena farmakognozija obuhvata i otkrivanje novih aktivnih komponenata biljaka, kao i definisanje njihove biološko-farmakološke aktivnosti, farmakološko-toksikološka ispitivanja i ispitivanja mehanizama dejstva, to znači da u velikom delu obuhvata aspekte terapeutske vrednosti i upotrebe biljnih droga, imeno fitoterapiju. Fitoterapija se definiše kao metod lečenja koji se zasniva na upotrebi lekovitog bilja i fitofarmaceutskih preparata, no, danas svakako pretstavlja posebnu naučnu disciplinu koja proizlazi i koja se razvija iz farmakognozije.
Farmaceutski fakultet u Skopju je uložio velike napore u optimizaciji programskih sadržina predmeta koji proizlaze iz farmakognozije. Fitohemija se više od 15 godina izučava kao poseban predmet i pretsavlja preduslov za izučavanje farmakognozije, a oba predmeta su preduslov za izučavanje Osnova fitoterapije. Predmetna sadržina Osnova fitoterapije obuhvata u uvodnom delu farmakodinamske karakteristike savremene fitoterapije, metode evaluacije efikasnosti i procenu bezbednosti fitofarmaceutskih preparata i ispitivanje i kontrolu kvaliteta, dok se u specijalnom delu izučavaju strategije i koncepti fitoterapeutskih tretmana bolesti sistema i organa čovekovog organizma, kao i pojedinačne biljne droge i njihovi preparati. U najvećem delu, predmet obuhvata identifikovanje aktivnih principa i mehanizme njihovog dejstva, izučavanje kliničke efikasnosti i nivoa bezbednosti, te regulatorne aspekte. Uvođenjem predmeta fitoterapije stiču se poznavanja koja su od velikog značaja za budući profesionalni angažman farmaceuta, posebno u javnom sektoru.

Ključne reči: farmakognozija, fitoterapija, dodiplomska edukacija farmaceuta, optimizacija programskih sadržina

OPTIMIZATION OF THE SUBJECT CONTENT OF PHARMACOGNOSY AND NEEDS FOR LEARNING PHYTOTHERAPY AS SEPARATED SUBJECT IN GRADUATED EDUCATION OF PHARMACIST - CURRICULA MODEL OF THE FACULTY OF PHARMACY FROM SKOPJE, REPUBLIC OF MACEDONIA

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Pharmacognosy is a compulsory subject in undergraduated education of pharmacists, incorporated in the list of obligatory disciplines defined by Directive 2005/36 EEC. The subject in some European pharmacy curricula is studied through several semesters while there also curricula where the subject matter is not present at all. Continuous development in the field of pharmacognosy leads to definition of new scientific subfields. Current concept of pharmacognosy except knowledge on herbal drugs covers studding of secondary plant metabolites, isolation and structure identification as well as bio-synthetic pathways and possibilities of their biotechnological production. Therefore, in up to date curricula the name of the subject pharmacognosy most often is altered with Pharmacognosy with phytochemistry, with intention to put accent on the particular content of the subject. At the same time in some curricula besides Pharmacognosy, a separated subject Phytochemistry is included. Contemporary Pharmacognosy content also cover new active constituents of herbal drugs and their bio-pharmacological activity, toxicological aspects of the active constituents as well as molecular bases of the mechanism of activity, as important attributes of herbal drugs therapeutic values and their use in healing purposes, in phytotherapy. Phytotherapy defined as a method of healing based on uses of herbal substances, today is a new scientific discipline arise and developed from pharmacognosy.
Faculty of Pharmacy, University Ss. Cyril and Methodius, Skopje, has made efforts in optimization of the contents of the subjects emerged from Pharmacognosy. Phytochemistry for more than 15 years is studied as separate subject as obligatory precondition for Pharmacognosy, while both Phytochemistry and Pharmacognosy are preconditions for Basic Phytotherapy. The introductory of Basic Phytotherapy covers pharmacodinamic aspects of modern phytotherapy and efficacy, safety and quality control evaluation methods of herbal drugs. Additionaly, strategies and concepts of healing and treatment of diferent deseases of organs and systems of humans are covered in special part. Active constituents of herbal substances and molecular mechanisams of their activity, as well as clinical efficacy, safety and regulatory aspects of phytopharmaceuticals make the core of the subject.

Keywords: pharmacognosy, phytotherapy, undergraduated education of pharmacists, optimization of subject contents

RAZVOJ KOMPETENCIJA FARMACEUTA KAO OSNOVA ZA RAZVOJ I NAPREDAK FARMACIJE - ISKUSTVA IZ HRVATSKE

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Svjetska federacija farmaceuta (International Pharmaceutical Federation - FIP) posljednjih godina s posebnom pozornošću razvija programe za evaluaciju i razvoj kompetencija u ljekarništvu, kao i edukacijske modele koji omogućavaju porast kompetencija. Iako postoje znatne razlike u edukacijskim programima, metodama učenja i prenošenja znanja, svi praktičari u farmaciji imaju isti cilj – poboljšanje zdravstvenog statusa pacijenata. Da bi se taj plemeniti cilj postigao, u svojem svakidašnjem radu, bez obzira na pripadnost okružju, naciji ili kulturi, potrebno je razviti stručno- znanstvene kompetencije.

GbCF je u primjeni u Engleskoj, Škotkoj, Irskoj, Litvi, Singapuru, Novom Zelandu, Australiji, Srbiji, Bosni i Hercegovini, Crnoj Gori, Cipru, Makedoniji, Turskoj. U Hrvatskoj je u primjeni od 2010. u više od 300 ljekarni, te su na temelju evaluacije organizirani brojni projekti i edukacijske aktivnosti koje su dovele do povećanja kompetencija i uvođenja novih usluga za pacijente.

Uzimanje medikacijske povijesti, usluga osobnog ljekarnika, savjetovalište o kontracepciji, škole mršavljenja i odvikavanja od pušenja, nutricionistička savjetovališta, astma škola, procjena rizika od metaboličkog sindroma, značajan rast prijava nuspojava lijekova, bilježenje intervencija u protfolio farmaceuta, aktivan program za uočavanje interakcija samo su neke od novih usluga koje se nude u hrvatskim ljekarnama.

Dokumentirani dokazi doveli su do jake pregovaračke pozicije ljekarnika sa Zavodom za osiguranje i u tijeku je implementacija ljekarničkih usluga na 4 razine u obliku tzv. DTP-ova (dijagnostičko-terapijskih postupaka). U predavanju ćemo pokazati detalje ovog modela, rezultate testiranja kompetencija i edukacijske programe koji su doveli do povećanja kompetencija i razvoja same struke, sada već vidljivog i prepoznatljivog, na nacionalnoj razini.

COMPETENCY DEVELOPMENT OF PHARMACIST- FOR DEVELOPMENT AND ADVANCEMENT IN PHARMACY – CROATIAN EXPERIENCE

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International Pharmaceutical Federation (FIP) is dedicated to develop evaluation competency frameworks for pharmacy development and advancement. Despite the differences in educational activities, teaching methods and programs internationally, all pharmacy practitioners have the same goal – to improve the status of the patients by improving therapeutic outcomes in pharmacotherapy. To achieve this noble goal in everyday pharmacy practice, in every environment, nation and culture – it is necessary to develop pharmacists' competencies.
GbCF has been used in England, Scotland, Ireland, Lithuania, Singapore, New Zeeland, Australia, Serbia, Bosnia and Herzegovina, Monte Negro, Cyprus, Macedonia and Turkey. In Croatia, this Framework has been used since 2010 and successfully implemented in more than 300 pharmacies.
As a result of this evaluation, numerous educational activities were organised, as well as the pharmaceutical care and public health projects, which were leading to the competency development and implementation of new services for our patients.
Medication review, personal pharmacist service, contraception counselling, weight management, smoking cessation, nutrition plan, asthma school, metabolic syndrome risk management, increased number of adverse reaction reports, documentation of pharmacists intervention in pharmacists portfolio, interaction management are only few of many activities and new services offered in Croatian community pharmacies.
Documentation of evidence is growing, assuring good position for pharmacists in negotiation with health insurance agency. New model of services, described on 4 levels of practice is in implementation just now. Diagnostic-therapeutical procedures will be presented in this presentation with details in implementation, as a direct result of competency evaluation and development. Advancement of pharmacy practice in Croatia is now recognized and visible on national level.

ZNAČAJ PRETKLINIČKE I KLINIČKE FARMAKOVIGILANCE ZA FARMAKOTERAPIJU

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Farmakovigilanca je relativno nova disciplina, koja ima za cilj da identifikuje, prati, sakuplja, analizira i reaguje na nove podatke koji su u vezi sa bezbednošću leka. Aktivnosti u okviru farmakovigilance su takođe usmerene ka proceni odnosa između rizika i koristi pri upotrebi leka, kao i praćenju interakcije lekova.
Pretklinička farmakovigilanca je nov termin za sa pretkliničku procenu bezbednosti leka i obuhvata pretkliničku toksikologiju(klasična toksikološka ispitivanja na životinjama, akutna, subakutna, hronična, toksičnost za jetru i bubrege, teratogenost, onkogenost...) i istorijski je glavni razlog uvođenje dobre laboratorijske prakse.
Izvori podataka za farmakovigilancu mogu biti: Spontano prijavljivanje neželjenih reakcija na lekove od strane zdravstvenih profesionalaca, kliničke i epidemiološke studije, medicinska literatura, informacije dobijene od farmaceutske industrije, informacije dobijene od drugih regulatornih tela. Postoji više aspekata farmakovigilance: Saopštavanje postojanja rizika, identifikacija mogućih rizika, intenzivno prijavljivanje i edukacija, nadzor studija i kontrolisana ispitivanja.
Jedna petina pacijenata primljenih u bolnice u svetu je zbog neželjenih i toksičnih dejstava lekova. Smrtnost od neželjenih dejstva u vezi lekova je na 5. mestu na listi vodećih uzroka smrti u bolnicama. Ovakav ishod neželjenih dejstava je moguće izbeći u skoro 50% slučajeva zbog čega odgovarajuća aktivnost u oblasti farmakovigilance, pre svega edukacija, prijavlijvanje i podizanje svesti o neželjenim dejstvima lekara, farmaceuta i pacijenata su ključni za pobolšanje kvaliteta farmakoterapije. Stoga je neophodna bliska saradnja svih zdravstvenih profesionalaca sa Agencijom za lekove i medicinska sredstva.

Ključne reči: farmakovigilance, neželjena dejstva, interakcije

THE IMPORTANCE OF PRECLINICAL AND CLINICAL PHARMACOVIGILANCE FOR PHARMACOTHERAPY

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Pharmacovigilance is a relatively new discipline that aims to identify, monitor, collect, analyse and react to new information that is related to the safety of the drug. Activities within pharmacovigilance are also aimed at assessing the relationship between risk and benefit in the use of the drug, as well as the monitoring of drug interactions.
Preclinical pharmacovigilance is the new term for the preclinical drug safety assessment and includes preclinical toxicology (classic toxicology tests on animals, acute, subacute, chronic, toxicity for the liver and kidneys, teratogenicity, oncogenicity etc.). Historically it is the main reason for the introduction of Good Laboratory Practice .
Data sources for pharmacovigilance can be: spontaneous reporting of adverse drug reactions by health professionals, clinical and epidemiological studies, medical literature, the information obtained from the pharmaceutical industry, the information obtained from other regulatory bodies. There are several aspects of pharmacovigilance: notification of the risk, identification of risks, intensive reporting and education, surveillance studies and controlled trials.
One-fifth of patients admitted to hospitals in the world are due to adverse effects and toxic effects of drugs. The mortality rate of adverse effects related drugs is ranked 5th in the list of leading causes of death in hospitals. Such outcome of adverse effects can be avoided in almost 50% of the cases for which the activity in the field of pharmacovigilance, primarily education, reporting and raising the awareness about the adverse effects amongst physicians, pharmacists and patients are crucial for the improvement of the quality of pharmacotherapy. Finally, very important is cooperation in between health professionals with Medical agency for drugs and medical devices.

Key words: pharmacovigilance, adverse effects, interactions

PROCENA PROPISIVANJA LEKOVA U STARIJOJ POPULACIJI U PRIMARNOJ ZDRAVSTVENOJ ZAŠTITI

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Specifičnosti starije populacije pacijenata ogledaju se u većem broju komorbiditeta i lekova koji se propisuju u ovoj populaciji, što povećava rizik od stupanja lekova u interakcije kao i neželjenih reakcija na lek. Takođe, promene u farmakokinetici i farmakodinamici koje nastaju starenjem mogu dovesti do potrebe za prilagođavanjem režima doziranja lekova. Istraživanja su pokazala da u starijoj populaciji često dolazi do neodgovarajućeg propisivanja lekova, odnosno propisuju se lekovi čiji je rizik od ispoljavanja neželjenog događaja veći od kliničke koristi, posebno ukoliko postoji bezbednija ili efikasnija alternativa. Sa druge strane, pacijentima ponekad nedostaje terapija sa dokazanom efikasnošću kod pojedinih bolesti što se takođe može smatrati neodgovarajućom terapijom. Poslednjih godina razvijeni su i validirani STOPP i START kriterijumi za procenu potencijalno neodgovarajućih lekova kod starijih. STOPP obuhvata 65 indikatora potencijalno neodgovarajuće terapije, uključujući lek-lek i lek-bolest interakcije i terapijske duplikacije. Pomoću START kriterijuma procenjuje se nedovoljna upotreba lekova za nekoliko najčešćih bolesti/stanja. U Republici Srbiji je 2012. godine sprovedena prospektivna studija preseka usklađenosti terapije starijih pacijenata sa STOPP/START kriterijumima u primarnoj zdravstvenoj zaštiti.

U istraživanju je učestvovalo 509 pacijenata, starosti 74,8±6,5 god, 57% ženskog pola. U 139 pacijenata zabeležene su 164 potencijalno neodgovarajuće proskripcije. Najčešći uzroci su bili dugotrajna upotreba dugo-delujućih benzodiazepina, upotreba nesteroidnih antiinflamatornih lekova u pacijenata sa umerenom-teškom hipertenzijom i primena teofilina kao monoterapije u pacijenata sa hroničnom opstruktivnom bolesti pluća. Takođe, u 257 pacijenata zabeleženo je odsustvo ukupno 439 potrebna leka. Najčešće su bili izostavljeni statini u pacijenata sa dijabetesom, acetilsalicilna kiselina u pacijenata sa povišenim rizikom od kardiovaskularnih događaja i beta-blokatori u terapiji hronične stabilne angine pektoris.

Istraživanje je ukazalo da farmaceuti moraju posvetiti više pažnje identifikaciji neodgovarajućeg propisivanje kod starijih kako bi se izbegli neželjeni ishodi i obezbedila optimalna terapija za individualnog pacijenta.

Ključne reči: stariji, pacijenti, STOPP i START kriterijumi, terapija

ASSESSING PRESCRIBING IN ELDERLY PATIENTS IN PRIMARY CARE SETTING

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Elderly patients are associated with comorbidities and usually need more than one medicine which further increases the risk of drug-drug interactions and adverse reactions. Also, changes in pharmacokinetics and pharmacodynamics, which occur due to aging, may cause the necessity of medicine dose adjustment. Studies have shown frequent occurence of inappropriate prescribing in the elderly, which means that medicines with unfavourable risk efficacy profile are being administered to patients although more efficient or safer medicines are available. Moreover, patients sometimes lack treatment with medicines of proven efficacy in some diseases or conditions which is also characterised as inappropriate. In the past years, STOPP and START criteria for the evaluation of potentially inappropriate prescribing in elderly patients, were developed and validated. STOPP comprises 65 indicators for potentially inappropriate medicines, including drug-drug, drug-disease interactions and therapy duplication. START criteria are used to evaluate inappropriate treatment omissions for several most common diseases/conditions. In 2012., in the Repulic of Serbia, a prospective cross-sectional study was perfomed with the aim of evalauating potentially inappropriate prescrbing in elderly patients, according to STOPP/START criteria, in primary care.

A total of 509 patients, aged 74.8±6.5 years, 57% female, participated in the study. 164 potentially inappropriate prescriptions were observed in 139 patients. The most frequent potentially inappropriate medications were long-term use of long-acting benzodiazepines, use of non-steroidal antiinflammatory drugs in patients with moderate-severe hypertension and use of theophylline as monotherapy for chronic obstructive pulmonary disease. Moreover, 439 potentially inappropriate omissions were observed in 257 patients. Most common omissions were omission of statins in patients with diabetes, omission of aspirin in patients with increased risk of cardiovascular events and omission of beta-blockers in the treatment of chronic stable angina pectoris.

The study revealed that pharmacists should pay more attention to the identification of inappropriate prescribing in elderly patients, in order to avoid adverse outcomes, and ensure optimal treatment for the individual patient.

Keywords: elderly, patients, STOPP and START criteria, therapy

VREDNOVANJE ZNAČAJA, DOSTUPNOSTI I SAVETODAVNE ULOGE FARMACEUTA U PRIMARNOJ ZDRAVSTVENOJ ZAŠTITI

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Zdravstvena ustanova apoteka Farmanea, Beograd, Republika Srbija

Cilj istraživanja bio je da se utvrdi da su farmaceuti najdostupniji zdravstveni radnici, njihov značaj za pacijente i mera u kojoj farmaceuti u javnim apotekama svojom dostupnošću i savetovanjem pacijenata kod manjih zdravstvenih problema i preporukom terapije, smanjuju posete lekarima i time doprinose efikasnosti sistema zdravstvene zaštite.
Istraživanje je sprovedeno u apotekama ZUA Farmanea u Srbiji i obuhvatilo je evidentiranje poseta i anketiranje pacijenata. Evidentirane su sve posete pacijenata u 9 izabranih apoteka u periodu 03.01.- 28.02.2014. Pacijenti (posete) su klasifikovani u 3 kategorije: oni koji dolaze po savet, oni koji dolaze sa receptom po propisanu terapiju i oni koji dolaze zbog kupovine konkretnog proizvoda. U istom periodu je sprovedeno i anketiranje pacijenata u 26 apoteka.
Evidentirano je 72,360 poseta i prikupljeno 3.656 anketa. Evidentiranje poseta je pokazalo da 29,09% pacijenata dolazi u apoteku kako bi mu farmaceut savetom ili preporukom terapije rešio manji zdravstveni problem i da na taj procenat ne utiče lokacija apoteke, osim u slučajevima kada je apoteka u ruralnim područjima kada taj procenat raste i do 48%, usled odsustva ambulante. S druge strane, 21,4% anketiranih je kao glavni razlog dolaska u apoteku navelo savetovanje sa farmaceutom, dok je 27,10% anketiranih istaklo podizanje terapije na recept. Rezultati ankete su pokazali da 83,5% pacijenata dolazi u apoteku najmanje jednom mesečno, dok 32,4% odlazi kod izabranog lekara u istom periodu. 65% anketiranih se prvo konsultuje sa farmaceutom kada ima lakši zdravstveni problem, a 81% ovih pacijenata se naknadno ne konsultuju sa lekarom. Čak 96.3% anketiranih je odgovorilo da im farmaceut uvek ili često pomogne kada mu se obrate u vezi lakšeg zdravstvenog problema. Na pitanje šta bi uradili kada bi se apoteke zatvorile na jedan dan, 58,5% ne bi otišlo kod lekara, već bi sačekalo da se apoteke otvore.
Rezultati istraživanja su pokazali da su pacijentima farmaceuti prvi izbor među zdravstvenim radnicima i da pacijenti visoko vrednuju dostupnost farmaceuta i savete. Preporukom terapije, farmaceuti mogu da reše manje zdravstvene probleme, a mogu i da prepoznaju simptome težih oboljenja i upute pacijenta lekaru. U značajnoj meri smanjuju broj poseta lekarima opšte prakse, čime smanjuju troškove fonda zdravstva.

ASSESSMENT OF THE ACCESSIBILITY, ADVISORY ROLE AND CONTRIBUTION OF COMMUNITY PHARMACIST IN PRIMARY HEALTH CARE

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The aim of this study was to prove that community pharmacists are the most accessible and relevant health care professionals, and to measure their contribution to health system efficiency by solving patients` minor ailments without visiting GP`s.
The study was carried out in pharmacies ZUA Farmanea in Serbia and involved recording patients` visits and questionnaires for patients. All patients` visits were recorded in 9 selected pharmacies from 03.01.- 28.02. 2014. The patients (visits) were classified into three categories: those seeking advice regarding health issue, those with a doctor's prescription, and those looking to buy a particular product. In the same period, patients in 26 pharmacies were asked to fill in the questionniares.
A total of 72,360 visits were evidenced and 3,656 patients` questionnaires were surveyed. The record of visits showed that 29.09% patients come to the pharmacy to seek advice for minor health problem. This percentage is not affected if there is a helath center near pharmacy. However, if the pharmacy is in rural areas, the percentage can rise up to 48%. The questionnaire data showed that 21,4 % of patients come to pharmacy asking for health advice, while 27,1 % of them primarily come for reimbursed medicines. These data also indicate that 83.5% of patients visit pharmacy at least once a month, while 32.4% visit GP as frequently. 65% of survey participants first consult a pharmacist when they have a minor health problem and 81% of these patients do not consult a doctor afterwards. For 96.3% of total survey participants, minor health problem is always or often solved by the at pharmacist. When asked what they would do in case that pharmacies were closed for a day, 58,5 % of patients said that they would wait for pharmacies to reopen, rather than visit a GP.
The results showed that pharmacists are patients' first choice among health care professionals and that highly value the pharmacists' accessibility and advice. Pharmacists can recommend therapy for minor health problems, but also recognize symptoms of severe illnesses and refer patient to GP's. By reducing the number of visits to GP`s, pharmacists reduce health budget expenditures.

DA LI JE TERAPIJA DEPRESIJE U DEPRESIJI, MOŽE LI FARMAKOGENOMSKI PRISTUP PONUDITI IZLAZ?

Vesna Pešić

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Depresija postaje široko rasprostranjeni problem i značajno opterećuje zdravstvene sisteme velikog broja zemalja. Ukoliko se meri godinama koje se izgube usled bolesti, deprsija ima najveći skor na svetskom nivou. Sa druge strane, nedostatak jasne, precizne dijagnoze i adekvatnih alata za razumevanje kompleksnosti mozga, usporava terapiju i istraživanja. Urgentno je pitanje kako da se ove prepreke prevaziđu te postoji više potencijalnih rešenja: može se naučiti iz mehanizama dejstava postojećih antidepresiva, značajno obećava preciznije razotkrivanje neuronskih veza uključenih u patofiziologiju depresije dok prikupljanjem informacija o lekovima koji se koriste u terapiji drugih oboljenja, može se neočekivano pojaviti neki koji ima uticaja i na poremećaje ponašanja. Naravno, identifikacija gena koji su povezani sa depresijom je izazovan zadatak i trenutno mu se pristupa kroz studije koje uključuju više hiljada pacijenata, aktivnošću MDD radne grupe za psihijatrijske GWAS studije. Analizirano je 1.2 miliona SNP-ova (single-nucleotid polymorphism) u 18759 uzoraka. Na žalost, ni ova mega analiza sprovedena u više zemalja nije ukazala na konkretnu mutaciju koja bi bila od statističkog značaja i imala prediktivnu vrednost (Mol Psychiatry 2013).

Ipak, farmakogenomski pristup pojedinih istraživačkih timova počinje da daje prve ohrabrujuće rezultate. Laboratorija pod rukovodstvom prof. Gurwitza koja se bavi ispitivanjem uticajem različitih antidepresiva iz grupe SSRI, pokazala je značajnu razliku u ekspresiji gena ITGB-3 i CHL-1, kao i dve mikroRNA: miR-221 i miR-222, prilikom in vitro tretmana LCL linija paroksetinom (Pharmacogenomics 2012).

Takođe, grupa prof. Ingelman-Sundberga sa Instituta Karolinska, koja se bavi ispitivanjem polimorfizma citohroma P450 i odgovora na antidepresive, pokazala je da je polimorfizam CYP2C19 i CYP2D6 značajan za regulaciju specifičnih neuronskih puteva, uslovljavajući inter-individualne razlike u riziku od razvoja depresije i pojave suicida kao i odgovora pacijenta na terapiju (Pharmacogenomics 2014).

Ohrabruje činjenica da sve više novih farmakogenomskih studija pokušava kako da razjasni molekularne mehanizme manifestacije depresivnih poremećaja, tako i da ukaže na biomarkere predikcije dobrog odgovora pacijenta na pojedinu klasu/vrstu antidepresiva, pa i dozu koja bi bila optimalna kod svakog pojedinačnog pacijenta. Možemo očekivati da će buduća farmakogenomska ispitivanja otvoriti perspektivu farmakoterapije pacijenata obolelih od ovog ozbiljnog i sve učestalijeg oboljenja.

Ključne reči: depresija, farmakogenomska istraživanja, farmakoterapija

IS DEPRESSION TREATMENT IN DEPRESSION, COULD PHARMACOGNOMIC APPROACH OFFER A WAY OUT?

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Depression is becoming a widespread problem and a significant burden on the health systems of many countries. In years lost to disability, depression has the highest score at the global level. On the other hand, the lack of a clear, precise diagnosis and adequate tools to understand the complexity of the brain is slowing down progress in treatment and research. There is an urgent issue of how to overcome these obstacles, and there are several potential solutions: finding more accurate information of neural connections involved in the pathophysiology of depression, exploring profoundly mechanisms of effects of existing antidepressants, or collecting information about drugs used in the treatment of other diseases, that could unexpectedly appear to have an impact on behavior disorders.

Identification of genes associated with depression is a challenging task, and now it is being accessed through studies activity of the MDD working group, involving thousands of patients, for psychiatric GWAS studies. Approximately 1.2 million SNPs (single-nucleotide polymorphism) in 18759 samples were analyzed. Unfortunately, even this mega analysis carried out in several countries couldn't indicate a specific mutation that would be of statistical significance and had predictive value (Mol Psychiatry 2013).

However, pharmacogenomic approach of several research teams is beginning to show the first encouraging results. Laboratory of prof. Gurwitz examines the influence of different antidepressants of the SSRI group, showed a significant difference in expression of ITGB-3 and CHL-1 genes, and two microRNAs: miR-221 and miR-222, after in vitro treatment of cell lines with paroxetine (Pharmacogenomics 2012).

Furthermore, the group of prof. Ingelman-Sundberg from the Karolinska Institute, which deals with the study of polymorphism of cytochrome P450 and response to antidepressants, showed that polymorphism of CYP2C19 and CYP2D6 is important for the regulation of specific neural pathways, causing inter-individual differences in the risk of developing depression and suicide phenomenon as well as responses of the patient to therapy (Pharmacogenomics 2014).

It is encouraging that more and more new pharmacogenomic studies attempt to clarify the molecular mechanisms of manifestation of depressive disorders, and to point out the good biomarker predictors of a patient's response to a particular class / type of antidepressants, including the dose that would be optimal for each individual patient. We expect that the future pharmacogenomic testing will open perspective for pharmacotherapy of patients suffering from this serious and frequent mental disorder.

Key words: depression, pharmacogenomic studies, pharmacotherapy

FARMACEUTSKI FAKULTET U PODGORICI- SADAŠNJOST I PERSPEKTIVE

Zorica Potpara

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Farmaceutski fakultet u Podgorici, osnovan je 2007.god. kao samostalni studijski program Univerziteta Crne Gore, a 2010.god. transformisan u Farmaceutski fakultet. Razlozi za osnivanjem fakulteta su bili prvenstveno nedostatak farmaceuta u Crnoj Gori i motivacija farmaceuta iz Crne Gore za daljom edukacijom. Farmaceutski fakultet ima jedan studijski program koji je uskladjen sa Direktivama EU, preporukama i smjernicama medjunarodnih farmaceutskih udruženja, kao i stavovima Evropske asocijacije farmaceutskih fakulteta (The European Association of Faculties of Pharmacy) o statusu visokog obrazovanja na polju farmacije i farmaceutskih nauka. Prema akreditovanom i reakreditovanom nastavnom programu, studenti tokom školovanja polažu 55 predmeta. Kurikulumi i nastavni programi koncipirani su da kroz kombinaciju fundamentalnih i izbornih predmeta omoguće ispunjavanje osnovnim ciljeva.

Teorijska i praktična nastava se odvija na fakultetu i nastavnim bazama sa kojima je ostvarena intenzivna saradnja. Fakultet je takođe ostvario i saradnju sa svim fakultetima u okruženju, a prihvatio je saradnju za otvaranje zajedničkih doktorskih studija sa farmaceutskim fakultetima iz Ljubljane i Sarajeva.

Farmaceutski fakultet upisuju najbolji srednjoškolci iz Crne Gori, koji i tokom studija pokazuju odlične rezultate, a po završetku studija, njihovi poslodavci daju pozitivne kritike o njihovom radu. Studenti ovog Fakulteta su dobitnici mnogobrojnih nagrada (nagrade UCG za najbolje studente, nagrade grada Podgorice, Bara, Nikšića, dobitnici su Atlas stipendija i korisnici su mnogih Fondova). Tokom studija studenti Farmaceutskog fakulteta su kroz programe mobilnosti bili na edukaciji u Ljubljani, Zagrebu, Gracu i tamo stečena znanja prenosili kolegama i iskoristili za dalja usavršavanja. Aktivno učestvuju na studentskim kongresima u zemlji i regionu, a njihovi radovi su bili jako zapaženi u Evropi i svijetu. Aktivnosti studenata Farmacije ogledaju se i učestvovanjem na mnogobrojnim manifestacijama (Svjetski dan farmaceuta, Otvoreni dani nauke i Noć istraživača, seminar povodom Evropskog dana svjesnosti o antibioticima, i mnoge druge).

Fakultet je jedan od organizatora I i II Kongresa farmaceuta Crne Gore sa međunarodnim učešćem.

Fakultet očekuje punu podršku od strane Vlade Crne Gore, Univerziteta Crne Gore i drugih relevantnih činilaca iz oblasti farmaceutske djelatnosti u smislu rešavanja prostornih i drugih kapaciteta, kako bi mogao da obavlja svoju djelatnost u punom obimu.

Ključne riječi: farmaceuti, edukacija, razvoj

FACULTY OF PHARMACY IN PODGORICA, PRESENT TIME AND PERSPECTIVES

Zorica Potpara

Faculty of Pharmacy, University of Montenegro, Podgorica, Montenegro

Faculty of Pharmacy in Podgorica, was established in 2007 as an independent study programme of The University of Montenegro, and in 2010 it was transformed into Faculty of Pharmacy. The reasons for establishing this faculty at the first place were the lack of pharmacists in Montenegro and the motivation of the pharmacists in Montenegro for further education.Faculty of Pharmacy has one study programme coordinated with the directive of the EU, recommendations and guidelines of international pharmaceutical organizations, and the attitude of The European Association of Faculties of Pharmacy) about the status of higher education in the field of Pharmacy and the pharmaceutical studies. According to accredited and reaccredited curriculum, students take 55 subjects. Curriculums and syllabus are composed through a combination of the fundamental and optional subjects which can enable achieving main objectives. Theoretical and practical part of teaching is held at the faculty and teaching bases with which there is intensive cooperation Faculty has also established cooperation with all the other faculties in the region and it has also accepted cooperation with the faculties in Ljubljana and Sarajevo for opening of the doctoral studies. The best high school students in Montenegro go to Faculty of Pharmacy in Podgorica, and they show excellent results during their studies , and after finishing the studies their employers give positive references about their work. Students of this faculty are the winners of numerous awards (Best student awards of The University of Montenegro , City of Podgorica, Bar and Niksic awards, and they are also the winners of Atlas grants and users of many funds).

Students of Faculty of Pharmacy were on trainings through mobility programmes in Ljubljana, Zagreb, and Grac during their studies and have passed on their acquired knowledge to their colleagues and used them for further training. They actively participate in Students Congresses in the country and the region, and their papers were noticed in Europe and in the world.

Activities of students of Pharmacy are seen in participating in numerous manifestations(World Pharmacist Day, Open Days of Science, Researchers' Night in Montenegro, seminar on the occasion of the European Antibiotic Awareness Day and many others)

Faculty of Pharmacy is one of the organisers of the I and II Congress of Pharmacist of Montenegro with international participation. Faculty expects full support of the Government and the University of Montenegro and other relevant factors from the pharmaceutical business for resolving spatial and other capacities in order to operate at full volume.

Key words: pharmacists, education, development

KONTINUIRANO UNAPREĐENJE SARADNJE SA INSTITUCIJAMA U SISTEMU ZDRAVSTVA - IMPERATIV U RADU CALIMS

Maja Stanković

Agencija za lijekove i medicinsa sredstva Crne Gore (CALIMS)

Agencija za ljekove i medicinska sredstva Crne Gore (CALIMS) je institucija od velikog značaja za očuvanje javnog zdravlja. Svojim brojnim nadležnostima, koje kao konačno ishodište imaju kvalitetan, bezbjedan i efikasan lijek na tržištu Crne Gore, uz nezavisnu, objektivnu informaciju koja prati njegovu primjenu, CALIMS je direktno upućena na zdravstvene radnike i cjelokupan zdravstveni sistem u Crnoj Gori. Preduslov ostvarivanja uloge CALIMS i zdravstvenih institucija u očuvanju javnog zdravlja je međusobna saradnja i informisanost zdravstvenih radnika o nadležnostima CALIMS, koje su od značaja u njihovom svakodnevnom radu. U interesu je zdravstvenih radnika i zdravstvenih ustanova da postoji referentna institucija u sistemu zdravstva, kao adresa za pružanje objektivnih, nezavisnih, na naučnim dokazima zasnovanim informacijama u cilju njihove primjene prilikom donošenja odluke o propisivanju/izdavanju i primjeni određenog lijeka.

Od samog osnivanja CALIMS je prepoznala svoju ulogu u očuvanju javnog zdravlja i u kontinuitetu unapređuje modalitete saradnje sa svim institucijama u sistemu zdravstva. Prvi korak u tom smislu je imenovanje koordinatora za farmakovigilancu u javnim zdravstvenim ustanovama, na svim nivoima zdravstvene zaštite. Uloga koordinatora za bezbjednu primjenu ljekova je da posreduje u komunikaciji između CALIMS i ostalih zdravstvenih radnika u zdravstvenoj ustanovi, da prima i prosleđuje ostalim zdravstvenim radnicima najnovije informacije o bezbjednosti ljekova I medicinskkoje dobije od CALIMS i da afirmiše među kolegama ulogu i značaj farmakovigilance. CALIMS će u ovoj godini, kroz komunikaciju sa zdravstvenim ustanovama, analizirati i ukoliko se ukaže potreba revidirati postojeću listu koordinatora, sve u cilju efikasne i uspješne saradnje sa zdravstvenim ustanovama, kao preduslova ostvarenja misije CALIMS i bolje bezbjednosti pacijenata. Značajan iskorak u pogledu unapređenja saradnje ostvaren je kroz informatičko povezivanje i mogućnost slanja prijava neželjenih dejstava kroz informacioni sistem zdravstvene zaštite, direktno u nacionalnu bazu podataka o neželjenim dejstvima, koju vodi CALIMS. Ovaj način prijavljivanja neželjenih dejstava funkcioniše u primarnoj zdravstvenoj zaštiti (domovi zdravlja) i u opštim bolnicama sa idejom uvođenja mogućnosti prijavljivanja neželjenih dejstava i u ostalim zdravstvenim ustanovama. Naglašavamo da smo u razvijanju ovog načina prijavljivanja pioniri u regionu i šire. Mogućnost postojanja jedninstvenog informacionog sistema u zdravstvenoj zaštiti je podstaklo CALIMS da u komunikaciji sa zdravstvenim ustanovama i Fondom za zdravstveno osiguranje, predloži mogućnost korišćenja informacionog sistema zdravstvene zaštite u svrhu slanja značajnih, najnovijih informacija o bezbjednoj primjeni ljekova, od strane CALIMS, zdravstvenim radnicima koji propisuju/izdaju/primjenjuju ljekove, na koje se informacija odnosi.

BIOLOŠKI SLIČNI LIJEKOVI

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Biološki lijek se definira kao onaj koji sadrži aktivnu supstancu koja je proizvod živih organizama i koja se ne može na drugi način sintetizirati. Danas su biološki lijekovi uglavnom proizvod tehnologije rekombinantne DNK i predstavljaju najsloženije medicinske proizvode koji djeluju na usko specifične receptore ili stanice. Procjenjuje se da je tržište biotehnoloških lijekova 2012. vrijedilo 89,8 milijardi dolara, dok su u 2014. godini biotehnološki lijekovi predstavljali 10% svih lijekova koji se izdaju na recept, a za SAD se pretpostavlja da to iznosi 20%. U ovakvoj situaciji je potpuno očekivano da će se na tržištu pojaviti kopije inovativnih bioloških lijekova odmah nakon isteka patentne zaštite.

Cilj ovog izlaganja je da se slušatelji upoznaju s činjenicom da ne postoje generici bioloških lijekova, nego se govori o biološki sličnim lijekovima (biosimilarima) za koje vrijede posebni zahtjevi prilikom izdavanja odobrenja za stavljanje u promet.

Svi biološki lijekovi koji se odobravaju u EU odobravaju se centraliziranim postupkom, uz specifične zahtjeve koje moraju ispuniti biološki slični lijekovi. Razlog za ovo je što biološki lijek kao aktivnu supstancu ima makromolekulu koja je proizvod žive ćelije koju je veoma teško u potpunosti karakterizirati. Tokom procesa proizvodnje su moguće varijacije koje na kraju utječu i na djelotvornost i na sigurnost biološki sličnog lijeka. Imunogenost je najznačajniji sigurnosni problem biološkog lijeka, a može biti posljedica post-translacijskih modifikacija na molekuli proteina, nedovoljnog prečišćavanja ili variranja u procesu proizvodnje ili formulacije gotovog oblika.

Zaljučak je da ne postoji nešto što se može nazvati biogenerik. Bez dodatnih pretkliničkih i kliničkih ispitivanja nije moguća automatska ekstrapolacija indikacija sa referentnog lijeka na biološki sličan lijek, kao što nije moguća ni automatska izmjenjivost inovativnog lijeka biosimilarom.

Ključne riječi: biološki sličan lijek, imunogenost, izmjenjivost

BIOSIMILARS

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Biologic medicinal product (pharmaceutical) is any medicinal product that cannot be produced in any other way, except synthesized in living cell. Nowadays biopharmaceuticals are produced almost exclusively using recombinant DNA technique and it represent the most sophisticated medicinal products acting on highly specific receptors or cells. It is estimated that biopharmaceutical market was worth 89.8 billion US dollars in 2012 while 10% of all prescription drugs in 2014 were biologic medicines. Even more, it is estimated than in US biopharmaceuticals market share was 20% of all prescribed drugs. It is reasonable to expect copies of biological medicines on the market after innovative drugs patent expiration.
The aim of this lecture is to make audience familiar with the fact that there are no biologic generics, but we can only talk about similar biopharmaceuticals (biosimilars).
All biologic medicinal products in EU are approved through centralised procedure, with certain specific requirements for biosimilars. That is because biologic medicine has a macromolecule as active pharmaceutical ingredient which is product of living cell and which is hard to fully characterise. There are possible variations that may occur during manufacturing and purification process which can lead to lack of efficacy and/or safety. Immunogenicity is the most important safety issue of biological medicine product and may be due to post-translational variations, insufficient purification and variation of processes in production of active ingredient or pharmaceutical formulation.
The final conclusion is that something like generic biopharmaceutical cannot exist. We can only talk about similarity between biological medicines. Automatic extrapolation of indications from referent drug to biosimilar is not possible without additional preclinical and clinical trials, neither is an automatic switch between innovative drug and biosimilar possible.

Key words: biosimilar, immunogenicity, therapeutic switch

ISTORIJA I RAZVOJ FARMACEUTSKE PRAKSE

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Tradicionalno, farmacija se posmatra kao tranziciona nauka koja se nalazi između zdravlja i hemije. Razvoj farmacije u XX veku se može posmatrati kroz četiri razdoblja.
Početkom veka farmaceuti su imali ulogu apotekara koji ima značaj u obezbeđivanju i distribuciji lekova. Farmaceuti su bili odgovorni za pripremanje lekovitih preparata iz prirodnih izvora i očekivalo se da poseduju znanja iz oblasti farmakognozije i galenske farmacije. Kako u ovom razdoblju nije postojala zakonska regulativa kojom se definiše lek koji se izdaje na recept i bez recepta farmaceuti su indirektno imali ovlašćenja propisivanja lekova.
Razvoj farmaceutske industrije, otkrivanje antibiotika i drugih novih i efikasnih lekova zahtevalo je od farmaceuta naučni pristup novim lekovima i literaturi i razumevanje mehanizma delovanja i načina korišćenja leka. Ove promene rezultiraju izmenom tradicionalne uloge farmaceuta, kao osobe zadužene za pripremanje lekova, ka profesionalnoj, savetodavnoj ulozi. Obrazovanje farmaceuta zasniva se na farmakologiji i farmaceutskoj tehnologiji.
U periodu od 1960. do 1990. povećan je broj raspoloživih lekova. Istovremeno korišćenje većeg broja lekova tokom terapije dovelo je do pojave alergijskih reakcija, interakcija lekova sa drugim lekovima i hranom, neželjenih efekata. Posao farmaceuta se usmerava ka pacijentu i profeionalnoj usluzi a sve manje prema proizvodu. Obrazovanje farmaceuta se zasniva na farmakokinetici i patofiziologiji.
U razdoblju koje je označeno kao farmaceutska zdrvastvena zaštita naglašena je uloga farmaceuta u pobiljšanju kvaliteta života pacijenta i pozitivne kliničke ishode u okviru realnih ekonomskih troškova.
Kako će se razvijati farmaceutska praksa u XXI veku da bi zadovoljila potrebe zdravstvene zaštite ? Postoji veliki broj faktora koje treba uzeti u obzir. U uslovima brzih promena u pružanju usluga zdravstvene zaštite, promena uloge farmaceuta će biti obavezna.

Ključne reči: farmaceutska praksa, istorija, farmaceutska zdravstvena zaštita

HISTORY AND EVOLUTION OF PHARMACEUTICAL PRACTICE

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Traditionally, pharmacy was considered as a transitional discipline between the health and chemical sciences. During the twentieth century, the pharmacy has evolved through four stages. At the beginning of this century pharmacists played the apothecary role and continued to be engaged in the roles as drug provider and dispenser. The Pharmacist was responsible for preparing and dispensing drug products from natural sources. They were expected to have knowledge in the field of Pharmacognosy and Galenical pharmacy. In this traditional era there was no formal legislation addressed to no prescribed and prescribed products. Indirectly, the pharmacist had some prescribing authority.

The development of the pharmaceutical industry, discovering of antibiotics and many other new and effective drug substances required a scientific background to interpret literature and understand the mechanism of action and proper use of drug products. These significant changes resulted in moving the role of pharmacist from the traditional compounding and dispensing of medication towards a more professional advisory role. The pharmacy education emphasized sciences disciplines: Pharmacology and Pharmaceutical technology.

During the Patient-care era (1960-1990) a number of available medicines were increased. Multiple drug therapy led to complications like allergic reactions, multiple drug interactions with other drugs and food and side effects. The primary focus of the pharmacy profession has shifted from a product-oriented to patient-oriented, professional service. A pharmacist's education is focused on Pharmacokinetics and Pathophysiology.

Pharmaceutical-care Era-by the early 1990s the pharmaceutical care model was adopted to emphasize that the role of the pharmacist is to optimize the patient's health-related quality of life, and achieve positive clinical outcomes, within realistic economic expenditures.

How will pharmacy practice evolve to meet the needs of the 21st-century health care system? There is a considerable range of factors to be taken into account. In a period of rapid changes in health care delivery the changing of pharmacist role is going to be mandatory.

Keywords: Pharmaceutical Practice, History, Pharmaceutical-Care Era, Health Care System

O ČEMU GOVORIMO KADA GOVORIMO O LEKOVIMA I MEDICINSKIM SREDSTVIMA?

Aleksandra Vujačić Simić

Sektor za medicinska sredstva Agencije za lekove i medicinska sredstva Srbije - ALIMS

Agencija za lekove i medicinska sredstva Srbije je svojim dugogodišnjim radom izgradila imidž institucije kojoj se veruje da će obezbediti da se samo kvalitetni, efikasni i pre svega bezbedni lekovi i medicinska sredstva nađu na tržištu Republike Srbije, kao i da se kontinuirano nadziru u posle stavljanja u promet. Postići tako nešto je zahtevalo sveobuhvatan pristup u pogledu komunikacionih aktivnosti prema svim ključnim akterima zdravstvenog sistema, od državnih institucija preko zdravstvenih ustanova do samih pacijenata. Agencija je naročito ponosna na skorašnju primenu dobrih praksi Evropske agencije za lekove u pogledu saradnje sa udruženjima pacijenata i zdravstvenih profesionalaca i nevladinim sektorom uopšte. Najvažnije teme poput farmakovigilance i vigilance medicinskih sredstava, racionalne upotrebe lekova, kliničkih ispitivanja ili borbe protiv falsifikovanih lekova i medicinksih sredstava su obrađivane od strane Agencije kroz kampanje i akreditovane skupove, dok je decenijska tradicija simpozijuma vezanih za najrazličitije regulatorne izazove omogućila redovan otvoren dijalog sa predstavnicima farmaceutske industrije organizovanim u asocijacije. Agencija ostvaruje saradnju sa visokoškolskim ustanovama, ali i srednjim pa čak i osnovnim školama, a takođe ima i brojne sporazume i ugovore kojima uređuje odnose sa raznim drugim institucijama važnim za njen rad i ostvarivanje rezultata, naročito kada zakonski propisi nisu dovoljno uredili neku oblast.

USMENA PREDAVANJA

DAVANJE PUNIH I OBAVEZNIH UPUTSTAVA ZA BEZBEDNU UPOTREBU LEKOVA

Zehadin Gashi, Driton Shabani, Armend Jashari, Sali Tolaj

Komora Farmaceuta Kosova

Puna uputstva za upotrebu lekova obezbeđuju pacijentu uspešno lečenje, sprečavanje neželjenih efekata i poverenje u njihovoj upotrebi kao i stvaraju jedan dobar imidž o farmaceutu. Cilj ovoga istraživanja je bio analiziranje poštovanja davanja u apoteci punih uputstava za upotrebu lekova. Metod istraživanja je osnovana na sakupljanju informacija u apotekama na Kosovu i u regionu, u vezi davanja upustava koje se trebaju davati pacijentu, tokom vremenskog perioda 2010-2014 godina. Dobiveni rezultati pokazuju da u 62% slučajeva, uputstva su skračena, izražena u brojkama i sa nepotpunim specifikacijama o načinu upotrebe, vremenu uzimanja, neželjenim efektima, inkompatibilnosti sa drugim lekovima i hranom, trajanju uzimanja, naćinu početka i završavanja upotrebe lekova, itd. Rezultati govore o nespremnosti farmaceuta za davanje uputstava bez pacijentovog zahteva, ali i o nezainteresovanosti pacijenata za uzimanje punih uputstava. Konačno možemo zaključiti da davanje uputstava pacijentima je nepotpuna i u nekim slučajevima i zabrinjavajuča. Komora farmaceuta treba vršiti neprekidnu edukaciju sa posebnim akcentom na informacijama koje se trebaju izdavati pacijentu, dodatno stručno nadgledanje i pritisak nad apotekama, da bi se sa preciznošču poštovalo davanje punih uputstava za koriščene lekove, obezedeći pacijentu bezbedno lečenje i sprečavanje neželjenih efekata.

Ključne reči: uputstvo, lek, pacijent

GIVING FULL AND NECESSARY INSTRUCTIONS FOR THE SAFE USE OF MEDICATION

Zehadin Gashi, Driton Shabani, Armend Jashari, Sali Tolaj

Pharmacist's Chamber of Kosova

The full instructions for the use of the medication provide the patient a successful treatment, prevention of side effects and a full confidence in their use as well as create a positive image of the pharmacist. The aim of this research is the analysis of the compliance on giving full instructions in the pharmacy, for the use of the medication. The method of the research is based on the collection of the information in the pharmacies in Kosovo and in the region, with regard to the instructions supposed to be given to the patient during the period of time 2010-2014 years. The obtained results show that in 62% of the cases, the instructions are shortened, expressed in numbers not specifying fully the way of the use, time of use, side effects, possible incompatibility with other medication and food, duration of the use, the way of starting and ending the use, etc. The results talk about the unwillingness of pharmacists to give instructions without the request of the patient, but also about the lack of interest of the patients to get full instructions. In the end we may conclude that providing the patient with instructions is not full and in some cases concerning. The Chamber of Pharmacists should do a continuous professional education for pharmacists with a stress on the information that should be given to the patient, additional supervision and pressure on the pharmacies, in order they fully comply with giving full

instructions for the medication used, thus providing the patient a safe treatment and prevention of the side effects.

Key words: instructions, medication, patient

EVALUATING COMMUNITY PHARMACISTS' KNOWLEDGE AND PRACTICE TOWARDS DRUG-DRUG INTERACTIONS AND TAKING MEASUREMENTS IN IMPROVING THEIR PROFESSIONAL SKILLS

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Order of Pharmacists of Albania

Estimates of the prevalence and adverse events resulting from drug-drug interactions (DDIs) vary widely. Co-administration of drugs that may interact appears to be relatively common. Even with drug dispensing safety measures, in some developed countries, such as computerized DDI checking, a pharmacist's knowledge of DDIs can facilitate evaluation of risk and mitigating factors, and selection of non- interacting therapeutic alternatives. In our country efforts have began from the Pharmacists' Order of Albania, within the Continuing Education process from 2010, by organizing different conferences, seminars and lessons with thematic consisting in safe medication use and the latest developments in pharmaceutics.
This descriptive study included a random sample of 107 pharmacies in Tirana. Data were gathered via a questionnaire designed and distributed to each pharmacy, consisting of 24 questions, with a first part designed to test competence of the pharmacists in monitoring DDIs and a second part in which recipients were asked to classify 15 drug pairs as interacting, or not. 87% of pharmacists reported their education prepared them to monitor DDIs and 81% feel confident for this role. According to the results from the classification of the 15 drug pairs, it is noticed that correct answers were only in 40% of the respondents. In contrast, only 13% of respondents assessed themselves as insufficiently prepared for monitoring DDIs.
This study ascertains that pharmacists' knowledge of potential clinically significant DDIs is generally poor. These findings suggest the need for improvement in DDIs education in pharmacy curricula, emphasize the need to develop systems that alert about potential interactions that are clinically relevant. It is also our obligation, as Pharmacists' Order of Albania to keep our professionals up to date with the latest developments in pharmaceutics and make them access the newest information on drugs' safe use.

Key words: Interaction, drugs, pharmacists, practice, education.

POINT OF CARE U APOTEKAMA

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Težnja da se osigura kvalitetna zdravstvena usluga, uključujući i „point of care“ (POCT) sistem, dovodi do suočavanja sa novim izazovima, kako u razvijenim zemljama, tako i u onim koje su u razvoju. Laboratorijska dijagnostika je konstantno podvrgnuta radikalnim promjenama kako unutar mreža bolničkih laboratorija, liječničkim ambulantama, „blizini pacijentova kreveta“, tako i u apotekarskim ustanovama. Koristeći metode jednostavnih biohemijskih ispitivanja može se pomoći pacijentima u ranom otkrivanju određenih poremećaja, te provođenjem ranog liječenja smanjiti razvoj bolesti. Sve ovo ukazuje na raznolikost stručnih kompetencija farmaceuta u promociji zdravlja, informisanju i savjetovanju pacijenata o prevenciji, liječenju i kontroli bolesti. Cilj svega navedenog je da dobro educiran farmaceut, ljekar i pacijent usko sarađuju da bi optimizirali ishod terapije, kao i uključivanje apoteke u multidisciplinarni pristup liječenju.
Obzirom da su neki POCT testovi zastupljeni kako u državnoj tako i u privatnoj apotekarskoj praksi, od značaja je bilo istražiti koliko apoteke primjenjuju ovaj vid usluga, koji testovi su zastupljeni i od kakvog je to značaja za rad apoteke, te dobrobit pacijenta. Istraživanje je provedeno u 33 apoteke, gdje su uposlenici bili upoznati sa svrhom, ciljem ispitivanja i načinom popunjavanja upitnika.
Od 33 apotekarske ustanove, njih 69,7% nudi POCT usluge, a u 87,8% se ovakvi testovi mogu kupiti. Od POCT usluga koje se nude najzastpljenije su mjerenje glukoze (53,33%), mjerenje holesterola i triglicerida (23,3%), te mjerenje krvnog pritiska (19,6%). Od testova koji se nude u prodaji najveći procenat otpada na testove za trudnoću, ovulaciju, trakice za mjerenje glukoze, te vrlo mali postotak testova za detekciju helicobakter pylori, hepatitis C, HIV, droge i sl.
Danas se POCT smatra brzo rastućim područjem kliničke dijagnostike zbog niza prednosti koje uključuju jednostavnu upotrebu, minimalnu tehničku podršku, rano postavljanje dijagnoze, malu cijenu održavanja i veću komfornost pacijenta.

Ključne riječi: Point of care, profesionalne kompetencije, multidisciplinarni pristup liječenja, klinička dijagnostika

POINT-OF-CARE IN PHARMACIES

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Striving to ensure quality health services, including the „point of care“ (POCT) system, leads to new challenges, both in the developed countries, and in those that are in developed as well as developing countries. Laboratory diagnosis is constantly subjected to radical changes in hospital laboratories, medical clinics, “ patient’s bedside”, and in pharmacy institutions.

Using the methods of simple biochemical tests can help patients in the early detection of certain disorders, and implementation of early treatment to reduce disease development. All this points to a variety of professional competencies of pharmacists in health promotion, information and counseling patients about prevention, treatment and control of disease. The aim of all this is that a well-educated pharmacist, doctor and patient work closely to optimize the therapy outcome, as well as the inclusion of pharmacies in the multidisciplinary approach to treatment.
Some POCT tests are present in both state and private pharmacy practice, and it is important to explore how many pharmacies apply this type of service, which tests are available in their pharmacies, what is the benefit for these pharmacies and what is the benefit for patient's well-being. The study was conducted in 33 pharmacies, where the employees were informed of the research purpose and aim and questionnaire comletion procedure.
69.7% of 33 pharmacies, offers POCT services, and 87.8% are selling these tests. The most common POCT services are measuring of glucose (53.33%), measuring cholesterol and triglycerides (23.3%), and measuring of blood pressure (19.6%). From the tests offered in the sale, pregnancy tests, ovulation tests, strips for measuring glucose, make up highest percentage and a very small percentage are tests for detection of helicobacter pylori, hepatitis C, HIV, drugs, etc.
POCT is rapidly growing field of clinical diagnostics because of the numerous advantages that include ease of use, minimal technical support, early diagnosis, low maintenance cost and greater comfort for the patient.

Keywords: point of care, professional competencies, multidisciplinary approach to treatment, clinical diagnostics

EVALUATION OF THE QUALITY OF BIOLOGICAL/BIOSIMILAR DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

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Biosimilar is a biological medicine that contains a version of the active substance of an already authorized, original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference medicinal product in terms of quality, biological activity, safety and efficacy. In the last decade in the field of rheumatology, biological therapies have revolutionized disease management, however their cost often strongly influence their access, benefiting and affordability. Therefore, in order to improve patient access, ensure affordable alternatives and increase overall benefiting for pharmacists, clinicians and above all for patients, it is encouraged the development of biosimilars medicines as high-quality and cost-effective therapies to patients. In this presentation we report the evaluation of two-dimensional gel electrophoresis and MALDI-TOF MS analysis for the quality study of therapeutically relevant biopharmaceuticals used as a targeted therapy in rheumatology area, rituximab and CTLA4-Ig (abatacept). In addition, new perspectives concerning the application of modern analytical techniques for the study of biopharmaceuticals and biosimilars are discussed.

Key words: gel electrophoresis, MALDI TOF MS, rituximab, abatacept

STVARNOST I PERSPEKTIVA SAMOLIJEČENJA

Mirna Radošević

Salveo, Središnja i Istočna Europa
CASI - Hrvatska udruga proizvođača bezreceptnih proizvoda

Danas financijska kriza pogađa i farmaceutsko tržište što dovodi do brojnih restriktivnih mjera. Zdravstvo je pod stalnim pritiskom, zdravstveni novac na raspolaganju je ograničen, a demografske promjene i povećana učestalost kroničnih bolesti veliki su izazovi za zdravstveni sustav Hrvatske. U okviru tih promjena samoliječenje bi trebalo postati važan stup i učinkovit način u unapređenju i očuvanju zdravlja.
Hrvatska udruga proizvođača bezreceptnih proizvoda, HUPBR/CASI (u daljnjem tekstu CASI) osnovana je 2010-te godine kao udruga proizvođača i distributera bezreceptnih proizvoda s ciljem zastupanja interesa i prava članica te unapređenjem kompetitivnog i transparentnog tržišnog natjecanja. CASI danas zastupa interese 24 članice te predstavlja 85% hrvatskog tržišta samoliječenja. CASI svojim aktivnostima promiče sigurno i učinkovito samoliječenje te unapređenje zdravlja.
Rezultati istraživanja agencije GfK iz 2011-te godine pokazuju da opća populacija u Hrvatskoj minorne bolesti najčešće rješava samostalno „prirodnim metodama“, a nakon 3-5 dana ukoliko nema poboljšanja odlaze liječniku. Njihov posjet liječniku u čak 30-50% slučajeva završava propisivanjem lijeka koji se izdaje na liječnički recept. Liječnici procjenjuju da pacijenti s minornim bolestima čine u prosjeku čak 20-30% svih pacijenata koje vide na mjesečnoj razini. Liječnici se načelno slažu da bi o tim pacijentima ljekarnici mogli brinuti jednako kompetentno kao i oni sami.
Rezultati istraživanja također pokazuju da se ljekarnici smatraju važnom karikom u procesu samoliječenja, a čak polovica ljekarnika smatra da nedovoljno vremena posvećuju savjetovanju pacijenata. Očekivanja opće populacije od ljekarnika idu u pravcu više savjetovanja u odnosu na trenutno stanje.
CASI smatra da treba težiti sljedećem konceptu samoliječenja:
-Pojedinac preuzima odgovornost o vlastitom zdravlju i prvo konzultira ljekarnika za sve manje zdravstvene tegobe.
-Ljekarnik aktivno sudjeluje u brizi za zdravlje pojedinca i preuzima ključnu ulogu za odgovorno samoliječenje i unapređenje zdravlja.
-Liječnik ima pozitivan stav o odgovornom samoliječenju te vjeruje u znanje i vještine ljekarnika.
Fokusirana suradnja svih zainteresiranih skupina trebala bi dovesti do poboljšanja zdravlja i kvalitete života populacije te manjeg broja posjeta liječnicima primarne zdravstvene zaštite za manje zdravstvene tegobe.

REALITY AND PROSPECTIVES OF SELF-MEDICATION

Mirna Radošević

Salveo CEE
CASI - The Croatian Association of Self-Medication Industry

Many countries are nowadays affected by the financial crisis which also reflects on the pharmaceutical market, bringing numerous restrictive measures in force. Health care system is under continuous pressure, available health care funds are limited while demographic changes and increased incidence of chronic diseases stand as the challenge for Health care system in Croatia. Within such changes, self-medication should become an important issue and efficient way of improving public health and preventing diseases.
The Croatian Association of Self-Medication Industry, was established in 2010 as an association of manufacturers and agents of OTC products, aiming to represent the interests and rights of its members and improving the competitive and transparent market race. With its 24 member companies, CASI represents 85% of the Croatian self-medication market. By its activities, CASI promotes safe and efficient self-medication and improvement of health.
Results of the GfK agency survey carried out in 2011 show that the general population in Croatia choose to solve minor ailments by using “natural methods” for self-curing and see their doctor after 3-5 days if the symptoms persist. As much as 30-50% of patients visiting physician finally get the prescription medicine. Physicians estimate that patients with minor ailments make even 20-30% of all patients seen within one month. In general, physicians agree that pharmacists could take care of such patients as competent as they do.
The results of the aforesaid survey also show that pharmacists are considered as an important link in the process of self-medication and even half of them admit that time set aside to advise patients is insufficient. The general population expects more pharmacy consulting services compared to what they get now.
CASI considers that the solution should be found in the concept of self-medication:
- Each individual takes responsibility of its own health and consults pharmacist as the first line health care professional for common health issues.
- Pharmacist takes an active role in individual’s health care and holds a key role in responsible self-medication and improvement of health.
- Physician has a positive attitude on responsible self-medication and show confidence in pharmacists’ expertise.
Focused cooperation of all stakeholders should result in improved health and life quality of the population with fewer visits to general practitioners related to common health issues.

PHARMACOVIGILANCE: MONITORING OF THE ADVERSE DRUG REACTIONS

Monika Sonc

Institute of Oncology Ljubljana, Slovenia

At the Institute of Oncology Ljubljana monitoring, recording and reporting of adverse drug reactions is particularly important because a lot of new drugs are used in cancer treatment.

Even after the drug receives marketing authorization and can be used in hospitals or doctors may prescribe it, we have to monitor the safety of medicines. These activities, which are related to the detection, assessment, understanding and prevention of adverse effects, are known as pharmacovigilance.
By collecting and analyzing the information on adverse drug reactions we may help to complement the leaflets and thereby improve the safety of the treatment. It is particularly important to record and collect reports of serious adverse drug reactions, which is obligatory for all healthcare professionals.
Hospital pharmacists, who operate under the auspices of the Slovene Chamber of Pharmacy, took the initiative to prepare the web application which facilitates the collection of data on adverse drug reactions and provides comparable data. We are monitoring especially adverse drug reactions of anticancer drugs, which are used to treat the patients in our hospital.
The therapy of cancer patients requires continuously supervision of the progress of treatment by the physician and pharmacist, since patient often gets his oral medication at the community pharmacy. Developed web application is used as a tool to collect and monitor adverse drug reactions and thus improve patient safety receiving antitumor drugs.

Key words: Phamacovigilance, adverse drug reaction, cancer treatment, web application.

POSTER PREZENTACIJE

NOVEL IZOXAZOLO- AND THIAZOLOHYDRAZINYLDIENE-CHROMAN-2,4-DIONES AS POTENTIAL ANTI-BREAST CANCER AGENTS

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Breast cancer is still the most frequent malignancy cancer in women and principal cause of cancer death for females worldwide.Despite tremendous progress in its treatment, severe toxic side-effects and de novo and acquired resistance to the existing therapies present a major clinical problem urging for design and development of novel drugs and treatment combinations. Medicinal chemists are intrigued for decades to explore the natural coumarin or their synthetic analogs for their applicability as anticancer drugs due to the antiproliferative and cytotoxic effect on malignant cells and usefulness in prevention of recurrence and metastases of malignant cells. In search for novel coumarin based anti-breast cancer drugs, we have synthesized compounds that combine the coumarin core and five-member heterocycles (isoxazoles and thiazoles) in hydrazinylidiene-chroman-2,4-diones. Eight compounds were synthesized, structurally characterized and their antiproliferative effects were testedon breast cancer cells (MCF7 and MDA-MB-231) and bone and lung metastatic cell lines from breast cancer (SCP1833 and SCP4175, respectively) using MTT assay. Cell viability was evaluated after 48h-treatment and the ICs50 of the coumarin derivatives were determined.The apoptotic effect was evaluated by detection of PARP cleavage and reduced activity of the survival kinase Akt.
The results demonstrated cell-, dose- and time-dependent activity. Three of the eight compounds tested, having thiazole moiety, without or with additional methyl group(s) attached to the carbon(s) at the position(s) 5 and/or 4 in the thiazole ring showed to be the most potent, possessing significantly higher potency against all tested cell lines compared to the leading compound, 4-hydroxycoumarin. These compounds may be considered as new candidates that could contribute to the development of a large chemical library or related compounds by a combinatorial synthesis approach. Further studies are needed to elucidate with precision the type of receptor involved in their activity and their mechanism of action, including binding mode.

Key words: hydrazinyldiene-chroman-2,4-diones, breast cancer cells, antiproliferative effect, apoptosis

ODREĐIVANJE SADRŽAJA ANASTRAZOLA U FARMACEUTSKIM DOZIRANIM OBLICIMA PRIMENOM VISOKO EFIKASNE TEČNE HROMATOGRAFIJE

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Anastrazol (2- [3- (1-cijano-1-metil-etil) -5- (1 H-1,2,4-triazol-1-ilmetil) fenil] -2-metil-propannitril pripada novoj generaciji nesteroidnih inhibitora aromataze. Anastrazol se reverzibilno vezuje za enzim i mehanizmom kmpetitivne inhibicije inhibira konverziju androgena u estrogene u perifernim tkivima i pojedinim regionima unutar CNS. Anastrazol se primenjuje u postoperativnom tretmanu kod žena u menopauzi koje su obolele od karcinoma dojke. Snižavajući nivo estrogenih hormona anastrazol usporava rast i razvoj tumora. U ovom radu opisana je jednostavna i precizna RP-HPLC metoda koja je razvijena i validirana za određivanje anastrazola u doziranim farmaceutskim oblicima. Hromatografska analiza je izvedena korišćenjem ZORBAX Eclipse C8 (150 x 4,6 mm) 3,5μm kolone pod izokratskim uslovima sa radnom temperaturom od 30° C. Eluiranje je ostvareno mobilnom fazom koja uključuje acetonitril i vodu u odnosu 45:55 (v/v), pri brzini protoka od 1 ml/min. Detekcija je rađena na 215 nm. Razvijena metoda je validirana prema ICH smjernicama u pogledu specifičnosti, linearnosti, preciznosti, tačnosti i robusnosti. Metoda je linearna u opsegu koncentracija od 0,1212 mg/ml do 0,2828 mg/ml (r ≥0,9990). Dokazana je dobra preciznost (RSD < 2%) , tačnost (Recovery u opseg 98-102%) i robusnost metode.

Ključne reči: anastrazol, inhibitori aromataze, validacija RP-HPLC metode

DETERMINATION OF ANASTROZOLE IN PHARMACEUTICAL DOSAGE FORMS BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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Anastrozole,2-[3-(1-cyano-1-methyl-ethyl)-5-(1H-1,2,4-triazol-1-ylmethyl)phenyl]-2-methyl-propanenitrile is a new generation non-steroidal aromatase - inhibitor. Anastrozole binds reversibly to the aromatase enzyme through competitive inhibition, inhibits the conversion of androgens to estrogens in peripheral tissues (outside the CNS), and a few CNS sites in various regions within the brain . Anastrozole is used to treat advanced breast Cancer in women who have gone through “the change of life” (menopause) . Anastrozole works by lowering estrogen hormone levels to help shrink tumors and slow their growth.
In this study described the simple and precise RP-HPLC was developed and was validated for the determination of anastrazole in pharmaceutical dosage forms. Chromatography was carried by using ZORBAX Eclipse C8 (150 x 4,6 mm) 3,5μm column under isocratic
conditions at 30°C. Eluation was achived with a mobile phase comprising acetonitrile and water in ratio 45:55 (v/v). Flow rate was 1 ml/min. Detection was worked on 215 nm. Development

method was validated as per ICH quidelines with respect to specificity, linearity, accuracy, precision and robustness. Method is linear over the range of concentrations 0.1212 mg/ml to 0.2828 mg/ml ($r \geq 0,9990$). It was proved good precision (RSD < 2%), accuracy (Recovery in the range 98-102%) and robustness.

Key words: anastrozole, aromatase inhibitors, validation of RP-HPLC method

MARIJUANA ONCE AND TODAY

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Marijuana is very popular nowadays because of its medical use. This paper gives a short survey and review on the historical development of the ideas associated with marijuana. The aim of this paper is to look inside all faces of marijuana through history. Marijuana represents the dried top parts of female hemp plant in flower, which contains up to 6% tetrahidrokanabinol THC. Throughout human history hemp has been used for many purposes such as recreation, therapy, art, religion, medicine as a textile. The origin of marijuana dates from six thousands years ago when many different tribes used it for different celebrations and rituals. There are documents that show that marijuana was used even in the time of Chinese Emperor Shen Nung in 2337 BC. They used it in their funeral rituals. Seeds of this plant were found in their funeral urns. This plant was also used for treating insomnia, healing and also as painkiller. Each culture and subculture from prehistory up to now use this plant because it causes selective changes in consciousness of its consumers strictly dosing what is beyond reality, and also for medical reasons. Medicinal use of marijuana arrived in Europe from the East during the 18th century. It was brought to Europe much later, but it was not less popular. It reaches the high society very soon. In Paris, a club was open where many famous people, even Balzac, enjoyed marijuana. The first comprehensive description of the medical use of Indian hemp in Europe was written in 1830 by the German pharmacist Friedrich Ludwig Nees von Esenbeck. Until that point in time, use of marijuana for medical purposes had remained at a low level. Thanks mainly to the work of W.B.O'Shaugnessy in 1839 marijuana become recognized within European – school medicine. He used various hemp compounds in his investigations, partly with great success, against rheumatism, rabies, cholera, tetanus, convulsions and delirium tremens. The prestigious US Institute of Medicine published its report Medical Use of Marijuana in 1999. Recent studies reviewed by Park et al. 2004 that marijuana, THC and other exogenous cannabinoids exert potent effects on the endocannabinoid system in both the gonads and during pregnancy. These reports established the evidence base to support the further examination of cannabis products for medical use. Today marijuana is forbidden in many countries for its narcotic and negative influence to the nerve system. In some cultures marijuana was a protected mark, other cultures were its big admirers and third do not know or do not look on that way about marijuana. The use of marijuana was legalized in the Netherlands in 2003 and extended for a five – year period in 2007.

Key words: marijuana, cannabis, pharmaceutical use, medicinal use, history

FARMAKOEPIDEMIOLOŠKA ANALIZA VANBOLNIČKE POTROŠNJE ANTIINFEKTIVNIH LIJEKOVA ZA SISTEMSKU UPOTREBU U REPUBLICI SRPSKOJ U ODNOSU NA CRNU GORU

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Neracionalna potrošnja antiinfektivnih lijekova predstavlja jedan od najvažnijih faktora za nastajanje i širenje antimikrobne rezistencije, sve većeg ozbiljnog javnozdravstvenog problema, koji prijeti efikasnoj prevenciji i liječenju infekcija izazvanih mikroorganizmima i zahtijeva multidisciplinarno djelovanje na svim nivoima.
Cilj ove retrospektivne studije je bio da se procijeni vanbolnička potrošnja antiinfektivnih lijekova u Republici Srpskoj u odnosu na Crnu Goru u petogodišnjem periodu (od 2009. do 2013. godine). Podaci su dobijeni iz Instituta za javno zdravstvo Republike Srpske i Agencije za lijekove i medicinska sredstva Crne Gore (www.calims.me).
Podaci o potrošnji su standardizovani pomoću definisanih dnevnih doza na 1000 stanovnika na dan (DDD/1000 stanovnika/dan), u skladu sa ATC/DDD klasifikacijom i metodologijom Svjetske zdravstvene organizacije.
Vanbolnička potrošnja antiinfektivnih lijekova u Republici Srpskoj od 2009. do 2013. godine iznosila je 18.74, 21.30, 17.10, 15.17 i 17.33 DDD/1000 stanovnika/dan, redom. Od toga je najveća potrošnja amoksicilina, a zatim cefaleksina. Ako se uzme u obzir i ukupna potrošnja lijekova u apotekama, potrošnja antiinfektivnih lijekova je bila prosječno 2,9% od ukupne potrošnje lijekova u ovom periodu. Iz rezultata se vidi da se u ovom petogrodišnjem periodu potrošnja antiinfektivnih lijekova nije drastično mijenjala, sa najvećom potrošnjom u 2010. godini (21.30 DDD/1000 stanovnika/dan), te trendom opadanja potrošnje do 2012. godine, kada je dostigao najmanju potrošnju (15.17 DDD/1000 stanovnika/dan), da bi opet u 2013. godini potrošnja porasla za 2.16 DDD/1000 stanovnika/dan.
Ukupna potrošnja antiinfektivnih lijekova u Crnoj Gori od 2009. do 2013. godine iznosila je 42.50, 41.45, 39.05, 33.02 i 35.81 DDD/1000 stanovnika/dan, redom, što je u prosjeku 2,2 puta veća potrošnja u odnosu na Republiku Srpsku. Dalje, rezultati pokazuju kontinuiran trend pada potrošnje antiinfektivnih lijekova u Crnoj Gori u ovom periodu, izuzev 2012. godine, sa još uvijek izuzetno velikom potrošnjom.
Uočeni trendovi ukazuju na potrebu daljeg istraživanja i djelovanja u pogledu racionalne upotrebe antiinfektivnih lijekova u obe zemlje. Ovi koraci će omogućiti bolji uvid u potencijalno prisustvo iracionalnog propisivanja i dovesti do poboljšanja racionalne farmakoterapije.

Ključne riječi: farmakoepidemiologija, antiinfektivni lijekovi, potrošnja

PHARMACOEPIDEMIOLOGICAL ANALYSIS OF OUTPATIENT CONSUMPTION OF ANTIINFECTIVES FOR SYSTEMIC USE IN THE REPUBLIC OF SRPSKA COMPARED TO MONTENEGRO

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Irrational use of antiinfectives is one of the most important factors for the emergence and spread of antimicrobial resistance, increasingly serious threat to global public health, which threatens to effective prevention and treatment of infections caused by microorganisms and requires multisectoral action at all levels.
The aim of this retrospective study was to assess the outpatient consumption of antiinfectives in the Republic of Srpska compared to Montenegro in five-year period (2009 to 2013). Data were obtained from the Public Health Institute of the Republic of Srpska and the Agency for Drugs and Medical Devices of Montenegro (www.calims.me).
Consumption data were standardized using the defined daily doses per 1000 inhabitants per day (DDDs / 1000 inhabitants / day), in accordance to the ATC/DDD classification and methodology prescribed by the World Health Organization.
Outpatient consumption of antiinfectives in the Republic of Srpska was 18.74, 21.30, 17.10, 15.17 and 17.33 DDDs/1000 inhabitants/day, from 2009 to 2013 respectively. The consumption was the highest for amoxicillin and cephalexin. Considering the total outpatient consumption of drugs, the average consumption of antiinfectives was 2.9% of total drug consumption during this period. The results show that consumption of antiinfectives has not drastically changed, with the highest consumption in 2010 (21.30 DDDs / 1000 inhabitants / day), then the trend of decreasing until 2012, when it reached the lowest rate (15.17 DDDs / 1000 inhabitants / day), but again in 2013 the level was increased for 2.16 DDDs / 1000 inhabitants / day.
Total consumption of antiinfectives in Montenegro was 42.50, 41.45, 39.05, 33.02 and 35.81 DDD / 1000 inhabitants / day, from 2009 to 2013 respectively, which is on average 2.2 times higher consumption than in the Republic of Srpska. Furthermore, the results show a continued downward trend of antiinfectives consumption in Montenegro during this period, except 2012, and still extremely high consumption.
The results indicate a need for further research and action in terms of rational use of antiinfectives in both countries. These steps will provide better insight into the potential presence of irrational prescribing and lead to improvements to rational pharmacotherapy.

Keywords: pharmacoepidemiological, antiinfectives, consumption

ZNANJE PACIJENATA O RACIONALNOJ UPOTREBI ANTIBIOTIKA U REPUBLICI SRPSKOJ

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Racionalna upotreba antibiotika je najvažniji preduslov za sprečavanje pojave i širenja antibiotske rezistencije. Jedan od ključnih segmenata racionalne potrošnje antibiotika je upotreba antibiotika isključivo u svrhu liječenja infekcija izazvanih bakterijama, pri čemu se pravilna antibiotska terapija određuje na osnovu rezultata antiobiograma.
Osnovni cilj studije je bio da se procijeni znanje o racionalnoj upotrebi antibiotika među pacijentima u Republici Srpskoj.
U istraživanju je korišten upitnik sa pitanjima o racionalnoj upotrebi antibiotika, a koji je kreiran u skladu sa eurobarometrom za antibiotsku rezistenciju. Istraživanje je provedeno u novembru 2014. godine, a anketirano je 144 pacijenta oba pola, životne dobi od 18 do 85 godina, od kojih je najveći procenat bio sa srednjom (49,30%), zatim visokom (28,45%) i višom stručnom spremom (16,01%).
Od ukupnog broja anketiranih 54,20% ispitanika je koristilo antibiotike u posljednjih 12 mjeseci. Na pitanje da li antibiotici ubijaju viruse čak 72,20% pacijenata je odgovorilo potvrdno, što predstavlja netačan odgovor. Takođe, 46,50% ispitanika smatra da su antibiotici efikasni protiv prehlade i gripa. Nasuprot tome, 80,60% od ispitanih pacijenata je svjesno da nepotrebna upotreba antibiotika smanjuje njihovu efikasnost, odnosno da dovodi do pojave neefikasnosti, dok 72,20% pacijenata zna da upotreba antibiotika često ima neželjena dejstva, kao što je dijareja.
Rezultati dobijeni anketiranjem pacijenata u Republici Srpskoj ukazuju na potrebu podizanja svijesti o racionalnoj upotrebi antibiotika. Pacijenti su svjesni da nepravilna upotreba antibiotika dovodi do neželjenih dejstava i pojave rezistencije, međutim nivo znanja o pravilnoj upotrebi je izuzetno nizak, naročito ako se uzme u obzir nivo stručne spreme ispitanika. Zabrinjavajući je podatak da u najvećem procentu ispitanici smatraju da su antibiotici efikasni u liječenju prehlada i gripa. Dakle, podizanje nivoa svijesti i znanja o racionalnoj upotrebi antibiotika i antibiotskoj rezistenciji među stanovništvom Republike Srpske je ključni korak za sprječavanje pojave i širenja antibiotske rezistencije.

Ključne riječi: racionalna upotreba antibiotika, pacijenti, znanje

KNOWLEDGE OF PATIENTS ABOUT RATIONAL ANTIBIOTIC CONSUMPTION IN THE REPUBLIC OF SRPSKA

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Rational antibiotic use is the most important precondition for preventing emergence and spread of antibiotic resistance. One of the key segments of rational antibiotic consumption is antibiotic use solely for the treatment of infections caused by bacteria, with the proper antibiotic therapy based to the antibiogram results.
The main objective of the study was to assess the knowledge about rational antibiotic use among patients in the Republic of Srpska.
The study used a questionnaire containing questions about rational antibiotic use and it was created according to the Eurobarometer of antibiotic resistance. The survey was conducted in November 2014, and 144 patients of both sexes were interviewed, aged 18 to 85, of which the highest percentage was high school (49.30%), university (28.45%) and associate degree (16.01%).
Of the total number of respondents, 54.20% had used antibiotics in the last 12 months. Even 72.20% patients responded affirmatively to question if antibiotics kill viruses, which is an incorrect answer. Also, 46.50% of respondents believe that antibiotics are effective against cold and flu. On the other hand, 80.60% of the examined patients are aware that unnecessary use of antibiotics reduces their effectiveness and leads to the emergence of inefficiency, while 72.20% patients know that antibiotic use often has side effects, such as diarrhea.
The results obtained by interviewing the patients in the Republic of Srpska show the need to raise awareness about the rational antibiotic use. Patients are aware that improper antibiotic use leads to adverse effects and the emergence of resistance. However, level of knowledge about rational use is extremely low, especially considering the educational level of respondents. It is worrisome that the highest percentage of respondents believe that antibiotics are effective in treating cold and flu. Thus, raising awareness and knowledge about rational antibiotic use and antibiotic resistance among population of the Republic of Srpska is a key step to prevent the emergence and spread of antibiotic resistance.

Keywords: rational antibiotic use, patients, knowledge

BIODEGRADABILNE MIKROEMULZIJE KAO NOSAČI ZA DERMALNU ISPORUKU ANTIFUNGALNOG LIJEKA

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Sertakonazol-nitrat (SN) je derivat imidazola koji inhibicijom sinteze ergosterola ispoljava antifungalnu aktivnost. Praktično je nerastvorljiv u vodi i ima veoma ograničenu dermalnu raspoloživost nakon primjene konvencionalnih farmaceutskih oblika. Kao termodinamički stabilne i optički izotropne disperzije, mikroemulzije predstavljaju efikasne nosače za isporuku lijekova. Osim što pojačavaju perkutanu penetraciju lijekova, imaju i mnoge druge prednosti, kao što su visok kapicitet solubilizacije teško rastvorljivih lijekova, jednostavnost izrade i dugoročna stabilnost. Cilj ovog rada je bio formulacija mikroemulzija kao nosača za dermalnu isporuku SN zasnovanih na nejonskim biodegradabilnim surfaktantima, niskog iritacionog potencijala – gliceret-7-kaprilat/kapratu i polisorbatu 80.

Sprovedena su ispitivanja rastvorljivosti sertakonazol-nitrata u različitim uljima (izopropilmiristat, propilenglikol monokaprilat ili kaprilno/kaprinski trigliceridi) i kosurfaktantima (propilenglikol, dietilenglikolmonoetiletar, etanol ili izopropanol). Pseudoternarni fazni dijagrami dobijeni su metodom titracije vodenom fazom (visokoprečišćena voda), korišćenjem gliceret-7-kaprilat/kaprata u kombinaciji sa 4 različita kosurfaktanta ili polisorbata 80 u kombinaciji sa dietilenglikolmonoetiletrom kao kosurfaktantom. Nakon uspostavljanja ravnoteže, uzorci su vizuelno pregledani kako bi se procijenila njihova transparentnost. Odabrano je 5 formulacija mikroemulzija koje su pokazale najveći kapacitet solubilizacije terapijske koncentracije SN (2% (m/m)). Izotropnost dobijenih mikroemulzija, kao i odsustvo kristala lijeka, potvrđeni su polarizacionom mikroskopijom. Odabranim formulacijama (placebo uzorci i uzorci sa SN) su određeni indeks refrakcije, pH vrijednost, provodljivost i viskozitet.

Rastvorljivost SN je bila najveća u propilenglikol monokaprilatu (46,26 mg/ml) i dietilenglikolmonoetiletru (44,68 mg/ml). Kapacitet odabranih mikroemulzija za rastvaranje terapijske koncentracije SN je bio sličan, nezavisno od vrste korišćenog surfaktanta ili kosurfaktanta. Vrijednosti viskoziteta nisu bile veće od 51,01 mPas, pH vrijednosti su bile u opsegu 4,42 – 7,47 (placebo uzorci) i 3,67 – 4,87 (uzorci sa SN). Električna provodljivost je bila niža kod mikroemulzija bez lijeka (21,5 – 94,63 μS/cm) nego kod uzoraka sa SN (182 – 445,67 μS/cm) i ukazivala je na bikontinualnu strukturu sistema.

Kako su dobijene mikroemulzije imale zadovoljavajuće karakteristike, njihov potencijal kao nosača za dermalnu isporuku SN je neophodno dalje ispitati primjenom odgovarajućih metoda karakterizacije.

Ključne riječi: sertakonazol-nitrat, mikroemulzije, gliceret-7-kaprilat/kaprat, dermalna isporuka

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BIODEGRADABLE MICROEMULSIONS AS POTENTIAL CARRIERS FOR DERMAL DELIVERY OF AN ANTIFUNGAL DRUG

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Sertaconazole nitrate (SN), an imidazole derivative, maintains the antifungal activity by inhibiting the ergosterol synthesis. SN is poorly water soluble and dermal availability after topical administration of conventional pharmaceutical forms is limited. As thermodynamically stable, optically isotropic dispersions, microemulsions (MEs) are considered as an efficient carrier for topical drug delivery. In addition to their known enhanced penetration properties, they offer further advantages such as good solubilization capacity, ease of preparation and long-term stability. The aim of this study was to develop ME formulations based on two nonionic biodegradable surfactants with low skin irritation potential – glycereth-7-caprylate/caprate and polysorbate 80.

The solubility study of SN in various oils (isopropyl myristate, propylene glycol monocaprylate or caprylic/capric triglyceride) and cosurfactants (propylene glycol, diethylenglycolmonoethylether, ethanol or isopropanol) was carried out by shake-flask method. Pseudoternary phase diagrams were constructed by aqueous titration method, using glycereth-7-caprylate/caprate with 4 different cosurfactants and using polysorbate 80 with diethylenglycolmonoethylether as cosurfactant. After equilibrium, the balanced samples were observed visually to evaluate their transparency. Five MEs which showed maximum loading capacity for SN therapeutical concentration (2% (w/w)) were selected. Isotropy of MEs and the absence of undissolved drug crystals were confirmed using polarizing microscopy. Index of refraction, pH, electrical conductivity and rheological behavior of blank and SN-loaded MEs were evaluated.

The highest solubility of SN was in propylene glycol monocaprylate (46.26 mg/ml) and diethylenglycolmonoethylether (44.68 mg/ml). The loading capacity of MEs for SN was similar regardless of the cosurfactant used. Viscosity of selected MEs was not more than 51.01 mPa*s, pH ranged from 4.42 to 7.47 (blank ME) and from 3.67 to 4.87 (drug loaded MEs). The conductivity values were lower for blank MEs (21.5 - 94.63 μS/cm) than for SN-loaded MEs (182 - 445.67 μS/cm) and suggested bicontinuous structure..

The potential of these carriers to deliver SN in skin will be subject of further investigations.

Key words: sertaconazole nitrate, microemulsion, glycereth-7-caprylate/caprate, dermal drug delivery

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SADRŽAJ TOKSIČNIH METALA U KOMERCIJALNIM BILJNIM ČAJEVIMA

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Pored široke upotrebe biljnih proizvoda u terapiji mnogih bolesti, u današnje vrijeme ljudi često uzimaju biljne preparate kako bi se osjećali „zdravije“ ili zbog njihovog prijatnog ukusa. Međutim, veliki problem predstavlja široko rasprostranjena kontaminacija ljekovitog bilja, između ostalog, i teškim metalima.
Cilj ovog ispitivanja bio je da se odredi sadržaj teških metala (Cd, Pb, Cu, Zn, Mn, Ni) u uzorcima čajeva od najprodavanijih proizvođača u apotekama u Podgorici, Crna Gora. Analizirani su sledeći čajevi: Hypericum perforatum (4 uzorka), Achillea millefolium (3 uzorka), Thymus serpyllum (3 uzorka), Salvia officinalis (3 uzorka).
Uzorci su pripremljeni metodom suve mineralizacije, a sadržaj teških metala je određen ICP–OES metodom.
Dobijeni rezultati ukazuju na visoke koncentracije kadmijuma u svim uzorcima kantariona (0,32–0,51 mg/kg). Takođe, u jednom od tri uzorka hajdučke trave koncentracija kadmijuma je veća od one koju je predložila Svetska zdravstvena organizacija (0,3 mg/kg) i iznosi 0,41 mg/kg dok je u druga dva uzorka njegova koncentracija bila neznatno ispod predloženog limita. Sa druge strane, sadržaj kadmijuma u svim uzorcima majčine dušice nije bio veći od dozvoljenog, dok je u svim uzorcima žalfije bio ispod nivoa detekcije. Rezultati ukazuju i na visoku koncentraciju nikla u dva od tri uzorka majčine dušice (4,02 i 5,01 mg/kg). U svim ostalim uzorcima koncentracija nikla je bila manja od 4 mg/kg. Sa druge strane, koncentracije Cu, Pb, Zn i Mn u svim analiziranim uzorcima bile su niže od njihovih maksimalno dozvoljenih koncentracija.
Ispitivani komercijalni biljni čajevi kantariona i hajdučke trave mogu da predstavljaju značajan izvor kadmijuma, a majčine dušice nikla. Sa ciljem da se osiguraju bezbijednost i kvalitet neophodna je provera sadržaja toksičnih metala u ljekovitom bilju pre puštanja u promet ili izrade biljnih lekova i preparata. Takođe, kako bi se smanjila koncentracija toksičnih metala u ljekovitom bilju proizvođači bi trebali pažljivo odabrati mjesto uzgoja.

Ključne riječi: Toksični metali, komercijalni biljni čajevi, ICP–OES

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THE CONTENT OF HEAVY METALS IN COMMERCIAL HERBAL TEAS IN PODGORICA, MONTENEGRO

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Apart from widespread use of herbal products for treatment of different diseases, nowadays people, in order to feel better and to be fit, often take herbal preparations without any control. However, one of the main problems is extensive contamination of medicinal plants, inter alia, with heavy metals.
The aim of this study was to determine heavy metal concentrations (Cd, Pb, Cu, Zn, Mn, and Ni) in four samples of Hypericum perforatum, three of Achillea millefolium, three of Thymus serpyllum and three of Salvia officinalis from the best-selling manufacturers collected in the pharmacy in Podgorica.
The sample preparation has been performed using dry digestion and the content of heavy metals was determined by ICP–OES.
The results of the study indicate high concentrations of Cd in all samples of Hypericum perforatum (0.32–0.51 mg/kg). Also, in one of three samples of Achillea millefolium Cd concentration was higher than the one proposed by World Health Organization (0.3 mg/kg) and amounted 0.41 mg/kg while in other samples was slightly below established limit. On the other hand, Cd concentration in all samples of Thymus serpyllum did not exceed permissible level and in Salvia officinalis samples was below the detection limit. The obtained results indicate high concentration of Ni in two samples of Thymus serpyllum (4.02 and 5.01 mg/kg). Nickel concentration in other medicinal plant samples was lower than 4 mg/kg. Concentration of Cu, Pb, Zn and Mn were below their maximum permissible concentrations in all analyzed samples. Investigated best-selling commercial herbal teas of Hypericum perforatum and Achillea millefolium could appear as significant source of Cd, as well as, Thymus serpyllum of nickel. Medicinal plants should be tested on toxic metals content before processing it for human use ensuring their safety and quality. In order to minimise concentration of cadmium and nickel in medicinal plants, growers should carefully choose the growing sites.

Key words: Toxic metals, commercial herbal tea, ICP–OES

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UNOS FLUORIDA PUTEM VODE ZA PIĆE I PASTE ZA ZUBE KOD DECE UZRASTA DVE I TRI GODINE U ZEMUNU, SRBIJA

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Fluoridi imaju značajnu ulogu u prevenciji karijesa, međutim, povećan unos fluorida može dovesti do toksičnih efekata na zube i kosti. Prekomerni unos fluorida može predstavljati značajan rizik za decu uzrasta dve do tri godine, pošto se u tom periodu razvoj zuba odvija kroz faze sekrecije i maturacije.
Cilj ovoga rada je bio da se proceni dnevni unos fluorida puta dva najznačajnija izvora, vode za piće i paste za zube, kod dece uzrasta 2 i 3 godine sa opštine Zemun u Beogradu, Srbija.
Podaci o vrsti vode (česmenska/flaširana) i paste za zube koju deca koriste, kao i o učestalosti pranja zuba na dnevnom nivou dobijeni su putem upitnika koji su popunjavali roditelji. Koncentracija fluorida u vodi i pasti za zube određivana je elektrohemijskom metodom sa kombinovanom jon selektivnom elektrodom (Tip 800, WTW, Weilheim, Nemačka). Unos fluorida je procenjen korišćenjem matematičkog modela datog od strane Američke agencije za zaštitu životne sredine.
Procenjene srednje vrednosti ukupnog dnevnog unosa fluorida putem vode i paste za zube za decu uzrasta 2 i 3 godine iznose 0,401 i 0,412 mg F-/dan. Dobijene vrednosti su znatno niže od tolerišućeg dnevnog unosa fluorida za decu uzrasta 1-3 godine (1,3 mg/dan, Svetska zdravstvena organizacija-SZO) i čak niže i od preporučenog dnevnog unosa za isti uzrast (0,7-1 mg/dan, SZO). Međutim, 95-ti percentil procenjenog ukupnog dnevnog unosa fluorida za dvogodišnjake i trogodišnjake izražen na telesnu masu (0,102 i 0,057 mg F-/kg/dan) veći je od optimalnih vrednosti preporučenih od strane Evropske agencije za bezbednost hrane (0,05 mg F-/kg/dan).
Dnevni unos fluorida kod najvećeg broja ispitivane dece bio je ispod optimalnog unosa preporučenog za prevenciju karijesa, dok je povišen unos zapažen samo kod pojedine dece što ukazuje da u ovom uzrastu unos fluorida putem ispitivanih izvora treba da bude kontrolisan od strane roditelja.
(Projekat III 46009)

Ključne reči: fluoridi, pijaća voda, pasta za zube, procena unosa, deca

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FLUORIDE INTAKE VIA DRINKING WATER AND TOOTHPASTE IN TWO- AND THREE-YEAR-OLDS FROM ZEMUN, SERBIA

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It is known that fluoride have important role in caries prevention, as well as that increased fluoride intake can induce toxic effects on teeth and bones. High fluoride intake can be of special risk in children two and three years old because this is a period when tooth development is in the phase of secretion and maturation.

The aim of this study was to assess the daily fluoride intake via most important sources of fluoride, i.e. via drinking water and toothpaste in children aged 2 and 3 from the municipality of Zemun, Serbia.

Data on the water type (tap and/or bottled water) and toothpaste used by children, as well as the daily frequency of tooth brushing were obtained from questionnaire for parents. Fluoride concentrations in water and toothpaste samples were determined electrochemically, using fluoride-selective electrode (Combined ISE type 800, WTW, Weilheim, Germany). Fluoride intake was assessed using a mathematical model given by US EPA (United States Environmental Protection Agency).

The estimated mean values of total daily fluoride intake via water and toothpaste in children aged 2 and 3 were 0.401 and 0.412 mg F-/day, respectively. These results were far below the tolerable upper level of fluoride intake for children aged 1 to 3 (1.3 mg/day, World Health Organization-WHO) and even lower than the recommended optimal intake (0.7-1 mg/day, WHO) for this age. However, the 95-percentile of estimated daily fluoride intake for children aged 2 and 3 expressed per body weight (0.102 and 0.057 mg F-/kg/day, respectively) were higher than the optimal intake value given by European Food Safety Authority-EFSA (0.05 mg F-/kg/day).

Daily fluoride intake in the majority of studied toddlers was lower than the optimal intake needed for the caries prevention, although higher intake was determined in some children indicating that this is a period of childhood during which fluoride intake via these sources should be controlled by parents.

(Project III 46009)

Key words: fluoride, drinking water, toothpaste, intake assessment, children

HOMEOPATSKI LEK – OSOBINE I PRAVILNA UPOTREBA

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Individualizovana terapija svakog pacijenta ponaosob, primenjena je i u posologiji homeopatskog leka, kao osnovni princip klasične homeopatije.

Upoznavanje stručne javnosti sa osobenostima homeopatskog leka, kao i razlike u primeni

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odnosu na alopatski lek.
U klasičnoj homeopatiji je u upotrebi isključivo jednokomponentni homeopatski lek. Homeopatski lek se najčešće koristi u decimalnoj potenciji gde je odnos lekovite supstance i vehikuluma 1:10 (D potencija), centizimalnoj (C) potenciji 1:100, M potenciji (1:1000) i LM potencijama (1 : 50 000). Broj upotrebljenih tableta, globula ili peleta nema isti značaj kao u alopatiji, jer se njima ne unosi u organizam materijalna doza leka, već informacija koju lek poseduje. Od 1938. god. SAD reguliše homeopatske lekove i zvanično priznaje oko 1300 lekova čije se monografije nalaze u Homeopatskoj američkoj farmakopeji. Za homeopatske lekove referentne su i homeopatske farmakopeje drugih zemalja (nemačka, engleska, indijska itd.)
Hanemanova knjiga „Organon" sadrži važna uputstva za pravilan homeopatski tretman. Homeopatski lek stimuliše organizam da mobiliše sopstvenu snagu što dovodi do izlečenja. Poreklo homeopatskog leka može biti: biljno, životinjsko, mineralno. Ostale grupe lekova se nazivaju nozodi, sarkodi i imponderabilia. Homeopatski lekovi u čvrstom obliku su tablete, globule ili pelete. Globule su krupnije (85% saharoze i 15% laktoze), a pelete su sitnije (100% laktoze). Haneman je upoređivao efikasnost upotrebe čvrstih oblika homeopatskog leka i vodenih rastovora.
Poredeći evoluciju Hanemanovih zaključaka kroz izdanja „Organona" i knjige „Hronične bolesti" uočava se da je u četvrtom izdanju „Organona" Haneman preporučio upotrebu 1-2 pelete, a iste godine u knjizi „Hronične bolesti" kao efikasniju upotrebu vodenih rastvora leka. U petom izdanju „Organona" (1833. god.) njegov konačan stav je da više ne treba upotrebljavati suve doze peleta, već lek treba davati pacijentu u obliku vodenog rastvora.

Ključne reči: homeopatija, posologija, homeopatski lek, „Organon"

HOMEOPATSKI LEK – OSOBINE I PRAVILNA UPOTREBA

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Basic principle of homeopathy is an individualized therapy, which is present also in the posology of homeopathic medicines.
This work has the aim to help health professionals get acquanted with characteristics of a homeopathic medicine and the points that distinguish its posology of an alopathic remedy.
Classical homeopathy uses exclusively homeopathic remedies made of a single substance. Homeopathic remedies are used most often in D potency which is made of substance and vehicle in the ratio 1:10, in C potency (ratio 1: 100), in M potency (ratio 1:1000) and in LM potency (ratio 1 : 50 000). The number of tablets, globules or pellets used by a patient is not significant as it is in allopathic medicine, due to the lack of materialistic dose of the homeopathic remedy which instead carries information. Homeopathic remedies are offically approved in the US by Homeopathic American Pharmacopoeia which recognizes about 1300 remedies. Homeopathic drugs are regulated also by pharmacopoeias of other countries (German, British, Indian etc.)
Hanneman's book „Organon" contains important guidelines for the correct homeopathic treatment. Homeopathic remedy stimulates organism to self-healing. Origin of homeopathic remedies is herbal, mineral or animal. Other groups of homeopathic remedies are called

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nosodes, sarcodes and imponderabilia. Solid forms of homeopathic remedies are tablets, globules or pellets. Globules are bigger (85% of saccharose and 15% of lactose) and pellets (100% of lactose) are smaller. Hanneman compared efficacy of homeopathic remedies after administration of solid dosages vs. water solutions.
Comparing the evolution of Hanneman's conclusions on posology of homeopathic medicine which he presented in different editions of „Organon" and „Chronic diseases", it can be observed that Hahnemann suggested administration of 1-2 pellets in the 4th edition of „Organon", while during the same year in „Chronic diseases" he suggested as more efficient use of water solutions. In the 5th edition of Organon (1833) his final opinion is that dry doses should not be administred and he favors the water solutions of homeopathic remedy.

Key words: homeopathy, posology, homeopathic medicine, „Organon".

HELIANTHUS TUBEROSUS L. ASTERACEAE KAO SASTOJAK FUNKCIONALNE HRANE

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Helianthus tuberosus L. Asteraceae, čičoka, je potencijalni sastojak funkcionalne hrane. Sadrži osim vode u velikom procentu, ugljene hidrate (inulin) i proteine, a lipide u tragovima. Inulin je rastvorljivo dijetno vlakno i nakon oralne primene ne podleže enzimskoj digestiji. Uočen je prebiotski efekat, sniženje serumskih lipida i prevencija osteoporoze i kardiovaskularnih bolesti, nakon konzumiranja hrane bogate inulinom. Ugljeno-hidratna hrana se karakteriše vrednošću glikemijskog indeksa (GI) koji je specifična neimenovana vrednost za svaku namirnicu. GI je za različite namirnice naveden u internacionalnim tablicama, a vrednosti ispod 55 se smatraju povoljnim i niskim GI vrednostima. Za inovativne proizvode sa ugljenim hidratima je važno odrediti vrednosti GI. Čičoka je slabo zastupljena u ishrani.
Karakterizacija različitih proizvoda sa sadržajem čičoke. Napravljeno je dve vrste proizvoda: hleb i ekstrudovani proizvodi sa sadržajem čičoke.
Hleb je napravljen od pšeničnog kvasnog testa i obogaćen sa 25% brašna od suvih krtola čičoke. Okarakterisan je parametrima nutritivne vrednosti (sadržaj vode, suve materije, ugljenih hidrata, proteina, lipida i dijetnih vlakana) i glikemijskim indeksom (GI). Ekstrudovani proizvodi su dobijeni primenom tehnologije ekstruzije na mešavinu pirinčanog brašna i brašna od čičoke (odnos 70/30) i okarakterisani su vrednošću GI. Nutritivna vrednost i GI su odredjivani standardnim metodama.
Parametri nutritivne vrednosti hleba bili su: sadržaj vode 41,46%, sadržaj suve materije 58,36%, sadržaj ugljenih hidrata 47,64%, sadržaj proteina 8,25%, sadržaj lipida 0,27%, sadržaj dijetnih vlakana 6,15%. Vrednost glikemijskog indeksa za hleb sa sadržajem čičoke je bila 53,7, a za ekstrudovane proizvode 91,26.
Analizirani hleb je optimalne nutritivne vrednosti, sa niskim sadržajem masti i značajnom količinom dijetnih vlakana. Glikemijski indeks hleba je povoljan i niži od GI ekstrudovanih proizvoda, uprkos nižem sadržaju čičoke. Incidenca hroničnih bolesti uslovljava razvoj novih

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proizvoda za dijetetski režim, a koji mogu da dovedu do unapređenja zdravlja. Inkorporiranjem brašna od čičoke u inovativne dijetetske proizvode moguće je dobiti proizvod optimalnih osobina.

Ključne reči: čičoka, nutritivna vrednost, glikemijski indeks

HELIANTHUS TUBEROSUS L. ASTERACEAE AS AN INGREDIENT OF FUNCTIONAL FOOD

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Helianthus tuberosus, L. Asteraceae (Jerusalem artichoke) is a potential ingredient of functional food. It contains water in large percent, carbohydrates (inulin) and proteins, while lipids are present in traces. Inulin is soluble dietary fiber, which is not digested in the small intestine after oral administration. The consumption of inulin-containing food has prebiotic effect, lowers serum triglyceride levels and can prevent osteoporosis and cardiovascular diseases. Food rich in carbohydrates is characterized by glycemic index (GI), which is a specific value for each food. It is classified in international tables of GI for different food and values lower then 55 are considered beneficial as low GI values. Therefore it is valuable to determine GI for innovative carbohydrate products. Jerusalem artichoke is rarely used in diet.
Characterization of different products with Jerusalem artichoke. The bread and extrudates were made with content of Jerusalem artichoke.
The bread was made from wheat, yeast dough and enriched with 25% of Jerusalem artichoke flour. The bread was characterized by nutritional value parameters (the content of water, dry matter, carbohydrates, proteins, lipids and dietary fiber), and glycemic index value (GI). The extrudates were obtained by extrusion technology from mixture of rice and Jerusalem artichoke flour (70/30 ratio). The obtained samples were characterized by glycemic index. Nutritional value and glycemic index of investigated products were determined by standardized methods.
Nutritional value of the bread was: content of water 41.64%, content of dry matter 58.36%, content of carbohydrates 47.64%, content of proteins 8.25%, content of lipids 0.27%, and 6.15% of dietary fiber. The obtained value of glycemic index for bread was 53.70, and 91.26 for extrudates.
The analyzed bread has optimal nutritional value, low lipid content and significant content of dietary fibers. The glycemic index of bread is beneficial and is lower then GI of extrudates, though content of Jerusalem artichoke in bread was lower then in extrudates. The incidence of chronic diseases leads to development of new dietary products which may have health maintaining effects. Incorporation of Jerusalem artichoke flour in inovative dietary products may provide a product of optimal diet values.

Key words: Jerusalem artichoke, nutritive value, glycemic index.

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ASSESSMENT OF THE CHEMICAL COMPOSITION OF SAGE ESSENTIAL OIL FROM ADRIATIC COAST IN ACCORDANCE TO EUROPEAN PHARMACOPOEIA AND OTHER QUALITY STANDARDS

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Although the knowledge and use of sage can be dated back to Greek Era and have a long history of culinary and effective medicinal use, even now there is a remarkable interest concerning its phytochemistry as many aspects are still unknown. There is large demand for chemically characterized and standardized plant material from the Balkans and the Mediterranean region, as native area of distribution of this commercially and economically exploited species.
Therefore, 14 populations of wild growing Dalmatian sage (S. officinalis L.) from 5 Adriatic countries (Slovenia, Croatia, Montenegro, Bosnia and Herzegovina and Albania) were analyzed regarding the essential oil yield and composition. The oil yield ranged from 0.39 % to 3.80 %. The highest yields were recorded in 2 indigenous populations from Croatia, (3.80 % and 3.39 %). Overall, 8 populations of sage met the Ph.Eur.8.0 minimal requirements concerning the essential oil yield, while 5 populations complied with the ISO 6571 standard.
Performing GC/FID/MS analysis, a total of 67 components were detected. Fourteen components (α-pinene, camphene, β-pinene, myrcene, p-cymene, limonene, 1,8-cineole, cis-thujone, trans-thujone, camphor, borneol, bornyl acetate, trans-(E)-caryophyllene and α-humulene) that were identified in all samples represent 66.57 % to 87.60 % of the total oil chemical composition. Only one Bosnian population of S. officinalis met the quality requirements for the composition of the essential oils according to the German Drug Codex and another Montenegrin population complied with the ISO 9909 standard. Overall, only one Croatian population met both, the ISO 9909 and the German Drug Codex requirements as well as complies with the minimal pharmacopoeial and ISO 6571 standard requirements for the oil yield.

Keywords: Dalmatian sage, GC/FID/MS analysis, essential oil quality.

UČESTALOST SAMOMEDIKACIJE PRIMARNE DISMENOREJE KOD STUDENTKINJA CRNOGORSKIH FAKULTETA

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Primarna dismenoreja (PD) je zdravstvena tegoba karakteristična po bolnim menstruacijama, često praćena mučninom, migrenom ili nesvjesticom i utiče na kvalitet života žene. Samomedikacija se definiše kao upotreba lijekova bez preporuke ljekara ili drugog zdravstvenog radnika, u cilju tretmana samodijagnostifikovanih smetnji ili simptoma.

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Ispitati učestalost PD, način na koji je studentkinje deset crnogorskih fakulteta ublažavaju, zastupljenost samomedikacije i upotrebu analgetika.
Ispitivanje je rađeno tokom školskih 2011/2012. i 2012/2013. godina. Anonimnom i dobrovoljnom anketom obuhvaćeno je 156 studentkinja treće i četvrte godine osnovnih studija 10 fakulteta iz Crne Gore koje su podijeljene u dvije grupe: studentkinje medicinske grupe fakulteta (SMGF): Farmaceutskog fakulteta njih 37, Medicinskog 28, Samostalnog studijskog programa stomatologije 17 i studentkinje nemedicinske grupe fakulteta (SNMGF): Pravnog fakulteta 16, Ekonomskog 27, Elektro-tehničkog fakulteta 4, Metalurško-tehnološkog 2, Arhitektonskog 14, Građevinskog fakulteta 5 i Montenegro Business school-a 6. Anketa se sastojala od 26 pitanja otvorenog i zatvorenog tipa o demografskim podacima, opštem zdravstvenom stanju, regularnosti menstrualnog ciklusa, PD i načinu ublažavanja tegoba. Podaci su statistički obrađeni putem deskriptivne statistike i primjenom hi-kvadrat ($\chi 2$) testa; $p<0.05$ smatrano je statistički značajnom razlikom.
Ukupno 152 studentkinje (97.4%) su prijavile tegobe PD. Najveći broj ispitanica, njih 125 (82,2%), tegobe PD liječe analgeticima, bez statistički značajne razlike između SMGF i SNMGF. Samomedikaciju analgeticima praktikuje 81 (64,8%) ispitivanih studentkinja, bez statistički značajne trazlike između SMGF i SNMGF. Najčešće korišteni analgetici kod obje grupe su ibuprofen (68,8%), diklofenak (31,2%), paracetamol (5,6%), acetilsalicilna kisjelina (4,8%) i naproksen (4,8%).
Samomedikacija je u visokom procentu zastupljena u obje grupe ispitivanih studentkinja. Najčešće korišteni analgetik ibuprofen je iz grupe nestereoidnih antiinflamatornih lijekova što upućuje na potrebu za edukacijom zbog potencijalnih neželjenih efekata karakterističnih za pomenuti lijek.

Ključne riječi: samomedikacija, primarna dismenoreja, studentkinje, analgetici

THE SELF-MEDICATION FREQUENCY OF PRIMARY DYSMENORRHEA BY FEMALE STUDENTS IN MONTENEGRO

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Primary dysmenorrhea (PD) is a health problem characterized by painful menstruation, often accompanied by nausea, migraine, or fainting and affects the quality of women's life. Self-medication is usually defined as intake of any type of drugs for treating oneself without professional supervision to relieve an illness or a condition.
To determine the frequency of PD by ten Montenegrin faculties students, how they reduce PD discomfort, self-medication usage and analgesic application.
Survey was performed during 2011/2012 and 2012/2013 school years. Anonymous questionnaire consisted of 26 items was filled by 156 female students separated in healthcare (Faculties of Medicine 28 students, Pharmacy 37 and Dentistry 17) (HC) and non-healthcare

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students (Faculties of Law 16 students, Economics 27, Architecture 14, Civil Engineering 5, Metallurgy 2, Electrical Engineering 4 and Montenegro Business school 6) (NC). Questions were about demographic data, general health condition, regularity of menstrual cycle and ways of alleviating PD. Data were statistically analyzed, Chi-square test used and $p<0.05$ considered as significant.
Number of students reported PD symptoms was 152 (97.4%). Largest number of respondents, 125 (82.2%) of them, are treating PD symptoms with analgesics, with no statistically significant differences between HC and NC. Self-medication with analgesics practiced 81 (64.8%) examined student, with no statistically significant between HC and NC. Between the analgesics, the most popular is ibuprofen (68.8%), then diclofenac (31.2%), paracetamol (5.6%), acetylsalicylic acid (4.8%) and naproxen (4.8%).
Prevalence of self-medication was high among the examined population.
Most frequently used analgesic ibuprofen belongs to group of non-steroidal anti-inflammatory drugs and this fact may indicate the need for further education due to probable side effects from mentioned analgesic.

Key word: self-medication, primary dysmenorrhea, students, analgesic

UTICAJ FORMULACIJE I USLOVA SKLADIŠTENJA NA STABILNOST LIZOZIMA IZRAŽENO PREKO „AKTIVNOSTI“ LIZOZIMA

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Lizozim Hidroklorid je visoko kvalitetan enzim koji se dobija ekstrakcijom i sofisticiranim tehnološkim postupkom iz svježeg bjelanceta. Bakteriostatsko i baktericidno djelovanje lizozima našlo je široku primjenu u farmaceutskoj industriji.
Lizozim je prisutan u ljudskom organizmu uglavnom u pljuvački, majčinom mlijeku i suzama. Lizozim je visoko efikasan lijek dostupan za pacijente u različitim ljekovitim formama, kao što su bezreceptni (OTC) preparati za liječenje prehlade, otopine i lozenge za grlobolju i kreme. Obzirom na atraktivnu primjenu Lizozima kao lijeka važno je razumjeti odnos između stabilnosti proteina i njegove aktivnosti u različitim dozažnim formama pri različitim eksperimentalnim uslovima.
Cilj rada je evaluacija korelacije enzimske aktivnosti sa različitim formulacijama komercijalnih preparata pri različitim uslovima skladištenja.
Za ispitivanje uticaja formulacije i uslova skladištenja na stabilnost Lizozima korištene su tri različite formulacije: vodena otopina (20mg/ml), krema (20mg/g) i komprimovane lozenge (200mg – upakovane u dva različita primarna pakovna materijala).
Formulacije su skladištene 12 mjeseci pri ubrzanim (40°C/75%RH), intermedijarnim (30°C/65%RH) i dugotrajnim (25°C/60%) uslovima starenja.
Aktivnost Lizozima je praćena odgovarajućom biološkom metodom koja podrazumijeva spektrofotometrijsko određivanje na principu bakteriolize.
Ispitivan je uticaj uslova skladištenja (temperature i relativne vlažnosti) na stabilnost proizvoda izražena kao “aktivnost” enzima.

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Može se zaključiti da je Lizozim prilično stabilan te da dozažna forma lijeka i uslovi skladištenja imaju uticaja na enzimsku aktivnost kao i pH vrijednost za tečne i polučvrste forme. Aktivnost Lizozima raste u vodenim otopinama pri ubrzanim i intermedijarnim uslovima skladištenja. Pod uticajem povišene temperature i slabo kisele sredine (pH 5-6), termalna modifikacija Lizozima dovodi do polimerizacije enzima i povećane antibakterijske aktivnosti.

Ključne riječi: lizozim, stabilnost, aktivnost, formulacija

INFLUENCE OF FORMULATION AND STORAGE CONDITIONS ON LYSOZYME STABILITY MEASURED AS "ACTIVITY" OF LYSOZYME

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Lysozyme Hydrochloride is a high quality enzyme made from fresh egg white by original extraction and refining technology. The bacteriostatic and bactericidal properties of lysozyme have generated numerous applications in the pharmaceutical industry. Lysozyme is present in humans, mainly in saliva, breast milk and tears. Lysozyme, a highly effective therapeutic drug, is available for the consumers in a variety of forms, such as an over-the-counter (OTC) cold remedy, solutions and lozenges for sore throats and creme. Due to the enzyme's attractive application as a drug, it is highly important to understand the relationship between the protein's stability and activity in different dosage forms at different experimental conditions.
The aim of this work was to evaluate how the enzyme activity in commercial preparations correlates to the drug product formulas and storage conditions.
The effect of formulation and storage conditions on Lysozyme stability has been investigated on three different formulations of Lysozyme: aqueous solution (20mg/ml), creme (20mg/g) and compressed lozenges (200mg- packed in two different primary packaging materials).
Formulations were stored for 12 months under accelerate (40C/75% RH), intermediate (30C/65%RH) and long-term conditions (25C/60%RH). Activity of Lysozyme was monitored by the proposed biological method, spectrophotometric determination on the basis of the bacteriolysis reaction.
Influence of storage conditions (temperature and relative humidity) on drug products stability, measured as "activity", was investigated.
It is possible to conclude that Lysozyme has a quite good stability. Dosage form and storage conditions has influence on activity of Lysozyme, as well as pH for liquid and semisolid forms.
It is observed that activity of Lysozyme in aqueous solution at accelerated and intermediate storage conditions increased. Under higher temperature and weakly acid environment (pH 5-6), thermal modification of Lysozyme promotes increased polymerization of enzyme and makes it possible to obtain higher antibacterial activity.

Key words: lysozyme, stability, activity, formulation

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ANALIZA ODNOSA TROŠKOVA I EFEKATA FINASTERIDA I DUTASTERIDA U TERAPIJI BENIGNE HIPERPLAZIJE PROSTATE - MARKOVLJEV MODEL BAZIRAN NA PODACIMA IZ CRNE GORE

Vera Dabanovic

Zdravstvena ustanova Apoteke Crne Gore "Montefarm"

Benigna hiperplazija prostate je jedno od najčešćih oboljenja kod muškaraca starijih od 50 godina i tijesno je povezano sa procesom starenja. Obzirom da životni vijek ima trend produženja, za očekivati je povećanje učestalosti ove bolesti, što će potencijalno dovesti do povećanja troškova zdravstvene zaštite. Ukoliko se ne liječi ima progresivan tok i dovodi do teških komplikacija. Inhibitori 5 alfa reduktaze, finasterid i dutasterid, ublažavaju simptome bolesti, povećavaju kvalitet života i smanjuju rizik od komplikacija. Dutasterid značajno smanjuje progresiju bolesti i komplikacije, kao što su akutna retencija urina i hirurške intervencije, u odnosu na finasterid, ali je skuplji od finasterida 2,3 puta. Cilj ove studije je da pokaže da li je sa aspekta odnosa troškova i efikasnosti opravdano finansiranje upotrebe dutasterida od strane Fonda za zdravstveno osiguranje u Crnoj Gori.
Studija je sprovedena Markovljevim modelom, koji je razvijen na osnovu podataka iz literature o efektivnosti i na osnovu troškova liječenja u Crnoj Gori. Trajanje jednog ciklusa u modelu je jedna godina a vremenski horizont praćenja je iznosio 20 godina. Za troškove i ishode korišćena je perspektiva društva i oni su diskontovani po stopi od 3% godišnje. Urađena je Monte Karlo mikrosimulacija modela sa 1.000 virtuelnih pacijenata.
Primjena dutasterida je imala nešto bolji odnos troškova i kliničke efikasnosti od finasterida (539,51 €/QALY u odnosu 544,11€/QALY). Jedna dobijena godina života prilagođena za kvalitet, upotrebom dutasterida, košta Fond za zdravstveno osiguranje Crne Gore 1.245,68 €, što ukazuje da je terapija sa dutasteridom farmakoekonomski isplativa.
Ova studija je pokazala da dutasterid ima bolji odnos troškova i kliničke efikasnosti u odnosu na finasterid, pa je finansiranje dutasterida od strane Fonda za zdravstveno osiguranje Crne Gore farmakoekonomski opravdano.

Ključne riječi: dutasterid, finasterid, benigna hiperplazija prostate, odnos troškova i efikasnosti.

COST EFFECTIVENESS COMPARISON OF DUTASTERIDE AND FINASTERIDE IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA / MARKOV MODEL BASED ON DATA FROM MONTENEGRO

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Benign prostatic hyperplasia (BPH) is one of the most commonly disease among male aging 50 years and more. The rise of the prevalence of BPH is related to aging, and since duration of life time period has tendency of rising the prevalence of BPH will rice as costs of treatment BPH and its influence on health economic budget. Dutasteride is a new drug which similar to finasteride

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inhibits enzyme 5- alpha reductase, diminish symptoms of BPH, reduce risk complications and increase quality of life in patients with BPH. But, use of dutasteride is limited by its high costs. The aim of this study was to compare cost effectiveness of dutasteride and finasteride from the perspective of purchaser of health care service (Republic Institute for health Insuranse, Montenegro).

We constructed Markov model to compare cost effectivenss of dutasteride and finasteride using data from available published pharmacoeconomic literature and data which reflects socio economic sphere actual in Montenegro. Time horizon was estimated on 20 years, with duration of on cycle of 1 year. The discount rate was 3%. We performed Monte Carlo simulation for virtual cohort of 1000 patients with BPH.

Total costs for one year treatment of BPH with dutasteride were estimated on 6.458,00 € which is higher comparing with finasteride which coststs were 6.088,56 € . The gain in qality adjusted life years were higher with dutasteride (11,97 QALY) than with finasteride (11,19 QALY). The results of our study indicate that treating BPH with dutasteride comparing to finasteride is cost effective option since the value of ICER is 1.245,68 €/QALY which is below estimated threshold (1.350,00 Euros per one gained year of life).

Dutasteride is cost effective option for treating BPH comparing to finasteride. Results of this study put up new information for health care decision makers about treatment of BPH in socio economic environment which is actual as well in Montenegro as well in other countries with recent history of socio economic transition.

Key words: dutasteride, finasteride, benign prostatic hyperplasia, cost efffectiveness.

DIJETETSKI SUPLEMENTI NAMIJENJENI REDUKCIJI TJELESNE MASE – KORISTI I PROBLEMI NJIHOVE PRIMJENE

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Broj osoba čija telesna masa je veća od idealne je svakim danom sve veći. Prema nekim procjenama 2/3 odraslih osoba želi da redukuje tjelesnu masu ili spriječi njeno povećanje usvajajući nove modele ponašanja ali uz nerealna očekivanja.

Dijetetski suplementi su namirnice koje dopunjuju normalnu ishranu i predstavljaju koncentrovane izvore vitamina, minerala ili drugih supstanci sa hranjivim ili fiziološkim efektom, pojedinačno ili u kombinaciji, a u prometu su u doziranim oblicima dizajnirane da se uzmu u odmjerenim pojedinačnim količinama (kapsule, tablete, kesice praška, ampule tečnosti, bočice za doziranje u kapima i dr.)

Dijetetski suplementi obuhvataju širok spektar proizvoda, bez obzira na oblik u kome se nalaze, koji može biti neobičan za namirnice, ali ipak pripadaju kategoriji namirnica. Prodaju se u apotekama, prodavnicama bezbjedne hrane, ali i putem Interneta. Agresivno promovisani u medijima, veoma često sa zvučnim obećanjima o efikasnosti, i često bez upozorenja o eventualnoj opasnosti. Ogroman broj suplementa namenjenih smanjenju telesne mase je prisutan na tržištu,vrlo često ih prate zvučne izjave, od kojih su mnoge obmanjujuće a većina prisutnih dijetetskih suplemenata na tržištu nikad nije ispitivana.

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Ne postoje čarobni napici među dijetetskim suplementima, oni mogu djelovati jedino ako su u kombinaciji sa dobro izbalansiranom dijetom i povećanom fizičkom aktivnošću. Osnovna pitanja koja moramo postaviti za svaki dijetetski suplement pa i onaj namijenjen smanjenju tjelesne mase su:
- Da li je bezbjedan?
- Da li je efikasan?
- Da li je legalan?

Potrošači moraju da budu zaštićeni od neadekvatnih proizvoda i netačnih tvrdnji da se njihovom upotrebom za kratko vrijeme gubi višak kilograma u čemu značajnu ulogu treba da ima savremena regulativa usklađena sa naučnim procjenama i međunarodnim standardima.
Za osobe sa povećanom tjelesnom masom i one osobe koje su nezadovoljne svojim punačkim izgledom, važeća preporuka je pridržavajte se dijete i vježbajte.

Ključne riječi: dijetetski suplementi, namirnice, dijeta, fizička aktivnost

DIETARY SUPPLEMENTS FOR WEIGHT REDUCTION-THE BENEFITS AND PROBLEMS OF THEIR USE

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Persons whose body weight is higher than ideal is increasing every day. According to some assessment, two third of adults want to reduce body weight or prevent its increase by adopting new models of behavior but with unrealistic expectations.
Dietary supplements are foods that supplement normal diet and which are concentrated sources of vitamins, minerals or other substances with nutritional or physiological effect, alone or in combination, marketed in dosage forms designed to be taken in measured small unit quantities (capsules, tablets, sachets of powder, liquid ampoules, vials with dropwise dosing etc.)
Dietary supplements include a wide range of products, regardless of form in which they are situated, which can be unusual for foodstuffs but still belong to the category of food. They sale in pharmacies, shops for safe food, but also through the Internet. Aggressively promoted in the media, often with sound promises of efficiency and without warning about possible dangers. Huge number of supplements designed for reducing body weight is present in the market, often are accompanied with sound statements and also many of them are misleading and the majority of the dietary supplements in the market has never been analyzed.
There are no magic drinks among dietary supplements, they can only act if they are combined with well balances diet and increased physical activity. The basic questions that we must ask for any dietary supplement, even those intended for weigh reduction, are:
- I s it safe
- Is it effective?
- Is it legal?

Consumers must be protected from inappropriate and false product claims that using them for a short time will lose extra pounds a significant role need to have modern legislation aligned with scientific assessments and international standards.

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For the persons with increased body mass and those who are dissatisfied with their plump appearance, valid recommendation is follow the health dietary and exercise.

Keywords: dietary supplements, foods, diet, physical activity

ULOGA KLINIČKOG FARMACEUTA U LIJEČENJU DEPRESIJE

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Depresija kao jedna od vodećih bolesti u svijetu, je također u istoj mjeri prisutna u Bosni i Hercegovini. Socijalni faktori, kao što su nezaposlenost, egzistencijalna nesigurnost pogoduju uslovima za razvoj depresije, a također kao bitan faktor za njen razvoj je post traumatski stresni poremećaj (PTPS), koji je u velikoj mjeri posljedica rata s kraja XX vijeka u BiH. U BiH ne postoji zvaničan registar osoba oboljelih od depresije. (1)
Prikazati neophodnost uključivanja kliničkog farmaceuta u tim za liječenje depresije.
Podaci prikupljeni sa Klinike za psihijatriju Sveučilišne kliničke bolnice Mostar
Studija sprovedena od strane Američke farmaceutske asocijacije
Studija sprovedena od strane američkih farmaceuta, (University of Michigan College of Pharmacy)
U studijama provedenim od strane Američke farmaceutske asocijacije i američkih farmaceuta sa Univerziteta Mičigen, klinički farmaceut je bio dio tima zdravstvenih radnika koji su bili uključeni u liječenje i skrining depresije. Od ukupnog broja pacijenata 80% je imalo vidno smanjenje težine simptoma između njihove prve i posljednje posjete. Srednji rezultat samoprocjene simptoma depresije je bio smanjen sa 11.5 (umjerena težina), na početku liječenja, na 5.3 (blaga težina). Ukupni troškovi zdravstvene zaštite bili su manji nego što su na početku predviđeni. (2,3)
U periodu od januara 2014. godine do 31. avgusta 2014. godine, na Klinici za psihijatriju Sveučilišne kliničke bolnice Mostar hospitalizovano je 2214 bolesnika, od toga je 12.54% hospitalizovano zbog depresije. Međutim u liječenju pacijenata u BiH, klinički farmaceut nije dio ljekarskog tima.
Uz međusobnu saradnju, sa ljekarskim timom, klinički farmaceuti imaju sposobnost da započnu terapiju određenim lijekovima, prekinu i prilagode lijekove koji se koriste prilikom liječenja ovih bolesti.

Ključne riječi: Depresija, klinički farmaceut, liječenje i skrining depresije

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ROLE OF CLINICAL PHARMACIST IN DEPRESSION TREATMENT

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Depression as one of the leading diseases in the world, is also equally present in Bosnia and Herzegovina. Social factors, such as unemployment and socioeconomic status are favorable conditions for the development of depression, but also as an important factor for its development is post traumatic stress disorder (PTSD), which is largely a result of the war in the late twentieth century in BiH. In BiH, there is no official register of persons suffering from depression.
Aim of this work is to show the necessity of including a clinical pharmacist in the team for the treatment of depression.
Data collected from the Department of Psychiatry, University Clinical Hospital Mostar
A study conducted by the American Pharmaceutical Association
A study conducted by the American Pharmacists, (University of Michigan College of Pharmacy)
In studies conducted by the American Pharmaceutical Association and the American Pharmacists with the University of Michigan, a clinical pharmacist was part of a team of health professionals involved in treatment and screening for depression. Of the total number of patients, 80% had a visible reduction in symptom severity between their first and last visit. The average result of self-assessment of depressive symptoms was reduced from 11.5 (moderate severity), at the beginning of treatment, at 5.3 (mild severity). Total health care costs were lower than initially foreseen.
In the period from January 2014 to 31 August 2014, at the Department of Psychiatry, University Clinical Hospital Mostar 2,214 patients were hospitalized, of which 12,54% were hospitalized for depression. However, in the treatment of patients in BiH, clinical pharmacist is not part of the team of health professionals.
Clinical pharmacist as part of the team of health professionals have ability to start and stop treatment with certain drugs, and also adjust drug dose for right treatment of depression.

Keywords: Depression, clinical pharmacist, treatment and screening for depression

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KNOWLEDGE, EXPECTATIONS AND SELF MEDICATION IN THE ADULT POPULATION IN THE REPUBLIC OF MACEDONIA

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Self-medication ie using of medications without doctor's prescription becomes a problem, most of all because the patients are not informed for the possible consequences from the willfully taking of medications, as interactions medicine – medicine and increased risk from the appearance of harmful effects from the medicines taken in doses bigger than usual wherein

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appears potential abuse of the medicines. Self-medication allows quick access to the medicines because of their permanent and wide availability on the market itself.
Using of medicines for self-medication is constantly increasing and one of the most often used medicines for self-medication are the medicines that are used for treating the symptoms of cold, slightly increased temperature, headache and other types of pain, diarrhea and so on. In Republic of Macedonia medicines that are used for self-medication (self-treating) are safe and efficient if they are given in recommended doses and also if are followed the recommendations given from the World Health Organizations.
We have made research on a patients from different ages with purpose to determine the most often reasons for using of the self-medication, knowing the possible indications and contraindications, how often they use the medicines for self-medication, and also if the commercials for the medicines for self-medications have influence on the opinion of the patients.

Key words: contraindications, indications, pain, security, efficiency.

AFINITET RAZLIČITIH ŽUČNIH KISELINA PREMA TRANSPORTNIM PROTEINIMA ZA LEKOVE U BIFIDOBACTERIUM LONGUM NCC2705

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Zbog uloge crevne mikroflore u inter- i intra- individualnim razlikama u metabolizmu lekova, kao i zbog uloge žučnih kiselina (ŽK) u modifikaciji prodora lekova kroz biološke membrane, cilj rada bio je da se ispita afinitet različitih ŽK (holna (CA), 12-monoketoholna (12-MKC) i deoksiholna (DCA) kiselina) prema multidrug transporterima prisutnih kod probiotske bakterije Bifidobacterium longum NCC2705 (BL), kako bismo pretpostavili koja od njih ima najveći uticaj na transport lekova.
Kako bi se uporedili afiniteti posmatranih ŽK prema multidrug transporterima kod BL (6 iz ABC familije i 8 sekundarnih transportera), urađena je docking studija. Ona je izvršena pomoću programa SwissDock. I-Tasser server je korišćen za predviđanje strukture trasnportnih proteina na osnovu njihove amino-kiselinske sekvence. Rezultati dokinga dati su kao FullFitness energije pri čemu manja energija ukazuje na jači afinitet liganda prema određenom proteinu.
Najniže energije sa svim ispitivanim transportnim proteinima pokazala je DCA, dok su CA i 12-MKC imale nešto više, međusobno slične energije. Za sve tri ŽK, najveći afinitet pokazan je za BL1767 transporter iz ABC porodice. S druge strane, najviša energija i posledično najmanji afinitet procenjen je za BL1703, sekundarni transporter. Dobijeni rezultati ukazuju da sve ispitivane ŽK imaju generalno jači afinitet ka ABC transporterima u odnosu na sekundarne transportere.
Na osnovu dobijenih rezultata docking studija može se pretpostaviti da se uticaj ŽK na transport lekova kroz membranu BL očekuje pre uticajem na ABC transportere nego na sekundarne transportere. Osim toga, zbog najjačeg afiniteta vezivanja za bakterijske transportere, najveći

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uticaj na transport lekova očekuje se od DCA. Kako bi se potvrdili ovi rezultati, potrebno je preduzeti dalja in vivo istraživanja ovih interakcija na molekulskom nivou.

Ključne reči: docking, žučne kiseline, transporteri, interakcije sa lekovima

THE AFFINITIES OF DIFFERENT BILE ACIDS TOWARDS MULTIDRUG TRANSPORTERS IN BIFIDOBACTERIUM LONGUM NCC2705

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Due to implication of gut microflora in inter- and intra- individual differences in drug metabolism and the role of bile acids (BAs) in modification of drug penetration through biological membranes, the aim of this study was to predict the affinities of different BAs (cholic (CA), 12-monoketocholic (MKC) and deoxycholic acid (DCA)) towards multidrug transporters of Bifidobacterium longum NCC2705 (BL), in order to predict which of them could have the greatest influence on drug transport.
Docking study was carried out to compare the affinities of selected BAs towards multidrug transporters in BL (6 ATP-binding cassette transporters [ABC] and 8 secondary transporters). Docking step was performed using molecular docking program SwissDock. I-Tasser server was used to predict the protein structures of transporters, based on their amino-acid sequences. Results of docking study were given as Full Fitness energies. The lower estimated Full Fitness energy indicates the higher binding affinity of ligands towards a certain protein.
The lowest energies for all studied transporters had DCA, while CA and MKC showed a bit higher, but similar energies. For all three BAs, the highest affinity was for ABC transporter BL1767. On the other hand, the highest energy and consequently the lowest affinity was estimated for secondary transporter BL1703. The obtained Full Fitness energies indicate that all examined BAs have generally higher affinities towards ABC transporters compared to secondary transporters.
Based on the obtained docking results, it could be assumed that the influence of BAs on drug transport through the membrane of BL is expected to be more likely through ABC than secondary transporters. Furthermore, due to highest binding affinities, the major influence on drug transport is expected from DCA. In order to confirm these results, further in vivo investigations of their interactions at molecular level need to be undertaken.

Keywords: docking, bile acids, transporters, drug interactions

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UTICAJ DEOKSIHOLNE KISELINE NA DISTRIBUCIONI KOEFICIJENT SIMVASTATINA

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Oktanol-voda particioni koeficijent ima široku primenu u farmaceutskoj industriji kao kvantitativna mera za procenu afiniteta leka ka biološkim membranama. S druge strane, poznato je da su žučne kiseline modifikatori transporta lekova kroz biološke membrane. Stoga, cilj rada je bio da se ispita uticaj deoksiholne kiseline (DCA) na distribucioni koeficijent simvastatina (SV), koji predstavlja visoko lipofilno jedinjenje sa ekstremno niskom rastvorljivošću u vodi i malom bioraspoloživošću.
Distrbucioni koeficijent i logD vrednost SV sa i bez DCA određivani su tečno-tečnom ekstrakcijom u n-oktanol/pufer sistemu na pH 5 i pH 7.4, simulirajući gastrointestinalno okruženje. Koncentracije SV u vodenoj fazi određene su HPLC-DAD metodom.
Kao visoko lipofilno jedinjenje i slaba kiselina, u kiselijoj sredini se očekuje da SV bude više u neutralnoj formi koja može lakše da prolazi kroz biološke membrane što objašnjava veće vrednosti distribucionog koeficijenta na nižem pH (4.70±0.01 na pH5 i 4.59±0.06 na pH7.4). Dodatak DCA doveo je do statistički značajnog smanjenja distribucionog koeficijenta SV na obe posmatrane pH vrednosti (4.52±0.08 at pH 5, and 4.38±0.09 at pH 7.4).
Pokazano je da dodatak DCA u n-oktanol/pufer sistem smanjuje vrednosti distribucionog koeficijenta SV. Ovo bi moglo biti posledica formiranja hidrofilnog kompleksa, što bi kao posledicu moglo da ima povećanje bioraspoloživosti. Kako bi se potvrdili ovi rezultati, potrebno je preduzeti dalja in vivo istraživanja ovih interakcija na molekulskom nivou.

Ključne reči: distribucioni koeficijent, žučne kiseline, simvastatin, hidrofilnost, transport lekova

THE INFLUENCE OF DEOXYCHOLIC ACID ON THE DISTRIBUTION COEFFICIENT OF SIMVASTATIN

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The octanol-water partition coefficient is widely regarded in the pharmaceutical industry as a quantitative measure for assessing a drug molecule affinity for the biological membranes. Bile salts are known for their function as modifiers of drug penetration across biological membranes. Accordingly, the aim of this study was to estimate the influence of deoxycholic acid (DCA) on the distribution coefficient of simvastatin (SV) which is a highly lipophilic compound with extremely low water-solubility and bioavailability.

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Distribution coefficients and logD of SV with or without DCA were measured by liquid-liquid extraction in n-octanol/buffer systems at pH 5 and pH 7.4, resembling gastrointestinal environment. SV concentrations in aqueous phase were determined by HPLC-DAD.
As a highly lipophilic molecule and weak acid, in more acidic environment, SV is expected to be more in its neutral form that can more easily penetrate biological membranes which explains higher values of distribution coefficient at lower pH (4.70±0.01 at pH5 vs. 4.59±0.06 at pH7.4). Upon addition of DCA, the distribution coefficient SV significantly decreased at both selected pH (4.52±0.08 at pH 5, and 4.38±0.09 at pH 7.4).
Our data indicate that the addition of DCA into the n-octanol/buffer system decreases the values of SV distribution coefficient. This may be the result of the formation of hydrophilic complexes increasing the solubility of SV that could consequently lead to the increase of SV bioavailability. In order to confirm these results, further in vivo investigations of their interactions at molecular level need to be undertaken.

Keywords: distribution coefficient, bile salts, simvastatin, hydrophilicity, drug transport

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VITAMINI I MINERALI KOJE NAJČEŠĆE KORISTE STUDENTI STUDIJSKOG PROGRAMA FARMACIJA U BANJA LUCI

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Dijetetski suplementi se proizvode u dozno zavisnim oblicima kao kapsule, tablete, sirupi, kapi i slično. Direktiva EU definiše dijetetske suplemente kao namirnice koje dopunjuju normalnu ishranu i predstavljaju koncentrovane izvore nutrijenata, vitamina, minerala i drugih supstancija sa hranljivim i fiziološkim efektom, a u prometu su u doziranim farmaceutskim oblicima, predviđeno da se uzimaju u odmjerenim pojedinačnim količinama (kapsule, tablete, kapi i sl.). Cilj nam je bio odrediti koje vitamine i minerale studenti najčešće uzimaju kroz dijetetske suplemente.
U istraživanju je korišten originalni upitnik kojim su anketirana 72 studenta. Od svih upitnika izdvojen je jedan upitnik koji nije ispravno popunjen i on nije dalje analiziran.
Vitamin C je najčešće korišten pojedinačni vitamin kojeg koristi 23,3% studenata a od minerala najčešće je korišten kalcijum kojeg je koristilo 6,7% studenata.
Najčešće korišteni minerali među anketi¬ranim studentima bili su kalcijum, magnezijum i gvožđe. Najčešće korišćeni vitamini među anketi¬ranim studentima su vitamin C i vitamini B kompleksa.

Ključne riječi: dijetetski suplementi, studenti, upotreba

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VITAMINS AND MINERALS WHICH ARE MOST COMMONLY USED BY STUDENTS OF THE STUDY PROGRAM PHARMACY IN BANJA LUKA

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Dietary supplements are produced in a dose-related forms such as capsules, tablets, syrups, drops etc. The EU Directive defines dietary supplements as addition to the normal diet which are concentrated sources of nutrients, vitamins, minerals
and other substances with a nutritional or physiological effect and, on the market they are in dosed pharmaceutical forms, meant to be taken in measured small unit quantities (capsules, tablets, drops, etc.). Our goal was to determine which vitamins and minerals are taken by students through dietary supplements.
The study used the original questionnaire which surveyed 72 students. Of all the questionnaires, one was singled out, because it was not properly filled out and will not be further analyzed.
Vitamin C is the most commonly used single vitamin used by 23.3% of students, and calcium is most commonly of the minerals used by 6.7% of students.
The most commonly used minerals among the surveyed students were calcium, magnesium and iron. The most commonly used vitamins among the surveyed students are vitamin C and B complex vitamins.

Keywords: dietary supplements, students, consumption.

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ISPITIVANJE RASPADLJIVOSTI EFERVESCENTNIH TABLETA PRISUTNIH NA TRŽIŠTU REPUBLIKE SRPSKE

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Efervescentne tablete su neobložene tablete koje obično sadrže kiselu supstancu i karbonate ili hidrogenkarbonate koji u prisustvu vode brzo reaguju i oslobađaju ugljen dioksid. Prije upotrebe rastvaraju se ili disperguju u vodi. U posljednje vrijeme veliki je broj prisutnih dijetetskih suplemenata u obliku efervescentnih tablete na našem tržištu i oni imaju veoma široku upotrebu. Naš cilj je bio analizirati raspadljivost efervescentnih tableta prisutnih na tržištu.
Uzorci su analizirani metodom prema Petoj Jugoslovenskoj farmakopeji (Ph. Jug V). Uzorci su bili dijetetski proizvodi sa vitaminima i mineralima, u obliku efervescentnih tableta. Ukupno je analizirano 12 različitih uzoraka.
Raspadljivost je ispitivana prema metodi po kojoj svih šest tableta mora da se raspadne za 5 minuta, kako je i bilo sa svim našim uzorcima.
Rezultati su dobri, ali treba napomenuti da je broj proizvoda koji se danas nalaze u prometu veliki, i u apotekama i u supermarketimaa a i u ostalim prodavnicama robe široke potrošnja, pa

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smatramo da je potrebna kontinuirana provjera kvaliteta ovih proizvoda.
U svim ispitivanim uzorcima raspadljivost efervescentnih tableta je bila u skladu sa propisom Pete Jugoslovenske farmakopeje.

Ključne riječi: efervescentne tablete, raspadljivost, ispitivanje

TESTING DEGRADABILITY OF EFFERVESCENT TABLETS AVAILABLE ON THE MARKET OF THE REPUBLIC OF SERBIAN

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Effervescent tablets are uncoated tablets generally contain acidic substances and carbonates or bicarbonates, which in the presence of water quickly react and release carbon dioxide. Before use they are dissolved or dispersed in water.
Lately a large number of present dietary supplements in the form of effervescent tablets are in the market and they have a very wide use. Our aim was to analyze the disintegration of effervescent tablets available on the market.
Samples were analyzed according to the Fifth Yugoslav Pharmacopoeia (Ph. Jug V). Samples were dietetic suplements with vitamins and minerals, in the form of effervescent tablets. A total of 12 different samples were analyzed.
Degradability is tested according to the method by which all six tablets must disintegrate in 5 minutes, as it was with all our samples.
The results are good, but it should be noted that the number of products that are now in the market is big, in pharmacies, supermarkets and in other stores of consumer goods, so we believe that we need a continuous check on the quality of these products.
In all cases of testing degradability of effervescent tablets, tablet was was in accordance with the regulation Ph. Jug V

Keywords: effervescent tablets, degradability, testing

SADRŽAJ TEŠKIH METALA U ZEMLJIŠTU PARKOVA I IGRALIŠTA U PRIMORSKIM OPŠTINAMA CRNE GORE

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Određivanje sadržaja potencijalno štetnih teških metala u uzorcima zemljišta parkova i igrališta je imperativ u cilju procjene rizika kako po stanovništvo tako i po turiste. Do danas u Crnoj Gori postoji veoma malo naučno istraživačkih rezultata o zagađenosti zemljišta. Da

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bi se odredila koncentracija i porijeklo teških metala, kao i procjena kvaliteta zemljišta, uzeto je 54 uzorka zemljišta iz parkova i igrališta u primorskim opštinama Crne Gore. U uzorcima zemljišta određivan je sadržaj Cd, Cu, Pb i Zn. Zagađenost zemljišta je procijenjena na osnovu geohemijskog indexa (Igeo) i potencijalnog indeksa ekološkog rizika (RI).
Vrijednost geohemijskog indeksa Igeo je bila 0, uglavnom negativna, za Cd, Cu i Zn, ukazujući na nedostatak kontaminacije. Međutim Igeo za Pb je bio između 1 i 2, što odgovara klasi 2 za kvalitet zemljišta, što odgovara srednje zagađenom zemljištu.
Na osnovu dobijenih rezultata za vrijednost RI može se zaključiti da ispitivana zemljišta pokazuju značajan stepen zagađenja, jer se RI kretao između 100 i 200, tj. 132.5. Ovakvi podaci nam pružaju dovoljno dokaza o zagađenosti zemljišta u primorskim opštinama Crne Gore pri čemu prisustvo toksičnih teških metala u životnoj sredini može prouzrokovati različite vrste zdravstvenih problema. Posebnu pažnju treba posvetiti ovom problemu, nastaviti dalja istraživanja i razmisliti o mogućim načinima remedijacije lokacija na kojima je primjećena kontaminacija.

Ključne riječi: teški metali, parkovi, igrališta, Igeo, RI

HEAVY METALS CONCENTRATION IN SOILS FROM URBAN PARKS AND GREEN AREAS IN COASTAL MUNICIPALITIES OF MONTENEGRO

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Determination of concentration of potentially harmful heavy metals in the soil of urban parks and playgrounds is imperative in order to evaluate the potential risks to residents and tourists. Until now days there is a little scientific research data on soil pollution in Montenegro. To identify the concentrations and sources of heavy metals, and to assess the soil environmental quality, soil samples were collected from 54 urban parks and playgrounds located in coastal municipalities of Montenegro. The concentrations of Cd, Cu, Pb and Zn in the samples have been analyzed. The contamination of soils was assessed based on the index of geoaccumulation (Igeo) and potential ecological risk index (RI).
The index of geoaccumulation (Igeo) was below 0 for Cd, Cu and Zn, mostly negative, pointing to the lack of contamination. But Igeo for Pb was between 1 and 2, belongs to class 2 for soil quality, which means moderately contaminated soil.
Based on the result for RI it can be concluded that the investigated soil samples showed considerable pollution, because RI was between 100 and 200, i. e. 132.5. This data provide enough evidence about soil pollution in coastal municipalities of Montenegro and it is well documented that the presence of highly toxic heavy metals in environment can cause various types of health problems. Special attention should be paid to this problem, to continue further research and to consider possible ways of remediation of the sites where contamination has been observed.

Key words: heavy metals, parks, playgrounds, Igeo, RI

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DIZAJN NOVIH ANALOGA VITAMINA E KAO POTENCIJALNIH ANTITUMORSKIH LEKOVA

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Tokom poslednje decenije brojni eksperimentalni podaci su pokazali da individualne forme vitamina E ispoljavaju diferencijalnu antiproliferativnu aktivnost na raznim tipovima tumorskih ćelija. Analozi vitamina E koji su izgubili antioksidativnu aktivnost, uglavnom estri, su pokazali poboljšanu antitumorsku aktivnost i stabilnost u odnosu na polazna jedinjenja. Studije kvantitativnog odnosa između strukture i dejstva (Quantitative Structure-Activity Relationship - QSAR) su primenjene na seriji derivata tokoferola i tokotrienola čija je antiproliferativna aktivnost (izražena kao pIC50) testirana na MCF-7 ćelijama karcinoma dojke. Na osnovu formiranih 2D- i 3D-QSAR modela identifikovane su najvažnije strukturne karakteristike koje utiču na antitumorsku aktivnost derivata vitamina E. Dizajnirano je devet novih jedinjenja i predviđena je njihova aktivnost. 3D-farmakoforna slika najaktivnijih dizajniranih jedinjenja uključuje prisustvo dva akceptora vodoničnih veza- predstavljena sa dva karbonilna kiseonika na optimalnom rastojanju, prisustvo hidrofobnog regiona, akceptora i donora vodonične veze u estarskom lancu na položaju C6, što je u saglasnosti sa rezultatima 3D-QSAR studije. Vrednosti in silico izračunatih ADMET (absorption, distribution, metabolism, excretion, toxicity) parameteara (MWt, MlogP, PrUnbnd, HBD, HBA, RuleOf5, CYP_Risk, TOX_hERG, TOX_Risk) dizajniranih jedinjenja su upotrebljene za finalni odabir potencijalno najboljih jedinjenja za sintezu i ispitivanje na ćelijama karcinoma dojke.

Ključne reči: vitamin E, karcinom dojke, QSAR, dizajn lekova

DESIGN OF NEW VITAMIN E DERIVATIVES AS POTENTIAL ANTICANCER AGENTS

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Over the last decade numerous experimental data have shown that individual forms of vitamin E exert differential antiproliferative activity against various types of tumor cells. Redox-silent analogs of vitamin E, mainly esters, showed improved anticancer activity and stability relative to the parent compounds. Quantitative Structure-Activity Relationship (QSAR) studies were performed on data set composed of tocopherol and tocotrienol derivatives whose antiproliferative activity (expressed as pIC50) was tested on MCF-7 breast cancer cell line. Based on the created 2D- and 3D-QSAR models we were able to identify the most important structural determinants that influence antiproliferative activity of vitamin E derivatives. Nine new compounds were designed and their activity was predicted by use of the created 3D-QSAR

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model. 3D-pharmacophoric feature of most active designed compounds includes presence of two hydrogen bond acceptor groups, represented by two carbonyl oxygens, at optimal distance, presence of the hydrophobic region, hydrogen bond donor and hydrogen bond acceptor group in the ester chain at C6, which is in accordance with 3D-QSAR results. In silico ADMET properties (MWt, MlogP, PrUnbnd, HBD, HBA, RuleOf5, CYP_Risk, TOX_hERG, TOX_Risk) of designed compounds were used for final selection of the most promising candidates for synthesis and in vitro study on breast cancer cell lines.

Keywords: vitamin E, breast cancer, QSAR, drug design

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ISPITIVANJE MIKROBIOLOŠKE ISPRAVNOSTI FARMACEUTSKO-TEHNOLOŠKE FORMULACIJE GELA SA 1% KLINDAMICIN HLORIDA

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Da bi magistralni preparat izrađen u laboratoriji pri apoteci ili galenski preparat proizveden u galenskoj laboratoriji kao samostalnoj zdravstvenoj ustanovi bio efikasan i bezbedan za primenu kod pacijenata, farmaceuti se moraju u toku svog rada pridržavati i poštovati sve propisane principe Dobrih praksi. Jedan od važnijih segmenata je svakako da dobijeni preparat bude i mikrobiološki ispravan i da se tokom čuvanja i primene njegova mikrobiološka ispravnost očuva. Ispitivanje mikrobiološke ispravnosti magistralno pripremljene formulacije gela, koji sadrži klindamicin hidrohlorid u koncentraciji od 1%.
Prvi korak pre same izrade preparata podrazumevao je pripremu radnog prostora kako bismo u skladu sa principima DLP smanjili mogućnost kontaminacije, kao i priprema posuđa za izradu lekovitog preparata i ambalaže u koje će se pakovati gotov preparat bio je sledeći korak. Prema protokolu uzorci su podeljeni u tri grupe, a svaka od ovih grupa imala je i podgrupu sa namernim onečišćenjem, koje je uz oznaku grupe imalo i slovo „p“.
I grupa uzoraka (po 5) je prema protokolu čuvana na (T 25oC) i ispitivana je mikrobiološka ispravnost nakon izrade formulacije, zatim nakon 8 dana i nakon 14 dana. II grupa uzoraka je čuvana u frižideru (T 4-8oC) pa je nakon toga zasejavana dok je III grupa uzoraka je čuvana u termostatu na 36,6oC.
Svi preparati su bili bakteriološki ispravni nakon izrade. Neki preparati su bili kontaminirani nakon upotrebe (normalna flora kože), a samo dva preparata od kontaminiranih upotrebom u trećoj sedmici rada nisu odgovarala normi za bakteriološku ispravnost leka, po broju ukupnih mezofila, koji je diskretno prelazio 1000/ ml. Svi izolovani mikroorganizmi nisu preživeli u gelu duže od 6 dana. Uz poštovanje principa dobre laboratorijske prakse u toku izrade željene farmaceutsko-tehnološke formulacije za lečenje akni 1% Klindamicin hlorid gela, u uslovima laboratorije na fakultetu, dobijen je lekoviti preparat koji je svojim izgledom i mikrobiološkom ispravnošću zadovoljio najstrožije zahteve za efikasnost i bezbednost dobijenog galenskog preparata.

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THE STUDY OF MICROBIOLOGICAL SAFETY OF 1% CLINDAMYCIN CHLORIDE GEL

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In order for the main preparation is made in the laboratory at a pharmacy or galenical preparation produced in galenic laboratory as an independent medical institution was effective and safe for administration to patients, pharmacists must be in the course of their work and adhere to appreciate all the regulative principles of good practice. One of the most important segments is sure to be a preparation obtained and microbiologically correct and that during storage and application of microbiological safety of his preserve.
The aim of study of microbiological safety masterly prepared gel formulations comprising clindamycin hydrochloride at a concentration of 1%.
The first step before the actual production of preparations included the preparation of the working area in order to comply with the principles of GLP reduce the possibility of contamination, as well as the preparation of dishes for making medicinal products and packaging in which it will be packed ready preparation was the next step. According to the protocol, samples were divided into three groups and each group had a subgroup of intentional contamination, which is a mark group, had the letter “p”.
Group I samples (5) according to the protocol stored at (T 25 ° C) and examined the microbiological safety after making the formulation, then after 8 days and after 14 days. The second group of samples was stored in a refrigerator (T 4-8oC) and is then inoculated while the III group of samples was stored in a thermostat at 36,6oC.
All preparations were bacteriologically correct after placement. Some preparations were contaminated after use (the normal flora of the skin), and only two preparations of using contaminated in the third week of work did not fit the norm for bacteriological quality of the drug, according to the total number of mesophyll, which is discreetly exceeded 1000 / ml. All isolated microorganisms did not survive in the gel more than 6 days. With respect to the principles of good laboratory practice during the preparation of the desired pharmaceutical technological formulations for the treatment of acne 1% Clindamycin gel chloride, in laboratory conditions at the college, obtained a medicinal preparation which is its appearance and microbiological correctness meet the most stringent requirements for efficiency and safety resulting galenical preparations.

Key words: clindamycin gel, galenic preparation, bacteriologically

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MENADŽMENT ZBRINJAVANJA FARMACEUTSKOG OTPADA NA TERITORIJI NOVOG SADA

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Farmaceutski otpad može postati opasan otpad ako se ne zbrinjava na zakonom propisan način i ako se neodgovorno i bez kontrole odlaže i baca u smeće, kontejnere, izliva u kanalizaciju ili zakopava u zemlju.
Sagledati kako i na koji način se zbrinjava farmaceutski otpad koje građani odlažu u specijalno postavljene kontejnere u okviru apoteka pri Apotekarskoj Ustanovi Novi Sad (AUNS).
Korišćeni su podaci su dobijeni u Transfer stanici za prikupljanje lekova sa isteklim rokom, koja priprada AUNS, a koja je osnovana 2011.godine.
Na godišnjem nivou skupi se oko 1 tona farmaceutskog otpada. Farmaceutski otpad se sastoji većinom od lekova koji se izdaju na recept, delom iskorišćenih a nalaze se i neotvorene kutije. Pored organizovanog sakupljanja i klasifikovanja, AUNS je organizovala i odgovarajuće skladištenje farmaceutskog otpada, i do sada je samo mali deo uništen preko registrovane kompanije, dok većina otpada stoji propisno uskladištena i klasifikovana zahvaljujući postojanju Transfer stanice i predanom radu koleginice koja rukovodi ovom stanicom.
Akcija sprovedena od strane farmaceuta u okviru AUNS je sigurno doprinela zbrinjavanju jednog dela farmaceutskog otpada sa teritoriji Novog Sada i okoline ali je to nedovoljno jer se ostali mogući „proizvođači“farmaceutskog otpada poput bolnica, lekarskih i stomatoloških ordinacija, domova zdravlja, instituta, zavoda, privatnih apoteka, veterinarskih ordinacija i dr. nisu uključili te je stoga neophodna akcija širih razmera radi organizovanog sakupljanja farmaceutskog otpada od svih mogućih „proizvođača“, njegovog klasifikovanja i uništavanja u skladu sa propisima.

Ključne reči: farmaceutski otpad, zaštita sredine, opasan otpad

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MANAGEMENT OF DISPOSAL OF PHARMACEUTICAL WASTE IN NOVI SAD

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Pharmaceutical waste can become a hazardous waste if it is not disposed of in accordance with law and if you are irresponsible and out of control delayed and thrown in the trash container , poured into drains or buried in the ground. Hazardous waste at its origin, composition or concentration of hazardous substances can cause harm to the environment and human health. To see how and in what manner pharmaceutical waste that citizens stored in special containers placed within the pharmacies of Pharmacy Institution of Novi Sad (AUNS) is disposed.
We used the data obtained in the collecting unit within the pharmacies of Pharmacy Institution of Novi Sad, which was established in 2011.
Based on the collection and classification of drugs that people dispose in containers placed in pharmacies, it can be seen that the percentage of deferred and unused medications is large. Boxes and blisters that make pharmaceutical waste, indicating that some of the prescribed drugs, because most of the drugs are from list of prescription, half- used and unopened. It would be a huge harm that drugs were not used and did not contribute to improving therapeutic outcomes, were not collected as pharmaceutical waste, and accidentally found exposed to the influence of atmospheric factors and reaches the soil or water, which is an immense and immeasurable danger to the environment and for human health.
In addition to the organized collection and classification, AUNS organized and proper storage of pharmaceutical waste for transport and destruction are is done by registered companies. This waste with appropriate documentation is exported and destroyed in the neighboring countries that have organized incinerators.
The action performed by pharmacists within AUNS contributed to the disposal of a part of pharmaceutical waste arising in the territory of Novi Sad and its surroundings, but it is not sufficient- since remained uncovered other possible " producers " of pharmaceutical waste such as hospitals, outpatients department, within the dental, medical centers, institutes, private pharmacies, veterinary clinics and others. It is necessary a large-scale action that will lead to the organized collection of pharmaceutical waste from all sorts of "producers" and then the waste must be classified and kept until destruction.

Keywords: pharmaceutical waste, environmental protection, hazardous waste

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LEGAL AND ETHNICAL DILEMMA IN PRESCRIBING AND USING BIOSIMILARS IN EU AND USA

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Biosimilars which are present on the EU market from 2006, and on the USA market since 2010 still are hot topic from a clinical, regulatory and economical aspect. Due to their complex structure, biosimilars are not identical copies of biological medicines and the generic approach cannot be applied. The licensing of biosimilars is based on abbreviated registration process and biosimilar manufacturers must submit robust data to demonstrate a product's efficacy and safety profile and provide substantial data to show that its product is sufficiently similar to the original biomedical product. Although EMA and FDA had set up a legal framework and a licensing pathway for biosimilars, the decisions on interchangeability and/or substitution rely on national authorities. Several EU countries issued recommendation against automatic substitution of reference biologicals and their biosimilars, and they do not recommend the use of international nonproprietary names for biologicals. In last three biosimilar guidance's issued by FDA in April 2015, interchangeability is not covered.

There is relatively little data available on the number of patients that have been switched or substituted between biological and biosimilars in clinical practice, and this should be done in an agreement between patients and their doctor or pharmacist. Separate clinical trials will be required to prove interchangeability, which will ensure that switching between products does not affect the safety or efficacy of the product. Robust follow up and close monitoring of the effects of introducing the biosimilars will be required in the following years to ensure their safety and efficacy.

The most important conditions for market uptake of biosimilar medicines are driven by factors in the commercial market such us physician perception and patient acceptance of biosimilars, local pricing and reimbursement regulation, procurement policies and terms. Physicians practice frequently is driven by cost of the medicine, insurance companies and the regulations which limit the freedom to practice the art and science of patient-centered care. It is thus essential that physicians and patients share a thorough understanding of brand name biological medicines and biosimilar, and express confidence in using either type of therapy. This can be achieved by maintaining a robust regulatory framework and effective risk management, transparency with regard to biological medicinal products, and continued education on biological medicines, including biosimilar medicines.

Key words: biosimilars, licensing, interchangeability, EMA, FDA

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SIDE EFFECTS RESEARCH OF ANTIPSYCHOTICS AT PATIENTS WITH SCHIZOPHRENIA

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It is a research of side-effects of antipsychotics used on the schizoprenical patients of the Regional Hospital of Prizren.
Data were collected prospectively; it has been done the analization of the material taken from the evaluation, opinions and attitudes of the subjects, tracing the side-effects of the anitpsychotics and from generation into numerical values taken from 34 cases. Target group in this study was subjects with schizophrenia at the department of psychiatry in the Regional Hospital of Prizren (n=34). Data collection were realiyed from 1 october 2013 – 31 march 2014.
At all subjects (34) of different ages and genders with schizophrenia disease treated with antipsicotis tablets, capsules and injections, were observed side effects in all subjects such: diskinezia tardiva was shown to 9(26%) subjects, hipotension to 1 (3%) subject, parkinsonism to 8 (23%) subjects, obesity to 3 (9%) subjects, hyperkinezia to 2 (6%) subjects, galaktore to 1 (3%) subject, tortikolis to 2 (6%) subjects, okulogire crises to 1 (3%) subject, acatizia to 1 (3%) subject, sijalore to 1 (3%) subject, hypokinezia to 3 (9%) subjects, distonia to 1 (3%) subject and hirzutismus to 1 (3%) subject.
Invest in professional education of psychiatrists and other health personnel, so that the health services especially in psychiatry to be as qualitative and success. According to this study the risk from antipsychotic lies in that, that if we do not have enough professional knowledge, we are based on works “Routine” and on work without protocol, patients can pay with their life.
Evidence research shows that even psychiatrist has or not enough knowledge from theoretically approach regarding antipsychotics, patients should be educated according the process before and after taking the antipsychotics and early signs of side effects from the antipsychotic.

Key words: schizophrenia, side effect, antipsychotic, treatment side effects, time appearance of side effects

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HRANA I PROBIOTICI KOD DJECE

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Djeca su najveći problem što se tiče ishrane ne samo kod nas nego u cijelom svijetu. Jako je važno da od prvih dana forsiramo ispravnu i uravnoteženu ishranu koja će pomoći normalnom razvoju djeteta, sačuvati i pravilno formirati gastrointestinalni trakt i crijevnu floru. Pravilno unošenje tvrde hrane, korišćenje mliječnih formula do 2 godine života, suplementacija probioticima, izbjegavanje prerađene hrane bogate nitratima i radioaktivnim materijama jedan su od glavnih stvari koje treba savjetovati roditeljima.

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Ono sto želimo da postignemo ovim radom jeste da probudimo svijest kod roditelja za pravilnu ishranu djece. Nepravilna ishrana se manifestuje raznim bolestima i ozbiljnim situacijama. Sve više imamo gojaznu djecu, i taj stepen je tokom perioda 1989-2009. god. povećao za 300 odsto. Loša apsorpcija nutrientata, odnosno loše formirani gastrointestinalni trakt sve češće su razlog raznih intolerancija, anemija, ekcema, atopije i alergija.
Analiza raznih svjetskih studija i studija zemalja u regionu o načinu ishrane kod djece i pozitivni efekti probiotika na formiranje gastrointestinalnog trakta.
Pothranjenost, gojaznost i anemija kod djece posljedica su neodgovarajuće ishrane i nedovoljnog kretanja. Probiotici pomažu formiranje crijevne flore i opuštanju GLP-1hormona i butirata koji smanjuju mogućnost za gojaznost i dijabetes.

Ključne riječi: hrana, probiotici, djeca

FOOD AND PROBIOTICS IN CHILDHOOD

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Children nutrition is big problem not only in our country but throughout the world. It is very important from the first day to support correct and balanced diet that will help the normal development of the child gut and metabolism. Proper intake of food, the use of milk formula for babies until 2 years, supplementation with probiotics, avoiding foods rich in nitrates, conservans, nitrates and radioactive materials are one of the main things to advise parents.
With this work we want to achieve to help parents to reduce their mistakes about children nutrition. Improper nutrition is manifested by a variety of diseases and serious situations. We have more and more obese children, and their number is increased by 300 percent during the period 1989-2009. Bad absorption of nutrient and bad formed intestinal flora are various reasons for intolerance, anemia, eczema, atopic dermatitis and allergy.
We have analyzed several of international studies and studies of countries in the region about the diet of children and how probiotics can show positive effects in the formation of the gastrointestinal tract.
Malnutrition, anemia and obesity during the childhood are the result of inadequate nutrition. Probiotics help the formation of intestinal flora and relaxation GLP-1hormon and butyrate, which reduce the possibility of obesity and diabetes.
Parents usually buy the babies food at the pharmacy and the best advice about it they should get from pharmacists.
Pharmaceutical advice for child nutrition, about food intolerance, properly combine foods, toxic foods, supplementation with probiotics are very important to help parents raise their children properly and reduce the consequences that may accompany their children in the future.

Keywords: food, probiotics, children

CELL RELEASE CHARACTERISTICS OF MICROENCAPSULATED LACTOBACILUSS CASEI PREPARED BY SPRAY-DRYING

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Among different microencapsulation techniques used for probiotics protection against adverse conditions to which they are exposed during gastrointestinal passage, spray-drying is an appropriate for industrial application on a large scale. However, due to process hurdles like extreme temperatures or pressure, even the most robust probiotics are sometimes ruled out. In this study, Lactobacillus casei was encapsulated in alginate or soy-protein matrix using spray-drying (inlet and outlet temperature 120oC and 60oC, aspiration 90%, flow 5-6 mL/min), with subsequent cross-linking in solution of CaCl2 (3%w/v), coating of alginate microparticles only by soy-protein and freeze-drying (50oC, 0.05mbar, 24h). The aim of the study was to determine the influence of the preparation procedure, biomaterials and cross-linking on probiotic release/viability in different gastrointestinal conditions. Series of (non-)cross-linked probiotic microparticles were prepared, with alginate to soy-protein concentration varying from 0:4 to 4:0. The probiotic viability was investigated during the encapsulation process and after incubation of the particles in simulated gastric (pepsin 0.3% w/v, pH 1.5, 3h) and intestinal juice (PBS, pancreatin 0.1% or 1% w/v, bile salts 0.6 or 1% w/v, pH 6.8, 3h and pH 7.4, 4h) at 37 oC. Viability of the probiotic was determined after bead dissolution/cell release in PBS pH 8.0, using the plate-count method.
After spray-drying, probiotic microparticles with a cell load of ca.11.5 log10CFU were obtained. After freeze-drying, 71% to 89% of the probiotic viability was preserved. The viability in simulated gastric juice ranged from 71% to 86%, while in pH 6.8, from 55% to 90%. No significant difference in cell viability was observed when higher concentrations of bile and pancreatic enzyme were used for cell release/viability studies. Inclusion of soy-protein and cross-linking procedure increased probiotic viability by 10-35%. The highest viability was obtained when cross-linked microparticles were prepared with 4:1 alginate to soy-protein ratio.

Key words: probiotic, microencapsulation, spray-drying, viability

SAMODISPERGUJUĆI SISTEMI ZA PERORALNU PRIMENU ACIKLOVIRA: IN VITRO DIFERENCIJACIJA TIPA NANODISPERZNOG NOSAČA

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Aciklovir (ACV) je antivirotik čija je apsorpcija iz gastrointestinalnog trakta spora, biološka raspoloživost niska (~15–30%), a poluvreme eliminacije kratko (t1/2 2,5h). Dizajn samodispergujućih sistema razmatra se kao potencijalna strategija za poboljšanje apsorpcije aktivnih supstanci. Cilj istraživanja bio je formulacija samodispergujućih sistema tipa III sa ACV i kategorizacija in situ formiranih koloidnih sistema u pogledu disperzibilnosti i in vitro kinetike oslobađanja aktivne supstance. Kao sastojci samodispergujućih sistema korišćeni su: trigliceridi srednje dužine lanaca (ulje), nejonski surfaktanti (makrogol-glicerolhidroksistearat i poligliceril-3-dioleat) i hidrofilni korastvarači (polietilenglikol-8 i glicerol). U pripremljenim sistemima određena je rastvorljivost ACV spektrofotometrijski (Evolution 300, Thermo Scientific)(252nm). U nastavku istraživanja procenjena je disperzibilnost sistema sa ACV u vodenim medijumima različitog pH (0,1M HCl i fosfatni pufer pH 7,2) spektrofotometrijski i fotonskom korelacionom spektroskopijom Zetasizer NanoZS90 (Malvern Instruments). Kinetika oslobađanja ACV iz samodispergujućih sistema ispitana je in vitro korišćenjem aparature sa rotirajućom lopaticom (Erweka DT70, Erweka), 900ml fosfatnog pufera pH 7.2 kao medijuma, na 37±1oC tokom 60 min. Formulisani su samodispergujući sistemi koji su se razlikovali u pogledu udela surfaktanta i vrste i koncentracije korastvarača. Formulacioni parametri imali su značajan uticaj na rastvorljivost ACV u formulisanim samodispergujućim sistemima (od 6,39-63,32%). Spektroskopskom karakterizacijom utvrđeno je da je proces dispergovanja ispitivanih sistema u korišćenim vodenim medijumima brz. Formirane nanodisperzije bile su mikroemulzije (prosečna veličina kapi Zave≤100 nm i indeks polidisperziteta (PdI≤0,250)), pri masenom odnosu surfaktant/kosurfaktant (Km) 0,11 i Km 1, odnosno, nanoemulzije (100nm<Zave≤250 nm; PdI≤0,250) za Km 1, sa 20% i 30% korastvarača. Celokupna količina ACV se detektuje u medijumu posle 10-60min iz samomikroemulgujućih sistema (SMEDDS), a nakon 60min detektovano je manje do 12,5% ACV iz samonanoemulgujućih sistema (SNEDDS). Optimalan sastav u pogledu postavljenih kriterijuma (maksimalna rastvorljivost i brzina oslobađanja ACV) ispunjavaju SMEDDS pripremljeni sa 20% korastvarača (Km 0,11) i može se dalje razmatrati njihov potencijal za poboljšanje apsorpcije ACV.

Ključne reči: aciklovir, samodispergujući sistemi, fotonska korelaciona spektroskopija, SNEDDS, SMEDDS

SELFDISPERSING SYSTEMS FOR ORAL ADMINISTRATION OF ACYCLOVIR: IN VITRO DIFFERENTIATION OF A NANOCARRIER TYPE

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Acyclovir (ACV) is an antiviral agent whose absorption from gastrointestinal tract is slow, bioavailability is low (~ 15-30%), and half-life short (t1/2 2.5h). Novel approach for improving drug absorption is based on the design of selfdispersing delivery systems (SEDDS). Type III SEDDS were formulated and evaluated in this study for drug loading capacity, dispersibility in aqueous media of different pH and in vitro release kinetics. Potential selfdispersing systems were formulated using: an oil (medium chain length triglycerides), surfactants (macrogol-glycerolhydroxystearate and polyglyceryl-3-dioleate) and a co-solvent (glycerol or polyethyleneglycol-8). The dissolved amount of the drug in prepaired systems was determined spectrophotometricaly (Evolution 300, Thermo Scientific) (252nm). Dispersibility of the systems in aqueous media of different pH (0.1M HCl or phosphate buffer pH 7.2) was determined spectrophotometricaly and by photon correlation spectroscopy using Zetasizer NanoZS90 (Malvern Instruments). In vitro drug kinetics study was performed using rotating paddle method (Erweka DT70, Erweka) in 900ml phosphate buffer pH 7.2 (dissolution media), at 37±1oC for 60 min. Prototype SEDDS were prepared with different type and concentration of co-solvent and surfactant/cosurfactant mass ratio (Km) The formulation parameters had a significant effect on the solubility of ACV in formulated SEDDS (6,39-63,32%). The dispersibility of studied systems in aqueous media was fast. Formed nanodispersions were microemulsions (SMEDDS) (average droplet size Zave≤100 nm and polydispersity index PdI≤0,250) at Km 0.11 and Km1, or nanoemulsions (SNEDDS)(100nm<Zave≤250 nm; PdI≤0,250) at Km 1, with 20% or 30% co-solvents. The entire amount of ACV was detected in the medium after 10-60min from SMEDDS, and after 60min detected less to 12.5% ACV from SNEDDS. The results showed that SMEDDS with 20% cosolvent (Km 0.11) has satisfactory capacity to solubilize ACV and release profile that is potentially suitable to improve its absorption.

Keywords: acyclovir, selfdispersing drug delivery systems, photon correlation spectroscopy, SNEDDS, SMEDDS

ANALOZI RESVERATROLA KAO POTENCIJALNI AGENSI U TERAPIJI METABOLIČKIH OBOLJENJA: IN SILICO PRISTUP

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Resveratrol je polifenol sa utvrđenim kardioprotektivnim, hemopreventivnim, anti-inflamatornim i antioksidativnim efektima. Nedavno je pokazano da se resveratrol vezuje za PPAR-γ receptor, kao i da smanjuje insulinsku rezistenciju povezanu sa gojaznošću. S obzirom da je slaba rastvorljivost resveratrola u vodi glavni ograničavajući faktor za široku primenu u farmaciji, cilj našeg rada je bio da se identifikuju analozi resveratrola sa poboljšanim farmakokinetičkim osobinama i sa većim afinitetom vezivanja za PPAR-γ receptor.
Strukture resveratrola i analoga su preuzete iz ZINC baze jedinjenja, dok je struktura PPAR-γ receptora preuzeta iz Protein Data Bank baze. Docking studije su urađene pomoću Molegro Virtual Docker softvera. Molekulski deskriptori koji ukazuju na rastvorljivost i farmakokinetiku su izračunati upotrebom VolSurf+ softvera.
Metodom pretrage po strukturnoj sličnosti u ZINC bazi, 57 jedinjenja je identifikovano i podvrgnuto docking analizama. Energije vezivanja (MolDock skor) su bile u opsegu od -136,69 do -90,89 kcal/mol. MolDock skor za resveratrol je iznosio -118,04 kcal/mol i 16 jedinjenja je imalo niže energije vezivanja, odnosno veći afinitet ka PPAR-γ. Izračunate vrednosti SOLY deskriptora, kao logaritma intrinzičke rastvorljivosti, iznosile su od -5,05 do -3,24. Za 23 ispitivana jedinjenja je utvrđeno da su rasvorljivija u vodi od resveratrola. Kombinovanjem ovih rezultata, pokazano je da samo dva ispitivana jedinjenja, tetrahidroksi derivati stilbena - piceatanol i oksiresveratrol, imaju i bolju rastvorljivost i veći afinitet ka PPAR-γ u odnosu na resveratrol. Izračunati farmakokinetički parametri ukazuju da su oba ova jedinjenja metabolički stabilnija od resveratrola, kao i da imaju veći volumen distribucije, ali je samo za oksiresveratrol utvrđena veća vrednost amfifilnog momenta, koji određuje sposobnost jedinjenja da prolazi biološke membrane, odnosno apsorpciju.
Rezultati naše studije sugerišu da je oksiresveratrol jedinjenje koje bi trebalo detaljnije ispitivati kao potencijalni lek u terapiji metaboličkih oboljenja.

Ključne reči: docking, PPAR, resveratrol, deskriptori, ADME

IN SILICO DISCOVERY OF RESVERATROL ANALOGUES AS POTENTIAL AGENTS IN THERAPY OF METABOLIC DISEASES

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Resveratrol is a polyphenol with demonstrated cardioprotective, chemopreventive, anti-inflammatory and antioxidant effects. Recently it was shown that resveratrol binds to PPAR-γ receptor and that can reduce insulin resistance associated with obesity. Low solubility in water is the major limiting factor for widespread pharmaceutical use of resveratrol. Therefore, the aim of our study was to identify analogues of resveratrol with improved pharmacokinetic properties and higher binding affinities towards PPAR-γ receptor.
3D structures of resveratrol and its analogues were retrieved from ZINC database, while PPAR-γ structure was obtained from Protein Data Bank. Docking studies were performed using Molegro Virtual Docker software. Molecular descriptors relevant to solubility and pharmacokinetics were

calculated from ligand structures using VolSurf+ software.
Using structural similarity search method in ZINC database, 57 compounds were identified and subjected to docking analyses. Binding energies (MolDock Scores) were ranged from -136.69 to -90.89 kcal/mol. MolDock Score for resveratrol was -118.04 kcal/mol and 16 compounds exerted lower binding energies, i.e. higher affinities towards PPAR-γ. Calculated values of SOLY descriptor, as logarithms of intrinsic solubility, were ranged from -5.05 to -3.24, and 23 studied compounds were found to be more soluble in water than resveratrol. By combining these results, it was revealed that only two tetrahydroxy stilbene derivatives, piceatannol and oxyresveratrol, had both better solubility and affinity towards PPAR-γ. Calculated pharmacokinetic parameters showed that both these compounds were more metabolically stable and wider distributed in body than resveratrol, but only oxyresveratrol had higher value of amphiphilic moment, which determines the ability to permeate membranes and absorption.
The results of our study demonstrate that oxyresveratrol is a promising drug candidate that should be more in-depth investigated in terms of potential use in metabolic diseases.

Keywords: docking, PPAR, resveratrol, descriptors, ADME

MEDICAL DEVICES REGULATION IN EU, USA AND CHINA

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The term medical device includes huge and heterogeneous products, from simple tongue depressors to sophisticated pacemakers. Together with the medicinal products and applied medicinal procedures, medical devices are equally important part in health care. Today, there are more than 8000 groups of generic medical devices on the market and the manufacturer designed and place on market more and more sophisticated products.
The medical devices legislation must follow this trend, which is a challenge for the regulators, because they must ensure and guarantee the quality and safety of medical devices on the market. The current EU regulatory framework governing medical device includes Directive 93/42/EEC, Directive 90/385/EEC, Directive 98/79/EC и Directive 2007/47/EC. But, the medical device regulation must follow the globalization of the medical devices market. The activities of the International Medical Device Regulators Forum (IMDRF) are moving toward harmonization of medical devices regulation.
The aim of this paper is to compare the medical device regulation in EU, USA and China. Special attention was put on actual revision of Europe’s medical device regulation. The proposed changes were compared with the actual USA medical devices regulation and the level of their harmonization was evaluated. China was chosen as a member state of IMDRF, from the one side, and from the other side, China is the fourth largest market in the world and one of the world’s most promising markets for medical devices. As a result of the rapid growth of the Chinese medical devices industry, the original medical device regulation was no longer effective and it was revised in 2013. In 2014, the newly revised Medical Device Regulation took effect. The China’s regulation was compared with that of the EU and USA. Finally, the level of the harmonization of all tree regulations with the IMDRF guidelines was evaluated.

Key words: medical device, regulation, harmonization

VALIDACIJA ČIŠĆENJA OSTATAKA NIFUROKSAZIDA SA PROIZVODNE OPREME METODOM BRISA

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Validacijom čišćenja se potvrđuje efikasnost postupka čišćenja kojim je potrebno postići odgovarajuću čistoću opreme u cilju sprečavanja kontaminacije proizvoda. Cilj validacije čišćenja jeste da utvrdi i dokumentuje da primjenjeni postupak čišćenja je efikasan u otklananju ostataka aktivne supstance, sredstva za čišćenje i mikrobioloških ostataka.
Nifuroksazid spada u kategoriju teško topivih i teško perivih supstanci. Praktično je netopiv u vodi, slabo topiv u etanolu, netopiv u metilen kloridu. Osim toga, podliježe fotolizi pri čemu nastaje nifuroksazid nečistoća E ((Z) -4-hidroksi-N '- [(5-nitrofuran-2-il) metiliden] benzohidrazid).
Kromatografski uslovi HPLC metode su sljedeći: kao mobilna faza korištena je smjesa vode i acetonitrila u omjeru 650:350, brzina protoka 1,0 ml/min. Stacionarna faza je bila
kromatografska kolona C18, 250 mm x 4,6 mm; 5 µm. Temperatura kolone je postavljena na 30°C, a detekcija na 280 nm. Otapalo za bris je etanol, a za otopanje uzoraka je 10% N, N-dimetilformamid u 35% acetonitrilu. Metoda je validirana kroz parametre tačnost, preciznost i linearnost. Faktor korelacije (r) za nifuroksazid je 0,9995. Također, ne postoji utjecaj placeba. Metoda opisana u ovom radu je pogodna za kvantiziranje nifuroksazida u koncentracijama 0,06 ppm.

Ključne riječi: nifuroksazid, validacija čišćenja, metoda brisa

SWAB SAMPLING FOR CLEANING VALIDATION OF NIFUROXAZIDE RESIDUAL ON MANUFACTURING EQUIPMENT

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Cleaning validation is performed in the pharmaceutical industry to confirm that manufacturing equipment has been properly cleaned. The aim of cleaning validation is also to prevent ingress of foreign matter and cross-contamination by drug products.
Nifuroxazide is difficult to dissolve and difficult washable substance. Practically is insoluble in water, slightly soluble in ethanol, practically insoluble in methylene chloride. Besides, it is very sensitive to day light and is subject to photolysis to form it's impurity E ((Z)-4-hydroxy-N′-[(5-nitrofuran-2-yl)methylidene]benzohydrazide).
HPLC method mobile phase consisted of water and acetonitrile in ratio 650:350, with flow rate of 1.0 ml/min. Column type C18, 250 mm x 4.5 mm; 5 µm was used. Column temperature was set to 30°C and UV detection was performed at 280 nm. Solvent for swab was ethanol, and for solutions was 10% N,N- dimethylformamide in 35% acetonitrile (v:v).
Method has been validated with reference to accuracy, precision and linearity. Correlation factor (r) for nifuroxazide was 0.9995. Also, there is no influence of placebo. The method described in this study is suitable to quantized concentrations of nifuroxazide to 0.06 ppm.

Keywords: nifuroxazide, cleaning validation, swab sampling

ODREĐIVANJE MEMANTIN HIDROHLORIDA U FILM TABLETAMA GASNOM HROMATOGRAFIJOM

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Memantin se koristi za liječenje simptoma Alzhajmerove bolesti. Memantin djeluje tako da smanjuje abnormalnu aktivnost mozga. Memantin može da poboljša mogućnost razmišljanja i pamćenja, ili može da uspori gubitak ovih mogućnosti kod ljudi koji boluju od Alzhajmerove bolesti. Cilj rada je bio da se razvije i validira odgovarajuća metoda za određivanje memantin hidrohlorida u film tabletama metodom gasne hromatografije. Metoda se bazira na korištenju kapilarne kolone CP-Sil 8 CB, 30 m x 0.32 mm x 0.25 µm. Gasni hromatograf je bio opremljen sa FID detektorom. Temperatura injektrora je bila 240°C, a temperatura detektora 250°C. Temperatura pečnice je bila 130°C, i drži se na toj temperaturi 4.5 minute, onda se temperatura povećava 5°C/min do 180°C, i drži na toj temperaturi 1 minut. Zatim se ponovo temperatura povećava 30°C/min do krajnje temperature 240°C, i drži na toj temperaturi 5 minuta. Volumen injiciranja je bio 5µl. Rastvori su pripremljeni ekstrakcijom sa n-heptanom. Metoda je validirana prema ICH Q2(R1) smjernicama. Faktor korelacije (r) za memantin hidrohlorid je bio 0,9999. Recovery je bio od 98%-101%, granica povjerenja za preciznost metode je bila 0,6%. Također, nije bilo uticaja placeba. Validacioni parametri su pokazali da je metoda selektivna i robusna za određivanje memantin hidrohlorida u film tabletama.

Ključne riječi: Memantin hidrohlorid, GC- FID, validacija metode, n-heptana

DETERMINATION OF MEMANTINE HYDROCHLORIDE IN FILM-COATED TABLETS BY GAS CHROMATOGRAPHY

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Memantine is used to treat the symptoms of Alzheimer's disease. Works by decreasing abnormal activity in the brain. Memantine may improve the ability to think and remember or may slow the loss of these abilities in people who have Alzheimer's disease.
The objective of this study was to develop and validate stability indicating method for determination of memantine hydrochloride bay gas chromatography in film-coated tablets.
The method is based using capillary column CP-Sil 8 CB, 30 m x 0.32 mm x 0.25 µm. The gas chromatograph is equipped with FID. The injection port temperature was 240°C and detector temperature was 250°C. Oven temperature was 130°C, hold for 4.5 minutes, then rate 1 was 5°C/min to 180°C, and hold for 1 minute. Rate 2 was 30°C to final temperature 240°C, and hold for 5 minutes. Injection volume was 5µl. Solutions were prepared by extraction with n-heptane. Method was validated according to ICH Q2(R1).
Correlation factor (r) for memantine hydrochloride was 0.9999. Recovery was from 98%-101%, confidence limit for method precision was 0.6%. Also, there is no influence of placebo.

Validation parameters showed that method is selective and robust for simultaneous determination of memantine hydrochloride in film-coated tablets.

Keywords: memantine hydrochloride, GC- FID, validation of method, n-heptane

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GENERIČKI LJEKOVI USKE TERAPIJSKE ŠIRINE: KRITERIJUM ZA BIOEKVIVALENCIJU

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Dokaz bioekvivalentnosti generičkog preparata u poređenju sa referentnim preparatom predstavlja osnov terapijske zamjenljivosti ljekova. Bioekvivalencija se definiše kao odsustvo značajne razlike u brzini i stepenu, u kome aktivna supstanca iz farmaceutskih ekvivalenata ili alternativa dospijeva na mjesto djelovanja, kada se ekvivalenti ili alternative primijene pod istim uslovima u istoj dozi u okviru odgovarajuće dizajnirane studije bioekvivalencije.
Bioekvivalencija se određuje komparativnom statističkom analizom logaritamski transformisanih vrijednosti farmakokinetičkih parametara PIK0-t i Cmax, uz primijenjen interval pouzdanosti od 90 % i kriterijum za bioekvivalenciju od 80.00-125.00%.
Ne postoji opšta definicija za ljekove uske terapijske širine, međutim generalno se podrazumijeva da male promjene u doziranju ovih ljekova ili promjene koncentracija u krvi mogu izazivati značajne kliničke implikacije kao što su izostanak terpijskog odgovora ili toksičnost odnosno pojavu ozbiljnog neželjenog dejstva.
Radi obezbjeđivanja sigurnije primjene ovih ljekova javila se potreba da se u novoj Smjenici o sprovođenju ispitivanja bioekvivalencije CPMP/EWP/QWP/1401/98 Rev.1/Corr** propiše suženi kriterijum za bioekvivalenciju od 90.00%-111.11% za specifične slučajeve ljekova uske terapijske širine. U smjernici se naglašava da nije moguće definisati kriterijum za kategorizaciju ljekova uske terapijske širine i da se mora razmotriti „case by case“ da li neki lijek spada u ovu grupu ljekova, na osnovu kliničkih razmatranja. Neke države u EU kao što su Danska i Beligija, pojedine države SAD, Kanada i Japan su objavile listu ovih ljekova kao i kriterijum za bioekvivalenciju ljekova uske terapijske širine. Ove liste se međusobno razlikuju. Evropska agencija za ljekove (EMA) je definisala par INN (ciklosporin, takrolimus i sirolimus) kao ljekove uske terpijske širine, kao i kriterijum za bioekvivalenciju, koje i Agencija za ljekove i medicinska sredstva Crne Gore primjenjuje prilikom procjene dokumentacije o ispitivanju bioekvivalencije i donošenja odluke o odnosu benifita/rizika lijeka.
Harmonizacija standarda, objavljivanje jedinstvene liste ljekova uske trapijske širine kao i definisanje kriterijuma za bioekvivalenciju za ove ljekove od strane EMA, bila bi od velikog značaja kako za bezbjedniju primjenu generičkih ljekova uske terapijske širine tako i za regulatorne organe koje odobravaju stavljanje u promet ovih ljekova.

Ključne riječi: generički lijek uske terapijske šine, bioekvivalencija

GENERIC NARROW THERAPEUTIC INDEX DRUGS: CRITERIA FOR BIOEQUIVALENCE

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Proof of bioequivalence of generic products compared to reference produst is the basis of therapeutic interchangeability of medicinal products. Bioequivalence is defined as the absence of a significant difference in the rate and extent at which active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.
Bioequivalence is determined by comparative statistical analysis of log-transformed values of pharmacokinetic parameters AUC0-t and Cmax, with the 90% confidence interval for the ratio of test and reference products should be within 80.00-125.00%.
There is no general definition for narrow therapeutic index drugs (NTIDs), but generally, small changes in the dose of these drugs or changes in concentration in blood can cause significant clinical implications such as loss of efficacy or toxicity i.e. occurrence of serious adverse effect. In order to provide safer administration of these products, there was a need to prescribe stricter criteria for bioequivalence of 90.00%-111.11% in new Guideline CPMP/EWP/QWP/1401/98 Rev.1/Corr** for specific cases of narrow therapeutic drugs. According to the same guideline it is not possible to define a set of criteria to categorise drugs as narrow therapeutic index drugs and it must be decided case by case and based on clinical considerations weather an active substance is an NTID. Some countries in the EU such as Denmark and Belgium, some of US states, Canada and Japan have published a list of these medicinal products as well as the criteria for bioequivalence of narrow therapeutic index drugs. These lists differ. European Medicines Agency (EMA) has defined a couple INN (cyclosporine, tacrolimus and sirolimus) as narrow therapeutic index drugs, as well as the criteria for bioequivalence, which have been applied by the Agency for Medicines and Medical Devices of Montenegro during evaluation of bioequivalence studies and making decision about benefit/risk ratio of the medicinal products.
Harmonization of standards, publishing a unique list of narrow therapeutic index drugs as well as defining criteria for bioequivalence for these drugs by the EMA would be of great importance both for safe administration of generic narrow therapeutic index drugs as well as for regulatory authorities that approve marketing of these drugs.

Keywords: generic narrow therapeutic index drugs, bioequivalence

STAVOVI I INFORMISANOST OPŠTE JAVNOSTI O KLINIČKIM ISPITIVANJIMA

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Klinička ispitivanja ljekova ključna su za dobijanje relevantnih informacija o efikasnosti i

bezbjednosti ljekova. Literaturni podaci pokazuju da opšta javnost nije dovoljno informisana o svrsi i značaju kliničkih ispitivanja. Cilj ovog rada je da se istraže stavovi i informisanost opšte javnosti u Crnoj Gori o kliničkim ispitivanjima.
Prikupljeni su podaci iz upitnika koji je popunilo 400 nasumično odabranih odraslih ispitanika. Za statističku obradu podataka korišćen je SPSS software.
Pokazana je statistički značajna razlika između ispitanika muškog i ženskog pola u odnosu na informisanost o kliničkim ispitivanjima. Samo 44,2% ispitanika muškog pola u odnosu na 70,8% ispitanika ženskog pola je informisano o definiciji kliničkih ispitivanja (p <0,001). Dok 49,8% žena smatra da su ljekovi na tržištu klinički ispitani, 47,5% muškaraca nijesu bili sigurni da su ljekovi u prometu klinički ispitani (p = 0,037). Glavni motiv za kliničko ispitivanje kod ispitanika mlađih od 25 godina i starijih od 50 godina bilo bi liječenje postojeće bolesti, dok bi kod ispitanika uzrasta od 26 do 50 godina glavni motiv bila finansijska nadoknada (37,6% i 44,2% u odnosu na 34,9%, p <0,001).
Dobijeni rezultati pokazuju da su potrebne dodatne edukativne mjere kako bi se unaprijedila svijest opšte javnosti o značaju kliničkih ispitivanja. Stoga će Agencija za ljekove i medicinska sredstva Crne Gore nastaviti sa započetim aktivnostima u cilju promocije kliničkih ispitivanja prema opštoj i stručnoj javnosti.

Ključne riječi: kliničko ispitivanje, informisanost opšte populacije.

PUBLIC ATTITUDES AND AWARENESS OF CLINICAL TRIALS

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Clinical trials of medicines are crucial for obtaining relevant information on the efficacy and safety of medicines. Literature data showed that the general public is not sufficiently informed about the purpose and importance of clinical trials. The aim of this study is to investigate awareness of general public in Montenegro regarding clinical trials.
The data from questionnaire completed by 400 randomly selected people aged 18 and over was collected. SPSS software was used for statistical analysis.
There were statistically significant gender differences with regards to clinical trials awareness. Only 44,2% of all male subjects versus 70,8% of all female ones were informed about the definition of clinical trials (p<0,001). While 49,8% women thought that medicines on the market were clinically tested, 47,5% men were not sure about that (p=0,037). The main motive for clinical trial enrolment for subjects under the age of 25 and over the age of 50 was curing the existing disease, while for subjects aged 26-50 was financial reimbursement (37,6% and 44,2% versus 34,9%; p<0,001).
These results indicate that additional educational efforts are needed in order to improve the awareness of significance of clinical trials. Therefore, the Agency for Medicines and Medical Devices of Montenegro will continue its activities in order to promote clinical trials to the general and professional public.

Keywords: clinical trial, informing the general population.

DETERMINATION OF CAPSAICINOIDS IN DIFFERENT GENOTYPES OF CAPSICUM SPECIES BY VALIDATED HPLC METHOD

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Capsaicin is a commonly used phytochemical, well-known by its pharmacological properties as analgesic, antidiabetic, hypolipidemic and antitumor agent. Development of a simple method for extraction and quantification of capsaicin from hot pepper fruits (Capsicum annuum L.) gives a chances for effective exploitation of this highly represented agro culture in Republic of Macedonia, and brings an opportunity for further investigations on its pharmacological activity. Therefore, the aim of this study was to determine capsaicinoids (capsaicin, dihydrocapsaicin and nordihydrocapsaicin) in ethanolic extracts of 11 different genotypes of hot pepper fruits from Republic of Macedonia with a validated simple and sensitive HPLC method.
Fruits, dried and grounded, were used as a plant material for Soxlet extraction by using a 96 % (V/V) ethanol as a solvent (70˚C, for 5 hours). Quantification of a capsaicin and dihydrocapsaicin was performed on a RP-HPLC (reverse phase-high performance liquid chromatography) system by using a Zorbax SB-C18 column, (5 µm, 250 × 4.6 mm), mobile phase: H2O/CH3CN, 50:50 (V/V), flow rate: 1.5 mL/min and UV detection at 220 nm.
The analytical method was validated by using the protocols set out in the International Conference on Harmonization (ICH) guidelines. The required validation parameters, specificity, linearity, accuracy, precision, limit of detection, and limit of quantification, were studied for capsaicin and dihydrocapsaicin. The linearity range was found to be 1.52 – 380.00 µg/mL for capsaicin, and 1.12 – 279.00 µg/mL for dihydrocapsaicin, respectively. Limit of detection for capsaicin and dihydrocapsaicin was 0.075 and 0.109 µg/mL, and limit of quantification was 0.230 and 0.331 µg/mL for capsaicin and dihydrocapsaicin, consequently. The highest concentration of capsaicin, 2835 µg/g and for dihydrocapsaicin 2443 µg/g was found in the extract obtained from genotype Feferona.
The results showed that this method can be employed as quantification method for determination of capsaicinoids in the Capsicum oleoresins.

Key words: capsaicinoids, peppers, liquid chromatography, validation parametars.

KARAKTERIZACIJA I KVANTIFIKACIJA HIDROKSICIMETNIH KISELINA I FLAVANOLA U ZRNU SORTI EVROPSKE HELJDE

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Heljda (Fagopyrum esculentum Moench) predstavlja važan izvor funkcionalne hrane. Bogata je vitaminima, esencijalnim aminokiselinama i fenolima koji su odgovorni za njenu zdravstvenu korisnost i antioksidantnu aktivnost. Heljda je pseudocerealija koja sadrži monomerne flavan-3-ole (katehin i epikatehin) i proantocijanidine niskog stepena polimerizacije. Katehini pokazuju važna farmakološka svojstva kod ljudi, poput antioksidantnog, antikarcinogenog, antihipertenzivnog i antiinflamatornog efekta. Proantocijanidini se ubrajaju u prirodne proizvode sa najvećom antioksidantnom aktivnosti.
Cilj ovog istraživanja bio je da se odredi sastav i sadržaj fenolnih komponenti u zrnu sorti heljde iz Zapadne i Centralne Evrope, kao i sa Balkana. Zrno dvanaest uzoraka samleveno je do praha u tečnom azotu. 0.3 g uzorka zatim je ekstrahovano sa 5 ml MeOH rastvora sa 1% 2.6-di-terc-butil-4-metilfenolom (BHT). Određivanje individualnih fenolnih komponenti izvršeno je pomoću HPLC-DAD analize, na Thermo Finnigan Surveyor HPLC sistemu na 280 nm, na koloni Gemini C18 (150×4.6 mm 3 µm). Rastvarači za eluciju bili su 0.1% rastvor mravlje kiseline u bidestilovanoj vodi (A) i 0.1% mravlja kiselina u acetonitrilu (B). Ukupni antioksidantni kapacitet ekstrakata određen je pomoću njihove sposobnosti da uklanjaju 1,1-difenil-2-picrilhidrazil (DPPH) slobodne radikale.
Od hidroksicimetnih kiselina najviše su bili zastupljeni derivati kafene i hlorogene kiseline. Izolovano je i preko deset različitih procijanidina, a sorte heljde su podeljene u dve grupe na osnovu sadržaja flavanola: one sa visokim sadržajem propelargonidina (epiafzelehin-epikatehin, do 5.3 mg 100 g-1), i one sa visokim sadržajem procijanidina (prosečno oko 3.3 mg 100 g-1). Sorta `Novosadska` imala je najveći sadržaj fenolnih kiselina i proantocijanidina. Što se tiče antioksidantnog kapaciteta zrna heljde, sve sorte su pokazale veoma visoku antioksidantnu aktivnost. Najveća je zabeležena u češkim sortama ´Bamby´ i ´Češka´ (87.3% neutralizovanih DPPH radikala).

Ključne reči: heljda, hidroksicimetne kiseline, flavanoli, antioksidantna aktivnost

CHARACTERIZATION AND QUANTIFICATION OF HYDROXYCINNAMIC ACIDS AND FLAVANOLS IN SEEDS OF EUROPEAN BUCKWHEAT CULTIVARS

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Buckwheat (Fagopyrum esculentum Moench) represents an important functional food. It is a rich source of vitamins, essential amino acids and phenolics which are responsible for many of the health benefits and antioxidant properties. Buckwheat is a pseudocereal that contains monomeric flavan-3-ols (catechin and epicatechin) and proanthocyanidins with a low degree of polymerization. Catechins have important pharmacological properties in humans, such as antioxidant, anticancer, antihypertensive and anti-inflammatory effects. Proanthocyanidins

exibit high antioxidant ability.
The aim of this study was to investigate composition and content of phenolic compounds in seeds of cultivars from Western, Central Europe and Balkans. Seeds of twelve specimen were ground to a fine powder in liquid nitrogen. Seed powder 0.3 g, were extracted with 5 ml methanol containing 1% (w/v) 2.6-di-tert-butyl-4-methylphenol (BHT). Determination of individual phenolic compounds was performed using HPLC-DAD analysis, on a Thermo Finnigan Surveyor HPLC system with a diode array detector at 280 nm, on a Gemini C18 (150×4.6 mm 3 μm) column. The elution solvents were aqueous 0.1% formic acid in twice distilled water (A) and 0.1% formic acid in acetonitrile (B). The total potential antioxidant activity of investigated seeds extracts was assessed by their ability to scavenge 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radicals.
Mostly detected hydroxycinnamic acids in seeds of the investigated cultivars were caffeic and chlorogenic acid derivatives. More than ten different procyanidins were detected and all cultivars were divided into two groups according to flavanols contents: those with high propelargonidins (epiafzelechin-epicatechin, up to 5.3 mg 100 g-1) and those with high procyanidins contents (3.3 mg 100 g-1, in average). Cultivar `Novosadska` had the highest level of phenolic acids and proanthocyanidins. As for antioxidant abilities of investigated buckwheat seeds extracts, all cultivars exibited quite high antioxidant capacity. The highest DPPH activity was recorded in ´Bamby´ and ´Češka´ cultivars (87.3% of neutralized radicals).

Key words: buckwheat, hydroxycinnamic acids, flavanols, antioxidant activity

ODREĐIVANJE SADRŽAJA FENOLNIH SPOJEVA I ISPITIVANJE ANTIOKSIDATIVNOG KAPACITETA PIVA NA TRŽIŠTU BOSNE I HERCEGOVINE

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Pivo predstavlja prirodni proizvod sa većim ili manjim sadržajem alkohola, ali i značajnim antioksidativnim kapacitetom. Antioksidativne karakteristike ovog proizvoda zavise u prvom redu od sadržaja polifenolnih jedinjenja. Najveći dio antioksidanasa u pivu predstavljaju jednostavne fenolne kiseline koje su biodostupne. Njihova uloga je velika, imajući u vidu moderan način života, te napredak razvoja ateroskleroze, kardiovaskularnih, malignih i ostalih bolesti, što je potkrijepljeno i statističkim podacima.
Cilj ovog rada bio je ispitati sadržaj ukupnih fenolskih spojeva i antocijanidina u različitim vrstama piva koje su prisutne na bh tržištu, te odrediti njihov antioksidativni kapacitet. Za određivanje fenolnih spojeva korištene su četiri spektrofotometrijske metode (Folin- Ciocalteu-ova metoda, vanilin-HCl metoda, te kolorimetrijske metode sa aluminijum (III) hloridom i modifikovana metoda sa natrijum nitritom), a antioksidativna aktivnost utvrđena je pomoću DPPH, FRAP, TEAC eseja i određivanjem ukupnog antioksidativnog kapaciteta.
Ukupni sadržaj fenola u uzorcima kretao se između 218,2 i 323,94 mg/l TAE (ekvivalent taninske kiseline) za svijetla piva i između 345,10 i 507,89 mg/l TAE za tamna piva. Sadržaj flavonoidnih komponenti bio je u svim ispitivanim uzorcima oko dva puta viši u odnosu na sadržaj neflavonoidnih spojeva. Sadržaj antocijanidina u uzorcima tamnog piva bio je nešto

viši u odnosu na sadržaj nađen u uzorcima svijetlog piva i kretao se u granicama od 111,57 do 152,11 mg/l katehina.
Antioksidativni kapacitet ispitivanih uzoraka bio je viši za uzorke tamnih piva u DPPH (34,7-62,2 %) i FRAP (4,08-7,49 mmol Fe+2/l) eseju, dok je ukupni antioksidativni kapacitet bio otprilike jednak za sve ispitivane uzorke. Antioksidativna aktivnost ispitivanih uzoraka piva izražena kao TEAC (TE, mmol/l) kretala se u rasponu od 5,26 do 14,60 mmol/l TE. Antioksidativna aktivnost ispitivanih uzorka bila je značajno viša u odnosu na rezultate sličnih ispitivanja i odgovarala je aktivnosti nađenoj za neke uzorke crnih vina.

Ključne riječi: pivo, antioksidativni kapacitet, polifenoli

DETERMINATION OF TOTAL PHENOLIC CONTENT AND ANTIOXIDANT CAPACITY OF BEER AT MARKET IN BOSNIA AND HERZEGOVINA

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Beer is a natural alcoholic beverage with different alcohol content, but also significant antioxidant capacity. The antioxidant properties of this product depend primarily on the content of polyphenolic compounds. The most important antioxidants in beer are simple phenolic acids that can be easily absorbed. Statistics support their great role in prevention of atherosclerosis, cardiovascular, cancer and other diseases that are resulting from the modern way of life.
The aim of this study was to determine the content of total phenolic compounds and anthocyanins in certain types of beer that are present on the local market, and determine their antioxidant capacity. Polyphenolic compounds were determined with four spectrophotometric methods (Folin- Ciocalteu's method, vanillin-HCl method, and colorimetric methods with aluminum (III) chloride and modified method with sodium nitrite), and the antioxidant capacity was determined by DPPH, FRAP, TEAC assays. The total antioxidant capacity was also determined.
Total phenolic content in the samples ranged between 218.2 and 323.94 mg /L TAE (tannic acid equivalent) for light beers and between 345.10 and 507.89 mg / L TAE for dark beers. The content of flavonoids in all the investigated samples was about two times higher than the content of non flavonoids. Dark beers contain slightly more anthocyanins than light beers, ranging between 111.57 to 152.11 mg / L of catechine.
Antioxidant capacity of tested samples was higher in samples of dark beer in DPPH (34.7 to 62.2%) and FRAP (4.08 to 7.49 mmol Fe + 2/L) assay, while the total antioxidant capacity was approximately equal for all tested samples. The antioxidant activity of beer samples expressed as TEAC (TE, mmol /L) ranged from 5.26 to 14.60 mg /L of TE (Trolox equivalent). The antioxidant capacity of our samples was significantly higher compared to the results of similar samples and corresponds with the activity that was found for some samples of red wines.

Keywords: beer, antioxidant capacity, polyphenols

ODREĐIVANJE SADRŽAJA FENOLNIH SPOJEVA I ISPITIVANJE ANTIOKSIDATIVNOG KAPACITETA VINA AUTOHTONIH HERCEGOVAČKIH SORTI

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Nekoliko epidemioloških studija pokazuje da povećani unos neutralnih fenolnih antioksidanasa (prisutni u vinu) korelira sa smanjenjem nastanka koronarnih srčanih bolesti. Ovaj podatak objašnjava tzv. “Francuski paradoks”. Osim toga, dokazano je da polifenolni spojevi, prisutni u vinu imaju također i antiviralno, antiinflamatorno, antitrombocitno i karcinostatsko djelovanje. Antioksidativni potencijal direktno je povezan s mogućnošću fenolnih spojeva, da predaju elektron ili vodonik i na taj način “ugase” radikal i spriječe njegovu reaktivnost u daljnjim lančanim reakcijama.
Cilj istraživanja ovog rada bio je odrediti sadržaj ukupnih fenolnih spojeva i antioksidativni potencijal hercegovačkih sorti vina spektrofotometrijskim metodama, te na osnovu dobijenih rezultata evaluirati njihov kvalitet. Hercegovačke sorte su glavne sorte koje se proizvode u BiH, pa se može pretpostaviti da se u značajnoj mjeri konzumiraju u lokalnoj populaciji. Do sada je provedeno vrlo malo ispitivanja antioksidativnog kapaciteta autohtonih bh sorti, te iz tog razloga rezultati ovih ispitivanja predstavljaju vrlo vrijedne podatke.
Ispitivanja kvantitativnog sastava fenolnih spojeva pokazala su veći sadržaj istih u crnim u odnosu na bijela vina. Tako je Folin-Ciocalteu-ovom metodom pokazan oko 5 puta veći sadržaj ukupnih fenola u uzorcima crnog vina, u odnosu na bijelo vino (srednja vrijednost iznosila je 1175.65 mg/l TA i 256 mg/l TA, respektivno).
Sadržaj ukupnih flavonoida iznosio je 157,33 mg/l-565,96 mg/l kvercetina za crna vina i 43,79 mg/l-64,28 mg/l kvercetina za bijela vina. Postotak inhibicije DPPH u uzorcima crnog vina kretao se od 87,77 % do 93,75 % za crna i od 12,13% do 28,45% za bijela vina. Antioksidativni potencijal određen DPPH radikalskim testom dobro korelira sa sadržajem ukupnih fenola i flavonoida (R2=0.98 i R2=0.93, respektivno).
Antioksidativni kapacitet određen FRAP metodom odgovarao je sličnim prethodno provedenim istraživanjima i iznosio je 3,95-14,88 mmol Fe(II)/l. Rezultati ABTS eseja iznosili su 11,18 mmol TE/l -12,96 mmol TE/l, što otprilike odgovara rezultatima istih ispitivanja provedenih za hrvatska crna vina.

Ključne riječi: vina, Hercegovina, antioksidansi

DETERMINATION OF PHENOLIC COMPOUNDS AND ANTIOXIDANT CAPACITY OF INDIGENOUS VARIETIES OF WINES FROM HERZEGOVINA

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Several epidemiological studies have shown good correlation of consumption of neutral phenolic antioxidants (present in wine) with a decrease in the prevalence of coronary heart disease. This fact explains the so-called “French paradox”. In addition, it has been proven that polyphenolic compounds present in wine, also have antiviral, anti-inflammatory, antithrombotic and carcinostatic effects. Antioxidant potential is directly related to the ability of the phenolic compounds, to give electrons or hydrogen, and to scavenge radicals and prevent their reactivity in subsequent chain reactions.
The aim of this study was to determine the content of total phenolic compounds and antioxidant potential of varieties of wines from Herzegovina using appropriate methods, and to evaluate their quality. Herzegovinian varieties are the main varieties produced in the our country, and it can be assumed that they are substantially consumed by the local population. So far very few testing of antioxidant capacity of indigenous varieties of wines in BiH were conducted, and therefore the results of these tests represent valuable data.
Phenolic compounds showed higher content in red comparing to white wines, approximately 5 times higher, according to Folin-Ciocalteu’s method (the mean value was 1175.65 mg /L , TA and 256 mg/L, TA , respectively).
The content of total flavonoids was from 157.33 mg /L to 565.96 mg /L quercetin in red wine and from 43.79 mg /L to 64.28 mg /L quercetin for white wines. The percentage inhibition of DPPH in samples of red wine ranged from 87.77% to 93.75% and from 12.13% to 28.45% for white wines, that shows good correlation with the content of total phenols and flavonoids (R 2 = 0.98 and R2 = 0.93, respectively).
Antioxidant capacity determined by FRAP method correlates with similar previously conducted investigations and was from 3.95 to 14.88 mmol of Fe (II) /L. Results of ABTS assays were from 11.18 mmol TE /L to 12.96 mmol TE /L, which roughly corresponds to the results of the same tests conducted for the red wines from Croatia.

Keywords: wine, Herzegovina, antioxidants

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KORISNOST ODREĐIVANJA FREEPSA/TOTALPSA OMJERA KOD PACIJENATA S VRIJEDNOŠĆU TOTAL PSA OD 2.1 DO 10NG/ML

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Prostata specifični antigen i njegove izoforme danas su najznačajniji biokemijski biljezi za otkrivanje tumora prostate. Vrijednost total PSA u krvi od 4 ng/mL općenito se smatra normalnom. Trend je, međutim, obavljanje biopsije prostate u svih muškaraca s total PSA vrijednosti višom od 2,5 ng / mL, kako bi se tumor prostate otkrio u ranoj potpuno izlječivoj fazi. Izrazito povišene koncentracije total PSA prilično su jasna indikacija za biopsiju dok rezultati u području tzv, sive zone (od 2,1 do 10ng/mL) onemogućuju donošenje jasnih zaključaka. Naime kako i druga oboljenja prostate poput benigne hiperplazije pokazuju povećane vrijednosti total

PSA smanjena je sama specifičnost testa u tom području.
U našem ispitivanju željeli smo utvrditi opravdanost određivanja free PSA/total PSA omjera uz total PSA kako bi se doprinijelo dijagnozi te izbjegle nepotrebne biopsije kod pacijenata sa nejasnom vrijednosti total PSA.
U retrospektivnoj deskriptivnoj analizi sudjelovalo je 70 pacijenata prosječne dobi bi 66± 9.8 godina od kojih je 22 (31,4%) dijagnosticiran tumor prostate dok su kontrolnu skupinu činili pacijenti s različitim dijagnozama ito benigna hiperplazija prostate (n=28), tumor testisa (n=4) , prostatitis (n=7), tumor rektuma (n=5) te zdravi ispitanici (n=4) svi sa vrijednošću total PSA od 2,1 do 10ng/mL.
Potvrđena je statistički značajna razlika u vrijednosti omjera freePSA/totalPSA kod pacijenata oboljelih od karcinoma prostate u odnosu na kontrolnu skupinu. Pored toga utvrđena je niža vrijednost omjera kod pacijenata oboljelih od karcinoma u odnosu na ispitanike oboljele od benigne hiperplazije prostate ($p<0.05$).
Omjer free PSA/total PSA se pokazao specifičnijim pri razlikovanju tumora od ostalih oboljenja prostate napose benigne hiperplazije prostate.

Ključne riječi: prostata specifični antigen, tumor prostate, hiperplazija prostate

THE USEFULNESS OF DETERMINING FREEPSA/TOTALPSA RATIO IN PATIENTS WITH TOTAL PSA VALUE FROM 2.1 TO 10 NG/ML.

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Prostate specific antigen and its isoforms are now the most important biochemical markers for the detection of prostate tumors. 4 ng/mL value of total PSA in blood is generally considered normal. Trend is, however, to perform a prostate biopsy in all men with total PSA values above 2,5 ng/mL so the prostate tumor can be detected in early and hopefully completely curable stage. Extremely elevated total PSA concentrations are clear indication for biopsy while concentrations in field of so called grey zone (from 2.1 to 10 ng/mL) prevent reaching any firm conclusions. In fact, as other prostate pathologies such as benign prostatic hyperplasia show increased values of total PSA, the specificity of the test itself is reduced in this area.
In this paper we want to affirm usefulness of determination freePSA/totalPSA ratio with tPSA in order to contribute to diagnosis and avoid unnecessary biopsies in patients with unclear tPSA values.
In a retrospective descriptive analysis 70 patients had participated with the average age of 66 ± 9.8, of which 22 (31.4%) were diagnosed with a prostate tumor while the control group was consisted of patients diagnosed with benign prostatic hyperplasia (n=28), testicular tumor (n=4), prostatitis (n=7), cancer of the rectum(n=5) and healty subjects (n=4) all with a total PSA value from 2.1 to 10 ng/mL.

It has been statistically confirmed significant difference in freePSA/totalPSA ratio value in patients suffering from prostate cancer compared to the control group. In addition lower ratio was measured in patients suffering from prostate cancer compared to benign prostatic hyperplasia ($p<0.05$).
The ratio of fPA/tPSA was proved to be more specific in differentiating tumor from other prostate diseases especially benign prostatic hyperplasia.

Key words: prostate specific antigen, prostate tumor, prostatic hyperplasia.

LEKOVI U ŽIVOTNOJ SREDINI-POTENCIJALNI RIZICI ZA ČOVEKA

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Povećano prisustvo lekova u životnoj sredini i njihovi potencijalni toksični efekti predstavljaju značajan problem poslednjih decenija. Lekovi mogu dospeti u životnu sredinu iz proizvodnih postrojenja, preko otpada iz domaćinstva, deponija, usled poljoprivrednih aktivnosti, itd. Iako su dosadašnja istraživanja bila fokusirana na negativne posledice koje lekovi u životnoj sredini ispoljavaju na biljni životinjski svet, novija ispitivanja ukazuju na mogući rizik i po zdravlje ljudi. Među brojnim lekovima koji dospevaju u životnu sredinu, posebna pažnja je posvećena onima koji su perzistentni, koji se akumuliraju u organizmu i izazivaju toksične efekte u niskim koncentracijama. Stoga su brojna aktuelna istraživanja uglavnom usmerena na estrogene i antibiotike.
Estrogeni su uzročnici feminizacije mužjaka vodenih životinja koja je primećena u različitim vodenim ekosistema širom planete. Takođe, povišene količine estrogena u životnoj sredini dovode se u vezu i sa reproduktivnim problemima ljudi. Iako su oralni kontraceptivi „optuženi“ da najviše doprinose estrogenosti životne sredine, istraživanja su pokazala da je njihov udeo ipak relativno mali u odnosu na prirodne. Potencijalnu opasnost takođe predstavljaju i antibiotici prisutni u životnom sredini, a posebno penicilini koji čak u niskim dozama mogu izazvati ozbiljne alergije kod osetljivih osoba. Antibiotici u životnoj sredini imaju posebnu ulogu sa aspekta razvoja rezistencije. Procenjuje se da su milioni tona antibiotika pušteni u biosferu u poslednjih pola veka, što je dovelo do konstantne selekcije populacija otpornih bakterijskih sojeva u svim ekosistemima.
Svest o prisustvu lekova u životnom okruženju i njihovim mogućim toksičnim efektima na životnu sredinu i čoveka ukazuju na neophodnost bolje kontrole oslobađanja lekova u životnu sredinu. (Projekat III 46009)

Ključne reči: lekovi, životna sredina, čovek, rizik

PHARMACEUTICALS IN THE ENVIRONMENT-POTENTIAL HUMAN RISK

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The discharge, presence of pharmaceuticals in the environment and their potential toxic effects have became a burning issue during the last few decades. The pharmaceuticals may enter the environment by various routes such as manufacturing, household waste, landfills, agriculture, livestock. Investigations were previously focused on the adverse effects that extended levels of pharmaceuticals in the environment can have on nature and wildlife, while recent investigations indicate the possible risk these pharmaceuticals pose to humans.
Among numerous pharmaceuticals that enter the environment, special attention has been given to the ones that are persistent in the environment, can accumulate in the organism and cause toxic effects at low levels. Hence, up to date investigations were mainly targeted on estrogenic compounds and antibiotics.
Estrogenic compounds were connected to feminization of aquatic animals observed in different waterways worldwide. Furthermore, the increased estrogenicity of the environment and especially drinking water has been connected to the human reproductive problems. Although oral contraceptives were accused of being the most significant contributors to the overall estrogenicity, performed investigations indicated that involvement of synthetic estrogens is relatively small compared to the natural ones. Caution should also be taken with antibiotics present in the environment, especially those such as penicillin that in very sensitive individuals reacting on even a few molecules can cause serious allergies. Further, the predominant role of human activities in the generation of environmental reservoirs of antibiotic resistance cannot be disputed. It can be estimated that many millions of tons of antibiotic have been released into the biosphere over the last half-century, thus providing constant selection and maintenance pressure for populations of resistant strains in all environments.
The awareness of the presence of pharmaceuticals in the environment and their possible adverse effects on humans suggests the need for better control of pharmaceutical release into the environment. (Project III 46009)

Keywords: pharmaceuticals, environment, human, risk

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RODITELJI I NJIHOVA ZNANJA O LEKOVIMA KOJI SU NAMENJENI PEDIJATRIJSKOJ POPULACIJI

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Poseduju li roditelji adekvatna znanja o proceni zdravstvenog stanja svog deteta i odabiru

terapije, čak i kada je reč o lekovima sa režimom izdavanja bez recepta?
Ispitati ponašanje roditelja kada se dete razboli, da li i koje lekove samoinicijativno daju detetu i upoznatost sa pojmom antimikrobne rezistencije (AMR).
Tokom februara 2015. godine roditelji čija deca pohađaju predškolsku ustanovu u Majdanpeku popunjavali su upitnik sastavljen od 14 pitanja. Ispitivalo se iskustvo roditelja u lečenju dece bez konsultacije lekara, koje lekove su davali, pravilnost upotrebe antibiotika i poznavanje pojma AMR.
U dva objekta predškolske ustanove anketirano je 98 roditelja, što predstavlja polovinu ukupnog broja roditelja. Kada se dete razboli, roditelji najčešće dete vode kod lekara (85%), 8% ide u apoteku, posavetuje se sa farmaceutom, 4% ide u apoteku uzimajući za dete ono što smatra najboljim, 3% čeka da detetu bude bolje bez davanja lekova.
Bez konsultacije sa lekarom/farmaceutom roditelji detetu najčešće daju antipiretik (77,55%), biljne sirupe - 57,14%, kapi za nos - 46,94%.
9,18% roditelja je samoinicijativno dalo antibiotik detetu. Među njima 44,44% ne zna šta je AMR, a 77,78% ne poznaje uzrok AMR. 2% roditelja daje antibiotik do prvih znakova poboljšanja.
7% dece čiji su roditelji ispitivani ima neku vrstu alergije. Ipak, oralne antihistaminike samoinicijativno je kod svog deteta primenjivalo 20,41% roditelja.
4% roditelja je davalo detetu neki od lekova koji olakšavaju disanje (navedeni budezonid, fenoterol, ipratropijum bromid), a samo jedno od te dece ima alergiju, niko hroničnu bolest.
Imajući u vidu rezultate ovog istraživanja, u istoj predškolskoj ustanovi su održana 3 predavanja o pravilnoj upotrebi lekova, AMR i jačanju imuniteta deteta.
Zaključak: Roditelji dece predškolskog uzrasta nedovoljno poznaju rizike samoinicijativne upotrebe lekova u lečenju svoje dece, a farmaceuti zbog svoje pozicije u zdravstvenom sistemu, dostupnosti i znanja koje poseduju mogu doprineti edukaciji stanovništva, naročito roditelja.

Ključne reči: pravilna upotreba lekova, uloga farmaceuta, roditelji, deca, edukacija

PARENTS AND THEIR KNOWLEDGE ABOUT MEDICINES INTENDED FOR PEDIATRIC POPULATION

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Do parents have required knowledge for estimation of health status of their child, and to make right choices with therapy, even when it comes to medication that can be purchased without the medical prescription?
Test the parents behaviour when child gets sick, do they, and which medications they give to child on their own initiative, and test them if they are familiar with the term antimicrobial resistance (AMR).
During February 2015. parents who have children in preschool in Majdanpek were filling in a questionnaire which contained 14 questions. Tested topics were parents experience in curing children without a consultation with the doctor, which medications did they use, proper use of antibiotics and familiarity with the term AMR.

98 parents were tested in two preschool institutions, which represents half of total number of parents. When child gets sick, parents mostly take child to the doctor (85%), 8% goes to the pharmacy and consults with a pharmacist, 4% goes to the pharmacy and buys whatever they think is the best for the child, 3% wait for child to get better without giving them any medicines.
Without prior consultation with doctor/pharmacist parents mostly give to their child antipyretic (77,55%), herbal syrups - 57,14%, nose drops - 46,94%.
9,18% of parents gave an antibiotic to child on their own initiative. Among them 44,44% does not know what AMR is, and 77,78% does not know about the cause of AMR. 2% of parents give antibiotics to child until the first signs of health improvement.
7% of kids whose parents were tested have some kind of alergy. Still, 20,41% of parents used oral antihistaminics on their own initiative on their own child.
4% of parents gave to child one of the medicines that eases breathing (budesonide, fenoterol, ipratropium bromide were listed), and only one kid has alergy, none of them chronic disease.
Having in mind results of this research, 3 lectures were held in the same preschool institution about proper use of medications, AMR and improving childs immune system.
Parents of preschool kids are not knowledgable enough about risks of selfinitiative considering healing their own children, and pharmacists, given their position in healthcare system, availability and knowledge they possess, can contribute to populations education, especially in education of parents.

Key words: proper use of medicines, pharmacists role, parents, children, education.

INTERPOLIMERNI KOMPLEKSI CARBOPOL®-A 940 I RAZLIČITIH TIPOVA SURFAKTANATA KAO MATERIJALI ZA PRIMENU U FARMACIJI

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Polimeri i surfaktanti se zajedno nalaze u velikom broju različitih farmaceutskih i kozmetičkih proizvoda u cilju postizanja željenih osobina preparata u zavisnosti od specifične primene. Razvoj novih lekova i farmaceutskih formulacija unapređenih osobina u velikoj meri zavisi od prisustva sinergističkih ili antagonističkih interakcija u sistemima polimer-surfaktant. Umreženi polimeri akrilne kiseline, poznati pod zaštićenim imenom Carbopol®, glavna su komponenta lekova za okularnu, nazalnu, rektalnu, vaginalnu, bukalnu i transdermalnu primenu.
Interakcije Carbopol®-a 940 i anjonskog surfaktanta, natrijum dodecil sulfata (SDS), odnosno nejonskog Tween®-a 80, ispitane su primenom tenziometrije i skenirajuće elektronske mikroskopije (SEM). Površinski napon binarnih smeša polimer-surfaktant meren je na 25ºC ± 0,1 metodom prstena po du Noüy-u. Uzorci za SEM analizu su dehidrirani i presvučeni slojem zlata pre posmatranja na skenirajućem elektronskom mikroskopu (Jeol JSM 6460LV, Japan) na 25 kV.
Površinski napon smeša polimer-surfaktant meren je pri konstantnoj koncentraciji polimera. Različit izgled krive zavisnosti sa i bez prisustva polimera upućuje na formiranje kompleksa Carbopol® 940-Tween® 80 i Carbopol® 940-SDS. U slučaju Tween®-a 80, prisustvo Carbopol®-a 940

povećava površinski napon vodenih rastvora u poređenju sa čistim surfaktantom. Dodatak anjonskog surfaktanta u rastvor Carbopol®-a 940 uzrokuje smanjenje površinskog napona. Dobijena vrednost kritične agregacione koncentracije SDS-a približno je konstantna (1,99 mM) i ne zavisi od koncentracije polimera. Sa povećanjem sadržaja Carbopol®-a 940, u slučaju SDS-a i Tween®-a 80, tačka zasićenja polimera surfaktantom raste od 9,13 do 10,51 mM odnosno od 0,22 do 0,69 mM, respektivno. Pored toga, na mikrostrukturalnom nivou uočene su konformacione promene polimera u prisustvu surfaktanta.
Dobijeni rezultati potvrđuju da Carbopol® 940 formira interpolimerne komplekse sa ispitivanim surfaktantima.

Ključne reči:Carbopol® 940; natrijum dodecil sulfat; Tween® 80; površinski napon, mikrostruktura

INTERPOLYMER COMPLEXES OF CARBOPOL® 940 AND DIFFERENT TYPES OF SURFACTANTS AS MATERIALS FOR PHARMACEUTICAL APPLICATIONS

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Polymers and surfactants are used together in wide range of drug delivery systems and personal care products in order to provide desired properties required for specific application. Accordingly, the development of new drugs and improvement of pharmaceutical formulations is highly dependent on the synergistic or antagonistic interactions in mixed surfactant-polymer solutions. The cross-linked polyacrylate polymers commercially known as Carbopol® are major components of drug delivery systems for ocular, nasal, rectal, vaginal, buccal and trans-dermic applications.
The interactions between Carbopol® 940 and two types of surfactants: anionic sodium dodecylsulfate (SDS) and nonionic Tween® 80 were investigated by the combination of tensiometry and scanning electron microscopy (SEM). Surface tension measurements of binary mixtures of polymer and surfactant were done at 25 ºC ± 0.1using a du Noüy ring method. The SEM images of dried and sputter-coated with gold samples were taken with the Jeol JSM 6460LV scanning electron microscope (Japan) with a 25-kV acceleration voltage.
The surface tension of polymer-surfactant mixtures was measured at constant polymer concentration. The difference in the shape of curves with and without constant polymer concentration could be ascribed to Carbopol® 940-Tween® 80 and Carbopol® 940-SDS associations. Although, the addition of anionic surfactant SDS led to a decrease in the surface tension, the presence of Carbopol® 940 increased the surface tension of Tween® 80 compared to the pure surfactant solution. The critical aggregation concentration of SDS was particularly independent of polymer concentration and remained approximately constant (1.99 mM). The polymer saturation point for SDS and Tween® 80 increased with Carbopol® 940 concentrations from 9.13-10.51 mM and 0.22-0.69 mM, respectively. Additionally, the surfactant induced changes of polymer conformation at microstructural level were observed.
The obtained results confirmed the assumption about the formation of interpolymer complexes

between Carbopol® 940 and two types of surfactants.

Keywords: Carbopol® 940; sodium dodecylsulfate; Tween® 80; surface tension; microstructure

HAPLOTYPES OF SLCO1B1 GENE ENCODING OATP1B1 IN ALBANIAN ETHNIC GROUP

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OATP1B1 is an influx transporter, encoded by the SLCO1B1 gene, known to mediate the uptake of various endogenous compounds and xenobiotics. The aim of this study was to analyze the distribution of SCLO1B1 alleles at 7 variant sites (c.388A>G, c.521T>C, c.571T>C, c.597C>T, c.1086C>T, c.1463G>C and c.*439T>G) in 94 Albanians using TaqMan allelic discrimination assay. Genetic diversity was quantified between the members of this population and between this population and the global population. Allele and genotype frequencies were estimated with a gene counting method, while agreement with Hardy-Weinberg Equilibrium of the observed genotypic distribution and population comparisons with the Chi-square test (SPSS, v. 19.0). Odds ratios were calculated with 95%CI, with statistically significant differences set to $p<0.05$. For the analysis of linkage disequilibrium (r2 and D'), haplotype construction and genetic association at polymorphism loci, the SHEsis software platform was used (http://analysis2.bio-x.cn/myAnalysis.php).
The frequency of the c.521T>C SNP was the lowest (12%), while the frequencies of all other SNPs alleles were above 40%. Variant alleles of c.1463G>C and c.1086C>T SNPs were not identified in this ethnic group. The haplotype analysis revealed 21 different haplotypes. The most common haplotype, *1J/*1K/*1L, had a frequency of 27%. The variant alleles of the functionally significant c.521T>C and c.388A>G SNPs existed in one major haplotype (*15/*16/*17), with a frequency of 2.4%. In conclusion, sequence variations of SLCO1B1 gene in the studied population occur at high frequencies, which are similar to that of the Caucasian population. Further studies are needed to evaluate the clinical significance of these SNPs and/or the major SLCO1B1 haplotypes they form for a large number of substrates and for susceptibility to certain diseases. The results from this study could serve as baseline clinical data for dosing of all drugs substrates of OTAP1B1 and avoiding the adverse drug reactions.

Keywords: SLCO1B1, OATP1B1, SNPs, haplotypes

ANALIZA UPOTREBE LEKOVA ZA LEČENJE DIJABETES MELITUSA U REPUBLICI SRBIJI U PERIODU OD 2007. DO 2012. GODINE

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Dijabetes melitus je jedno od vodećih hroničnih nezaraznih oboljenja i u Srbiji je peti vodeći uzrok smrtnosti. Prema poslednjoj klasifikaciji WHO (World Health Organization), modifikovanoj za domaće potrebe prema nacionalnom vodiču za šećernu bolest Republike Srbije, postoje 4 osnovne grupe dijabetes melitusa.
Cilj rada bio je da se analizira potrošnja antidijabetika, lekova za lečenje dijabetes melitusa u Republici Srbiji u periodu od 2007. Do 2012. godine i da dobijene rezultate uporedimo sa potrošnjom istih lekova u dve skandinavske zemlje, Norveškom i Finskom, zemljama koje imaju dobro razvijenu farmakoterapijsku praksu.
Podaci o potrošnji i cenama lekova u Republici Srbiji za period od 2007. do 2012. godine dobijeni su od Agencije za lekove i medicinska sredstva Srbije, za Norvešku su preuzeti sa zvaničnog sajta Norveškog instituta za javno zdravlje, a za Finsku sa zvaničnog sajta Finske agencije za lekove.
U Srbiji je upotreba antidijabetika u kontinualnom porastu i prema analizi najčešće prepisivani lekovi su oralni antidijabetici i to derivati sulfonilureje, dok se u Norveškoj i Finskoj beleži najveća potrošnja bigvanida a sledeći na listi su derivati sulfonilureje.
Analizirajući potrošnju antidijabetika u Srbiji u periodu od 2007. do 2012. godine, uočavamo da je Srbija zemlja po potrošnji antidijabetika, između Norveške i Finske. Norveška prema analizi pokazuje ujednačenu potrošnju dok Finska pokazuje progresivan porast potrošnje antidijabetika.
Ovaj rad je finansijski podržan od strane Pokrajinskog sekretarijata za nauku i tehnološki razvoj, Autonomne Pokrajine Vojvodine projekta br 114-451-2458/2011 i od strane ministarstva za nauku Republike Srbije, projekat broj 41012.

Ključne reči: dijabetes mellitus, potrošnja antidijabetika, farmakoepidemiologija

THE ANALYZE OF CONSUMPTION OF DRUGS FOR THE TREATMENT OF DIABETES MELLITUS IN THE REPUBLIC OF SERBIA FROM 2007 TO 2012

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Diabetes mellitus is one of the leading chronic non-communicable diseases and in Serbia is the fifth leading cause of death. According to the latest classification of WHO (World Health Organization), modified for the needs of the national guide for diabetes Republic of Serbia, there are four main groups of diabetes mellitus.

The aim of this study was to analyze the consumption of serum antidiabetic drugs used in diabetis melitus therapy, in Serbia from 2007 to 2012, and to compare this data with Norway and Finland, countries with developed pharmacotherapeutic practice.
The data about the use of antidiabetic drugs in Serbia from 2007 to 2012 were taken from the Agency for Drugs and medical Devices of the Republic of Serbia, about Norway were taken from the official website of Norwegian Institute of Public Health and bout the use of antidiabetic drugs in Filand were taken from official webisite of Agency for Drugs of Filand.
In Serbia use of antidiabetics is in continuously increasing and by analyzing the most commonly prescribed drugs are oral antidiabetic drugs and sulfonylurea derivatives, while Norway and Finland record the highest consumption of a biguanide and the next on the list are sulfonylurea derivatives.
Analyzing the consumption of antidiabetic drugs in Serbia, Norway and Finland in the period from 2007 to 2012, Serbia is a country between Norway and Finland. Norway, shows a uniform consumption while Finland shows a progressive increase in the consumption of antidiabetic drugs.
Acknowledgement: This research was supported by Provincial Secretariat for Science and Technological Development, Autonomous Province of Vojvodina project No 114-451-2458/2011 and by Ministry of Science, Republic of Serbia, project no 41012

Key words: diabetes mellitus, consumption of antidiabetics drugs, pharmacoepidemiology

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SYNTHESIS OF NOVEL BENZAMIDOMETHYL DERIVATIVES OF CIPROFLOXACIN AND THEIR STRUCTURAL CHARACTERIZATION

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Ciprofloxacin is the first of the quinolones useful in a variety of infections, such as lower respiratory, skin, joint urinary infections and sexual transmitted diseases. Various derivatives of ciprofloxacin were synthesized and tested for their antimicrobial activities with an aim of improving its pharmacokinetic and pharmacodynamic properties. The prodrug concept has been modestly examined to improve the therapeutic efficacy, generally with an aim to increase its oral bioavailability and cell penetration. Herein, we present the synthesis of novel benzamidomethyl derivatives of ciprofloxacin as potential prodrugs, with higher lipophylicity than the leading compound. Four novel derivatives of ciprofloxacin were synthesized with substitution of the hydrogen atom at position N-4 of the piperazinyl ring with previously synthesized derivatives of (benzamidomethyl)triethylammonium chloride. To a mixture of ciprofloxacin and benzamidomethyl salts in water, triethylamine was added until pH 11 was achieved. Afterwards,

reaction mixture was extracted with dichloromethane, the extract was washed, dried over Na2SO4, filtered and concentrated in vacuo to give a white solid, which was purified by dissolving in DMSO and precipitation with water. The reactions were monitored by TLC at UV detection of 254 nm. Total spectral assignation by IR, 1H-NMR, 13C-NMR, 2D-NMR and MS was performed.
Pure compounds with high yields (72-98%) were synthesized, with melting points in a range 149-219 oC. In the IR spectra, characteristic Amide I and Amide II bands in the regions from 1717-1736 and 1626-1663 cm-1, respectively, were noticed. In the 1H-NMR in general the same singlet, doublets and multiplets to that of ciprofloxacin were seen. The doublet at 4.29 ppm from the hydrogen of the methylene group attached to N-4 of the pyperazinyl ring of ciprofloxacin was present in all derivatives, pointing to the substitution position.

Key words: ciprofloxacin, benzamidomethyl derivatives, prodrugs, structural characterization

POLIMORFIZAM CYP2D6 – FAKTOR RIZIKA ZA NASTANAK NEŽELJENIH DEJSTAVA BETA BLOKATORA

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Neželjena dejstva imaju veliku učestalost ispoljavanja kod hospitalizovanih pacijenata, čemu doprinose brojni faktori rizika. Glavni cilj rada je analiza učestalosti ispoljavanja neželjenih dejstava beta blokatora i njihovih karakteristika, kao i faktora rizika za njihov nastanak, na osnovu čega su predložene mjere za racionalizaciju farmakoterapijske prakse.
Sprovedeno je prospektivno ispitivanje kojim je obuhvaćeno 138 pacijenata hospitalizovanih u Centru za kardiologiju Kliničkog centra Crne Gore. Intenzivnim praćenjem prikupljeni su podaci o ispoljavanju neželjenih dejstava beta blokatora. Urađena je genotipizacija CYP2D6*3 (2549delA, rs35742686), CYP2D6*4 (1846G>A, rs3892097), CYP2D6*5 (delecija gena), CYP2D6*6 (1707delT, rs5030655) i CYP2D6*10 (100C>T, rs1065852) metodom RT- PCR, kako bi se utvrdila učestalost različitih tipova metabolizera.
Od svih ispitanika koji su dobijali beta blokatore, neželjena dejstva ove farmakoterapijske grupe ljekova ispoljila su se kod 15 (10,9%) ispitanika. Neželjena dejstva su se ispoljila kod 2,6% ispitanika iz grupe brzih i intermedijarnih metabolizera, 15,7% sporih metabolizera i 55,6% ispitanika iz grupe veoma sporih metabolizera i bez enzimske aktivnosti. Postoji statistički značajna razlika u učestalosti ispoljavanja neželjenih dejstava beta blokatora u odnosu na genetski determinisanu enzimsku aktivnost CYP2D6 (Hi-kvadrat=25,325; p<0,001). U modelu multivarijantne logističke regresije pokazano je da je enzimska aktivnost statistički značajan prediktor javljanja neželjenih dejstava beta blokatora (B=3,544; p<0,001). Postoji jaka pozitivna statistički značajna korelacija višeg stepena enzimske aktivnosti i doza beta blokatora koje su pacijenti dobijali tokom hospitalizacije.
Framakogenetske analize koje su po prvi put rađene u crnogorskoj populaciji pacijenata ukazuju da ovakve analize mogu predvidjeti odgovor pacijenata na određenu terapiju. Ostaje nada autora da će u Crnoj Gori zaživjeti farmakogenetika i da će se zdravstveni radnici uvjeriti da uvid u genetske varijacije i razumijevanje uticaja koje imaju na individualne reakcije u farmakoterapiji, povećava

mogućnost kontrolisanja i liječenja velikog broja oboljenja.

Ključne riječi: farmakogenetika, neželjena dejstva ljekova, beta-blokatori

CYP2D6 POLYMORPHISM – RISK FACTOR FOR DEVELOPING ADVERSE DRUG REACTIONS OF BETA BLOCKERS

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Adverse drug reactions (ADRs) are common causes of morbidity and mortality within the hospital setting, with contribution of numerous risks factors. Our main goal was to analyse risk factors, incidence and characteristics of ADRs of beta blockers in hospitalised cardiac patients and to consequently suggest measures for rationalization of pharmacotherapy practice

Prospective study, which included 138 patients hospitalized at Cardiology Centre of the Clinical Centre of Montenegro, was performed. ADRs of beta blockers were collected using intensive monitoring system. Genotyping of CYP2D6*3 (2549delA, rs35742686), CYP2D6*4 (1846G>A, rs3892097), CYP2D6*5 (gene deletion), CYP2D6*6 (1707delT, rs5030655) and CYP2D6*10 (100C>T, rs1065852) using RT- PCR method, in order to determine the frequency of different drug metabolizer status types of beta blockers.

Of all patients who received beta blockers, ADRs of this drug pharmacotherapeutic group, 15 (10.9%) experienced at least one of adverse drug reaction of beta blockers. 2,6% of fast and intermediate CYP2D6 metabolizers, 15,7% of poor metabolizers and 55,6% of very slow and those with no CYP2D6 enzyme activity experienced ADRs of beta blockers. There is a statistically significant difference in the enzyme activity level of CYP2D6 regarding the existence of ADRs (Hi2=25,325; p<0,001). In the multivariate logistic regression model showed that the enzyme activity of CYP2D6 is statistically important predictor of occurrence of beta blockers' ADRs B=3,544; p<0,001). There is a strong positive, statistically significant higher level correlation of the enzyme activity of CYP2D6 and the given dose of beta blockers during hospitalization.

Pharmacogenetics analyses that were done in the Montenegrin population of patients for the first time suggest that these analyses can predict patient response to the certain therapy. Authors hope that pharmacogenetics analyses will become a reality in Montenegro and will assure that health workers insight into the genetic variation and understanding of the impact they have on the individual response to pharmacotherapy will increase the possibility of controlling and treating a large number of diseases.

Key words: pharmacogenetics, adverse drug reactions, beta-blockers

ANALIZA POTROŠNJE LJEKOVA ZA KARDIOVASKULARNE BOLESTI U ZDRAVSTVENOJ USTANOVI APOTEKE CRNE GORE "MONTEFARM"

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Farmakoekonomija je nauka koja ima za cilj da racionalizuje primjenu ljekova na bazi ekonomskih i zdravstvenih pokazatelja. Kardiovaskularne bolesti su vodeći uzrok smrti u većini razvijenih zemalja. Crna Gora spada u grupu zemalja sa visokom stopom mortaliteta od kardiovaskularnih bolesti. Cilj ovog rada je da analizira potrošnju ljekova za liječenje kardiovaskularnih bolesti, u Zdravstvenoj ustanovi Apoteke Crne Gore "Montefarm" u periodu 2004- 2012. godine, i upoređivanje dobijenih podataka sa principima savremene farmakoterapijske prakse.
Analiza se zasniva na podacima dobijenim iz veledrogerije Zdravstvene ustanove Apoteke Crne Gore "Montefarm" u periodu 2004- 2012. godine. Podaci o potrošnji ljekova su analizirani prema metodologiji Svetske zdravstvene organizacije, anatomsko terapijsko hemijske klasifikacije, internacionalnim nezaštićenim imenima i definisane dnevne doze. Podaci o broju stanovnika u Crnoj Gori su preuzeti iz Zavoda za statistiku Crne Gore. U farmakoekonomskoj analizi primijenjen je deskriptivno-analitički metod i retrospektivna analiza.
U odnosu na promet svih lijekova najviši procenat zauzimaju ljekovi koji se koriste u liječenju kardiovaskularnih bolesti od 87,02 DDD/1000 stanovnika/dan (2004) do 212,98 DDD/1000 stanovnika/dan (2012). Najveću potrošnju su imali ljekovi koji deluju na renin - angiotenzin sistem (od 35,39 do 114,19 DDD/1000 stanovnika/dan). Finansijska zastupljenost ove grupe ljekova se kretala od 16,29% (2004) do 8,23% (2012). Najpropisivaniji ljekovi su ACE inhibitori koje prati pad cijena u 2012. u odnosu na 2004. godinu.
Prema podacima ukupno prometovanih ljekova po dnevno definisanim dozama, ljekovi koji djeluju na kardiovaskularni sistem nalaze se na prvom mjestu. Unutar grupe ljekova koji djeluju na kardiovaskularni sistem najveći udio imaju ACE inhibitori, što je u skladu sa savremenom farmakoterapijskom praksom. Finansijska sredstva utrošena za ovu grupu ljekova su u konstantnom porastu, ali nijesu parametar na osnovu kojeg bi ova grupa ljekova bila označena kao ATC grupa sa najvećim finansijskim izdacima.

Ključne riječi: farmakoekonomija, ljekovi u terapiji kardiovaskularnih bolesti, ACE inhibitori

THE ANALYSIS OF DRUG UTILIZATION FOR CARDIOVASCULAR DISEASES IN HEALTH PHARMACY INSTITUTION OF MONTENEGRO "MONTEFARM"

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Pharmacoeconomics is a science that aims to rationalize the application of medicines on the basis of economic and health indicators. Cardiovascular diseases are the leading cause of

death in most developed countries. Montenegro belongs to the group of countries with a high rate of mortality from cardiovascular disease. The aim of this stady is to analyze drug utilization for the treatment of cardiovascular diseases in a Health Pharmacy Institution of Montenegro "Montefarm" in the period 2004- 2012, to compare the obtained data with the principles of modern pharmacotherapy practice.
The analysis is based on data obtained from wholesalers Health Pharmacy Institution of Montenegro "Montefarm" in the period 2004- 2012. Drug utilization data were analyzed according to the methodology of the World Health Organization, anatomical therapeutic chemical classification, the international non-proprietary names and defined daily dose. Data on the number of inhabitans in Montenegro are taken from the Statistical Institute of Montenegro. In pharmacoeconomics analysis was applied descriptive-analytic method and retrospective analysis.
In relation to the utilization of all the medicines the highest percentage take drugs used in the treatment of cardiovascular disease than 87.02 DDD / 1000 inhabitants / day (2004) to 212.98 DDD / 1000 inhabitants / day (2012). The highest utilization had drugs that act on the renin - angiotensin system (from 35.39 to 114.19 DDD / 1000 inhabitants / day). Financial representation of this group of drugs ranged from 16.29% (2004) to 8.23% (2012). The most frequently prescribed drugs are ACE inhibitors which follows the fall in prices in 2012 compared to 2004.
According to the total utilization drugs per defined daily doses, drugs that act on the cardiovascular system are in the first place. Within the group of drugs that act on the cardiovascular system the largest percentage take ACE inhibitors, which coincides with the principles of modern pharmacotherapy practice. Financial resources spent for this group of drugs have been steadily rising, but are not a parameter by which to this group of drugs was identified as ATC group with the biggest financial outlay.

Key words: pharmacoeconomics, drugs in the treatment of cardiovascular disease, ACE inhibitors

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POTREBE ZA SAVJETOVANJEM O PRIMJENI TERAPIJE ODRASLIH I STARIJIH PACIJENATA

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U procesu pružanja farmaceutske zdravstvene zaštite, uloga farmaceuta ogleda se, između ostalog, u procjeni potreba i zabrinutosti pacijenata u vezi sa primjenom lijeka, na osnovu čega se može pružiti savjetovanje pacijenata skrojeno prema individualnim potrebama.
U periodu od mart-maj 2014., u apoteci ZUACG „Montefarm", Bijelo Polje, regrutovano je deset pacijenata, starosti od 18-65 godina, koji su započeli hroničnu terapiju novim lijekom i deset pacijenata, starosti >65 godina, koji su bili na hroničnoj terapiji sa najmanje 5 lijekova propisanih za liječenje kardiovaskularnih, digestivnih, muskulo-skeletnih i/ili respiratornih bolesti. Pacijenti su popunili upitnike odgovarajući na pitanja šta bi želeli da znaju o terapiji, kakva očekivanja

imaju od terapije, da li postoji (i koji je) razlog za zabrinutost u vezi primjene ili prekid terapije. Na osnovu dobijenih odgovora pruženo je savjetovanje prema individualnim potrebama pacijenta. Obije grupe pacijenata su pokazale podjednaka očekivanja vezana za efekat terapije. Zapažene su razlike u grupama vezane za zabrinutost zbog hronične upotrebe lijekova, koja je evidentirana kod 4 pacijenta >65 godina, dok mlađi pacijenti nijesu pokazali zabrinutost (0/10). Razlike su zabilježene i u razlozima samostalne obustave primjene lijekova. Polovina pacijenata starosti 18-65 godina bi samostalno obustavila terapiju u slučaju regulacije kliničkih parametara ili pojave neželjenih efekata. Nasuprot tome, pacijenti stariji od 65 godina ne bi vršili obustavu terapije bez prethodne konsultacije sa zdravstvenim radnikom. Pacijenti starosti 18-65 godina, pokazali su veću zainteresovanost za saznanja o neželjenim efektima i neophodnosti svakodnevne upotrebe lijeka (4/10), dok su pacijenti >65 godina, veću zainteresovanost pokazali za mehanizam delovanja lijekova (5/10). U grupi pacijenata >65 godina sprovedene su 3 intervencije od strane farmaceuta vezane za edukovanje o primeni lijekova.
Rezultati ukazuju na postojanje različitih potreba za znanjem u vezi primjene lijeka u odraslih i starijih pacijenata koje se moraju uzeti u obzir pri individualnom savjetovanju pacijenata o primjeni terapije.

Ključne riječi: pacijenti, savjetovanje, odrasli, stariji

MEDICATION USE COUNSELING NEEDS IN ADULT AND ELDERLY POPULATIONS

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In the process of pharmaceutical care, the role of pharmacist’s comprises, among other tasks, the assesment of patient’s needs and concerns regarding medication use, which provides a basis for individualized patient counseling.
In the period March-May 2014, in the pharmacy „Montefarm“, Bijelo Polje, 10 patients aged 18-65 years, who initiated chronic treatment with a new medicine, were recruited. Moreover, 10 patients aged >65 years, on chronic treatment with at least 5 medicines, proscribed for the treatment of cardiovascular, digestive, musculo-sceletal and/or respiratory diseases were included in the study as well. Patients filled in questionnaires answering questions related to knowledge about medicines, expectations from treatment and reasons for concern or discontinuation of treatment. According to their answers, counseling was offered adjusted to individual patient needs.
Both patient groups had similar expectations about treatment effects. Differences were observed regarding concerns about chronic medication use, which was documented in 4 patients aged >65 years, whereas younger patients showed no similar concerns (0/10). Differences were also observed regarding reasons for discontinuation of medication use. 50% of patients aged 18-65 years, would have discontinued the treatment in the case of clinical parameter regulation or adverse effects. In contrast, patients >65 years would not discontinue medication without prior consultation with a health professional. Patients aged 18-65 years showed more interest

in knowledge about adverse effects and the need of regular medication use (4/10), whereas patients >65 years showed more interest in mechanisms of medication action (5/10). In patients >65 years, pharmacists had 3 interventions regarding patient counseling about medication use. The results indicate that adult and elderly patients may have different needs regarding knowledge about medication use, which must be taken into consideration during individual patient counseling.

Key words: patients, counseling, adults, elderly

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ZAVISNOST IZMEĐU OSOBINA MOLEKULA BLOKATORA KALCIJUMOVIH KANALA I STEPENA NJIHOVOG VEZIVANJA ZA PROTEINE PLAZME

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Povišeni krvni pritisak danas predstavlja širom sveta rasprostranjeno oboljenje. Blokatori kalcijumskih kanala (BKK) primenjuju se u lečenju brojnih kardiovaskularnih oboljenja, uključujući hipertenziju, anginu pektoris, supraventrikularne poremećaje srčanog ritma, hipertrofičnu kardiomiopatiju i nakon infarkta miokarda.
Cilj ovog rada bio je da se prouči odnos između izračunatih osobina molekula devet blokatora kalcijumovih kanala (amlodipin, felodipin, isradipin, nikardipin, nifedipin, nimodipin, nislodipin, verapamil i diltiazem) i vrednosti njihovog stepena vezivanja za proteine plazme.
Vrednosti stepena vezivanja za proteine plazme ispitivanih BKK prikupljene su iz relevantne literature. Softverski paketi Virtual Computational Chemistry Laboratory kao i Molinspiration Depiction Software primenjeni su za isračunavanje nekoliko različitih molekulskih deskriptora ispitivanih lekova: rstvorljivosti (logS), polarne površine molekula (PSA), molekulske mase (Mr), volumena molekula (Vol) kao i parametara lipofilnosti, logP vrednosti.
U radu je ispitana zavisnost između izračunatih molekulskih osobina BKK i vrednosti stepena njihovog vezivanja za proteine plazme koje su dobijene iz relevantne literature. Međutim, u prvoj fazi istraživanja metodom jednostavne linearne regresije dobijene su niske vrednosti koeficijenta korelacije ($R2<0,35$). U nastavku proučavanja, primenjena je višestruka regresiona analiza (MLR) kako bi se dobila bolja zavisnost. Najbolja korelacija dobijena je za zavisnost između stepena vezivanja za proteine plazme blokatora kalcijumovih kanala i nihove lipofilnosti uz primenu dodatnih molekulskih desktiptora, izračunatih vrednosti Mr ($R2 = 0,623$) ili Vol ($R2 = 0,741$) kao nezavisnih promenljivih (uz prihvatljive vrednosti stepena verovatnoće $P < 0,05$)
Predložena tehika potvrđuje uticaj lipofilnosti, zajedno sa drugim osobinama molekula ispitivanih blokatora kalcijumovih kanala na stepen njihovog vezivanja za proteine plazme. Može se posmatrati kao dopunski in vitro pristup pogodan za modelovanje vezivanja za proteine plazme

ispitivane grupe lekova.

Ključne reči: Blokatori kalcijumovih kanala; lipofilnost; molekulska masa; stepen vezivanja za proteine plazme.

THE RELATION BETWEEN CALCIUM CHANNEL BLOCKERS' MOLECULAR PROPERTIES AND PLASMA PROTEIN BINDING DEGREE

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Today, high blood pressure or hypertension is a globally spread disease. Calcium channel blockers (CCBs) are widely used drugs in cardiovascular medicine for the treatment of hypertension, angina pectoris, supraventricular dysrhythmias, hypertrophic cardiomyopathy and after myocardial infarction.
The aim of this study was to investigate the relationship between computed molecular properties of nine CCBs (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nislodipine, verapamil and diltiazem) and their available plasma protein binding (PPB) data.
The PPB degree data for investigated CCBs were obtained from relevant literature. The values of CCBs several molecular descriptors, aqueous solubility (logS), electronic descriptor - polar surface area (PSA), constitutional parameter - molecular weight (Mw), geometric descriptor - volume value (Vol) and lipophilicity parameters, logP values were calculated using software packages, Virtual Computational Chemistry Laboratory and Molinspiration Depiction Software.
The relationship between CCBs computed molecular properties and PPB degree data collected from relevant literature were firstly investigated using simple linear regression analysis showing the low correlations ($R2<0.35$). In continuation, multiple linear regression (MLR) analysis was applied to access higher correlation of CCBs calculated molecular descriptors and PPB data. The best correlations were found for relationships between CCBs PPB data and their lipophilicity (ClogP) with application of additional molecular descriptors, Mw or Vol data as additional independent variables ($R2 = 0.623$ and $R2 = 0.741$ respectively) with acceptable probability value, $P < 0.05$.
The proposed technique confirmed that lipophilicity, together with other molecular properties, is essential in drugs PPB degree and could be regarded as additional, in vitro approach appropriate for its modeling for investigated group of calcium channel blockers.

Keywords: Calcium channel blockers; lipophilicity; molecular weight; plasma protein binding degree.

ANTIOKSIDATIVNA ODBRANA I INFLAMACIJA U RESTENOZI NAKON PERKUTANE KORONARNE INTERVENCIJE

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Angiografski benefit perkutane koronarne intervencije (PCI) često je ugrožen potrebom za ponovnom revaskularizacijom, zbog razvoja in-stent restenoze. Brojne studije su pokušale uspostaviti prediktivnu vrijednost brojnih biomarkera i restenoze, ali rezultati su cesto bili kontraverzni.
Cilj ovog rada je bio da se procijeni prognostički značaj antioksidativne odbrane, lipidnih markera i markera inflamacije za razvoj in-stent restenoze (ISR) nakon PCI.
Serumski, visoko senzitivni CRP (hs-CRP), rastvorljiva intracelularna adhezivna molekula-1 (ICAM-1), transformišući faktor rasta-beta (TGF-β), oksidovani niske-gustine lipoprotein (oxLDL), ceruloplazminski nivoi kao i serumska katalazna (CAT) aktivnost su određivani kod 44 pacijenta prije implantacije stenta kao i 6 mjeseci nakon praćenja od PCI.
Rezultati nakon praćenja, su otkrili da kod pacijenata koji su razvili angiografski potvrđenu ISR, porast nivoa hs-CRP je bio značajno viši u odnosu na pacijente bez stenoze. Stent implantacija indukuje kompenzatorno povećanje serumske antioksidativne zaštite tokom praćenja sa znatno nižom CAT aktivnosti kod pacijenata sa ISR, što vjerovatno doprinosi njenom razvoju. Nema značajnih promjena u cirkulaciji kod nivoa ICAM-1, TGF-β, oxLDL i ceruloplazmina unutar ispitivanih grupa.
U zaključku, nivo serumskog hs-CRP i aktivnost CAT se može smatrati korisnim prediktivnim biomarkerima u praćenju razvoja ISR kod pacijenata nakon implantacije stenta.

Ključne riječi: in-stent restenoza, antioksidativna odbrana, markeri inflamacije

THE ANTIOXIDANT DEFENSE AND INFLAMMATION IN RESTENOSIS FOLLOWING PERCUTANEOUS CORONARY INTERVENCTION

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Angiographic benefit of percutaneous coronary intervention (PCI) is often compromised by the need for repeated revascularization, due to the development of in-stent restenosis. Numerous studies have tried to establish the predictive value of different biochemical markers of restenosis, but the results were often controversial.

The aim of this study was to assess the prognostic significance of antioxidant, lipid markers and markers of inflammation in the development of in-stent restenosis (ISR) after PCI.
Serum, high sensitivity CRP (hs-CRP), soluble intracellular adhesion molecule-1 (ICAM-1), transforming growth factor-beta (TGF-β), oxidized low-density lipoprotein (oxLDL), ceruloplasmin levels and serum catalase (CAT) activity were determined in 44 patients before stent implantation procedure as well as 6 months after the monitoring of PCI.
The results of the follow-up, they found that patients who developed angiographic ISR, increase the level of hs-CRP was significantly higher than in patients without stenosis.Stent implantation induces a compensatory increase in serum antioxidant protection during follow-up with a much lower CAT activity in patients with ISR, which probably contributes to its development.No significant changes in the circulation at the level of ICAM-1, TGF-β, oxLDL and ceruloplasmin were observed between the groups.
In conclusion,serum hs-CRP and CAT activity may be considered as useful predictive biomarkers for monitoring patients during follow-up after stent implantation.

Key words: in-stent restenosis, antioxidant defense, markers of inflammation

KOMPARATIVNO ISPITIVANJE UTICAJA HENODEOKSIHOLNE I URSODEOKSIHOLNE KISELINE NA BIOHEMIJSKE PARAMETRE U SERUMU PACOVA SA HOLESTAZOM

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Holestatski poremećaji jetre obuhvataju bolesti hepatobilijarnog sistema različite etiologije, a koje karakteriše nagomilavanje žučnih kiselina, bilirubina i holesterola, kao posledica poremećaja u sekreciji žuči. Ursodeoksiholna kiselina (UDCA), kao hidrofilna žučna kiselina, se široko koristi u terapiji holestaze, dok je njen epimer, henodeoksiholna kiselina (CDCA), hidrofobno jedinjenje koje može da ispolji toksične efekte, ali takođe može da aktivira farnezoid X receptor (FXR). FXR je glavni regulator homeostaze žučnih kiselina i razvoj liganda za FXR predstavlja novi pristup u lečenju holestatskih poremećaja. Cilj našeg istraživanja je bio da se utvrde efekti niskih, netoksičnih doza CDCA na parametre holestaze kod pacova.
Akutna intrahepatična holestaza kod pacova je indukovana pomoću 17α-etinil-estradiola (EE) i efekti primene CDCA tokom 5 dana, u komparaciji sa UDCA, su određeni merenjem aktivnosti alanin aminotransferaze (ALT), aspartat aminotransferaze (AST) i γ-glutamiltransferaze (GGT), kao i nivoa bilirubina u serumu.
Indukcija holestatskog oštećenja jetre je bila povezana sa statistički značajnim povećanjem vrednosti ALT i konjugovanog bilirubina u serumu ($p<0,05$). Aktivnosti enzima AST i GGT su bile takođe povišene u serumu pacova tretiranih etinil-estradiolom, ali to povećanje nije bilo statistički značajno. Obe ispitivane žučne kiseline, UDCA i CDCA, su uspele da delimično vrate vrednosti svih biohemijskih pokazatelja holestaze i oštećenja jetre prema normalnim vrednostima, ali je to smanjenje parametara bilo statistički značajno ($p<0,05$) samo za aktivnost ALT. CDCA se

pokazala kao efikasnija u smanjenju vrednosti ALT u serumu, dok je UDCA uspela u većoj meri da smanji aktivnost GGT, kao specifičnog pokazatelja holestaze, u odnosu na CDCA.
Rezultati naše studije pokazuju da obe ispitivane žučne kiseline, UDCA i CDCA, iako imaju različite mehanizme delovanja, ispoljavaju protektivni efekat prema estradiol-indukovanoj intrahepatičnoj holestazi.

Ključne reči: žučne kiseline, holestaza, aminotransferaze, hepatoprotektivno dejstvo

COMPARATIVE STUDY ON EFFECTS OF CHENODEOXYCHOLIC AND URSODEOXYCHOLIC ACID ON SERUM BIOCHEMICAL PARAMETERS IN CHOLESTATIC RATS

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Cholestatic liver disorders encompass hepatobiliary diseases of diverse etiologies characterized by accumulation of bile acids, bilirubin and cholesterol as the result of impaired secretion of bile. Ursodeoxycholic acid (UDCA), as hydrophilic bile acid, is widely used agent for the treatment of cholestasis, while its epimer, chenodeoxycholic acid (CDCA), is hydrophobic compound that may exert toxic effects, but can also activate the farnesoid X receptor (FXR). FXR is the main regulator of bile acid homeostasis and the development of FXR ligands represents a new approach for the treatment of cholestasis. The aim of our study was to determine the effects of low, non-toxic doses of CDCA on parameters of cholestasis in rats.
Acute intrahepatic cholestasis in rats was induced by 17α-ethynylestradiol (EE), and the effects of treatment with CDCA during 5 days on cholestasis were explored and compared with UDCA by serum biochemical determination of alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT) and bilirubin.
The induction of cholestatic damage by EE was associated with significant increase of ALT and direct bilirubin ($p<0.05$). The values of AST and GGT were also elevated in serum of EE-treated rats, but it was not statistically significant. Both UDCA and CDCA could reverse all these biochemical parameters referring to cholestasis and liver injury, but that reduction was statistically significant ($p<0.05$) only for ALT activity. CDCA was shown to be more effective than UDCA in reducing ALT levels, while UDCA managed to decrease the activities of GGT, as specific markers of cholestasis, to a greater extent when compared to CDCA.
The results of our study suggest that both UDCA and CDCA, although having distint mechanisms of action, exhibit potential protection against estradiol-induced acute intrahepatic cholestasis.

Keywords: bile acids, cholestasis, aminotransferases, hepatoprotection

EPIMER-SPECIFIČNI EFEKTI ŽUČNIH KISELINA NA PROLIFERACIJU HT-29 ĆELIJA KARCINOMA KOLONA

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Hidrofobnost je glavna determinanta toksičnosti žučnih kiselina i zavisi od broja, pozicije i orijentacije hidroksilnih grupa. Ursodeoksiholna kiselina (UDCA) je hidrofilna dihidroksi žučna kiselina koja nastaje 7β-epimerizacijom henodeoksiholne kiseline (CDCA) u lumenu creva dejstvom normalne mikroflore. Za razliku od drugih sekundarnih žučnih kiselina, UDCA ispoljava citoprotektivne i antiapoptotske efekte sprečavanjem oksidativnog stresa. Cilj naše studije je bio da se analizira uticaj stereohemije hidroksilnih grupa u strukturi žučnih kiselina na njihovu antiproliferativnu aktivnost.
Citotoksičnost CDCA i UDCA je ispitana na HT-29 ćelijama humanog adenokarcinoma kolona pomoću kolorimetrijskog MTT testa. U cilju objašnjenja dobijenih rezultata MTT testa, pomoću VolSurf+ programa iz 3D struktura CDCA i UDCA izračunato je 12 molekularnih deskriptora koji ukazuju na polarnost, rastvorljivost i transport kroz membrane.
Ispitivane žučne kiseline su ispoljile različit nivo citotoksičnosti prema HT-29 malignim ćelijama na koncentracijski zavisan način. Koncentracije CDCA i UDCA koje inhibiraju ćelijski rast za 50% (IC50 vrednosti) iznosile su 19,6 μM i 351,9 μM. Oksidativni stres se smatra najznačajnijim mehanizmom citotoksičnosti žučnih kiselina, što je uslovljeno pre svega njihovom hidrofobnošću. Molekularni deskriptor pomoću kog se mogu objasniti ovi različiti citotoksični efekti žučnih kiselina jeste amfifilni momenat (A), koji se definiše kao vektor koji se pruža od centra hidrofobnog do centra hidrofilnog domena. Dužina vektora (5,62 za CDCA i 4,87 za UDCA) određuje sposobnost jedinjenja da prolazi kroz biološke membrane. Ovaj rezultat je dodatno potkrepljen vrednostima CACO2, SKIN i LgBB deskriptora koji ukazuju na bolji prodor CDCA u odnosu na UDCA kroz Caco-2 ćelije, kožu i krvno-moždanu barijeru.
Potvrdili smo izraženije citotoksične efekte CDCA u poređenju sa UDCA. Softverske tehnike koje izračunavaju fizičko-hemijske osobine molekula mogu biti u velikoj meri od pomoći u predikciji njihove citotoksičnosti.

Ključne reči: žučne kiseline, citotoksičnost, MTT test, maligne ćelije, stereohemija

EPIMER-SPECIFIC EFFECTS OF BILE ACIDS ON HT-29 COLON CANCER CELLS PROLIFERATION

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Hydrophobicity is the most important determinant of toxicity of bile acids (BAs) and depends on the number, position and orientation of hydroxyl groups. Ursodeoxycholic acid (UDCA) is a hydrophilic dihydroxy BA, which is formed by 7β-epimerization of chenodeoxycholic acid (CDCA) in the gut by intestinal bacteria. Unlike the other secondary BAs, UDCA exerts antiapoptotic effects by preventing oxidative stress. The aim of our study was to analyze the influence of stereochemistry of hydroxyl groups on antiproliferative activity of BAs.
Human colon adenocarcinoma HT-29 cells were used to assess the cytotoxicity of CDCA and UDCA using colorimetric MTT assay. In order to explain obtained results of MTT assay, 12 molecular descriptors relevant to solubility and membrane transport were calculated from structures using VolSurf+ software.
Studied BAs displayed distinct degrees of cytotoxicity towards HT-29 cancer cells in a concentration-dependent manner. Concentrations of CDCA and UDCA that inhibited cell growth by 50% (IC50) were 19.6 μM and 351.9 μM, respectively. Oxidative stress is considered to be the most plausible mechanism of cytotoxicity of BAs, which is determined mostly by their hydrophobicity. Calculated molecular descriptor that may explain these distinct cytotoxic effects is amphiphilic moment (A), which is defined as a vector pointing from the centre of hydrophobic domain to the centre of hydrophilic domain. The vector length (5.62 of CDCA and 4.87 of UDCA) determines the ability of compound to permeate a membrane. This was additionally substantiated with the values of CACO2, SKIN and LgBB descriptors that indicate higher Caco-2 permeability, skin permeability and blood-brain barrier distribution of CDCA in comparison to UDCA.
More pronounced antiproliferative activity of CDCA, compared to UDCA, was observed. We suggest that computational methods exploring the physicochemical properties of molecules may help in prediction of their cytotoxicity.

Keywords: bile acids, cytotoxicity, MTT assay, malignant cells, stereochemistry

UPOTREBA ANTISEPTIKA I SREDSTAVA ZA DEZINFEKCIJU U JAVNIM USTANOVAMA U REPUBLICI MAKEDONIJI U POSLIJEDNJIH PET GODINA

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Intrahospitalne ili bolničke infekcije nastaju kontaminacijom mikroorganizmina za vrijeme hospitalizacije pacijenata i klinički se manifestiraju od 48 do 72 sati poslije kontaminacije. Postupci dezinfekcije, vrsta i količine sredstava za dezinfekciju koji se koriste su direktno povezani sa efektima njihovog djelovanja.
Cilj rada je analiza korišćenja antiseptika i sredstava za dezinfekciju u javnim ustanovama u Republici Makedoniji u poslijednjih pet godina
Za izvođenje ovog istraživanja skupljeni su podaci bilježeni u evidentnim listama za korišćenje sredstava za dezinfekciju i antiseptika u različitim odjelima, kako i podatci iz evidentnih listi nabavke bolničkih apoteka u više zdravstvenih institucija u Republici Makedoniji. Za analizu efektivnosti upotrebljenih dezinficiensa skupljeni su podaci o izvršenim mikrobiološkim ispitivanjima.
Rezultati analize za svaku godinu i instituciju posebno ukazuju na značajno smanjenje kontaminacije sa patogenim mikroorganizmima ako je bila pravilno provedena dezinfekcija, kad se pravilno sprovode propisane procedure za njihovu upotrebu, pri čemu posebno treba obratiti pažnju gdje i koji dezinficijensi se koristi. Statistička obrada podataka u poslijednjih pet godina daje kompletnu sliku o povezanosti upotrebljenih sredstava za dezinfekciju i antiseptika s pojavom ili ne nozokomijalnih infekcija.
Obrađeni podaci koji se odnose na vrstu, količinu i način korišćenje dezinficijensa i antiseptika ukazuju na pravilno i racionalno korišćenje. Ova analiza se može koristiti za monitoring od strane nadležnih autoriteta i preveniranje bolničkih infekcija u samim zdravstvenim ustanovama.

Ključne riječi: sredstva za dezinfekciju, antiseptic, dezinfekcija

USE OF ANTISEPTICS AND DISINFECTANTS IN PUBLIC INSTITUTIONS IN THE COUNTRY IN THE LAST FIVE YEARS

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Intra-hospital or hospital infections are caused by organisms acquired during hospitalization of the patient and clinically manifest from 48 to 72 hours after their administration. Disinfection procedures, type and quantity of disinfectant used is directly related to the effects of their use.
Review of the use of antiseptics and disinfectants in public institutions in the country for five years.
For the implementation of this research collected data from the obvious lists using disinfectants and antiseptics in various departments of several health institutions in the country as well as the obvious lists procurement of hospital pharmacies. To monitor the effectiveness of disinfectants used collected data from the microbiological controls.

The results of the analysis for each year and each institution specifically indicate significant reduction of contamination with pathogens when properly conducted disinfection and reduce the quantity of disinfectant used when following procedures for use, with particular attention to where and who disinfectant used. Statistical processing of data from the last five years gives a complete picture of the connection used disinfectants and antiseptics to the appearance or absence of nosocomial infections.
The processed data on the type, amount and manner of use of disinfectants and antiseptics indicate their proper and rational use. The analysis can be used to monitor the situation by the competent authorities and prevention of hospital infections in the health facilities.

Keywords: means of disinfectants, antiseptics, disinfectants

ZNANJE I PONAŠANJE BUDUĆIH LJEKARA, STOMATOLOGA I MEDICINSKIH SESTARA U VEZI SA ANTIBIOTICIMA

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Antibiotici su ljekovi koji se koriste u liječenju bakterijskih infekcija. Racionalna antibiotska terapija je imperativ.
Ispitati osnovna znanja i ponašanje studenata studijskih programa Medicinskog fakulteta u Podgorici u vezi sa antibioticima.
Istraživanje je sprovedeno tokom oktobra 2014. godine, a obuhvatilo je 129 studenata medicine, stomatologije i visoke medicinske škole, od čega 65% studenata nisu imali položen ispit iz predmeta farmakologija u periodu istraživanja, a 35% jesu. Korišćen je upitnik koji se odnosio na znanje i ponašanje studenata u vezi sa antibioticima.
Nešto više od jedne trećine (34.1%) studenata smatraju da su antibiotici efikasni u liječenju povišene tjelesne temperature, a 30.2% u liječenju kijavice, kašlja i zapušenosti nosa. Jedna četvrtina (24.8%) studenata smatraju da su antibiotici efikasni u liječenju virusnih, gljivičnih i parazitarnih infekcija. Efikasnost antibiotika u liječenju bola u stomaku različitog uzroka navodi 14% studenata, a u liječenju različitih alergijskih stanja oko 12%. Nešto više od dvije trećine (67.4%) ispitanika se liječilo antibiotikom bez preporuke ljekara, a kao razlog tome najčešće navode prethodno pozitivno iskustvo sa primjenom lijeka (49.4%) i preporuke zaposlenih u apoteci (31%). Na pitanje šta misle o tzv. samoliječenju antibioticima 15.5% studenata smatraju da je to prihvatljivo i dobra praksa. Približno jedna četvrtina (23.3%) studenata smatraju da je antibiotik „čudesan lijek“ koji će uvijek biti efikasan u liječenju iste infekcije i u budućnosti.
Znanje i ponašanje studenata u vezi sa antibioticima nije na zadovoljavajućem nivou, bez obzira na to što većina studenata nisu imali položen ispit iz predmeta farmakologija u periodu istraživanja. Potrebna je dodatna edukacija kako bi se postojeće stanje poboljšalo i stvorili preduslovi za racionalnu primjenu antibiotika. Dobijeni rezultati bi mogli da ukažu i na to da znanje i ponašanje u vezi sa antibioticima ni u opštoj populaciji nije zadovoljavajuće.

Ključne riječi: antibiotici, znanje, ponašanje, studenti

KNOWLEDGE AND BEHAVIOR OF FUTURE PHYSICIANS, DENTISTS AND NURSES IN RELATION TO ANTIBIOTICS

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Antibiotics are medicines used to treat bacterial infections. Rational antibiotic therapy is an imperative.
To examine the elementary knowledge and behavior of students of Faculty of Medicine in Podgorica in relation to antibiotics.
The study was conducted during October 2014. and included 129 students of medicine, dentistry and nursing school. During the research, 65% of students had not yet passed the exam in pharmacology, while 35% did. We used a questionnaire about knowledge and behavior of students regarding antibiotics.
Slightly more than one-third (34.1%) of students believe that antibiotics are effective in the treatment of high body temperature, while 30.2% believe that antibiotics are effective in the treatment of cold, cough and nasal congestion. One-quarter (24.8%) of students believe that antibiotics are effective in the treatment of viral, fungal and parasitic infections. 14% of students stated that antibiotics are efficient in the treatment of abdominal pain of different causes, and about 12% of students stated they are efficient in the treatment of various allergic conditions. Slightly more than two-thirds (67.4%) of students were treated with antibiotics without a doctor's recommendation, and the reasons that most of them stated were previously positive experience with the use of medicine (49.4%) and recommendations of pharmacists (31%). When asked about their opinion on the so-called self-medication with antibiotics, 15.5% of students believe that this is acceptable and good practice. Approximately one-quarter (23.3%) of students believe that antibiotic is a "magic pill" that will always be effective in the treatment of the same infection in the future.
Knowledge and behavior of students in relation to antibiotics is not satisfactory regardless of the fact that a large number of them had not yet passed the exam in pharmacology during the research period. In order to improve the current situation and to create the conditions for rational use of antibiotics, additional education is necessary. These results suggest that knowledge and behavior in relation to antibiotics in the general population is also not satisfactory.

Key words: antibiotics, knowledge, behavior, students

ODREĐIVANJE RASTVORLJIVOSTI OLOPATADIN-HIDROHLORIDA PRIMJENOM TEČNE HROMATOGRAFIJE HIDROFILNIH INTERAKCIJA I UV SPEKTROFOTOMETRIJSKE METODE

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U radu je prikazano poređenje dvije metode za ispitivanje rastvorljivosti olopatadin- hidrohlorida. Olopatadin-hidrohlorid je antihistaminik sa selektivnom antagonističkom aktivnošću na H1-receptore, koji se koristi u obliku kapi za oči i sprejeva za nos. U preliminarnoj studiji ispitivana je rastvorljivost olopatadin-hidrohlorida s obzirom na njegov potencijal za upotrebu u različitim farmaceutskim oblicima. Ispitivane su tri različite serije supstance.
Pripremljeni su rastvori u vodi (konačna pH vrijednost 3,5) i fosfatnom puferu (pH 5,8). Prva korišćena metoda bila je tečna hromatografija hidrofilnih interakcija. Razdvajanje je izvršeno na Betasil Cyano koloni (100 mmx 4,6 mm, veličina čestica 5 □m). Mobilna faza se sastojala iz 85 % acetonitrila i 15 % vodenog rastvora koji je sadržavao 5 mM amonijum acetata, pH vrijednost je podešena na 4,5 dodavanjem glacijalne sirćetne kiseline. Protok je bio 1 mL min-1, a temperatura kolone 30 °C. UV detekcija je izvršena na talasnoj dužini od 257 nm. U drugoj metodi koncentracija olopatadin-hidrohlorida je određena spektrofotometrijskim mjerenjem na talasnoj dužini od 299 nm (Dvozračni Shimadzu UV-VIS spektrofotometar, model 1800). Kalibracione krive za oba medijuma su konstruisane u opsegu koncentracija od 10 do 100 μg/ml (r = 0,995).
Hromatografska analiza je pokazala da se lijek potpuno rastvorio (0,4 mg/ml). Dodatno, utvrđeno je da su pri nižoj pH vrijednosti prisutna dva oblika (jonizovani i nejonizovani), a pri višoj samo molekulski oblik lijeka. Spektrofotometrijska analiza je potvrdila visoku rastvorljivost olopatadin-hidrohlorida na obje pH vrijednosti. Rezultati studije su pokazali da se rastvorljivost olopatadin-hidrohlorida nalazi u opsegu terapijskih koncentracija (0,1 % – 0,7 %).
Prednost hromatografske metode je u mogućnosti razdvajanja udjela jonizovanog i nejonizovanog oblika lijeka što je značajno za formulaciju različitih farmaceutskih oblika.

Ključne riječi: Olopatadin-hidrohlorid, Rastvorljivost, Analiza, HILIC, UV spektrofotometrija

DETERMINATION OF OLOPATADINE HYDROCHLORIDE SOLUBILITY BY HYDROPHILIC INTERACTION LIQUID CHROMATOGRAPHY AND UV SPECTROPHOTOMETRIC METHODS

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In the present study comparison of two methods for solubility investigation of olopatadine hydrochloride was performed. Olopatadine hydrochloride is an antihistaminic drug used in eye drops and nasal sprays, with selective H1-receptor antagonist activity. In preliminary study solubility of olopatadine hydrochloride was investigated regarding its potential use in various dosage forms. Three different batches of the substance were tested.
The test solutions were prepared in water (final pH value was 3.5) and in a phosphate buffer (pH 5.8). The first method was hydrophilic interaction liquid chromatography (HILIC). Separation was performed on the column Betasil Cyano (100 mm x 4.6 mm, 5 □m particle size) with mobile phase consisted of 85% acetonitrile and 15% aqueous phase which containing 5 mM ammonium acetate and pH adjusted to 4.5 with glacial acetic acid. Flow rate was 1 mL min-1 and column temperature was 30 °C. UV detection was carried out at 257 nm. In the second method olopatadine hydrochloride concentration was determined spectrophotometrically at 299 nm (Double beam Shimadzu UV-VIS spectrophotometar, model 1800). Calibration curves in both water and a phosphate buffer were constructed within concentration range 10-100 μg/ml ($r = 0.995$).
Chromatographic analysis showed that the drug dissolved completely (0.4 mg/mL) at both pH levels. In addition, it was confirmed that at lower pH value two forms of olopatadine hydrochloride were eluted (ionized and molecular form) while at higher pH value only one form was eluted. Spectrophotometric analysis confirmed high solubility of olopatadine hydrochloride at both pH levels. The results of the study revealed that a solubility of olopatadine hydrochloride in water, at different pH values was within its therapeutic concentration range (0.1% – 0.7%).
Advantage of chromatographic method is the ability of determination concentration part of ionized and molecular form of the drug, which is important for formulation of dosage form.

Key words: Olopatadine hydrochloride, Solubility, Analysis, HILIC, UV spectrophotometry

ZNAČAJ SERUMSKIH KONCENTRACIJA MAGNEZIJUMA KAO MARKERA METABOLIČKOG ISCRPLJIVANJE ĆELIJA SRČANOG MIŠIĆA KOD VATERPOLISTA NAKON IZLAGANJA NAPORNOM TRENINGU

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Magnezijum (Mg) je element sa značajnim ulogama u fundamentalnim procesima ćelijskog metabolizma. Značajan je kao regulator fizioloških procesa u stanjima ishemije kardiovaskularnog sistema. Enzim glikogen fosforilaza tip bb (GP-BB) je visoko senzitivan i specifičan marker rane ishemije ćelija srčanog mišića, što je potvrđeno brojnim studijama.
Cilj ovog istraživanja je bio da se ukaže na značaj određivanje i praćenja dinamike serumskih koncentracija Mg i GP-BB kod vaterpolista nakon napornog treninga i da li dobijene koncentracije međusobno koreliraju.
Studija je obuhvatila 20 elitnih vaterpolista koji su podijeljeni i dvije grupe: prva grupa (eksperimentalna grupa) koja je bila izložena treningu izdržljivosti i druga grupa (kontrolna grupa) koja je služila kao kontrola. Materijal za ispitivanje su bili uzorci krvi (5 ml) koji su uzorkovani u definisanim vremenskim intervalima: prije treninga, 1, 30 i 60 minuta nakon treninga (isto i za kontrolnu grupu), a iz seruma su određivane koncentracije Mg i GP-BB. Dobijeni rezultati su statističi obrađeni primjenom SPSS programa verzija 17.0.
Odmah nakon treninga, nakon prvog minuta, dolazi do značajnog povećanja serumskih koncentracija Mg i GP-BB-a u odnosu na njegove koncentracije prije treninga ($p<0.001$; $p<0.011$). Serumske koncentracije Mg i GP-BB nakon treninga su bile u značajnim pozitivnim korelacijama: nakon prvog i tridesetog ($p<0.05$; $p<0.01$)) i nakon tridesetog i šezdesetog minuta ($p<0.05$; $p<0.05$). Međutim, samo u prvom minutu nakon fizičkog napora serumske koncentracije GP-BB i Mg su bile u značajnim pozitivnim korelacijama ($p<0.05$).
Metaboličko iscrpljivanje ćelija srčanog mišića kod vaterpolista uzrokovano fizičkim naporom je reverzibilnog karaktera. Adekvatna, individualno dozirana suplementacija magnezijuma je neophodna u cilju očuvanja funkcionalne homeostaze ćelija kardiovaskularnog sistema kroz brzi oporavak metaboličkih procesa u ćelijama.

Ključne riječi: megnezijum, metaboličko iscrpljivanje ćelija, vaterpolisti

IMPACT OF SERUM MAGNESIUM CONCENTRATION AS MARKER OF METABOLIC DEPLETION MYOCARDIAL CELLS IN WATER POLO PLAYERS AFTER STRENUOUS EXERCISE

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Magnesium (Mg) is an element with significant roles in fundamental processes of cellular metabolism. It is important as a physiological regulator cardiovascular system especially during ischemia. Enzyme glycoge phosphorylase type bb (GP-BB) is high sensitive and specific as

marker of early myocardial ischemia, acoording to published studies.
The aim of study was to point out the importance of measuring and monitoring of Mg and GP-BB serum concentration in water polo players after strenuous exercise and whether obtained concentration correlated.
The study include 20 elite water polo players who were divided into two groups: the first group (experimental group) exposed to strenuous exercise and the other group served as control (control group). Testing materials were blood samples (5 ml) collected at defined time intervals: 1, 30 and 60 minutes after strenuous exercise (same for control group) and from serum were measured Mg and GP-BB concentration. Obtained results were analyzed using SPSS version 17.0.
Immediately after strenuous exercise, 1 minute later, there were significantly increased serum concentration of Mg and GP-BB compared to its concentration before exercise ($p<0.001$; $p<0.011$). Obtained serum concentration of Mg and GP-BB after strenuous exercise were in significantly positive correlation: after 1 and 30 minutes ($p<0.05$; $p<0.01$) and after 30 and 60 minutes ($p<0.05$; $p<0.05$). However, only 1 minute after strenuous exercise concentration of Mg and GP-BB were in significant positive correlation ($p<0.05$).
Metabolic depletion of myocardial cells caused by strenuous exercise in water polo players are reversible. Adequate, individually dosed Magnesium supplementation in order to maintain homeostasis of cardiovascular cells through rapid recovery of metabolic intracellular processes.

Key words: magnesium, metabolic depletion cells, water polo players

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TRETMAN URSODEOKSIHOLNOM KISELINOM SMANJUJE DOKSKORUBICINOM-INDUKOVAN OKSIDATIVNI STRES U JETRI

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Hepatotoksičnost predstavlja značajno neželjeno dejstvo doksorubicina koje ograničava njegovu upotrebu. Povećana produkcija reaktivnih kiseoničnih vrsta je jedan od najznačajnijih uzroka ovog neželjenog dejstva. Cilj ove studije je ispitivanje potencijalnog hepatoprotektivnog dejstva žučne kiseline - ursodeoksiholne kiseline (UDK) preko njenog uticaja na lipidnu peroksidaciju (LP) i ekpresiju glutation-zavisnih antioksidativnih enzima u jetri DOK-om tretiranih pacova.
24 pacova soja Wistar muškog pola su podeljena u 4 grupe. Životinje su tretirane konstituensima (fiziološkim rastvorom i.p. (K1) ili naizmenično fiziološkim rastvorom i.p. i propilen glikolom p.o. (K2)), DOK-om (3 mg/kg i.p. svakog drugog dana ukupno 3 doze) ili kombinovaniim tretmanom sa UDK (25 mg/kg p.o.) svakog drugog dana ukupno 3 doze, počevši jedan dan pre primene DOK-a. 28-og dana izvršena je eutanazija životinja i jetre su odmah uzete u cilju ispitivanja ekspresije izabranih parametrara oksidativnog stresa.
Intenzitet LP je bio povišen u jetrama životinja tretiranih DOK-om u poređenju sa obe kontrolne

grupe, dok je intenzitet LP u grupi DOK+UDK bio snižen. U poređenju sa kontrolnim grupama, tretman DOK-om je značajno povćao specifičnu aktivnost glutation peroksidaze (GPx) ($p<0.01$ vs.K1 and K2), dok je kombinacija tretmana sa UDK smanjila aktivnost GPx. Specifična aktivnost glutation reduktaze je bila najviša u grupi životinja tretiranih DOK-om, dok je u grupi DOX+UDCA bila niža, ali bez statističke značajnosti. Specifična aktivnost glutation-S-transferaze je bila značajno viša u grupi tretiranoj DOK-om u poređenju sa kontrolama ($p<0.05$ vs. K1 and K2), a kotretman sa UDCA je snizio aktivnost ovog enzima.
UDK se može smatrati potencijalnim hepatprotektivnim agensom sa sposobnošću smanjenja oksidativnog oštećenja jetre indukovanog visokim dozama DOK-a.

Ključne reči: hepatotoksičnost, žučne kiseline, glutation, reaktivne kiseonične vrste

URSODEOXYCHOLIC ACID TREATMENT REDUCES DOXORUBICIN-INDUCED OXIDATIVE STRESS IN THE LIVER

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Hepatotoxicity commonly overshadows the anti-neoplastic effectiveness of doxorubicin (DOX). Overproduction of free radicals represents a significant cause of this side effect. The aim of our study was to evaluate the potential hepatoprotective properties of ursodeoxycholic acid (UDCA) through its influence on lipid peroxidation (LPO) and expression of glutathione-dependent antioxidative enzymes in the livers of rats treated with DOX.
Twenty four male Wistar rats were divided in four groups. Animals were administered either with vehicle (saline i.p. (K1) or saline i.p. with propylene glycol p.o. (K2)), DOX (3 mg/kg i.p. every other day for total 3 doses) or combined UDCA 25 mg/kg p.o. every other day for total 3 doses, starting one day before administering DOX. On the day 28 animals were euthanized and livers were immediately harvested in order to determine the expression of selected parameters of oxidative stress.
In the livers of animals administered with DOX, LPO was increased compared to both control groups, whereas in DOX+UDCA group the intensity of LPO was decreased, closely to control values. Treatment with DOX significantly increased the specific activities of glutathione peroxidase (GPx) compared to control groups ($p<0.01$ vs.K1 and K2). Combined treatment with DOX+UDCA decreased GPx activity. Similarly, the activity of glutathione reductase was highest in group treated with DOX and lower in group treated with DOX+UDCA. Specific activity of glutathione-S-tranferase was significantly increased in DOX-treated group compared to controls ($p<0.05$ vs. K1 and K2), and decreased in DOX+UDCA group, however without statistical significance.
According to its ability to decrease the LPO and modulate the activity of glutathione-dependent antioxidative system, UDCA represents an agent with potentially hepatoprotective properties

against oxidative liver damage induced by high doses of DOX.

Key words: hepatotoxicity, bile acids, glutathione, reactive oxygen species

ŽUČNE KISELINE U TERAPIJI METABOLIČKIH POREMEĆAJA

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Osim dobro poznate uloge u digestiji i resorpciji lipofilnih nutrijenata, žučne kiseline (ŽK) imaju značajnu ulogu kao signalni molekuli u različitim metaboličkim procesima. Fluks ŽK oslobođenih u duodenum nakon obroka kao i fluks ŽK koji se vraća u jetru enterohepatičkom cirkulacijom aktivira nuklearni farnesoid X receptor (FXR) u cilju regulacije metabolizma ŽK i postprandijalnog metaboličkog odgovora. ŽK takođe aktiviraju ovaj receptor u ne-enterohepatičkim tkivima. Cilj ovog rada je ispitivanje uloge ŽK kao FXR agonista u regulaciji metabolizma.
Detaljna analiza originalnih i preglednih radova objavljenih u period 1997-2015 godine.
Aktivacijom brojnih signalnih puteva i regulacijom genske ekspresije u različitim tkivima ŽK regulišu metabolizam ugljenih hidrata, lipoproteina, prenos insulinskih signala i energetsku homeostazu. Aktivacijom FXR-a ŽK regulišu vrednosti glikemije, trigliceridemije, holesterolemije, gojaznost i parametre sistemske inflamacije. ŽK predstavljaju integralni deo kompleksne metaboličke mreže koju reguliše njihov nuklearni receptor FXR kao jedan od najznačajnijih regulatora homeostaze metabolizma. Specifično ciljanje ovog receptora predstavlja novi atraktivni terapijski pristup u lečenju metaboličkih poremećaja, komponenti metaboličkog sindroma. Jedini značajan neželjeni efekt aktivacije FXR-a je blago smanjenje koncentracije HDL holesterola.
Identifikacija novih genski ili tkivno specifičnih FXR liganada može da poboljša specifičnost i redukuje neželjene efekte ovakvog terapijskog pristupa lečenja metaboličkih poremećaja. Modifikacija bočnih lanaca ili steroidnog jezgra ŽK može rezultovati u razvoju novih selektivnijih i specifičnijih FXR agonista.

Ključne reči: farnesoid x receptor, homeostaza, ligand, metabolički sindrom

BILE ACIDS IN THE THERAPY OF METABOLIC DISEASES

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In addition to well-established role in the digestion and absorption of lipophilic xenobiotics, bile acids (BAs) have emerged as important signalling molecules in a wide range of metabolic processes. Both the flux of BAs released in duodenum upon meal ingestion and flux of BAs arrived into liver by entero-hepatic circulation activate the liver and intestinal receptors including nuclear farnesoid X receptor (FXR) in order to regulate the BA homeostasis and to orchestrate the post-prandial metabolic response. Furthermore, BAs activate the FXR in the tissues not typically involved in BA metabolism. The aim of our study was to evaluate the role of the FXR agonists in the regulation of metabolism.
We have analysed original and review articles, published from 1997 to 2015 in order to get the insight into the FXR role in metabolism regulation.
The activation of multiple BA signalling pathways leads to altered expression of genes involved in carbohydrate and lipoprotein metabolism, insulin signalling and energy homeostasis. Given that BAs are an integrated part of the complex metabolic network regulated by FXR, acting as a major underlying pathway, specific therapeutic targeting of this nuclear receptor represents an attractive therapeutic approach for a wide range of disorders including metabolic syndrome. The activation of FXR may have potentially undesirable effects such as a slight decrease in HDL cholesterol level.
The identification of tissue- or gene-selective FXR modulators may enhance specificity and reduce the side effects of such approach in the therapy of metabolic diseases. Chemical manipulations of the side chain and the steroid nucleus of BAs could lead to the discovery of novel semi-synthetic BA derivatives that are more specific and selective FXR activators.

Key words: farnesoid x receptor, homeostasis, ligand, metabolic syndrome

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PROMJENE U POTROŠNJI DIKLOFENAKA KAO REZULTAT KOMUNIKACIJE PREMA ZDRAVSTVENIM RADNICIMA

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U julu 2013. godine, nakon usvajanja preporuka od strane Komiteta za farmakovigilancu i procjenu rizika Evropske Agencije za ljekove, Agencija za ljekove i medicinska sredstva Crne Gore je poslala pismo zdravstvenim radnicima koji propisuju/izdaju i primjenjuju ljekove koji sadrže diklofenakom u cilju racionalizacije njihove primjene koja će doprinijeti većoj bezbjednosti pacijenata. Ograničenje primjene koje podrazumijeva ograničenje indikacija, dužine primjene,

uvođenje novih kontraindikacija i upozorenja, uz poštovanje režima izdavanja treba da dovede do smanjenja visoke potrošnje ovih ljekova u Crnoj Gori.
Urađena je retrospektivna analiza podataka iz izvještaja Agencije o prometu ljekova u Crnoj Gori u 2011., 2012. i 2013. godini. Analizirana je potrošnja diklofenaka prije i nakon komunikacije od strane Agencije putem pisma zdravstvenim radnicima. Kao statistička jedinica za uporedni prikaz potrošnje, u skladu sa preporukama Svjetske zdravstvene organizacije, korišćena je ATC/DDD metodologija, tj. broj definisanih dnevnih doza na 1000 stanovnika po danu.
Analiza izvještaja o potrošnji ljekova u 2011. i 2012. godini pokazuje da se diklofenak nalazi na trećem mjestu najkorišćenijih ljekova po vrijednosti DDD/1000/dan, koja iznosi 48,95 za 2011. godinu, odnosno 46,74 za 2012. godinu. Analiza izvještaja o potrošnji ljekova u 2013. godini pokazuje da je diklofenak i dalje treći na listi najkorišćenijih ljekova, ali je potrošnja smanjena i DDD/1000/dan iznosi 39,86. Ukupna potrošnja diklofenaka je smanjena za 18.57% u odnosu na 2011. godinu, odnosno 14,72% u odnosu na 2012. godinu.
Regulatorne mjere preduzete od strane Agencije, koje su u skladu sa važećim propisima i zasnovane na novim informacijama o bezbjednosti primjene diklofenaka, kao rezultat su imale smanjenje potrošnje. Kako je potrošnja i dalje visoka, Agencija će ponoviti pismo zdravstvenim radnicima, a sve u cilju potpune implementacije regulatornih odluka donijetih u EU.

Ključne riječi: diklofenak, potrošnja, Agencija

CHANGES IN DICLOFENAC CONSUMPTION AS A RESULT OF DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION

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Pharmacovigilance Risk Assessment Committee of the European Medicines Agency in July 2013 issued the recommendation on new measures to minimise cardiovascular risks after use of medicines containing diclofenac. Agency for Medicines and Medical Devices of Montenegro, consequently took regulatory measure and sent letter to healthcare professionals who prescribe, dispense or administer medicines containing diclofenac. Restriction of indications, introduction of new contraindications, with respect to prescription status of diclofenac, should reduce high consumption of these medicines in Montenegro.
This is a retrospective analysis of data from the Agency's reports on medicines consumption in Montenegro, in 2011, 2012 and 2013. Comparation was performed, taking into consideration consumption of diclofenac before and after communication with healthcare professionals initiated by the Agency. For comparative view of consumption international standard was used, in accordance with the recommendations of the World Health Organisation - ATC/DDD methodology, number of defined daily doses per 1000 inhabitants per day.
Analysis of the Agency's reports in 2011 and 2012 showed that diclofenac was the third most frequently used medicine with 48,95 and 46,74 DDD/1000inhabitants/day, respectively. The same analysis in 2013 showed the same position on the list of most frequently used medicines, but with 39,86 DDD/1000 inhabitants/day. The data indicated that the total consumption was reduced by 18.57% and 14,72% in comparison with consumption in 2011 and 2012, respectively. The regulatory measures, taken by the Agency, in line with national legislation and based on

new information about safe use of diclofenac, have resulted in decreased consumption. As the consumption is still high, Agency is going to repeat communication in order to fully implement regulatory decisions made in EU.

Key words: diclofenac, consumption, Agency

REGULATORNI OSVRT NA BIOLOŠKI SLIČNE LJEKOVE

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Biološki slični ljekovi postaju sve dostupniji. Štaviše, isticanjem patentne zaštite nekih uspješnih originalnih bioloških ljekova i zbog ekonomskih prednosti koje pruža liječenje ovom grupom ljekova, biološki slični ljekovi su u izuzetno dinamičnom usponu primjene u praksi. Biološki ljekovi su velike molekule složene strukture, proizvedene pomoću/iz živih organizama, slične prirodnim supstancama u ljudskom tijelu, imunogeni su i nestabilni, a karakteriše ih i veliki uticaj procesa proizvodnje na gotov lijek. Zbog svega ovoga, mogu postojati velike razlike u bezbjednosti i efikasnosti biološki sličnih ljekova. Prema Direktivi Evropske unije (2001/83 EC) kod biološki sličnih ljekova se primarno ne dokazuje bezbjednost i efikasnost, već se dokazuje sličnost, tj. komparabilnost bezbjednosti i efikasnosti sa referentnim lijekom, kao i komparabilnost kvaliteta. Zbog ranije pomenutih razlika potrebno je priložiti dodatne dokaze, odnosno obezbijediti rezultate odgovarajućih pretkliničkih i kliničkih ispitivanja. Veliki izazov predstavlja određivanje regulatornih okvira koji će omogućiti dobijanje dozvole za stavljanje lijeka u promet. Stoga, Evropska agencija za ljekove je preuzela vođstvo u izdavanju dozvola, kao i donošenju brojnih smjernica za evaluaciju dokumentacije, od kojih su brojne još uvijek u razmatranju. Smjernice definišu pretklinička i klinička ispitivanja koja je neophodno sprovesti, uz prilagođeni plan farmakovigilance, prije dobijanja dozvole za lijek. Ove smjernice pružaju dragocjeni regulatorni okvir koji osigurava efikasnost i bezbjednost primjene lijeka.
Postoji mnogo neriješenih pitanja zdravstvenih radnika, pacijenata i odgovornih u zdravstvenim fondovima i agencijama za ljekove koja se tiču kriterijuma, dizajna i analize ocjene biološke sličnosti i zamjenljivosti bioloških ljekova, koji mogu u skoroj budućnosti bitno promijeniti dinamiku farmaceutskog tržišta.

Ključne riječi: biološki slični ljekovi, regulativa, smjernice

BIOSIMILARS: REGULATORY OVERVIEW

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Biosimilars are becoming more and more available. Moreover, with the patent expiration of some successful original biopharmaceuticals and the economic benefits of the therapy with this group of medicines, biosimilars have been emerging in practice extremely dynamically. Biopharmaceuticals are large molecules with complex structure, similar to natural substances in the human body; they are immunogenic, unstable and highly influenced by the manufacturing process of the finished product. Because of this, there can be significant differences in both safety and efficacy of biosimilars. According to the EU Directive (2001/83 EC), when it comes to biosimilars, what needs to be proven is not primarily the safety and efficacy, but the similarity, i.e. comparability of safety and efficacy with the reference medicinal product, as well as comparability of their quality. Due to the aforementioned differences, additional evidence, i.e. results of non-clinical and clinical trials needs to be provided. The challenge is the determination of regulatory framework which will allow obtaining a marketing authorization. Therefore, the European Medicines Agency has taken the lead in issuing marketing authorizations, as well as numerous guidelines for evaluation of documentation, many of which are still under consideration. The guidelines define non-clinical and clinical trials, along with the adjusted pharmacovigilance plan, which need to be conducted before obtaining a marketing authorization. These guidelines provide a valuable regulatory framework that ensures the efficacy and safety of the medicine. There are many unresolved issues of health care professionals, patients and those responsible in health care funds and Medicines Agencies concerning the criteria, design and analysis of evaluation of biological similarity and interchangeability of biopharmaceuticals, which might change significantly the dynamics of the pharmaceutical market in the near future.

Keywords: biosimilars, regulation, guidelines

ODREĐIVANJE P-FENILENDIAMINA U PRIRODNIM BOJAMA ZA KOSU

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Preparati za bojenje kose se upotrebljavaju u različitim oblicima već jako dugo. Sve je više prisutan trend bojenja kose i nanošenja privremenih tetovaža koje sadrže henu (Lawsonia inermis L.), prirodnu boju za kosu i tijelo. Međutim primjetan je porast upotrebe hene i sintetskih molekula za bojenje kose poput p-fenilendiamina (PPD) ili nekih drugih aromatskih amina. Preparati koji se koriste za bojenje kose sadrže PPD u maksimalnoj koncentraciji od 4%, a pri miješanju sa hidrogen peroksidom prije upotrebe do 2%. P-fenilendiamin je potentan

sentisizer, stoga je neophodno upoznati konzumenta sa rizikom od razvoja alergijske reakcije. On ispoljava lokalno i sistemsko djelovanje nakon topikalne ili oralne primjene. Značajne kliničke manifestacije trovanja su angioedem koji dovodi do disfazija i respiratornog kolapsa, rabdomioliza, intravaskularna hemoliza, akutno zatajenje bubrega i hepatička nekroza. Također može doći do miokarditisa i fatalne aritmije.
Osnovni cilj ovo rada bio je da se utvrdi da li proizvodi hene komercijalno dostupni na sarajevskom tržištu sadrže p-fenilendiamin. U te svrhe sadržaj PPD je određivan spektrofotometrijski primjenom tri različita reagensa za kuplovanje. Kao referentna metoda korištena je tečna hromatografija visoke moći razdvajanja prema postupku prethodno opisanom u literaturi. Hromatografijom na tankom sloju (TLC) ispitivano je prisustvo drugih amina i srodnih suspstanci u ispitivanim uzorcima, te je u svrhu njihove identifikacije provedena analiza primjenom IR spektroskopije.
Rezultati koji su dobiveni referentnom metodom su odudarali od onih koji su dobiveni primjenom spektrofotometrije, što je objašnjeno prisustvom drugih amina u ispitivanim uzorcima, a koji su mogli da se diazotiraju i daju obojene produkte nakon kuplovanja sa korištenim regensima. Naknadnim ispitivanjem TLC metodom je utvrđeno da uzorci osim PPD sadrže i druge aromatske amine od kojih je 8-amino-2-naftol identificiran u četiri od pet ispitivanih uzoraka.

Ključne riječi: p-fenilendiamin, boje za kosu, hena

DETERMINATION OF P-PHENYLENEDIAMINE IN NATURAL HAIR DYES

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Different products for hair colouring has been used for a long time. There is an increasing trend of colouring hair and applying temporary tattoos containing henna (Lawsonia inermis L.), natural colour for hair and body. However there is a noticeable increase in the use of henna together with synthetic molecules for hair colouring such as p-phenylenediamine (PPD) or other aromatic amines. Products used for dyeing hair can containe PPD in the maximum concentration of 4%, and the one that should be mixed with hydrogen peroxide prior to use up to 2%. P-phenylenediamine is a potent sentisizer, therefore it is necessary to inform consumers with the risk of developing allergic reactions. It exerts a local and systemic effects after topical or oral administration. Significant clinical manifestations of poisoning are angioedema that leads to dysphasia and respiratory collapse, rhabdomyolysis, intravascular hemolysis, acute renal failure and hepatic necrosis. Myocarditis and fatal arrhythmias can occure.
The main objective of this study was to determine whether products of henna commercially available at the Sarajevo market containe p-phenylenediamine. For these purposes, the content of PPD was determined spectrophotometrically using three different coupling reagent. As a reference method HPLC was used according to the procedure previously described in the literature. Thin layer chromatography (TLC) was used for detection of other amines and related substances in the analyzed samples. IR spectroscopy was used to identify these compounds.
Results obtained by the reference method differ from those obtained by spectrophotometric

methods, which is explained by the presence of other amines in the samples that could be diazotized and give coloured products after coupling with reagents used. Subsequent examination of samples with the TLC method showed presence of other aromatic amines, except of PPD, from which the 8-amino-2-naphthol was identified in four of the five analyzed samples.

Keywords: p-phenylenediamine, hair dyes, henna

ANALIZA UPOTREBE DIJETETSKIH SUPLEMENATA U FITNES CENTRIMA U PODGORICI

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Analiza upotrebe dijetetskih suplemenata (DS) predstavlja važan dio današnjice, jer može ukazati na potrebu i puteve racionalizacije upotrebe takvih proizvoda. Cilj ove studije bio je da se utvrdi učestalost upotrebe DS od strane samih sportista kao i uloge zdravstvenih radnika u tom procesu.
Deskriptivnim epidemiološkim ispitivanjem obuhvaćeno je ukupno 100 sportista (profesionalaca, amatera i rekreativaca) koji su dobrovoljno pristupili popunjavanju anonimne ankete. Istraživanje je sprovedeno u fitnes centrima u Podgorici. U cilju prikupljanja podataka korišćen je standardizovani upitnik.
Istraživanjem je obuhvaćeno 100 ispitanika (69 muškog i 31 ženskog pola) prosječne starosti 28 godina. Rezultati anketiranja pokazali su da je veći procenat onih ispitanika koji koriste DS u kontinuitetu 43%, povremeno ih upotrebljava 38%, a 19% uopšte ne koristi DS. Od ukupnog broja anketiranih 29% ispitanika se izjasnilo da trenutno koristi 2-3, a čak 8% se izjasnilo da koristi više od 5 različitih preparata istovremeno. Tri najčešće korišćena suplementa su vitamini 18.7%, proteinski suplementi 17.26% i aminokiseline 11.87%. Najveći broj ispitanika se izjasnio da DS kupuje u apoteci 25%, u fitnes centru/teretani 21.51% ili kod lokalnih distributera 18.02%. Anketiranjem su dobijeni podaci da ispitanici uglavnom dobijaju preporuke o upotrebi DS od fitnes instruktora/trenera ili prijatelja, a najmanje od strane ljekara, farmaceuta i nutricioniste. Veća polovina anketiranih se pridržava uputstva za upotrebu i isto toliko navodi da je prepoznalo korisne efekte tokom upotrebe DS. Oko 10% anketiranih je imalo neki neželjeni efekat koji vezuju sa upotrebom DS.
Studija pokazuje da veliki broj sportista koristi DS neracionalno, bez jasnih indikacija i preporuka od strane zdravstvenih radnika. Neophodno je uložiti dodatne edukativne napore ne samo prema zdravstvenim radnicima, već i prema svima onima koji rade u fitnes centrima radi boljeg informisanja korisnika o upotrebi DS.

Ključne riječi: dijetetski suplementi, zdravstveni radnici, sportisti.

ANALYSIS OF USING DIETARY SUPPLEMENTS IN THE FITNESS CENTERS IN PODGORICA

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Analysis of using dietary supplements (DS) is an important today as it may indicate the need and the ways of rationalizing the use of such products. The aim of this study was to determine the frequency of use of the DS by the very sportsmen as well as the role of health workers in the process.
A descriptive epidemiological investigation included a total of 100 sportsmen (professionals and amateurs) who voluntarily completed the anonymous survey. The research was conducted in fitness centers in Podgorica. In order to collect data we used a standardized questionnaire.
The study involved 100 subjects (69 males and 31 females) with an average age of 28 years. Survey results have shown that there are a major percentage (43%) of those respondents who use DS continuously, 38% use it occasionally, and 19% never use the DS. Among all respondents 29% of respondents said that they currently use 2-3, and even 8% said that they used more than 5 different products at the same time. The three most commonly used supplements are vitamins 18.7%, protein supplements 17.26% and amino acids 11.87%. Most of the respondents stated that they buy DS at the pharmacy 25%, in the fitness center / gym 21.51% or at local resellers 18.02%. The polling data have shown that respondents generally receive recommendations on the use of the DS from fitness instructors / trainers or friends, and at least from doctors, pharmacists and nutritionists. More than half of those surveyed follow the instructions for use and the same number of respondents stated that they recognized usefull effects during use of the DS. About 10% of respondents had some side effect associated with the use of the DS.
The study shows that a large number of sportsmen use the DS irrationally, without clear indications and recommendations by health professionals. It is necessary to make additional educational efforts not only regarding healthcare professionals, but also regarding those who work in fitness centers to better inform users about the use of the DS.

Keywords: dietary supplements, health workers, sportsmen.

UPOREDNA HEMIJSKA ANALIZA ETARSKIH ULJA IZOLOVANIH IZ CVIJETA LAVANDE (LAVANDULAE FLOS, *LAVANDULA ANGUSTIFOLIA* MILL., LAMIACEAE) RAZLIČITOG GEOGRAFSKOG PORIJEKLA

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Lavandula angustifolia Mill. (lavanda) je višegodišnja zeljasta biljka koja je bila i ostala jedna od omiljenijih aromatičnih i ljekovitih biljaka. Cilj ovog istraživanja je da se utvrdi i analizira hemijski sastav etarskih ulja izolovanih iz suvog cvijeta lavande sa područja Budve i Rovinja i da se dobijeni rezultati porede sa komercijalno dostupnim uzorkom u Crnoj Gori.
Etarsko ulje lavande je dobijeno metodom hidrodestilacije u aparaturi po Clevenger-u. Ispitivanje kvalitativnog i kvantitativnog sastava etarskog ulja izvršeno je gasnohromatografskom tehnikom (GC/MS i GC/FID).
Na osnovu gasnohromatografske analize u analiziranim uzorcima identifikovano je oko 100 komponenti, koje čine 96.95-99.74% prisutnih sastojaka u etarskim uljima. Analizom je utvrđeno da oksidovani monoterpeni predstavljaju dominantnu grupu jedinjenja i da postoji značajna razlika u uzorcima sa područja Budve (71.74%), Rovinja (91.79%) i komercijalnog uzorka (87.63%). Uzorak lavande sa područja Budve od oksidovanih monoterpena najviše sadrži: linalola (27.32%) i borneola (20.24%); uzorak iz Rovinja: linalola (47.67%) i kamfora (11.82%) i komercijalni uzorak: kamfora (21.23%) i linalola (19.92%). Drugu grupu jedinjenja čine monoterpenski ugljovodonici koji su zastupljeni u znatno manjem procentu u komercijalnom uzorku (2.64%) i uzorku iz Rovinja (3.57%), dok se visok sadržaj javlja u uzorku sa podneblja Budve (23.74%) u kojem dominira β-felandren (19.1%). Treću grupu jedinjenja po svojoj zastupljenosti, čine oksidovani seskviterpeni nešto manje zastupljeni u uzorku iz Rovinja (1.14%) i Budve (1.88%), a skoro dva puta više su prisutni u komercijalnom uzorku (4.37%). Kao dominantan sastojak u sva tri uzorka se javlja kariofilen oksid. Ugljovodonični seskviterpeni su znatno manje zastupljeni u ispitivanim uzorcima.
Varijabilnost u kvalitativnom i kvantitativnom sastavu najvjerovatnije zavisi od genotipa biljke i uticaja različitih ekoloških faktora. Sastav etarskog ulja lavande je značajan u kontekstu njegove primjene u terapijske svrhe pa su dobijeni rezultati značajni u cilju evaluacije kvaliteta biljne sirovine.

Ključne riječi: lavanda, etarsko ulje, hemijski sastav.

COMPARATIVE CHEMICAL ANALYSIS OF ESSENTIAL OILS FROM LAVENDER (LAVANDULAE FLOS, *LAVANDULA ANGUSTIFOLIA* MILL., LAMIACEAE) OF DIFFERENT GEOGRAPHIC ORIGINS

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Lavandula angustifolia Mill. (Lavender) is a perennial herbaceous plant being one of the favorite aromatic and medicinal plants. The aim of this study was to determine and analyze the chemical composition of essential oils of dry lavender flowers from the area of Budva and Rovinj and to compare to the results obtained in commercially available sample in Montenegro.
The essential oil of lavender was obtained by applying the method of hydro-distillation in the Clevenger type apparatus. Testing of qualitative and quantitative composition of the essential oil was carried out by using gas chromatography technique (GC/MS and GC/FID).
Based on gas chromatography analysis approximately 100 components were identified in the

analyzed samples, which makes 96.95% to 99.74% of the components present in essential oils. The analysis has shown that oxygenated monoterpenes were the dominant group of compounds. The significant difference between the samples from the area of Budva (71.74%) and Rovinj (91.79%) and the commercial available sample (87.63%) were noted. The most abundant oxygenated monoterpenes in the lavender oil sample from Budva region were linalool and borneol (27.32% and 20.24% respectively); sample from Rovinj contained linalool and camphor (47.67% and 11.82% respectively) and commercial sample camphor and linalool (21.23% and 19.92% respectively). Monoterpene hydrocarbons were present in a significantly lower percentage in the commercial sample (2.64%) and in a sample from Rovinj (3.57%), while the high content occurred in the sample from the climate of Montenegrin seaside (Budva) (23.74%) with the dominant constituent β-phellandrene (19.1%). The oxygenated sesquiterpenes were slightly less present in the sample from Rovinj (1.14%) and Budva (1.88%), and almost twice as much present in the commercial sample (4.37%). Caryophyllene oxide appears as the dominant ingredient in all three samples in the sample from Rovinj (0.36%); sample from Budva (0.43%) and commercial sample (2.78%). Hydrocarbon sesquiterpenes were insignificantly present in the analyzed samples.
Variability in the qualitative and quantitative composition most probably depends on the genotype of the plant and the influence of different environmental factors. The application of lavender essential oil for therapeutic purposes depends on its qualitative properties. The obtained results might be significant in order to evaluate the quality of the plant raw material.

Keywords: lavender, essential oil, chemical composition.

KREIRANJE EFIKASNIH KANALA KOMUNIKACIJE SA CILJEM UNAPREĐENJA INFORMISANOSTI I KOMPETENTNOSTI FARMACEUTA

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Farmaceutska komora Srbije (FKS) je profesionalno i regulatorno telo apotekara u Republici Srbiji. Naša misija je unapređivanje apotekarskog sektora Srbije i zaštita prava i interesa pacijenta uspostavljanjem standarda struke i etičkih načela. Da bi se to ostvarilo, potrebna je dobra informisanost i kompetetnost članova Komore.
Istraživanje je sprovedeno kako bi se utvrdilo koji su najprikladniji alati za informisanje farmaceuta o aktuelnim pitanjima, kao i utvrđivanja upoznatosti sa ponuđenim sadržajima važnim za odgovoran, kvalitetan i kompetentan rad.
Podaci su prikupljeni u periodu VII- X 2014. putem on line ankete sa sajta Komore. Anketu je popunilo ukupno 719 farmaceuta. Anketa je anonimna i dobrovoljna, i osim pitanja o preferiranim kanalima informisanja i njihovim sadržajima, sadrži i podatke o starosti ispitanika. Podaci su izraženi u procentima.
Anketu je popunilo oko 13% članova Komore. Većina ispitanika (59%) je starosti 25-40 godina, dok je najmanje iznad 55 (6%). Preferirani način informisanja je elektronski, sajt FKS i mejl (55-56%), potom časopis FKS (32%), a najmanje telefon (8%). Ispitanici su ukazali na nedostajuće informacije na sajtu, gde dominiraju opšta pitanja (44%) i pravna pitanja (38%). Samo 5% anketiranih smatra da je u potpunosti upoznata sa zakonskom regulativom, dok se 39% smatra veoma površno upoznatim. 55% smatra da časopis FKS omogućava da prate šta se dešava u

struci. Standarde Dobre apotekarske prakse, Etički kodeks i Nacionalni okvir kompetencija je pročitalo više od polovine anketiranih (51-79%).
Kvalitet farmaceutske zdravstvene zaštite zavisi od informisanosti i kompetentnosti farmaceuta. Da bi došlo do njihovog unapređenja, potrebno je da FKS modelira informacione kanale i informativne sadržaje prema preferencijama farmaceuta. Takođe, ovo istraživanje ukazuje i na potrebu afirmacije i promocije postojećih kanala informisanja i podizanja svesti farmaceuta o važnosti informisanosti i razvoja kompetentnosti.

Ključne reči: farmaceutska komora, farmaceuti, kanali informisanja, informisanost, kompetentnost.

ESTABLISHING EFFICIENT COMMUNICATION CHANNELS WITH THE AIM OF IMPROVING AWARENESS AND COMPETENCE OF PHARMACISTS

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The Pharmaceutical chamber of Serbia (FKS) is a professional and regulatory body for pharmacists in the Republic of Serbia. Our mission is to advance a pharmaceutical sector in Serbia and to protect the rights and interests of patients by establishing standards for the profession of pharmacy and ethic principles. To do so, requires a good level of information and competency of members of the Chamber.
The survey was conducted in order to determine the most appropriate tools for informing pharmacists about current issues, and to determine their familiarity with the offered contents which are relevant for responsible, high-quality and competent work.
Data were collected in the period July-October 2014., through an online survey which was set up on the web site of the Chamber. Survey was completed by a total of 719 pharmacists. The survey was anonymous and voluntary, and apart from the question of preferred channels of information and their contents, includes information about the age of the respondents. Data are expressed as a percentage.
Survey was completed by 13% of Chamber members. Most respondents (59%) were aged 25-40 years, while at least above 55 years (6%). The preferred way of acquiring information is trough digital media website of FKS and email (55-56%), followed by journal of FKS (32%) and at least by phone (8%). Respondents pointed out the missing information on the website, which is dominated by general issues (44%) and legal issues (38%). Only 5% of respondents consider that they are fully familiar with the applicable regulations, while 39% is considered only superficially familiar. 55% believe that the journal of FKS allows them to observe the trends in the profession. Standards of Good Pharmacy Practice, Code of Ethics and National competency framework has read more than half of the respondents (51-79%).

Keywords: pharmaceutical chamber, pharmacists, information channels, information, competence.

ISPLATIVOST UVOĐENJA REFIL PAKOVANJA I IZDAVANJE CILJANE INDIVIDUALNE TERAPIJE IZ APOTEKE - OD KOMPLIJANSE DO EKONOMIJE

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Adoc d.o.o, Apoteka ZZZZR Železnice Srbije

Uvidom u način pakovanja originalnih lekova koji se izdaju na obrazac LR1 (lekarski recept) u Republici Srbiji, pretpostavile smo da postoji značajan prostor za uštedu kao i za pravilnije praćenje terapije kod hroničnih pacijenata.
U cilju dokazivanja pretpostavke, izdvojile smo nekoliko originalnih pakovanja lekova koji se učestalo koriste u hroničnoj terapji. Izdavanje ovih lekova pratile smo kod pacijenata koji svoju terapiju podižu u apoteci ZZZZR Železnice Srbije u Beogradu u periodu od godinu dana.
Studijom smo pratile lekove koje se koriste u terapiji poremećaja srčanog ritma (metoprolol), povišenog holesterola (simvastatin), povišenog krvnog pritiska (ramipril), benigne hiperplazije prostate (finasterid) i u antibiotskoj terapiji (klaritromicin).
Na osnovu obrade podataka iz studije utvrdile smo da je, sa stanovišta racionalne potrošnje, izdavanje četvoronedeljne terapije najcelishodnije pri čemu se terapija u apoteci vrši iz refil pakovanja.
Ovim radom su definisani i potrebni alati, tehnički uslovi kao i potrebne promene u regulativi koje bi na jednostavan, praktičan i kroz GMP definisan način rada omogućili značajnu uštedu u izdavanju terapije kod hroničnih pacijenata i u značajnoj meri poboljšali komplijansu.

Ključne reči: pakovanje, terapija, refil, lek

COST EFFECTIVENESS OF A REFIL PACKAGE OF PRESCRIBING DRUGS FOR TARGETED THERAPY IN PHARMACY – FROM COMPLIANCE TO ECONOMICS

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With original packages of prescribing drugs that are used in Republic of Serbia, we are assumed that there is a significant way to make savings and to improve therapy monitoring and compliance, particularly with chronic disease patients.
To this end, we selected some of original drugs packages that are commonly used in chronical disease therapy. We monitored drug prescriptions with patients of Pharmacy ZZZZR Serbian Railways, Belgrade for a one year.
Throughout this study we monitored drugs in heart rhytm disorders (metoprolol), hyperlipidemia (simvastatin), hypertension (ramipril), benign prostatic hyperplasia (finasteride) and antibiotic therapy (clarithromycin).
According to the results of the processed data we found, from the standpoint of rational use, that four-week therapy should be the most expedient and drugs should be issued from the refill packages.
Within this paper we set up tools, technical conditions, necessary regulatory adjustments that would make possible a significant savings for prescription drugs in chronic disease patients as well as a improved compliance.

Key words: packages , therapy, refill, drug

VAŽNA ULOGA FARMACEUTA U PRIJAVLJIVANJU NEŽELJENIH DEJSTAVA LJEKOVA

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Uspostavljanje efikasnog sistema farmakovigilance podrazumijeva angažovanje farmaceuta u procesu prijavljivanja neželjenih dejstava ljekova. Prijavljivanje neželjenih dejstava ima važnu ulogu u dobijanju novih informacija o ljekovima koji su već u prometu. Farmaceuti ostvaruju neposredan kontakt sa pacijentom i u prilici su da prate bezbjednost terapije putem prijavljivanja neželjenih dejstava. Ključna uloga farmaceuta se ogleda u praćenju bezbjednosti ljekova koji se izdaju bez ljekarskog recepta, jer je farmaceut za ovu kategoriju ljekova najznačajniji izvor informacija za efikasnu i bezbjednu primjenu.
Urađena je retrospektivna analiza podataka iz izvještaja Agencije za ljekove i medicinska sredstva Crne Gore (CALIMS) o rezultatima prijavljivanja neželjenih dejstava ljekova od 2010. do 2014. godine. Analizirano je učešće farmaceuta u prijavljivanju neželjenih dejstava.
U toku 2010. godine farmaceuti nijesu poslali CALIMS nijednu prijavu neželjenog dejstva. U 2011. godini učešće farmaceuta u prijavljivanju je bilo 1%, 2012. 1.74%, 2013. 1.03%, dok je u 2014. taj procenat iznosio 11.32%. Porast broja prijava od strane farmaceuta u 2014. godini se može objasniti sve većim angažovanjem mladih farmaceuta, kojima je u toku studiranja ukazano na značaj farmakovigilance i prijavljivanja neželjenih dejstava. Zanemarljivo je malo učešće u prijavljivanju neželjenih dejstava farmaceuta koji rade na višim nivoima zdravstvene zaštite, a u pitanju su zdravstveni radnici koji se susreću sa ozbiljnim neželjenim dejstvima, koja se često javljaju kod hospitalizovanih pacijenata, koji primaju više ljekova i imaju kompleksnu patologiju.
Broj primljenih prijava od strane farmaceuta je i dalje nizak, posebno kada se uzme u obzir činjenica da su farmaceuti vrlo značajan izvor informacija o bezbjednosti primjene ljekova. Identifikujući problem nedovoljnog učešća farmaceuta u prijavljivanju neželjenih dejstava, CALIMS će inicirati održavanje radionica i kontinuiranu edukaciju o osnovnim principima i značaju farmakovigilance, a sve u cilju povećanja broja prijava koje bi mogle biti signal za rano otkrivanja potencijalnih rizika.

Ključne riječi: farmakovigilanca, neželjena dejstva, farmaceuti

THE IMPORTANT ROLE OF PHARMACIST IN REPORTING OF ADVERSE DRUG REACTIONS

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Establishing an effective pharmacovigilance system involves engagement of pharmacists in reporting of adverse drug reactions (ADR). Reporting of ADR is important for obtaining new information about medicines that are already on the market. Pharmacists are directly in contact with patients and have opportunity to monitor the safety of therapy by reporting ADR. Pharmacists play key role in monitoring the safety of over the counter medicines, because they

are the most important sources of information for this category of medicines.
This is a retrospective analysis of data from the Agency's reports on the results of reporting of ADR from 2010. to 2014. The partipication of the pharmacist in reporting of ADR was analyzed. Pharmacists did not send Agency any report during 2010. In 2011. the partipication of pharmacists in reporting of ADR was 1%, in 2012-1.74%, in 2013-1.03%, and in 2014-11.32%. An increase in the number of reports received from pharmacists could be explained by higher participation of young pharmacists, because the importance of pharmacovigilance and reporting was highlighted during their studies. The participation of pharmacists that work on higher level of healthcare is negligible, despite the fact that they are faced with serious ADR, which often occur in hospitalized patients receiving a lot of medicines and with complex pathology.
The number of reports received from pharmacists is still low, especially when the fact that pharmacists are important sources of information about safety use of medicines is taken into account. Identifying the problem of insufficient involvement of pharmacists in reporting of ADR, Agency will initiate holding of workshops and continuing education about basic principles and the importance of pharmacovigilance, with the aim of increasing the number of reports that might be the signal for early detection of potential risks.

Key words: pharmacovigilance, adverse drug reaction (ADR), pharmacists

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ULOGA OBRAZOVANJA U RAZVOJU ZDRAVSTVENE PISMENOSTI MLADIH O URGENTNOJ KONTRACEPCIJI

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Pod reproduktivnim zdravljem SZO podrazumeva stanje fizičkog, mentalnog i socijalnog blagostanja svih uzrasnih grupa u odnosu na reproduktivni sistem. Pod tim se podrazumeva zadovoljavajući i siguran seksualni život, sposobnost za reprodukciju i slobodno odlučivanje o reprodukciji. U ostvarivanju ovih prava , velika je uloga obrazovanja kod mladih u sticanju znanja i neophodnih informacija o očuvanju reproduktivnog zdravlja.
Cilj rada je ukazati na značaj obrazovanja mladih u okviru nastavnih predmeta o očuvanju reproduktivnog zdravlja. Mladi kroz nastavu stiču stavove i znanja o kontracepciji, kao i svest o aktivnom učešću u odlukama vezanim za reproduktivno zdravlje. Na osnovu ovih metoda analizirane su mogućnosti za dalji razvoj i unapredjenje zdravstvene pismenosti mladih o reproduktivnom zdravlju.
U toku školske 2013/2014 godine anketiranio je 240 učenika, Farmaceutsko-fizioterapeutske škole. Ispitivani su učenici raličitih smerova koji su prošli gradivo predmeta higijena, kao i oni kojima predstoji da taj predmet uče.
Statističkom analiziom resultata došlo se do podataka da učenici 1 .rareda u okviru predmeta higijena dobijaju osnovna znanja o reproduktivnom sistemu i oblicima kontracepcije, dok su učenici 4.razreda koji su slušali predmet farmakologija bolji u odgovorima o delovanju i dejstvu urgentne kontacepcije na organizam .
U očuvanju reproduktivnog zdravlja mladih neophodno je značajno unaprediti i proširiti nastavni program predmeta higijena, gde bi učenici pored osnovnih znanja o oblicima kontracepcije stekli širu sliku o načinu primene, efikasnosti i neželjenim efektima urgentne kontracepcije. U

školama koje nemaju predmete koji se bave reproduktivnim zdravljem neophodno je uvesti seksualno obrazovanje.

Ključne reči: urgentna kontracepcija, reproduktivno zdravlje, mladi

THE ROLE OF EDUCATION IN DEVELOPING HEALTH LITERACY OF YOUNG PEOPLE ABOUT EMERGENCY CONTRACEPTION

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Under the reproductive health WHO implies a state of physical, mental and social well-being of all age groups in relation to reproductive system. By this is meant a satisfying and safe sex life, ability to reproduct and opportunity to decide about reproduction. In realizing these rights, there is a big role of education of young people in gaining the knowledge and necessary informations about the maintenance of reproductive health.
The aim is to highlight the importance of education for young people within the subjects about preservating reproductive health. Young people through teaching gain attitudes and knowledge about contraception, as well as awareness about active participation in decisions related to their reproductive health. Based on this methods the possibilities are analyzed for further development and improvement of health literacy of young people about reproductive health.
During school year 2013/2014, 120 students of Pharmacy and Physioteraphy School were questioned. Students of different majors who have passed the subject of Hygiene were tested, as well as those who have remained to study that subject.
By statistical analysis of results was produced the data that students of the 1st grade within the subject Hygiene receive basic knowledge of the reproductive system and forms of contraception, while the 4th grade students who listened to the subject of Pharmacology better in answers about the activity and effects of emergency contraception on the organism.
In preservation of the reproductive health of young people is necessary to significantly improve and expand the curriculum subjects of hygiene, where the students in addition to basic knowledge about forms of contraception have gained a wider picture of usage, efficacy and side effects of emergency contraception. In schools that do not have subjects that deal with reproductive health it is necessary to introduce sexual education.

PRIMENA RAZLIČITIH IN VITRO TEHNIKA ZA PREDVIĐANJE PERMEABILNOSTI KROZ KRVNO-MOŽDANU BARIJERU LIGANADA IMIDAZOLINSKIH RECEPTORA

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Ligandi imidazolinskih receptora predstavljaju brojnu familiju biološki aktivnih jedinjenja koja imaju široku terapijsku primenu. Ovi ligandi mogu delovati na tri tipa imidazolinskih receptora (I1-IR, I2-IR and I3-IR) I na alfa2-adreno receptore. Imidazolinski receptori suodgovorni za različite biološke aktivnosti imidazolina. Stoga neki IRs ligandi su danas značajni za ispitivanje kao novi centralno delujući antihipertenzivi i potencijalni kandidati za lečenje različitih neuroloških oboljenja. Cilj ovog rada je bio da se proceni permeabilnost ovih liganada kroz Krvno-Moždanu Barijeru (KMB).
Test permeabilnosti na veštačkim paralelnim membranama (eng. Parallel Artificial Membrane Permeability Assay, PAMPA), bioparticiona micelarna hromatografija (eng. Biopartitioning Micellar Chromatography, BMC) i reverzno-fazna tečna hromatografija pod visokim pritiskom (eng. Reversed-Phase High-Performance Liquid Chromatography, RP-HPLC) su in vitro tehnike korišćenje za predviđnje permeabilnosti kroz KMB imidazolinsih liganada. Vrednosti dobijene korišćenjem PAMPA i BMC su ispitivane metodologijom kvantitativnog odnosa struktura i osobina jedinjenja (eng. Quantitative Structure-Property Relationship, QSPR).
Retencioni faktori dobijeni korišćenjem BMC I RP-HPLC su korelisani sa koeficijentima permeabilnosti dobijeni korišćenjem PAMPA. Pored toga, PLS (eng. Partial Least Square), MLR (eng. Multiple Linear Regression) i ANN (eng. Artificial Neural Networks) modeli su razvijeni korišćenjem retencionih podataka iz BMC sistema/efektivnih permeabilnosti iz PAMPA I molekulskih parametara izračunatih za optimizovane strukture. Dominantni molekulski/katjonski oblici jedinjenja na pH=7.4 su dobijeni korišćenjem MarvinSketch. Geometrijska optimizacija liganada je izvršena korišćenjem Chem3DBio Ultra. Molekulski deskriptori za optimizovana jedinjenja su izračunati korišćenjem Chem3DBio Ultra, Dragon and ADMET predictor programa. U ovoj QSPR studiji retencioni faktori/efektivne permeabilnosti jedinjenja su korišćene kao zavisne, dok izračunati deskriptori su korišćeni kao nezavisne varijable. SIMCA je korišćena za PLS analizu dok je postupno MLR i ANN modeliranje izvršeno korišćenjem STASTICA Neural Networks programa. Prognostički potencijal formiranih QSPR modela je potvrđen ukrštenom i eksternom validacijom.
Formirani QSPR modeli mogu biti korišćeni kao brzi skrining metod za procenu krvno-moždane permeabilnosti novih liganada imidazolinskih receptora, koji predstavljaju potencijalne kandidate u lečenju hipertenizije i neuroloških oboljenja.

Ključne reči: Imidazolini, PAMPA, BMC, RP-HPLC, QSPR

APPLICATION OF DIFFERENT IN VITRO TECHNIQUES FOR PREDICTING BLOOD BRAIN BARRIER PENETRATION IMIDAZOLINE RECEPTOR LIGANDS

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Imidazoline receptor ligands are a numerous family of biologically active compounds with many therapeutic applications. Those ligands can act at the three types of imidazoline receptors (I1-IR, I2-IR and I3-IR) and alpha2-adrenoceptors. Imidazoline receptors (IRs) are responsible for the versatile biological activities of imidazolines. Therefore some IRs ligands are examined as novel centrally

acting antihypertensives and drug candidates for treatment of various neurological diseases. The aim of this work was to evaluate Blood-Brain Barrier (BBB) permeability of these ligand.
Parallel Artificial Membrane Permeability Assay (PAMPA), Biopartitioning Micellar Chromatography (BMC) and Reversed-Phase High-Performance Liquid Chromatography (RP HPLC) are in vitro techniques used for predicting BBB penetration of imidazoline ligands. The values obtained using PAMPA and BMC were studied by the Quantitative Structure-Property Relationship (QSPR) methodology.
Retenion factors obtained using BMC and RP-HPLC were correlated with permeability coefficients obtained using PAMPA. Further, Partial Least Square (PLS), Multiple Linear Regression (MLR) and Artificial Neural Networks (ANN) models were developed using retention data from BMC system/effective permeabilities from PAMPA and molecular parameters calculated for the optimized compounds. The dominant molecules/cation species of compounds at pH=7.4 have been obtained using the MarvinSketch. Chem3DBio Ultra program was applied for geometry optimization. The molecular descriptors were calculated for the optimized compounds using ChemBio3D Ultra, Dragon and ADMET predictor software. Retention factors/effective permeabilities of compounds were used as dependant variable, while calculated molecular parametres were used as independent variables in the QSPR study. SIMCA was used for PLS analysis, while the stepwise MLR and ANN modeling were performed using STASTICA Neural Networks. Predictive potential of the formed models was confirmed by Leave-One-Out Cross- and external validation.
Formed QSPR models can be used as a fast screening method for assessment of brain penetration of novel imidazoline receptor ligands, as promissing drug candidates for treatment of hypertension or neurological diseases.

Key words: Imidazolines, PAMPA, BMC, RP-HPLC, QSPR

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POREĐENJE PUNOG FAKTORSKOG DIZAJNA, CENTRALNOG KOMPOZICIONOG DIZAJNA I BOX-BEHENKEN DIZAJNA U RAZVOJU HROMATOGRAFSKE METODE ZA ANALIZU FLUKONAZOLA I NJEGOVIH NEČISTOĆA

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Primjena savremenih hemometrijskih tehnika u razvoju metoda tečne hromatografije omogućava detaljnu analizu ispitivanog sistema i rješavanje složenih analitičkih problema koji se ne mogu riješiti jednostavnim procedurama. Metodologija eksperimentalnog dizajna (DoE) omogućava primjenu matematičkih modela s kojima je moguće predvidjeti ponašanje sistema izvođenjem minimalnog broja dobro isplaniranih eksperimenata.
Cilj ovog istraživanja je bio istovremeno poređenje četiri vrste eksperimentalnog dizajna: pun faktorski dizajn na dva nivoa (FFD 23), centralni kompozicioni dizajn (CCD), Box-Behnken dizajn (BBD) i pun faktorski dizajn na tri nivoa (FFD 33). Sve vrste dizajna primijenjene su za dizajniranje

eksperimenata namijenjenih za razvoj nove hromatografske metode za analizu flukonazola i njegovih nečistoća.
Eksperimenti su urađeni na hromatografskom sistemu Finnigan Surveyor Thermo Scientific koji se sastoji od HPLC pumpe, autosemplera Plus i UV/VIS detektora Plus. ChromQuest je korišćen za prikupljanje podataka. Kolona za hromatografsko razdvajanje bila je BDS Hypersil C18, 125 mm □ 4 mm, 5 □m veličine čestica, brzina protoka 1,2 mL min-1 i temperatura kolone podešavana prema planu eksperimenata. UV detekcija je vršena na 260 nm.
Metodologija eksperimentalnog dizajna primijenjena je za proučavanje hromatografskog ponašanja flukonazola i njegovih nečistoća, s čime je omogućen detaljan opis ponašanja ispitivanog sistema kroz praćene koeficijente matematičkih modela za retencione faktore k1, k2 i k3. Testirani su različiti dizajni u procesu optimizacije metode, te je CCD odabran kao najpogodniji. Optimalni hromatografski uslovi određeni su metodologijom pretrage mreže. Definisani su optimalni uslovi: mobilna faza sastava acetonitril–5 mM amonijum formijat (15:85, v/v) i temperatura kolone 25 oC.
Primjena metodologije eksperimentalnog dizajna pokazala se veoma korisno za što bolje razumjevanje ponašanja složenih sistema i određivanje optimalni uslov.

Ključne riječi: eksperimentalni dizajn, optimizacija, flukonazol, nečistoće, tečna hromatografija

COMPARISON OF FULL FACTORIAL DESIGN, CENTRAL COMPOSITE DESIGN AND BOX BENHKEN DESIGN IN CHROMATOGRAPHIC METHOD DEVELOPMENT FOR THE ANALYSIS OF FLUCANOZOLE AND ITS IMPURITIES

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The application of modern chemometrical techniques in LC method development provides detail analysis of the system and resolving of complex analytical problems that cannot be easily resolved by simple trial and error procedure. The Design of Experiments (DoE) methodology enables mathematical description of system behavior after performing minimal number of well-planned experiments.
The aim of this study will be simultaneous comparison of four experimental design types: two-level full factorial design, central composite design (CCD), Box-Behnken design (BBD) and three-level full factorial design on experimental example of chromatographic method development for the analysis of fluconazole and its impurities.
The experiments were performed on chromatographic system Finnigan Surveyor Thermo Scientific consisted of HPLC Pump, Autosampler Plus and UV/VIS Plus Detector. ChromQuest was used for data collection. The analytical column was BDS Hypersil C18, 125 mm □ 4 mm, 5 □m particle size. Flow rate was 1.2 mL min-1 and column temperature was adjusted according to the experimental plan. UV detection was carried out at 260 nm.
DoE methodology applied for the study of chromatographic behavior of fluconazole and its

impurities enabled detailed description of system behavior through k1 to k3 mathematical models. Different optimization designs were tested and CCD was selected as the most suitable design. Optimal chromatographic conditions were located by grid point search methodology. The optimal conditions were: acetonitrile content in the mobile phase 15%, ammonium formate concentration in the water phase 5 mM and column temperature 25 ºC.
The applied Design of Experiments methodology proved to be useful assistance for understanding of complex system behavior and location of optimal conditions.

Key words: design of experiments, optimization, fluconazole, impurities, liquid chromatography

PRAĆENJE STABILNOSTI AMLODIPIN-BESILATA STRES TESTOM PRIMJENOM TEČNE HROMATOGRAFIJE HIDROFILNIH INTERAKCIJA I TEČNOM HROMATOGRAFIJOM SA MASENIM DETEKTOROM

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Sve veći broj istraživanja danas su usmjerena na ispitivanje stabilnosti ljekovitih supstanci, u što kraćem vremenskom periodu, tretiranjem sa određenim stres agenasima, što za rezultat ima nastanak degradacionih proizvoda ispitivanog lijeka, ali i njihova identifikacija. Ispitivanje stabilnosti amlodipin-besilata (AB) pod uticajem različitih stres agenasa izvršena je primjenom tečne hromatografije hidrofilnih interakcija (HILIC) i UPLC metodom koja je spregnuta sa masenim detektorom.
HILIC uslovi: kolona Luna HILIC (100 mm x 4,6 mm, 5 µm veličine čestica), mobilna faza sastava acetonitril – 10 mM amonijum-acetat pH 4,0 podešen sirćetnom kiselinom (92:8, V/V), brzina protoka mobilne faze 1 mL min-1, temperatura kolone 30 oC, talasna dužina 230 nm. UPLC uslovi: kolona Acquity-C18 (100 mm x 2,1 mm, 1,7 µm veličine čestica), mobilna faza (A) metanol i (B) 5 mM amonijum-formijat i 0,5% mravlje kiseline sa gradijentnim eluiranjem, protokom mobilne faze 0,4 mL min-1 i temperaturom kolone 30 oC. MS određivanje urađeno je u ES+ modu.
Cilj ovog istraživanja je bio da se ispita stabilnost AB tretiranjem različitim stres agensima, kao i da se identifikuju nastali degradacioni produkti.
Rastvori AB tretirani sa različitim stres agensima praćeni su HILIC metodom. Pokazalo se da u baznoj sredini dolazi do nastajanja degradacionih proizvoda koji odgovaraju nečistoći D i nečistoći F. U cilju potvrde nastajanja nečistoća D i F urađena je analiza UPLC–MS/MS metodom. Identifikacija nečistoće D kojoj odgovara m/z 407,13, urađena je praćenjem sljedećih fragmenata 407,13→286,05 i 318,10, dok je identifikacija nečistoće F kojoj odgovara m/z 395,07 urađena je praćenjem sljedećih fragmenata 395,07→180,00 i 228,94.
Stabilnost AB pod uticajem različitih stres uslova uspešno je ispitana HILIC metodom, a nastajanje degradacionih proizvoda u baznoj sredini dodatno je potvrđeno UPLC–MS/MS metodom.

Ključne riječi: amlodipin-besilat, stabilnost, HILIC, UPLC-MS/MS

MONITORING THE STABILITY OF AMLODIPINE BESYLATE BY HYDROPHILIC INTERACTION LIQUID CHROMATOGRAPHY AND ULTRA PERFORMANCE LIQUID CHROMATOGRAPHY WITH MASS DETECTOR

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An increasing number of studies are now focused on stability testing of drugs within the shortest possible time period. Treatment with certain stress agents has resulted the formation of degradation products of the study drug, as well as their identification.
Stability testing of amlodipine besylate (AB) under various stress agents was performed using Hydrophilic Interaction Liquid Chromatography (HILIC) and Ultra Performance Liquid Chromatography with mass detector (UPLC-MS/MS) method.
HILIC conditions: column Luna-HILIC (100 mm × 4.6 mm, 5 μm particle size), mobile phase acetonitrile–10 mM ammonium acetate pH 4.0 adjusted with acetic acid (92:8, v/v), mobile phase flow rate 1 mL min-1, column temperature 30 °C, the wavelength of 230 nm. UPLC conditions: column Acquity-C18 (100 mm x 2.1 mm, 1.7 μm particle size), mobile phase (A) methanol and (B) 5 mM ammonium formate and 0.5% formic acid with gradient elution, the mobile phase flow rate of 0.4 mL min-1 and the column temperature 30 oC. MS determination was done in ES+ mode.
AB was subject of stress studies to different stress agents in order to examine its stability and identification of degradation products formed.
Solutions of AB treated with different stress agents were monitored by HILIC method. It has been shown that the alkaline medium leads to the formation of degradation products corresponding to impurity D and impurity F. In order to confirm the formation of impurities D and F, UPLC-MS/MS method analysis was done. Identification of impurity D with corresponding m/z 407.13, was done by following these fragments 407.13→286.05 and 318.10, while the identification of impurity F with corresponding m/z 395.07 was done by following these fragments 395.07→180.00 and 228.94.
Stability of AB under the influence of various stress agents was successfully followed by HILIC method, and the formation of degradation products was further confirmed by UPLC-MS/MS method.

Keywords: amlodipine besylate, stability, HILIC, UPLC-MS/MS

PRIMJENA DERIVATA SULFONILUREJE SA MODIFIKOVANIM OSLOBAĐANJEM KOD PACIJENATA SA DIJABETES MELLITUS-OM TIP 2 U CILJU PROCJENE KVALITETA GLIKOREGULACIJE

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Studija Action in Diabetes and Vascular disease (ADVANCE) pokazala je visoko značajnu efikasnost u sniženju vrijednosti glikoziliranog hemoglobina (HbA1c) primjenom derivata sulfonilureje sa modifikovanim oslobađanjem kod pacijenata sa dijabetes mellitus-om tip 2 (T2DM) posle 3 mjeseca liječenja, kod čak 80 % pacijenata. Procjena kvaliteta glikoregulacije primjenom derivata sulfonilureje sa modifikovanim oslobađanjem kod pacijenata sa T2DM.
U studiju su uključena 103 pacijenta sa T2DM i nezadovoljavajućom glikoregulacijom na prethodno ordiniranoj terapiji. Ekskluzioni kriterijum za uvođenje lijeka u terapiju bio je postojanje kontraindikacije za primjenu derivata sulfonilureje. Kao parametar za procjenu kvaliteta glikoregulacije korišćen je HbA1c (%). Pacijentima je uveden u terapiju derivat sulfonilureje gliklazid sa modifikovanim oslobađanjem u dozi od 60 mg u trajanju od 6 mjeseci. Po isteku navedenog vremenskog perioda u cilju procjene efikasnosti njegovog djelovanja na kvalitet glikoregulacije određen je kontrolni HbA1c. Za analizu podataka korišćene su deskriptivne (mjere centralne tendencije i mjere varijacije) i parametarske analitičke statističke metode (studentov t-test).
Među 103 pacijenta bilo je 48. muškaraca i 55. žena, prosječne starosne dobi 65.29 godina i prosječne dužine trajanja T2DM 7.26±4.96 godina. Grupisani su u tri grupe: grupa I HbA1c ≤ 7.5% (25 pacijenata), grupa II 7.6 < HbA1c < 9 % (57 pacijenata) i grupa III HbA1c ≥ 9 % (31 pacijent). HbA1c prije primjene lijeka 8.52 ± 1.66 %, a nakon primjene 7.41 ± 1.13 %. HbA1c prije i posle terapije u grupi I 10.76%...8.38%, u grupi II 8.12 %...7.21%, u grupi III 6.89%...6.43%. Dobijeni rezultati su pokazali visoku statističku značajnost $p < 0.0001$.
Primjena derivata sulfonilureje sa modifikovanim oslobađanjem kod pacijenata sa T2DM dovela je do značajnog poboljšanja kvaliteta glikoregulacije.

Ključne riječi: dijabetes melllitus tip 2, modifikovani derivat sulfonilureje, glikolizirani hemoglobin.

TREATMENT WITH SULFONYLUREA DERIVATIVES WITH MODIFIED RELEASE IN PATIENTS WITH DIABETES MELLITUS TYPE 2 IN ORDER TO ASSESS THE QUALITY OF GLYCEMIC CONTROL

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Study Action in Diabetes and Vascular Disease (ADVANCE) showed a highly significant efficacy in lowering glycosylated hemoglobin values (HbA1c) using sulfonylurea derivatives with modified

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release in patients with diabetes mellitus type 2 (T2DM) after 3 months of treatment, even at 80% of patients.
Evaluation of the quality of glycemic control using the sulfonylurea derivatives with modified release in patients with T2DM.
The study included 103 patients with T2DM and unsatisfactory glycemic control on previous treatment. Excluding criteria was the existence of contraindications for treatment with sulfonylurea derivatives. As a parameter for assessing the quality of glycemic control was used HbA1c (%). The sulfonylurea derivative gliclazide with modified release in a dose of 60 mg was introduced in the treatment for a period of 6 months. Upon expiry of the specified period, in order to assess the effectiveness of its action on the quality of glycemic control HbA1c was determined. To analyze the data, the descriptive (measures of central tendency and measures of variation) and parametric analytical statistical methods (Student's t-test).
Among the 103 patients, there were 48 men and 55 women, average age of 65.29 years and the average duration of T2DM 7.26 ± 4.96 years. They were grouped into three groups: group I HbA1c ≤ 7.5% (25 patients), group II 7.6 < HbA1c <9% (57 patients) and group III HbA1c ≥ 9% (31 patients). HbA1c before drug administration 8.52 ± 1.66%, and after the treatment of 7.41 ± 1.13%. HbA1c before and after the treatment in group I and 10.76% ... 8:38% in group II 8:12 ... 7:21%% in group III 6.89% ...% 6:43. The results showed high statistical significance of p <0.0001.
Treatment with sulfonylurea derivatives with modified release in patients with T2DM has led to significant improvements in the quality of glycemic control.

Keywords: Diabetes mellitus type 2, modified derivative of sulfonylurea, glycosylated hemoglobin.

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SVIJEST PACIJENATA O ZNAČAJU UPUTSTVA ZA LIJEK

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Uputstvo za lijek (PIL) je dokument koji je sastavni dio pakovanja lijeka, kao i dozvole za stavljanje lijeka u promet. Sadrži osnovne informacije o lijeku, namijenjen je pacijentu i mora biti napisan jasnim i razumljivim jezikom. Agencija za ljekove i medicinska sredstva Crne Gore (CALIMS) na svom portalu objavljuje ažurirana Uputstva za ljekove za koje je izdata dozvola za stavljanje lijeka u promet.
Procjena učestalosti čitanja, važnosti i razumljivosti informacija sadržanih u tekstovima Uputstva za lijek, kod pacijenata sa teritorije Podgorice.
Anketu koja je sadržala 22 pitanja zatvorenog tipa, popunilo je 95 ispitanika oba pola, starosti od 18 do 65 godina, u periodu od novembra 2014. do februara 2015. godine.
Prije započinjanja terapije 65% ispitanika čita PIL uvjek, 17% često, 14% rijetko, 4% nikad, za ljekove sa kojima se po prvi put susreću PIL čita 74% uvjek, 10% često, 3% rijetko i 3% nikad, PIL detaljeno čita 51% ispitanika, dok 49 % čita samo određene djelove. Ispitivanje je pokazalo da 73% ispitanika smatra da su informacije koje su sadržane u PIL veoma korisne dok 27% ispitanika misli da su donekle korisne. Termini i izrazi koji se koriste u PIL lako su razumljivi za 46% ispitanika, a djelimično razumljivi za 54% ispitanika.

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Rezultati pokazuju da skoro polovina ispitanika čita samo određene djelove PIL. Većina ispitanika je izjavila da su uputstva korisna ali su im samo djelimično razumljiva. Farmaceuti bi u kontaktu sa pacijentima trebali da promovišu i istaknu važnost čitanja PIL kao i da odgovore na sve nejasnoće vezane za termine i izraze korišćene u ovim dokumentima.

Ključne riječi: Uputstvo za lijek

AWARENESS OF PATIENTS ON THE IMPORTANCE OF PATIENT INFORMATION LEAFLET

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Patient information leaflet (PIL) is a document included in the package with a medicine, and also main part of marketing authorisation licence. It contains main information about medicine, intended for the patient and must be written clearly and understandably. The Agency for medicines and medical devices of Montenegro (CALIMS) on its portal publishes an updated PIL for drugs that have received marketing authorisation license.
Estimating the frequency of reading, importance and understanding of information included in Patient information leaflet of patients from the territory of Podgorica.
Questionnaire which containing 22 closed type questions were completed by 95 subject of both sexes, aged 18 to 65 years, in the period from November 2014 to February 2015.
Before starting therapy 65% of subjects read PIL always, 17% often, 14% seldom, 4% never, for medicines they have met for the first time PIL read 74% always, 10% often, 3% seldom, 3% never. PIL detailed read 51% of subjects, while 49% read only certain parts. Survey showed that 73% of subjects believe that the information contained in the PIL is very important, while 27 % of subjects think they are somewhat important. The terms and expressions used in the PIL are easily understood by 46% of subjects, and partially understood by 54% of subjects.
The results show that almost half of subjects read only certain parts of the PIL. Most subjects stated that the instructions are helpful but they are only partially understandable. Pharmacist should emphasise and promote importance of PIL to each patient. They also should explain any kind of unclearness due to the terms and phrases wich are mentioned in this documents.

Key words: Patient information leaflet

HRONOTERAPIJA U CILJU POBOLJŠANJA EFIKASNOSTI LJEKOVA

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Kako fiziološke funkcije variraju tokom 24. časovnog ciklusa, tako i patološka stanja imaju svoje cirkadijalne ritmove. Usklađivanje biološkog ritma sa mediciskim tretmanom poznato je kao hronoterapija. Jedna od strategija da se poveća efikasnost farmakoterapije je primjena

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ljekova u vrijeme u koje će oni biti najefikasniji sa manjim rizikom od neželjenih dejstava, kao i zadovoljenje terapijskih potreba vezanih za pojedinačne patološke slučajeve.
Analiza novije literature u cilju procjene djelotvornosti lijeka u odnosu na vrijeme primjene.
Pretraga je sprovedena u tri baze podataka Pubmed, Ebsco i Web of Science upotrebom termina "Chronotherapy", "Chronopharmaceutics", "Chronopharmacokinetics" "Chronopharmacodynamics", "Chronoefficacy", "Morning and Evening", i njihovih kombinacija. Kriterijum za selekciju članaka je bila godina objavljivanja 2000-2015, publikacije na engleskom jeziku, i studije sprovedene na ljudina.
Epidemiološke studije su pokazale da simptomi bolesti variraju tokom 24. časovnog ciklusa. Uzimajuci u obzir hronobiološke aspekte bolesti i hronokinetiku ljekova, dokazano je da vrijeme primjene ljekova može smanjiti broj neželjenih dejstava i povećati njihovu efikasnost. Vremenski zavisne promjene u kinetici ljekova mogu biti rezultat cirkadijalnih varijacija u apsorpciji, distribuciji, metabolizmu i eliminaciji. Potencijalni benefit od hronofarmaceutika je demonstriran u liječenju bolesti kao što su alergijski rinitis, reumatoidni artritis i srodne bolesti, astma, kancer, kardiovaskularne bolesti, dijabetes, hiperholesterolemija i peptički ulcer.
Hronoterapijske studije su pokazale da je optimizacija terapije moguća odabirom vremena primijene lijeka. Ispitivanja efikasnosti i bezbjednosti ljekova u odnosu na vrijeme primjene predstavljaju jedan od načina da se poboljšaja kvalitetna upotreba ljekova. S obzirom da su pojedinačne studije rađane na relativno malom broju ispitanika, u budućnosti hronoterapijske studije treba dizajnirati tako da istraže genetske, polne i starosne razlike.

Ključne riječi: hronoterapija, hronofarmaceutici, efikasnost, neželjena dejstva.

CHRONOTHERAPY CAN IMPROVE THE EFFICACY OF MEDICINES

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As human physiology vary during the 24. hours cycle, pathological conditions also exhibit circadian patterns. Matching biological rhythm with medical treatment is known as chronotherapy. Strategy to improve efficacy of pharmacotherapy is administration of medicines in time they will be the most efficacy with minimization of adverse drug reactions, as well as to meet the therapeutic needs related to individual pathological cases.
Analysis of the recent literature in order to assess the effectiveness of the drug in relation to the time of administration.
A literature search was conducted in three databases (Pubmed, Ebsco i Web of Science) using the search terms "Chronotherapy", Chronopharmaceutics", "Chronopharmacokinetics", "Chronopharmacodynamics", "Chronoefficacy", "Morning and Evening", and their combinations. The selection criteria for the inclusion of articles included currency 2000-2015, publication in English language, studies done in humans .
Epidemiological studies have documented that disease symptoms vary during the 24-hour cycle. Taking into account the chronobiological aspects of disease and the chronokinetic of medicines, it is demonstrated that moment of administration medicines may enhance the efficacy and reduce side effects. Time-dependent changes in kinetics may result from circadian

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variations at absorption, distribution, metabolism and elimination. The potential benefits of chronotherapeutics have been demonstrated in the management of diseases as a allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, hypercholesterolemia, diabetes and peptic ulcer disease.
Chronotherapeutic studies demonstrated that optimizing a drug therapy is possible by choosing the moment of administration of the drug. Examining the efficacy and safety of medicines in relation to the time of administration is one of the ways to improve quality use of medicines. Since the individual studies is carried out on a relatively small number of subjects in future chronotherapeutic studies should be designed to explore the genetic, gender, and age differences.

Key words: chronotherapy, chronopharmaceytics, efficacy, side effect

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ULOGA I ZNAČAJ SARADNJE IZMEĐU APOTEKE SUBOTICA I UDRUŽENJA BUBREŽNIH INVALIDA VOJVODINE U PROMOCIJI ZDRAVLJA I EDUKACIJI PACIJENATA KOJI SU NA HEMODIJALIZI

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Hronične bubrežne bolesti (HBB) u zadnjih deset godina imaju sva obeležja progresije kod stanovništva na teritoriji Republike Srbije.
Promocija zdravlja je proces osposobljavanja stanovništva i zajednice da unaprede svoje zdravlje i ujedno povećaju kontrolu nad njim.
Promocija zdravlja se sprovodi kroz:.zdravstveno promotivne programe i.zdravstvenu edukaciju.
Cilj rada je prikaz partnerskog odnosa između Apoteke Subotica (AS) i Udruženja bubrežnih invalida Vojvodine (UBIV), kao i aktivnosti sprovedene u promociji zdravlja i edukaciji pacijenata koji su na hemodijalizi
Za prikaz aktivnosti u periodu od 01.10.2014.- 13.03.2015.godine.primenjena je retrospektivna analiza
U analiziranom periodu održana su dva edukativna predavanja na temu Nutricionistički aspekt bubrežne dijete članovima UBIV. Publikovana je i javno prezentovana brošura pod nazivom Farmakoterapijski aspekti vitamina kod pacijenata na hemodijalizi. Povodom Svetskog dana bubrega 12.03.2015.godine podeljen je edukativni materijal o značaju donacije organa i transplantaciji bubrega. Sve javnozdravstvene aktivnosti su medijski propraćene gostovanjima na lokalnim televizijama, kao i na internet sajtovima Apoteke Subotica i UBIV.
Rezultat zajedničkog rada AS i UBIV predstavlja podršku važećim standardima, vodičima i protokolima, čijom se primenom postižu kvalitetni efekti lečenja bubrežnih pacijenata,
Edukacijom pacijenata koji su na hemodijalizi postiže se opšta informisanost o uzrocima HBB, prevenciji lečenja i primeni savremenih medicinskih sredtava i dijetetskih suplemenata.

Ključne reči: Hronične bubrežne bolesti (HBB), hemodijaliza, promocija zdravlja, edukacija pacijenata

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UPRAVLJANJE FARMACEUTSKIM OTPADOM- BUDUĆE AKTUELNOSTI U ZAKONSKOJ REGULATIVI REPUBLIKE SRBIJE

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Upravljanje farmaceutskim otpadom (UFO) zahteva multidisciolinaran pristup, koji uređuje Zakon o upravljanju otpadom (ZOUO) i Pravilnik o upravljanju medicinskim otpadom (POUMO). Predstaviti buduće aktuelnosti u Nacrtu Zakona o izmenama i dopunama ZOUO, s posebnim akcentom na delove koji se odnose na UFO u farmaceutskoj praksi.
Analiza Nacrta Zakona o izmenama i dopunama ZOUO i poređenje sa trenutno važećim ZOUO.
Nacrt zakona uvodi nov termin neopasnog farmaceutskog otpada (FO), u odnosu na važeći ZOUO gde su proizvođači i vlasnici FO dužni da sa njim postupaju kao sa opasnim otpadom. Član 56. iz ZOUO se redefiniše i prave se tri nova člana od kojih će jedan definisati način i postupanje sa medicinskim otpadom. Drugi član će definisati način i postupanje sa FO, dok će treći član definisati način finansiranja upravljanja medicinskog i FO. Prema Nacrtu zakona, građani će biti dužni da neupotrebljive lekove predaju apoteci koja je osnovana bilo kao državna ili privatna praksa. Kontejner za prikupljanje FO od građana postavljaće ovlašćeno pravno lice sa kojim apoteka sklopi ugovor, a koje ima sve dozvole u skladu sa ZOUO. Troškove UFO snosiće proizvođač otpada -apoteke, osim troškova UFO sakupljenim od građana. Troškove upravljanja, odnosno izvoza FO sakupljenog od građana snosiće proizvođač i/ ili uvoznik koji stavlja lek na tržište Republike Srbije, proporcionalno učešću u masi plasmana svojih proizvoda na tržistu, u skladu sa Zakonom. Troškove UFO podrazumeva: preuzimanje i prevoz FO, izradu Plana UFO, nabavku kontejnera, privremeno skladištenje, tretman FO, kao i vođenje evidencije i obaveštvanje prema Agenciji za zaštitu životne sredine.
Nacrt Zakona o izmenama i dopunama ZOUO definiše nedoumice i nedorečenosti koje se tiču UFO,.najviše u pogledu finansiranja njegovog zbrinjavanja. Usvajanje Nacrta zakona o izmenama i dopunama ZOUO omogućiće poboljšano i kontinuirano UFO.

Ključne reči: farmaceutski otpad (FO), upravljanje farmaceutskim otpadom (UFO), Zakon o upravljanju otpadom (ZOUO)

PHARMACEUTICAL WASTE MANAGEMENT – FUTURE TOPICS IN THE LEGISLATION OF THE REPUBLIC OF SERBIA

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Pharmaceutical waste management (PWM) requires a multidisciplinary approach which is regulated by the Law on Waste Management (LWM) and Statute on Medical Waste Management (SMWM).

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Presenting future topics in the Draft of Law of Amendments and Supplements (DLAS) for LWM, with emphasis on the parts related to the PWM in pharmaceutical practice.
Analysis of the DLAS for LWM and comparison with current LWM
The draft introduces new terms for non-hazardous pharmaceutical waste (PW), compared with the current LWM where the products and owners of PW are obliged to treat them as hazardous waste. Article 56 of LWM is redefined and three new articles are introduced, one of which will define how to deal with medical waste. The second article will define a way to handle PW, while the third article will define the method of financing medical and PWM. According to the draft, citizens will be obliged to hand over unusable medication to pharmacies which were established as either public or private practice. A container for collecting PW from the citizens will be appointed by the authorized legal entity with whom the pharmacy will enter into contract and whom has all the permits in accordance with the LWM. The costs of PWM will be borne by the waste producer – pharmacies, except for PW collected from the citizens. Handling costs, that is export of PW collected from the citizens will be borne by the manufacturer and/or importer who puts the medication on the market of the Republic Serbia, proportionally to the participation of mass marketing of their products on the market, in accordance with the law. Costs of PWM includes: PW acceptance and transport, PWM plan drafting, container procurement, temporary storage, PW handling, as well as record keeping and noticing the Agency for Environmental Protection.
The DLAS for LWM defines uncertainties and ambiguities which concern PWM, mostly in terms of financing its disposal. The adoption of the DLAS for LWM enables improved and continuous PWM.

Keywords: pharmaceutical waste (PW), pharmaceutical waste management (PWM), Law on Waste Management (LWM)

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ZNAČAJ PRAĆENJA SADRŽAJA OHRATOKSINA A U ŽITARICAMA

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Žitarice su često kontaminirane gljivicama i njihovim sekundarnim metabolitima-mikotoksinima. Zitarice su najčešće kontaminirane gljivicama roda Penicillium i Aspergilus koje produkuju ohratoksin A, najčešći kontaminent žitarica širom svijeta.
Akutna toksičnost ohratoksina A nije visoka. Brzo se apsorbuje iz želuca i crijeva a njegova koncentracija kao i koncentracija njegovih metabolita u krvi zavisi od doze i dužine ekspozicije. Deponuje se u tubulama bubrega odakle potiče njegova nefrotoksičnost.
Poluživot ohratoksina A u krvnoj plazmi je 35.55 dana. Nekoliko mehanizama ukljuceno je u njegovu toksičnost: inhibicija sinteza proteina, proizvodnja reaktivnog kiseonika, narušavanje homeostaze kalcijuma, inhibicija mitohondrijalnog disanja i cijepanje DNA.
Ohratoksin A je karcinogeni agens koji je prema IARC-u (International Agency for Research on Cancer) klasifikovan u grupu 2B (mogući karcinogen za ljude). Pored ovoga dokazano je da je teratogen , imunosupresivan i da učestvuje u etiologiji endemske nefropatije.
Sadržaj ohratoksina A praćen je u uzorcima žitarica metodom ELISA testa i tečne hromatografije. S obzirom na prošlogodišnju meteorološku situaciju (velika vlažnost) ohratoksin A je prisutan u svim ispitivanim uzorcima žitarica, u dozvoljenim koncentracijama. Njegov sadržaj je znatno veći u integralnim žitaricama. Dobijene koncenteracije kreću se u opsegu od 0.4 do 1.5µg/kg što je ispod

maksimalno dozvoljene koncentracije koja iznosi 5 μg/kg.
Izračunato je da dnevni unos ohratoksina A treba biti od 0.7-4.0 ng/kg, sedmični unos po FAO/WHO (Food and Agriculture Organization/World Health Organisation) iznosi 100 ng po kilogramu tjelesne mase.
Bez obzira na dobijene niske vrijednosti koncentracije ohratoksina A u žitaricama treba obratiti pažnju na dnevni unos ohratoksina A zbog njegove prisutnosti u kafi, kakau, kikirikiju, koštunjavom i sušenom voću i vinu. Zbog optimizacije dnevnog unosa potrebno je pratiti sadržaj ohratoksina A u svim navedenim namirnicama. Vrlo važno je pratiti sadržaj ohratoksina A u dječijoj hrani na bazi žitarica u kojoj su maksimalno dozvoljene koncentracije znatno niže.

Ključne riječi: mikotoksini, ohratoksin A, karcinogen, dnevni unos

THE IMPORTANCE OF MONITORING CONTENT OF OCHRATOXIN A IN CEREALS

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Cereals are often contaminated by fungi and their secondary metabolites-mycotoxins. Grains are usually contaminated by fungi of the genus Penicillium and Aspergillus, which produce ochratoxin A, the most common worldwide cereals contaminant.
Acute toxicity of ochratoxin A is not high. It is rapidly absorbed from the stomach and intestines and its concentration, as well as the concentration of metabolites in blood depends on the dosage and duration of exposure. It deposite in the kidney tubules where promotes its nephrotoxicity.
The half-life of ochratoxin A in blood plasma is 35.55 days. Several mechanisms involve in its toxicity: inhibition of protein synthesis, production of reactive oxygen, disruption of calcium homeostasis, inhibition of mitochondrial respiration and splitting of DNA.
Ochratoxin A is, according to IARC (International Agency for Research on Cancer) a carcinogenic agent which is classified in group 2B (possibly carcinogenic to humans). In addition to this it has been proven to be teratogenic, imunosupresivan and to participate in the etiology of endemic nephropathy.
The contents of ochratoxin A was monitored in samples of grain by ELISA assay and liquid chromatography. Due to last year's meteo conditions (high humidity) ochratoxin A is present in all analyzed samples of cereals, in permissible concentrations. Its content was significantly higher in whole grains. Concentrations which we found was from 0.4 to 1.5μg / kg, which is below the maximum allow concentration, which is 5 mg / kg.
It has been calculated that a daily intake of ochratoxin A should be from 0.7-4.0 ng / kg by FAO / WHO (Food and Agriculture Organization / World Health Organization) and weekly intake is 100 ng per kilogram of body weight.
Regardless that we found a low concentrations of ochratoxin A in cereals, it should pay attention to the daily intake of ochratoxin A due its presence in coffee, cocoa, peanuts, nuts and dried fruit and wine. Due to the optimization of the daily intake is necessary to monitor the content of ochratoxin A in all these foods. It is very important to monitor the content of ochratoxin A in children's cereal-based foods in which the maximum allowable concentrations much lower.

Keywords: mycotoxins, ochratoxin A, a carcinogen, daily intake

PREGLED I PODELA NAJČEŠĆE KORIŠĆENIH HIRURŠKIH KONACA U KLINIČKOM CENTRU SRBIJE

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Hirurški konci pripadaju grupi opštih i implantabilnih medicinskih sredstava i predstavljaju nit prirodnog ili sintetičkog materijala koja služi za ligiranje krvnih sudova ili ušivanje tkiva. Mogu se razvrstati po klasama: klasi II odgovaraju neresorptivni, a klasi III resorptivni hirurški konci.

Kako na tržištu postoji veliki broj različitih vrsta hirurških konaca, a i zbog toga što se jedni konci mogu menjati drugim u zavisnosti od trenutne raspoloživosti, bilo je neophodno olakšati proces planiranja nabavke i distribucije adekvatnim tabelarnim pregledom svih proizvođača koji su registrovani u Republici Srbiji.

Sekundarna, kvalitativna i kvantitativna analiza dostupnih tenderskih dokumentacija u 2013. i 2014. godini, analiza trebovanja klinika u pogledu dinamike isporuke, vrste i količine hirurških konaca.

Na osnovu dostupnih podataka napravljen je pregled najčešće korišćenih konaca u Kliničkom centru Srbije. Prikazane su osnovne podele i to: prema stepenu i vremenu resorpcije, sastavu i prirodi materijala. Predstavnici grupe polifilamentnih brzoresorptivnih su Polyglycolic acid i Polyglactin 910, polifilamentnih srednjeresorptivnih je Lactomer (kopolimer glikolida i laktida), a grupi monofilamentnih spororesorptivnih konaca pripadaju Polydioxanone, Poly-4-hydroxy-butyrate i Polyglyconate. Monofilamentni neresorptivni (Polyamid i Polypropylene) kao i polifilamentni neresorptivni konci izrađeni od poliestera, takođe su nezaobilazan deo hirurškog šavnog materijala. Prirodni šavni materijali se retko koriste, a najznačajniji su svila i lan. Pored navedenih osobina, analizirani su i debljina konca, vrsta, dužina i zakrivljenost igala, sva zaštićena imena koja se nalaze na tržištu Republike Srbije, kao i boja spoljašnjeg pakovanja.

U ustanovama sekundarnog i tercijarnog nivoa zdravstvene zaštite, farmaceuti aktivno učestvuju, kako u nabavci i distribuciji lekova, tako i medicinskih sredstava. Ovakve aktivnosti znatno olakšavaju svakodnevni rad apoteke ali i krajnjih korisnika, tj. celokupnog medicinskog osoblja u ambulantama i operacionim salama.

Ključne reči: hirurški konci, analiza, podele, karakteristike

THE REVIEW AND CLASSIFICATION OF THE MOST COMMONLY USED SURGICAL SUTURES IN THE CLINICAL CENTER OF SERBIA

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Surgical sutures are classified as general and implantable medical devices and represent the thread of natural or synthetic material used for ligating blood vessels or stiching of tissue. They can be sorted as non-resorbable (class II) and resorbable sutures (class III).

Despite the fact that the market has different types of sutures, and because they can be changed one to another, depending on the current availability, it was necessary to facilitate the planning of acqusition and distribution by making an overview of all manufacturers who are registered in Serbia.

The secondary, qualitative and quantitative analysis of procurement documentation available in 2013 and 2014, the analysis of demands of clinics in terms of delivery schedule, types and quantities of surgical sutures.

Based on the available data, it was made a review of the most commonly used threads. It has been shown a classification in main categories: according to the rate and time of absorption, the structure and nature of the material. The main representatives from the group of polyfilament rapidly resorbable are Polyglycolic acid and Polyglactin 910; polyfilament medium resorbable is Lactomer (copolymer of glycolide and lactide); Polydioxanone, Poly-4-hydroxybutyrate and Polyglyconate belong to a group of slowly resorbable monofilament threads. Non-resorbable monofilament (polyamide and Polypropylene) as well as non-absorbable polyfilament sutures made of polyester, are also an essential part of the surgical suture material. Natural suture materials are rarely used, but the most important are silk and linen. In addition to these characteristics, it was analyzed the thickness of suture, the type, lenght and curvature of the needles, all brand names that are on the market of the Republic of Serbia, as well as the color of the outer packaging.

In the institutions of secondary and tertiary health care, pharmacists actively participate in both the procurement and distribution of medicines and medical devices. These activities greatly facilitate the daily work of hospital pharmacy as well as of the end users, ie. the entire medical staff in clinics and operating rooms.

Keywords: surgical sutures, analysis, classification, characteristics

STUDENTSKI RADOVI

OPTIMIZACIJA FORMULACIJA ČVRSTIH DISPERZIJA SA KARBAMAZEPINOM - PRIMENA D-OPTIMALNOG EKSPERIMENTALNOG DIZAJNA I VEŠTAČKIH NEURONSKIH MREŽA

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Izradom čvrstih disperzija sa teško rastvorljivim lekovitim supstancama može se povećati rastvorljivost i brzina rastvaranja navedenih supstanci, a sa tim i njihova biološka raspoloživost. Cilj ovog rada bila je procena mogućnosti primene D-optimalnog eksperimentalnog dizajna (DOED) i veštačkih neuronskih mreža (VNM) u optimizaciji formulacija čvrstih disperzija sa karbamazepinom.

Formulisane su čvrste disperzije variranjem udela karbamazepina (30%-50%), lauroil makrogol-32 glicerida (Gelucire® 44/14) (20%-40%) i makrogol 6000-poli(vinilkaprolaktam)-poli(vinilacetat) polimera (Soluplus®) (30%-50%) (ulazni parametri). Izrađeno je 11 formulacija čvrstih disperzija, iz kojih je ispitana in vitro brzina rastvaranja karbamazepina, u aparaturi sa rotirajućim lopaticama. Sadržaj karbamazepina je određen UV spektrofotometrijski, na 287 nm. Kao izlazni parametri praćeni su procenati oslobođenog karbamazepina posle 10, 20, 30, 45 i 60 minuta. Nakon dobijanja matematičkih modela i optimizacije primenom DOED i VNN, izrađene su tri test formulacije. Uspešnost predviđanja formulacija, primenom DOED i VNM, izvršena je izračunavanjem faktora razlike (f1) i faktora sličnosti (f2) predviđenih i dobijenih profila brzine oslobađanja karabamazepina iz čvrstih disperzija.

Najveća brzina rastvaranja karbamazepina iz čvrstih disperzija (preko 80% za 30 minuta) postiže se pri udelima aktivne supstance od oko 35%, Gelucire® 44/14 oko 20% i Soluplus®-a oko 45%, što je potvrđeno primenom obe optimizacione tehnike. Poređenjem predviđenih i dobijenih profila brzine rastvaranja karbamazepina iz tri izrađene test formulacije uočava se veliko slaganje ($f1<15$; $f2>50$). Infracrvenom spektroskopijom (FT-IR) potvrđeno je da u tri optimalne formulacije čvrstih disperzija ne dolazi do interakcije između karbamazepina i ekscipijenasa i da se karbamazepin nalazi u jedinom farmakološki aktivnom kristalnom polimorfnom obliku III. Čvste disperzije sa pravilnim izborom udela karbamazepina, Gelucire® 44/14 i Soluplus®-a mogu značajno povećati brzinu rastvaranja aktivne supstance, a metode DOED i VNM se mogu sa uspehom koristiti u optimizaciji ovih formulacija.

Ključne reči: čvrste disperzije, optimizacija formulacija, brzina rastvaranja, Soluplus®, Gelucire® 44/14

SOLID DISPERSIONS OF CARBAMAZEPINE – OPTIMIZATION OF FORMULATIONS USING D-OPTIMAL EXPERIMENTAL DESIGN AND ARTIFICIAL NEURAL NETWORKS

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Solid dispersions prepared with poorly water-soluble drugs can increase solubility and dissolution rate of these drugs, as well as their bioavailability.
The aim of this study was optimization of carbamazepine-solid dispersion formulation, by using D-optimal experimental design (DOED) and artificial neural networks (ANNs).
Solid dispersions were formulated by varying the ratio of carbamazepine (30%-50%), lauroyl macrogol-32 glycerides (Gelucire® 44/14) (20%-40%) and polyvinyl caprolactam–polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®) (30%-50%) (input parameters). The dissolution profiles of eleven different carbamazepine-solid dispersions were determined using a rotating paddle apparatus. The carbamazepine concentration was determined spectrophotometrically, at 287 nm The observed output parameters were percentages of released carbamazepine after 10, 20, 30, 45 and 60 minutes. Three test formulations were created after developing mathematical models and optimization applying (ili using) DOED and ANNs. Prediction ability of DOED and ANNs models were compared by calculating the difference (f1) and similarity factor (f2) the obtained and predicted carbamazepine release profiles.
The highest dissolution rate of carbamazepine (more than 80% after 30 minutes) was achieved at carbamazepine ratio of about 35%, Gelucire® 44/14 of about 20% and Soluplus® of about 45%. By comparing the predicted and actual release rate profiles of carbamazepine from three optimal formulations, significant compliance of results was observed, application of both optimization techniques. FT-IR spectroscopy confirmed that there were no interactions between carbamazepine and excipients and carbamazepine is probably in polymorph form III, the only pharmacologically active form.
Proper selection of solid dispersion components may significantly increase release rate of carbamazepine. DOED and ANNs can be used for optimization of this formulations.

Key words: solid dispersions, optimization of formulations, dissolution rate, Soluplus®, Gelucire® 44/14

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PRIMJENA BILJNIH PREPARATA U PREVENCIJI STRESA U CRNOGORSKIM GRADOVIMA

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Savremeni način života doveo je do povećane izloženosti stresu, kako ko dmlađe, tako i kod starije populacije.Sve više ljudi se odlučuje za primjenu različitih preparata u cilju olakšavanja ovih tegoba. U tom smislu najvjerovatnije nijesu izuzetak ni stanovnici naše zemlje.
Cilj ovog istraživanja je bio da se utvrdi koliko su stanovnic i u gradskim sredinam anaše zemlje

izloženi stresu, koriste li neke preparate za ublažavenje stresa i koje, da li se radije odlučuju za biljne preparate ili konvencionalnu farmakoterapiju i kakav je njihov stav po pitanju efikasnosti i bezbjednosti istih.
Pilot istraživanje je rađeno tokom marta 2015.godine. U anonimnoj anketi je učestvovalo 100 ispitanika oba pola, starosti od 18 do 55 godina, različitih obrazovnih profila, iz nekoliko gradovaCrne Gore (Nikšić, Podgorica, Herceg Novi, Budva i Cetinje).Ispitanici su odgovarali na 17 pitanja koja su se odnosila na upotrebu preparata za ublažavanje stresa i o bezbjednosti njihove primjene.
Oko 80% ispitanika (n=83) su stresu izloženi na poslu, u školi ili fakultetu. Čak 56 ispitanika smatraju da stress remeti njihove svakodnevne aktivnosti, a dvije trećine korist ipreparate za ublažavanje stresa.Skoro polovina ispitanika (n=48) koriste biljne preparate, uglavnom u vidu čajeva. Samo 7% anketiranih se savjetuju sa ljekarom ili farmaceutom u vezi sa primjenom biljnih preparata. Među biljnim preparatima dominiraju oni na bazi kamilice (Matricaria chamomilla), lavande (Lavandula angustifolia) i kantariona (Hypericum perforatum).Većina (90%) ispitanika smatraju da su biljn ipreparati zdraviji, bezbjedniji i da ne izazivaju zavisnost. Standardne anksiolitičke ljekove (bromazepam, alprazolom, diazepam) anketirani znatno rjeđe koriste (7%) i to uglavnom po preporuci ljekara.Oko 40% ispitanika smatraju da su im preparati koje su koristil ipomogli u ublažavanju stresa.
U Crnoj Gori je veliki broj ljudi izložen stresu. Prema našim rezultatima, primjena biljnih preparata za ublažavanje istog je široko zastupljena, uz značajno manje korišćenje konvencionalne farmakoterapije.To što se ispitanici opredjeljuju za preparate prirodnog porijekla se može smatrati dobrom praksom, pod uslovom da su dovoljno informisani o pravilnoj primjeni imogućim neželjenim dejstvima ovih preparata.U tom smislu, veoma je važna edukativna uloga farmaceuta.

Ključne riječi: stres, biljni preparati, primjena

USE OF HERBAL PREPARATIONS IN PREVENTION OF STRESS IN MONTENEGRINS TOWNS

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The modern way of life has led to increased exposure to stress, in younger as well as inolder population.Today,many people decide to take various products in order to facilitate these discomforts. In this regard is likely neither an exception nor the inhabitants of our country.
Objective: The aim of this study was to determine the extent to which the inhabitants of our towns are exposed to stress, whether they use some preparation to relieve stress and which, if they prefer to use herbal supplements or conventional pharmacotherapy and what is their opinion about theefficacy safety of these preparations.
This pilot study was conducted during March 2015. In an anonymous questionnaire attended by 100 participants of both sexes, aged 18 to 55 years, of different educational backgrounds, from several towns of Montenegro (Podgorica, Herceg Novi, Budva and Cetinje) .Respodents

answered the 17 questionsabout the use of herbal and other preparations for relieving stress and about the safety of their application.

Approximately 80% of respondents (n = 83) were exposed to stress at work, at school or university. Even 56 respondents believe that stress disrupts their daily activities;two-thirds used preparations to relieve stress.Almost half of the respondents (n = 48) used herbal medicines, mainly in the form of teas. Only 7% of respondents consult with doctor or pharmacist about the application of herbal preparations. Dominant herbal preparations are based on Matricaria chamomilla, Lavandula angustifolia, and Hypericum perforatum.The majority (90%) of respondents believe that herbal preparations are healthier, safer and not addictive. Standard anxiolytic drugs (bromazepam, alprazolom, diazepam) are used less frequently (7%), mainly after the doctor's recommendation.About 40% of respondents believe that their preparations they used help them in relieving stress.

In Montenegro, the large number of people exposed to stress.According to our results, the use of herbal preparations to relieve the stress is widespread, with significantly less use of conventional pharmacotherapy. The use of preparations of natural origin can be considered as good practice, provided that people are sufficiently informed about the optimal use and possible side effects of these preparations. In that way, the educational role of pharmacistsis very important.

Key words: herbal preparations, stress, use

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COMMUNITY PHARMACY SECTOR IN KOSOVO, CURRENT SITUATION AND CHALLENGES

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The purpose of this research is to study actual situation in community pharmacy sector in Kosovo, particularly analyzing the provisions of the regulatory framework in force regarding pharmacy staff and new community pharmacy establishment and also challenges in future.

This research raises the question on how can we reach a satisfactory solution that would ensure quality pharmaceutical services in community pharmacies, addressing in one side the presence of the adequate pharmacy staff and the other side additional control in the pharmaceutical sector.

During this research, we have questioned 110 licensed pharmacists within 110 licensed community pharmacies throughout Kosovo. Also we have analyzed the official data from Ministry of Health and Kosovo Medicines Agency and regulatory framework in fields related with the purpose of this study.

From 110 community pharmacies in Kosovo where research was conducted, representing about 25% of licensed pharmacies in Kosovo, we have concluded that on average one community pharmacy has 1.1 licensed pharmacists, 1.03 pharmacy technicians, and due to absent of demographic or geographic restrictions in opening of new community pharmacies, made that community pharmacies mostly are opened in major urban centers and next to the health institution.

The results obtained from this research show that the number of pharmaceutical personnel in pharmacies in Kosovo is low and also, there is a need for more restrictions and improvement in opening of new community pharmacies procedure in order to achieve a better distribution and services in community pharmacies.

Key words: pharmacy staff, community pharmacies, pharmaceutical services, pharmaceutical regulatory framework.

FARMAKOVIGILANCA – PRAĆENJE UČESTALOSTI JAVLJANJA I PRIJAVLJIVANJA NEŽELJENIH DEJSTAVA LIJEKOVA U CRNOJ GORI

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Vrijeme u kome živimo karakteriše stalni porast upotrebe lijekova u prevenciji i liječenju različitih tegoba i oboljenja. Praćenje odnosa korist-rizik lijeka je važan parametar za procjenu njegove bezbjednosti. Spontano prijavljivanje neželjenih dejstava (ND) lijekova od strane zdravstvenih radnika je potrebno u cilju sprečavanja potencijalnih negativnih posledica njihove primjene.
Cilj istraživanja je utvrđivanje učestalosti javljanja nekih štetnih i nenamjerno izazvanih reakcija na lijek, stepen prijavljivanja ND od strane pacijenata, kao i upućenost pacijenata o mogućnosti prijavljivanja i svake sumnje na ND, odnosno praćenje onih aktivnosti koje obuhvata farmakovigilanca.
Istraživanje je sprovedeno tokom marta 2015. godine. U anonimnoj anketi učestvovalo je 260 ispitanika oba pola, starosti od 19 do 88 godina, različitog ekonomskog statusa i stepena obrazovanja iz nekoliko crnogorskih gradova (Podgorica, Budva, Nikšić, Cetinje, Mojkovac, Berane). Ispitanici su odgovarali na pitanja ankete koja se odnose na učestalost javljanja i mogućnost prijavljivanja ND lijekova zdravstvenim radnicima.
Od ukupno 260 ispitanika,13% (n=34) se ne pridržava uputstava koja mu ljekar propiše (vrijeme primjene, doza…). Čak 23,5 % ispitanika (n=61) uopšte ne čita uputstvo za upotrebu lijeka. Na pitanje koje lijekove češće koriste 52% ispitanika (n=135) je odgovorilo da koristi lijekove ,,na svoju ruku“ a njih 48% (n=125) na recept. Začuđujućih 41,5 % (n=108) ispitanika ne zna da postoji mogućnost prijavljivanja ND. Kod 28,5 % ispitanika (n=69) su se javile neželjene reakcije nakon primjene lijeka, od toga njih 80 % (n=55) ih je prijavilo, češće ljekaru nego farmaceutu.
Tokom istraživanja smo obišli i dvadesetak apoteka. U razgovoru sa farmaceutima smo zaključili da se mali broj prijavljenih sumnji na ND proslijedi dalje Agenciji za lijekove. U budućnosti treba raditi na poboljšanju informisanosti pacijenata i zdravstvenih radnika o značaju prijavljivanja ND kako bi se ona smanjila ili spriječila što je cilj farmakovigilance.

Ključne riječi: Neželjena dejstva, farmakovigilanca, prijavljivanje

PHARMACOVIGILANCE – MONITORING THE FREQUENCY OF OCCURRENCE AND REPORTING OF ADVERSE DRUG REACTIONS (ADR, OR ADVERSE DRUG EFFECT) IN MONTENEGRO

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The time in which we live is characterized by a steady increase in the use of drugs in the prevention and treatment of various ailments and diseases. Monitoring the risk-benefit ratio is an important parameter to evaluate its safety. Spontaneous reporting of adverse drug reactions (ADR) by healthcare professionals is necessary in order to prevent potential negative consequences of their use.
The aim of this study is to determine the frequency of occurrence of some harmful and unintentionally caused reactions to drugs, ADR reporting level by patients, as well as their familiarity with the possibility to report any suspected ADRs, ie. monitoring those activities which pharmacovigilance embraces.
The survey was conducted during March 2015. 260 respondents of both genders, aged between 19 and 88, of different socioeconomic status and level of education from several Montenegrin towns (Podgorica, Budva, Nikscic, Cetinje, Pljevlja, Berane) took part in an anonymous survey. Respondents answered the survey questions related to the frequency of occurrence and possibility of reporting ADRs to healthcare professionals.
Of the total number of respondents (260), 13% (n=34) fails to comply with the instructions prescribed by doctor (dosage, usage, time allowed between doses…). Even 23.5% does not read the PIL (Patient information leaflet) at all. When asked what kind of drugs they frequently use, 52% of respondents (n=135) said that they use drugs ‘’on their own hook’’, and 48% of them (n=125) with a prescription. An unbelievable 41.5% (n=108) of respondents does not know that there is a possibility to report ADRs. 28.5% of respondents (n=69) have had ADRs after drug administration, of which around 80% (n=55) reported them more more frequently to doctor than pharmacist.
During the survey, we have visited about twenty pharmacies. From a conversation with pharmacist we concluded that a small number of reported suspicions of ADRs is forwarded to the Agency for Medicines and Medical Devices. In the future we should work to improve the awareness of patients and healthcare professionals about the importance og reporting ADRs in order to reduce or prevent it, which is the purpose of pharmacovigilance.

Keywords: adverse drug reactions (ADR), pharmacovigilance, reporting

BRIGA O ZDRAVLJU - FITOFARMACIJA U SAMOMEDIKACIJI

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Nepravilna ishrana, nedovoljno kvalitetnog sna, izostanak fizičke aktivnosti, stres - sve su to tihe ubice našeg imunog sistema koji posljedično biva podložan, najprije, manje ozbiljnim, a zatim i teškim zdravstvenim poremećajima.
Ispred zdravlja se stavljaju drugi aspekti života, pa se njega, nažalost, velika većina sjeti tek po javljanju nekog problema, i to onda kada simptomi nastalog problema počnu da ometaju svakodnevne aktivnosti pojedinca.
,,Nemam vremena'' je najčešći razlog loših navika u održavanju zdravlja, neodlaska kod ljekara nakon javljanja problema i pristupanja samomedikaciji kao najlakšem rješenju. Istina je da postoje disbalansi u zdravlju koje možemo tretirati svojom kućnom apotekom, posebno onom biljnom, ali je neophodno znati ih prepoznati, pri čemu je potrebno adekvatno informisanje pojedinca (savjet farmaceuta, stručna literatura).
Podizanje svijesti stanovništva po pitanju vođenja zdravog života, a u cilju prevencije ozbiljnih zdravstvenih problema. U prilog ovome osvrćemo se na mjesto i ulogu fitofarmacije u sistemu primarne zdravstvene zaštite i samoliječenja.
Zasnovana na proučavanju dostupne literature, radova domaćih stručnjaka za fitoterapiju i vlastitim iskustvima.
Na osnovu sprovedene ankete, dokazujemo koliko je zauzimanje za ovu temu značajno radi iskorijenjavanja problema i pronaženja adekvatnog rješenja.
Greška je što se briga za zdravljem poistovjećuje samo sa tretiranjem bolesti, a izostavlja se onaj dio u kojem je ona prevencija bolesti. Greška može nastati i neadekvatnom samomedikacijom; istina, ona je manja ukoliko se koriste prirodni preparati, ali opet nezanemarljiva.
Pažljivije pristupanje samomedikaciji, spoznaja ljekovitosti prirodnih bogatstava, zatim njihovo udruživanje omogućiće eliminaciju navedenih grešaka.

Ključne riječi: zdravlje, prevencija, samomedikacija, fitofarmacija, fitopreparati.

HEALTH CARE – PHYTOPHARMACY IN SELF-MEDICATION

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Inadequate nutrition, shortage of quality sleeping, lack of physical activity, stress, these are all silent killers of our immune system which is consequently faced at first with less serious and then with more difficult health problems.
Other aspects of life come prior to health and that is why we come back to it only in case of we have some health problems. This usually comes at the point when the symptoms begin to disturb quotidian activities of a person.
“I have no time” is the most frequent reason for bad habits in maintaining good health, not visiting the doctors for health problem and starting with self-medication as the easiest solution.

It is true that there are health misbalances which can be treated by homemade pharmacy products, especially the herb ones. However, it is necessary to know how to recognize them, which implies adequate knowledge of a person (pharmaceutical advice, professional literature). Raising awareness of people when it comes to the living of healthy life, in order to prevent some serious health problems. Therefore, we look at the place and role of phytopharmacy within the system of primary health care and self-medication.
Based on study of available literature, publications of domestic experts for phytotherapy, as well as on our own experience.
On the ground of the conducted poll we are examining how much the interest for this topic is important for eliminating the problems and finding appropriate solutions.
The big mistake is equating the health care only with disease treatment, forgetting that health care refers also to disease prevention. Mistakes may also happen by inadequate self-medication, although smaller if the natural products are used, but they are still not negligible.
Cautious using of self-medication, recognizing healing effects of natural resources, and their joint use will ensure the elimination of the mentioned mistakes.

Keywords: health, prevention, self-medication, phytopharmacy, phytoproducts.

DETOKSIKACIJA ORGANIZMA OD ŠTETNIH AGENASA U NAŠEM OKRUŽENJU

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Naš organizam je opterećen ne samo probavljanjem teške i nezdrave hrane, već on takođe mora eliminisati pesticide, zagađivače i toksične agense koji ulaze u tijelo iz našeg okruženja i hrane. Ako se tome dodaju još i stres, prebrzi ritam života i nedostatak vježbe, sve ovo može preopteretiti i oslabiti organizam i spriječiti njegov pravilan rad. Nepravilan rad organizma može uzrokovati manje tegobe, kao što su umor i pospanost, a kasnije i veće probleme kao što su depresija, prerano starenje i različite bolesti. Toksine ne možemo izbjeći, zato što su oni svuda oko nas. Toksini i teški metali zagađuju vodu, vazduh i hranu. Svakodnevno koristimo kozmetiku i sredstva za ličnu higijenu, koji su puni opasnih hemikalija. Kada uđu u naš organizam, teški metali nagomilavaju se u unutrašnjim organima, tkivima i kostima. Naše tijelo ih ne može eliminisati bez naše pomoći. Detoksikacijska sredstva, i to vrlo pristupačna, osim fizičkih (glina, zeolit, hladno cijeđena i etarska ulja...) mogu biti i: tišina, zvuci prirode, opuštajuća muzika.
Da ukažemo na važnost pravovremenog djelovanja u smjeru čišćenja organizma od otrova, a u cilju vraćanja energije i poboljšanja cjelokupnog zdravlja.
Zasnovana na izučavanju dostupne literature, rada domaćih stručnjaka za detoksikaciju, iskustvima ljudi, kao i vlastitim iskustvima.
Pokazali su da je efekat detoksikacije, ili čišćenja organizma, pomogao mnogima da vrate prirodnu ravnotežu svom tijelu. Mnogi ljudi svjedoče o tome da su uspjeli da povrate energiju, koncentraciju i pozitivni stav.
Postoji više načina detoksikacije tijela. Iako skoro svaki wellness centar nudi tretman detoksikacije, ne treba žuriti, jer nam priroda nudi jednostavne i besplatne načine čišćenja organizma.
Ključne riječi: Detoksikacija, toksini, simptomi, detoksikacijska sredstva, detoksikacijske prakse.

BODY DETOXIFICATION OF HARMFUL SUBSTANCES IN THE ENVIRONMENT

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Our body is burdened not only with process of digestion of poor and unhealthy food, but also with elimination of pesticides, contamination and toxic substances which get into our body through the environment and food. In addition to this, there are stress, too fast way of living and lack of physical activities which also burden and weaken our body and disturb its regular functioning. Irregular body functioning may provoke some smaller issues such as tiredness and sleepiness, but further on it may cause bigger problems like depression, premature aging and many other conditions. We cannot avoid toxins because they are all around us. Toxins and heavy metals pollute water, air and food. On a daily basis, we use cosmetic as well as products for personal hygiene which are full of dangerous chemicals. Once they enter our body, heavy metals are being accumulated in internal organs, tissues and bones. The body itself cannot eliminate them without our help. Available detoxification tools, besides physical ones (clay, zeolite, cold-pressed and essential oils) include: silence, nature sounds, relax music.
To emphasize the importance of timely acting regarding the body cleaning of toxic substances, in order to recover the energy and improve overall health.
Based on study of available books, publications of domestic experts for detoxification, people's experience as well as on our own experience.
Showed that the detoxification or body cleaning effect helped people regain their natural body balance. Many people assert they managed to recover energy, concentration and positive state of mind.
There are many ways of body detoxifications. Although almost every wellness center offers the detoxification treatment, there should be no rush, because nature bestows simple and free ways of body cleaning on us.

Keywords: Detoxification, toxins, symptoms, detoxification products, detoxifications treatments.

3D-QSAR STUDIJA I RAZVOJ FARMAKOFORE ZA DIZAJN NOVIH ANTIDEPRESIVA SA DEJSTVOM NA TRANSPORTERE SEROTONINA I HISTAMINSKE H3 RECEPTORE

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Depresija je najčešći mentalni poremećaj koji pogađa oko 350 miliona ljudi širom sveta. Selektivni inhibitori preuzimanja serotonina (SSRIs- Selective Serotonine Reuptake Inhibitors) su lekovi izbora u lečenju depresije. Rezidualni simptomi (umor, kognitivna disfunkcija, poremećaji spavanja itd.) predstavljaju značajan problem u terapiji ovog poremećaja. Antagonisti H3 receptora poboljšavaju kognitivnu funkciju i povećavaju budnost, bez nespecifičnog stimulatornog efekta, što otvara mogućnost njihovog kombinovanja sa SSRIs u cilju prevazilaženja problema rezidualnih simptoma. Do danas su sintetisana mnoga jedinjenja sa dvostrukom aktivnošću inhibitora preuzimanja serotonina/antagonista H3 receptora.

Cilj rada je bio formiranje 3D-QSAR modela i strukture farmakofore jedinjenja sa dualnom aktivnošću inhibitora preuzimanja serotonina i antagonista histaminskih H3 receptora i dizajn novih antidepresiva koji ostvaruju efekat na oba ciljna mesta.
Iz literature su preuzeti podaci o strukturi i aktivnosti dualnih inhibitora preuzimanja serotonina/antagonista H3 receptora. Za pripremu molekula su korišćeni Marvin Sketch program, komponente ChemOffice paketa i Gaussian 98W. 3D-QSAR (3D Quantitative Structure-Activity Relationship) studija je sprovedena pomoću programa Pentacle 1.0.6.
Formiran je 3D-QSAR model SERT (Serotonin Reuptake Transporter) inhibitora i 3D-QSAR model antagonista H3R i konstruisane su 3D-strukture farmakofora za oba ciljna mesta. Definisane su strukturne karakteristike ispitivanih jedinjenja sa najvećim uticajem na aktivnost na SERT i H3R. Oba 3D-QSAR modela su ukazala na odgovarajućeg donora vodonične veze i supstituisanu fenil grupu sa optimalnim sternim i hidrofobnim osobinama kao značajne grupe za aktivnost na oba ciljna mesta. Stoga, uvođenjem odgovarajućeg supstituenta u fenil grupu, dizajnirani su novi ligandi. Dizajnirani ligandi sa predviđenom pKi(SERT)>8,42 i sa predviđenom pKi(H3R)>8,39 odabranu su za dalju studiju.
Formirane 3D-strukture farmakofora su upotrebljene za dizajn novih dualnih SERT/H3R inhibitora. Prednost dizajniranih jedinjenja u odnosu na polazna ogleda se u većoj aktivnosti na H3R uz zadržavanje optimalne aktivnosti inhibitora preuzimanja serotonina.

Ključne reči: Dizajn lekova, antidepresivi, 3D-QSAR, SSRI, antagonisti H3 receptora

3D-QSAR STUDY AND PHARMACOPHORE DEVELOPMENT OF NOVEL ANTIDEPRESSANTS AFFECTING SEROTONINE TRANSPORTERS AND HISTAMINE H3 RECEPTORS

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Depression is the most prevalent psychiatric disease, affecting 350 million people worldwide. Selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed antidepressant drugs. Residual symptoms (fatigue, cognitive dysfunction, sleep disturbance etc.) are important problem in therapy of depression. Since H3 receptor (H3R) antagonists improve cognition and increase wakefulness without showing nonspecific stimulant effects, development of novel dual acting antidepressants affecting serotonin transporters and histamine H3 receptors is potential solution to residual symptoms problem. To the present, many compounds with dual activity have been synthesized.
The aim of this study was to create 3D-QSAR models and pharmacophore structure of dual serotonin transporter/histamine H3 ligands and to design novel ligands as potential antidepressants.
Information about structure and activity of dual serotonin transporter/histamine H3 ligands was taken from references. Molecules were prepared in Marvin Sketch, ChemOffice and Gaussian 98W programs. 3D-QSAR (3D Quantitative Structure-Activity Relationship) analysis was performed by Pentacle 1.0.6 program.
Two 3D-QSAR models have been built, SERT (Serotonin Reuptake Transporter) model and H3R model, and 3D-pharmacophore structures have been constructed. Structural features

important for activity on both target sites have been defined. The 3D-QSAR models revealed specific hydrogen bound donor and substituted phenyl group with optimal steric and hydrophobic features as the structures significant for activity on both target sites. Therefore, by introducing the appropriate substituent into phenyl group, novel ligands have been designed. Designed ligands with predicted pKi(SERT)>8,42, and predicted pKi(H3R)>8,39 were selected for further evaluation.
Formed 3D-pharmacophore structures have been used for design of novel dual serotonin transporter/histamine H3 ligands. Advantage of designed ligands compared with the lead, is that designed ligands have higher activity on histamine H3 receptor, while they maintain optimal activity on SERT.

Key words: Drug design, Antidepressants, 3D-QSAR, SSRI, H3 receptor antagonist

PARENTERALNE NANOEMULZIJE DIAZEPAMA SA 20, 30 I 40% ULJANE FAZE: FIZIČKOHEMIJSKA I BIOFARMACEUTSKA KARAKTERIZACIJA

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Poznato je da parametri formulacije, kao i parametri procesa izrade, mogu značajno da utiču na fizičkohemijska svojstva i stabilnost nanoemulzija. Pored toga, od velikog značaja je i razumevanje uticaja same formulacije na ponašanje inkorporiranog leka – oslobađanje iz nanoemulzija, farmakokinetičko ponašanje i, posledično, terapijski efekat. Cilj ovog rada bio je da se razviju parenteralne nanoemulzije sa diazepamom kao model lekovitom supstancom i da se sprovede njihova sveobuhvatna fizičkohemijska i biofarmaceutska karakterizacija.
Metodom homogenizacije pod visokim pritiskom izrađene su nanoemulzije diazepama, stabilizovane smešom lecitina i polisorbata 80, variranjem udela uljane faze – 20, 30 i 40% (m/m) smeše triglicerida srednje dužine lanca i sojinog ulja u odnosu 4:1. U istraživanju je praćen uticaj koncentracije uljane faze na veličinu kapi (Z-Ave), indeks polidisperznosti (PdI), zeta potencijal (ZP) i fizičku stabilnost nanoemulzija. Takođe, praćen je uticaj broja ciklusa homogenizacije na Z-Ave i PdI u cilju identifikovanja optimalnih uslova za izradu nanoemulzija. Primenom reverzne tehnike sa dijaliznim vrećicama sprovedeno je in vitro ispitivanje brzine oslobađanja diazepama iz razvijenih nanoemulzija, uz karakterizaciju dobijenih profila oslobađanja primenom različitih matematičkih modela.
Nakon izrade, sve formulacije imale su prosečnu veličinu kapi u opsegu 197–211 nm, sa veoma uskom distribucijom veličine (PdI: 0,102–0,124), dok je ZP bio oko –50 mV. Tokom 2 meseca čuvanja na 25°C, sve nanoemulzije bile su fizički stabilne, bez značajnih promena u praćenim parametrima. In vitro ispitivanje brzine oslobađanja pokazalo je da su profili oslobađanja diazepama iz ispitivanih nanoemulzija sa 20, 30 i 40% uljane faze slični i da se 40–50% diazepama oslobodi iz ovih nanoemulzija u toku 1 h, pri čemu se kinetika oslobađanja može opisati Korsmeyer-Peppas modelom.

U zaključku, diskontinuiranim postupkom homogenizacije (9 ciklusa, 500 bar, 25°C) mogle su se dobiti nanoemulzije diazepama opimalnih karakteristika, pri čemu nije postojao značajan uticaj sastava formulacije na osobine i fizičku stabilnost ispitivanih nanoemulzija.

Ključne reči: nanoemulzija; diazepam; fizička stabilnost; in vitro oslobađanje leka; reverzna tehnika sa dijaliznim vrećicama.

PARENTERAL DIAZEPAM-LOADED NANOEMULSIONS WITH 20, 30 AND 40% OF OIL PHASE: PHYSICOCHEMICAL AND BIOPHARMACEUTICAL CHARACTERIZATION

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It is known that both, formulation parameters and processing conditions can affect physicochemical properties and stability of nanoemulsions. Furthermore, it is of great importance to understand the influence of the nanoemulsion system on its own on behavior of the incorporated drug – release from nanoemulsions, pharmacokinetics, and consequently its therapeutic effect. The aim of this study was to develop parenetral nanoemulsions with diazepam as model drug and to perform their comprehensive physicochemical and biopharmaceutical characterization.
For this purpose, diazepam-loaded nanoemulsions stabilized by lecithin/polysorbate 80 mixture and containing different concentration of oil phase – 20, 30 and 40% (w/w) of medium chain triglycerides–soybean oil mixture at 4:1 ratio, were prepared by high pressure homogenization. The effect of oil content on nanoemulsion droplet size (Z-Ave), polydispersity index (PDI), zeta potential (ZP), and physical stability was investigated. Also, the influence of number of homogenization cycles on Z-ave and PdI was studied to identify optimal conditions for nanoemulsion preparation. The in vitro release of diazepam from developed nanoemulsions was examined using reverse dialysis bag technique and drug release kinetics was evaluated through several mathematical models.
After preparation, all formulations revealed small Z-ave (197–211 nm), narrow droplet size distribution (PdI: 0.102–0.124), and ZP around –50 mV. During 2 months of storage at 25°C, all nanoemulsions remained physically stable, without considerable changes in monitored parameters. In vitro drug release study demonstrated that the release profiles of diazepam from the actual nanoemulsions with 20, 30 and 40% of oil were similar. The percent of diazepam released was 40–50% within 1 h, while the kinetic release process could be described by Korsmeyer–Peppas model.
To summarize, discontinuous homogenization process (9 cycles, 500 bar, 25°C) could yield nanoemulsions with optimal characteristics and there was no significant influence of formulation composition on nanoemulsion properties and physical stability.

Keywords: nanoemulsion; diazepam; physical stability; in vitro drug release; reverse dialysis bag technique.

ALERGIJE - NAJČEŠĆI SIMPTOMI I UZROČNICI

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Alergija je promijenjena reakcija imunološkog sistema na strane materije iz okruženja koje inače nijesu štetne, i bezopasne su za većinu ljudi.
Utvrđivanje zastupljenosti alergija među građanima Podgorice, alergena koji su najčešći uzročnici alergijske reakcije, kao i najčešćih simptoma do kojih dovodi.
U Podgorici je sprovedena anonimna i dobrovoljna anketa na koju je odgovaralo 150 ispitanika. Ispitanici stariji od 18 godina, oba pola, različitog stepena obrazovanja i različitog socio-ekonomskog statusa, odgovarali su na 11 pitanja, koja su se odnosila na to da li su nekada imali alergijsku reakciju, na koji alergen, koje su ljekove koristili za olakšavanje simptoma. Istražili smo na koji način ispitanici biraju lijek, kao i informisanost o novim načinima liječenja alergija.
Od 150 ispitanika, njih 110 (73,3%) je imalo alergijsku reakciju. Najčešći alergeni su polen (25,3%), hrana (20,7%) i prašina (20%). 6,7% ispitanika imalo je alergijsku reakciju na lijek. Najveći broj ispitanika koji su imali alergijsku reakciju na hranu, kao sastojak namirnice koji je njen uzročnik navode gluten. Alergija se najčešće manifestuje osipom na koži (37,3%), kijanjem i curenjem iz nosa (28,7%), crvenilom očiju (17,3%) i kašljem (17%). Ispitanici navode da se simptomi najčešće javljaju u spoljašnjoj sredini (30%), i da su najizraženiji u proljeće (28,7%). Pri izboru lijeka najčešće se savjetuju sa ljekarom (32%) i farmaceutom (27,3%), a za olakšavanje simptoma najčešće uzimaju antihistaminike (34,7%), prirodne ljekove (18%) i lokalne dekongestive (14%). Od ukupnog broja ispitanika 50% nije upoznato sa alternativnim načinima liječenja (akupunktura, BICOM, homeopatsko liječenje).
U Podgorici veliki broj ljudi pati od različitih vrsta alergija. Iz rezultata ankete možemo zaključiti da pri izboru lijeka veliki broj ispitanika ukazuje povjerenje farmaceutu. Alergeni se nalaze svuda oko nas, u vazduhu, hrani, kozmetičkim proizvodima i alergijske reakcije mogu remetiti svakodnevan život pacijenata tako da je veoma važno pravilno savjetovanje pacijenata.

Ključne riječi: alergija, alergeni, simptomi

ALLERGIES - THE MOST COMMON SYMPTOMS AND CAUSES

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Allergies are hypersensitive immune responses to foreign substances in the environment which are not harmful to most people.
To establish the incidence of allergies among the citizens of Podgorica, the most common causes of allergic reactions, as well as the most common symptoms which may occur.
An anonymous and voluntary survey was conducted in Podgorica, in which 150 respondents were participating. Respondents aged above 18 years, both sexes, different levels of education and different socio-economic levels, answered 11 questions which were related to the fact, whether they have ever had an allergic reaction to the allergen, which drugs they used to relieve

symptoms. We investigated how respondents choose medicine as well as how much they are informed about alternative treatments of allergies.
110 (73.3%) of the 150 respondents, had an allergic reaction. The most common allergens are pollen (25.3%), food (20.7%) and dust (20%). 6.7% of the respondents had an allergic reaction to the drug. The largest number of the respondents who have had an allergic reaction to the food, said that gluten was the cause. The most common manifestation of allergy is skin rash (37.3%), then sneezing and runny nose (28.7%), redness of eyes (17.3%) and cough (17%). Respondents answered that the symptoms most often occur in the environment (30%), and they are most pronounced in the spring (28.7%). When they choose a drug, they commonly consult with a doctor (32%) and pharmacists (27.3%), and for relieving the symptoms they usually take antihistamines (34.7%), natural medicines (18%) and local decongestants (14%). 50% of all respondents are not informed about the alternative ways of allergy treatments (acupuncture, BICOM, homeopathic treatment).
In Podgorica large number of people suffer from various kinds of allergies. From the survey results, we can conclude that when they choose a drug, large number of respondents have confidence in pharmacist. Allergens are all around us, in the air, food, cosmetic products and allergic reactions may disturb the daily life of patients, so proper counseling of patients is very important.

Keywords: allergies, allergens, the symptoms

KOMBINOVANI SMEŠA-PROCES EKSPERIMENTALNI DIZAJN U FORMULACIJI NANOEMULZIJA ACEKLOFENAKA STABILIZOVANIH BIODEGRADABILNIM EMULGATORIMA

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Tokom razvoja nanoemulzija (NE) kao nosača lekova, formulacioni i procesni parametri mogu uticati na fizičkohemijske karakteristike i stabilnost sistema, pa ih je stoga važno istovremeno optimizovati.
Cilj ove studije bio je da se ispitaju efekti smeše emulgatora, procesnih faktora i prisusutva aceklofenaka (ACF) kao model lekovite supstance na kritične karakteristike NE izrađenih metodom tople homogenizacije pod visokim pritiskom (HPH) uz primenu kombinovanog smeša-proces eksperimentalnog dizajna.
U studiji su odabrana tri emulgatora –lecitin iz jajeta (1-2%), saharoza palmitat (0-2%), saharoza stearat (0-2%) – sa ukupnim udelom 4% u formulacijama, dve procesne promenljive – pritisak (500/800 bar) i broj ciklusa homogenizacije (15/20), kao i jedna kategorička varijabla – prisustvo ACF-a. Prema D-optimalnom algoritmu, uključujući 5 lack-of-fit i 5 replikata, generisana su i nasumično sprovedena ukupno 52 eksperimenta. Kao odgovori praćeni su veličina kapi

(Z-ave) i distribucija kapi po veličini (indeks polidisperznosti, PDI) izrađenih NE. U cilju odabira kombinacija smeše i procesnih faktora koje dovode do formiranja NE prihvatljivih karakteristika sprovedene su numerička i grafička optimizacija. Odabrane optimalne ACF-NE su dalje temeljno okarakterisane u pogledu fizičkohemijskih karakteristika (površinsko naelektrisanje, viskozitet, morfologija, pH, elektična provodljivost, interakcije lek-nosač) i stabilnosti.
Izabrani dizajn je potvrdio da je kvadratni model, u slučaju smeše, ukršten sa modelom dvofaktorskih interakcija, u slučaju procesa, na odgovarajući način opisao oba posmatrana odgovora (Z-ave i PDI). Predloženi modeli su bili značajni i za model smeše i za model procesa. Takođe je pokazano da obe procesne promenljive, kao i prisustvo model leka, utiču, na određeni način, na efekte komponenti smeše. Optimalne formulacije NE sa lekom bile su različite u zavisnosti od procesnih uslova i posedovale su zadovoljavajuće fizičkohemjske karakteristike i stabilnost tokom 3 meseca čuvanja na sobnoj temperaturi.
Rezultati ove studije su jasno pokazali da je kombinovani smeša-proces eksperimentalni dizajn izuzetno pogodan za razvoj fizički stabilnih NE ACF-a stabilizovanih biodegradabilnim emulgatorima primenom HPH metode za njihovu izradu.

Ključne reči: kombinovani smeša-proces eksperimentalni dizajn, nanoemulzije, aceklofenak, šećerni estri, optimizacija.

COMBINED MIXTURE-PROCESS EXPERIMENTAL DESIGN IN FORMULATION OF ACECLOFENAC NANOEMULSIONS STABILIZED BY BIODEGRADABLE EMULSIFIERS

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During development of nanoemulsions (NEs) as drug carriers, formulation and processing parameters can affect NE physicochemical properties and stability and should be simultaneously optimized.
The aim was to evaluate the effect of emulsifier mixture composition, process variables and presence of aceclofenac (ACF) as model drug on critical NEs characteristics prepared using high pressure homogenization by employing combined, mixture-process experimental design.
Three emulsifiers – egg lecithin (1–2%), sucrose stearate (0–2%), sucrose palmitate (0–2%) – with the sum of all their proportions restricted to 4%, two process variables – homogenization pressure (500/800 bar) and number of cycles (15/20), and one non-mixture categorical variable – the presence of ACF, were selected in this study. According to the applied D-optimal algorithm, with 5 lack-of-fit and 5 replicate points, a total of 52 experimental runs were generated and randomly performed. As the response variables, the droplet size (Z-ave) and size distribution (polydispersity index, PDI) of the prepared nanoemulsions were evaluated. To find the mixture-process combination leading to the drug-loaded nanoemulsions with acceptable characteristics, numerical and graphical optimization procedures were conducted. Selected optimal ACF-loaded

nanoemulsions were further submitted to comprehensive physicochemical characterization (surface charge, viscosity, morphology, pH, electrical conductivity drug-excipient interaction) and stability testing.
The chosen design supported a quadratic mixture model crossed with a two-factor interaction process model for both Z-ave and PDI. The suggested models were significant for both the mixture and the process models. It was shown that each process variable as well as the presence of model drug influenced, in some way, the effects of mixture components. The optimal drug-loaded nanoemulsion formulations were different depending on the preparation conditions and exhibited satisfying physicochemical properties and stability during 3 months of storage at 25°C.
The results of present study showed the suitability of combined mixture-process experimental design approach for development of physically stable ACF-loaded nanoemulsions with biodegradable emulsifiers using HPH as fabrication method.

Keywords: combined mixture-process design, nanoemulsion, aceclofenac, sucrose esters, optimization.

ISPITIVANJE DIJATOMEJSKE ZEMLJE I PRIRODNOG ZEOLITA MODIFIKOVANIH SURFAKTANTOM KAO POTENCIJALNIH FARMACEUTSKIH EKSCIPIJENASA

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Literaturni podaci o prirodnim zeolitima modifikovanim određenim katjonskim surfaktantima u količini jednakoj ili većoj od spoljašnjeg kapaciteta izmene katjona (ECEC) ukazuju na proporcionalno povećanje kapaciteta adsorpcije ljekovite supstance sa povećanjem količine surfaktanta, kao i na posledično produženo oslobađanje ljekovite supstance iz dobijenih modifikovani zeolit/ljekovita supstanca kompozita. Cilj ovog istraživanja bio je ispitivanje modifikacije surfaktantom silikatnog minerala dijatomita, čija je uspešna neorganska modifikacija prethodno opisana, kao i procena njegove moguće primene kao funkcionalnog nosača za model ljekovitu supstancu diklofenak-natrijum (DS) u poređenju sa modifikovanim prirodnim zeolitom. Polazni uzorci dijatomita (D) ((d0,5): 38,4 μm; (d0,9): 78,7 μm) i prirodnog zeolita klinoptilolita (Z) ((d0,5): 13,3 μm; (d0,9): 159,8 μm) tretirani su heksadeciltrimetilamonijum-bromidom (HB) u jednostepenom postupku modifikacije. Karakterizacija polaznih i modifikovanih materijala (DHB i ZHB kompozita) sprovedena je merenjem zeta potencijala i ispitivanjem adsorpcije iz rastvora DS (4 mg/ml). Kompoziti DHB/DS i ZHB/DS pripremljeni su uparavanjem rastvarača, dok je ispitivanje brzine rastvaranja ljekovite supstance iz dobijenih kompozita izvedeno u aparaturi sa protočnom ćelijom u fosfatnom puferu pH 7,5.
Zeta potencijali uzoraka DHB (+5,7 mV) i ZHB (-18,1 mV) razlikovali su se u odnosu na zeta potencijale polaznih materijala: D (-28,96 mV) i Z (-27,4 mV), što upućuje na promjenu svojstava površine minerala nakon postupka modifikacije. Kapacitet adsorpcije DS na DHB (~23 mg/g) bio je nešto niži u odnosu na ZHB (~34 mg/g). Produženo oslobađanje DS iz organomineral/ljekovita supstanca kompozita (koji sadrže 75 mg DS-a) zapaženo je iz DHB/DS tokom 3h (do 94%) i ZHB/DS tokom 6h (do 92%).

Dobijeni rezultati ukazuju da modifikacija površine prirodnih silikatnih materijala (dijatomita i zeolita) katjonskim surfaktantima može poslužiti kao osnova za dalja ispitivanja u cilju dobijanja farmaceutskih ekscipijenasa poboljšanih svojstava - funkcionalnih nosača za ljekovite supstance.

Ključne riječi: dijatomit, klinoptilolit, katjonski surfaktant, nosač za ljekovite supstance, produženo oslobađanje

AN INVESTIGATION OF SURFACTANT MODIFIED DIATOMACEOUS EARTH AND NATURAL ZEOLITE AS POTENTIAL PHARMACEUTICAL EXCIPIENTS

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Literature data on natural zeolites modified with certain cationic surfactants in the amount equal or higher than its external cation exchange capacity (ECEC), showed proportional increase in adsorption capacity for drug molecules with increasing surfactant amounts, as well as subsequent prolonged drug release from the obtained modified zeolite/drug composites. The aim of this study was to investigate surfactant modification of a siliceous mineral diatomite, whose successful inorganic modification has been reported previously, and to access its potential use as a functional carrier for model drug-diclofenac sodium (DS) in comparison with modified natural zeolite.

The starting samples of diatomite (D) ((d0.5): 38.4 μm; (d0.9): 78.7 μm) and natural zeolite clinoptilolite (Z) ((d0.5): 13.3 μm; (d0.9): 159.8 μm) were treated with hexadecyltrimethylammonium bromide (HB) in the one step modification procedure. Characterization of the starting and modified materials (DHB and ZHB composites) was performed by zeta potential measurements and batch adsorption from DS (4 mg/ml) solution. Preparation of DHB/DS and ZHB/DS composites was done by solvent evaporation method while subsequent in vitro drug release was performed in a flow-through cell dissolution tester in phosphate buffer pH 7.5.

The zeta potentials of DHB (+5.7 mV) and ZHB (-18.1 mV) altered comparing with the zeta potentials of the starting materials: D (-28.96 mV) and Z (-27.4 mV), implying changes in surface properties after the modification procedure. DS adsorption capacity by DHB (~23 mg/g) was slightly lower than by ZHB (~34 mg/g). Prolonged DS release from the organomineral/drug composites (containing 75 mg of DS) was observed from DHB/DS during 3h (up to 94%) and ZHB/DS during 6h (up to 92%).

The obtained results revealed that surface modification of natural siliceous materials (diatomite and zeolite) with cationic surfactants can be further explored in order to obtain a pharmaceutical excipient with improved properties toward functional drug carriers.

Keywords: diatomite, clinoptilolite, cationic surfactant, drug carrier, prolonged release

ISPITIVANJE UTICAJA MANITOLA I POLYOX N60K NA PROFIL OSLOBAĐANJA KARVEDILOLA IZ TABLETA OBLOŽENIH KOMPRESIJOM PRIMENOM EKSPERIMENTALNOG DIZAJNA

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Hronoterapijski sistemi predstavljaju savremeni pristup terapije bolesti koje pokazuju cirkadijalnu zavisnost. Ovi sistemi mogu biti formulisani kao kompresijom obložene tablete koje omogućavaju odlaganje oslobađanja lekovite supstance (tlag – vreme bez oslobađanja leka), a potom i njeno pulsno oslobađanje u stanju najveće izraženosti simptoma bolesti. Tablete obložene kompresijom sastoje se iz jezgra i omotača. U sastav tabletnog jezgra često ulaze osmotski ekscipijensi koji generišu neophodni pritisak za pucanje omotača i omogućavaju rapidno oslobađanje leka nakon tlag. Omotač može biti formulisan sa različitim vrstama polimera koji će kontrolisati vreme odlaganja oslobađanja leka, kao i mehanizam oslobađanja leka. Cilj rada bio je ispitivanje uticaja koncentracije manitola i Polyox N60K na profil oslobađanja karvedilola iz tableta dobijenih oblaganjem kompresijom, korišćenjem eksperimentalnog dizajna.
Eksperimentalnim dizajnom varirana su dva faktora na dva nivoa (koncentracija manitola (20% i 50%) i koncentracija Polyox® WSR N60K (30% i 35%)). Izrađene su četiri formulacije (F1-F4) na ekscenter tablet masini. Za tabletna jezgra korišćen je alat dijametra 6mm, a za omotač 10mm. Brzina rastvaranja karvedilola ispitivana je u uređaju sa lopaticama u 0.1M HCl. Kao zavisno promenljive za eksperimentalni dizajn uzeti su tlag i količina karvedilola koja se oslobodi u toku 1h nakon tlag (Q1h).
Rezultati dobijeni u Design Expert® Softveru pokazuju da koncentracija manitola ima značajan uticaj na Q1h. Povećanjem nivoa ovog faktora sa 20 na 50%, Q1h se povećava za više od 20% u formulacijama sa 30% polimera, i više od 30% u slučaju 35% polimera u omotaču. Pokazano je da koncentracija Polyox® WSR N60K nema značajan uticaj na ovu zavisno promenljivu. Takođe, rezultati su pokazali da jedino udeo polimera u omotaču ima statistički značajan uticaj na tlag ($p<0.05$). Povećanjem koncentracije Polyox® WSR N60K u omotaču tableta dolazi do povećanja tlag. Koncentracija manitola nema statistički značajan uticaj na odlaganje oslobađanja karvedilola.

Ključne reči: oblaganje kompresijom, karvedilol, manitol, Polyox® WSR N60K

EXAMINATION OF INFLUENCE OF MANNITOL AND POLYOX N60K ON CARVEDILOL RELEASING PROFILE FROM COMPRESSION COATED TABLETS USING EXPERIMENTAL DESIGN

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Chronotherapeutic systems represent modern approach in therapy of diseases which are showing circadian dependency. These systems can be formulated as compression coated tablets, which are providing delayed drug release (tlag - time without drug releasing), and afterwards its pulsatile release when maximal expresion of disease symptomathology occures.

Compression coated tablets are composed of core and coat. Usually in the tablet core formulation are included osmotic excipients generating osmotic pressure necessary for coating rupture and providing rapid drug release after tlag. Tablet coat can be formulated with different types of polymers which will control delaying time and mechanism of drug releasing. The aim of work was to examine the influence of mannitol and Polyox N60K concentration on carvedilol releasing profile from compression coated tablets, using experimental design.
In experimental design two factors were varied on two levels (mannitol concentration (20% and 50%) and Polyox N60K (30% and 35%)). Four formulations were made (F1-F4) on excenter tablet press. Punches 6mm were used for tablet cores, and 10mm for coats. Dissolution rate was examined in paddle apparatus in 0.1M HCl. Dependent variables chosen for experimental design were tlag and amount of carvedilol released for 1h after tlag (Q1h).
Results obtained in Design Expert® Software showed that concentration of mannitol has statisticaly significant influence on Q1h ($p<0.05$). Increasing the level of this factor from 20 to 50%, Q1h is increasing for more than 20% in the tablet formulations containing 30% of polymer, and more than 30% in case of 35% of polymer in coat. It was shown that concentration of Polyox® WSR N60K does not have significante influence on this dependent variable. Also, results showed that only the concentration of polymer has statisticaly significant influence on tlag ($p<0.05$). Increase of Polyox® WSR N60K concentration lead to increasing of tlag. Mannitol concentration doesn't have statisticaly significant influence on tlag.
Key words: compression coating, carvedilol, mannitol, Polyox® WSR N60K

PRIMJENA RP-HPLC METODE ZA ISPITIVANJE STABILNOSTI DIHIDROKVERCETINA U EMULZIJI TIPA ULJE U VODI KOJA PODLJEŽE BRZOJ INVERZIJI FAZA NA KOŽI

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SWOP (eng. Switch-Oil-Phase) emulzije su prepoznate kao interesantni i korisni nosači posebno u proizvodima za zaštitu od ultravioletnog (UV) zračenja, zbog osobine da podležu brzoj inverziji faza tokom primjene na koži pri čemu prelaze iz emulzije tipa ulje u vodi u emulziju tipa voda u ulju. Poznato je da flavonoid dihidrokvercetin (DHK) djeluje kao jak antioksidans, slično α-tokoferolu i da apsorbuje zrake iz širokog UV spektra, pa bi se mogao iskoristiti za umanjenje oštećenja na koži nastalih djelovanjem UV zračenja. Cilj ovog istraživanja bio je da se DHK ugradi u SWOP emulziju i da se primenom RP-HPLC analize prati njegova stabilnost tokom vremena (nakon 48 h, 1 mjeseca i 2 mjeseca).
Postupkom toplo/toplo emulgovanja pripremljene su SWOP emulzija (označena kao S) i SWOP emulzija u koju je ugrađen 1% DHK (označena kao S-DHQ) i ostavljene 48 h da se stabilizuju pre RP-HPLC analize. Razdvajanje komponenti uzoraka izvršeno je na Zorbax Eclipse XDB-C8 150x4,6 mm, 5 μm koloni (45 °C, brzina proticanja 1 ml/min, λ=355 nm) sa mobilnom fazom acetonitril:voda=30:70 (v/v) (pH je podješen na 2,8 dodatkom fosforne kiseline).
Jednostavna i brza RP-HPLC metoda je razvijena za praćenje koncentracije DHK u analiziranim uzorcima. Rezultati dobijeni RP-HPLC analizom uzorka S-DHQ nakon 48 h pokazali su da

je sadržaj DHK čak viši (oko 120%) u odnosu na deklarisani, što je vjerovatno posljedica isparavanja vode tokom pripreme emulzije. Nakon mjesec dana sadržaj DHK se smanjio (99,92%) i nastavio je da opada do 78,43% koliko je određeno nakon dva mjeseca. Smanjenje sadržaja DHK u emulziji može biti posljedica njegove oksidacije u kvercetin pod djelovanjem spoljašnjih uticaja u toku čuvanja.
Dobijeni rezultati ukazuju na podložnost DHK oksidaciji, što dovodi do smanjenja njegovog sadržaja tokom vremena. Dalja istraživanja biće usmjerena ka poboljšanju stabilnosti DHK u SWOP emulziji promenom postupka izrade i/ili uvođenjem dodatnog antioksidansa u formulaciju.

Ključne rječi: RP-HPLC, dihidrokvercetin, SWOP emulzija, antioksidans, UV zaštita.

AN INVESTIGATION OF DIHYDROQUERCETIN STABILITY IN FAST INVERTED OIL-IN-WATER EMULSION BY RP-HPLC METHOD

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SWOP (Switch-Oil-Phase) emulsions are, due to their properties to invert from oil-in-water into water-in-oil emulsions during application on the skin, recognized as interesting and useful especially as a carrier in sun protection products. Since the flavonoid dihydroquercetin (DHQ) acts as a powerful antioxidant similarly to α-tocopherol and shows absorption activity over a wide range of ultraviolet (UV) spectrum, it may be used for diminishing skin damage caused by UV radiation. The aim of this study was to incorporate DHQ into SWOP emulsion and to monitor its stability during the time (after 48 h, 1 month and 2 months) by RP-HPLC analysis.
The SWOP emulsion base (labeled as S) and the SWOP emulsion with incorporated 1% DHQ (labeled as S-DHQ) were prepared using hot/hot emulsification procedure and left to equilibrate for 48 h before RP-HPLC analysis. Samples were separated on Zorbax Eclipse XDB-C8 150x4.6 mm, 5 μm column (45 °C, flow rate 1 ml/min, λ=355 nm) with acetonitrile:water=30:70 (v/v) as mobile phase (pH adjusted to 2.80 with phosphoric acid).
A simple and rapid RP-HPLC method has been developed for DHQ concentration monitoring in the analyzed samples. The results obtained by RP-HPLC analysis of S-DHQ after 48 h indicated that DHQ content was even higher (approximately 120%) than declared, probably as a consequence of water evaporation during the preparation procedure. After 1 month DHQ content decreased (99.92%) and continued to decline reaching 78.43% after 2 months. DHQ content reduce might be a consequence of its oxidation into quercetin, under the influence of external factors during storage.
Obtained results indicated oxidation susceptibility of incorporated DHQ, leading to a reduction in its content over time. Further research will be directed towards improving the stability of DHQ incorporated into SWOP emulsion by changing the preparation procedure and/or adding of extra antioxidants in the formulation.

Keywords: RP-HPLC, dihydroquercetin, SWOP emulsion, antioxidant, UV protection

FARMAKOLOŠKE KARAKTERISTIKE SUPSTANCI KOJE SE KORISTE U SVRHU DOPINGA U SPORTU

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Definicija dopinga je vremenom mijenjana, ali se sa farmakološkog aspekta može objasniti kao pokušaj da se poboljšaju sportske sposobnosti, posebno snaga i izdržljivost, nelegalnom primjenom određenih supstanci ili postupaka. Većina ovih supstanci su dobro poznate i mehanizam njihovog djelovanja je opisan u referentnoj literaturi. Cilj našeg istraživanja je bio da se opišu farmakološke karakteristike supstanci koje se koriste u svrhu dopinga u sportu, a nalaze se na najnovijoj Zabranjenoj listi (eng. The 2015 Prohibited List), izdatoj od strane World Anti-Doping Agency (WADA), koja važi od januara 2015. Najčešće i najznačajnije zabranjene supstance i postupci su anabolički androgeni steroidi, klenbuterol, eritropoetin, humani horionski gonadotropin, luteinizirajući hormon, hormon rasta, diuretici i maskirajući agensi, stimulansi, glukokortikoidi, krvni, kao i genetski goping. Neke supstance, kao što su kofein ili nikotin, nijesu zabranjene, ali se njihova upotreba mora pratiti. Ne treba zaboraviti ni mnogobrojne supstance koje se tajno sintetišu u labaratorijama, sa ciljem da se onemogući njihova detekcija na antidoping testovima. Nabrojana sredstva se prvenstveno koriste u terapijske svrhe i imaju dobro definisane terapijske indikacije. Međutim, i njihova upotreba u dopingu je značajna, kako sa aspekta povećanja mišićne mase, snage ili izdržljivosti, tako i zbog brojnih neželjenih dejstava koja se mogu očekivati kod skoro svih osoba koje ih koriste. Osim toga, organizam zdravih osoba drugačije reaguje na ove supstance, nego pacijentov, koji ih koristi za liječenje. Anabolički androgeni steroidi su, vjerovatno, najviše zloupotrebljavani, ali i najbolje proučavani, posebno u cilju povećanja anaboličkih, a smanjenja androgenih efekata. Sintetisan je jako veliki broj, egzogenih i endogenih steroida, sa različitim načinima primjene, što sve otežava njihovu detekciju, zahtijevajući od nadležnih institucija veliku posvećenost u razvoju što efikasnijih testova, ali i u edukaciji sportista, trenera i ljekara.

Ključne riječi: doping, sport, farmakološki aktivne supstance

PHARMACOLOGICAL PROPERTIES OF SUBSTANCES THAT ARE USED FOR THE PURPOSE OF DOPING IN SPORT

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The definition of doping has been modified over the years, but its meaning may be pharmacologically understood as attempt to enhance athletic performance, mainly strength and endurance, by illegal administration of certain substances or methods. Most of these substances are well known, and their modes of action have been reviewed in reference literature. Aim of our research was to describe pharmacological characteristics of substances used in

doping in sport, which are identified on The 2015 Prohibited List, published by the World Anti-Doping Agency (WADA), which came into effect in January 2015.
The most important and most often abused prohibited substances and methods are: androgenic anabolic steroids, clenbuterol, erythropoetin, human chorionic gonadotropin, luteinizing hormone, growth hormone, diuretics and masking agents, stimulants, glucocorticoids, blood doping and gene doping. Some substances, like coffeine and nicotine, are not prohibited, but their use must be monitored. It's also important to mention many substances, which are secretly manifactured in laboratories, with purpose to circumvent doping tests. The listed substances are primarily used as therapeutic agents, and have well definied therapeutic indications. However, their use as performance-enhancing drugs is important, because of their properties to increase muscle mass, strength and endurance, but also because of many adverse effects, which are almost always encountered. Besides that, organism of a healthy individual reacts on these drugs differently, than it is the case in patient's organism, who administers them to treat diseases. Anabolic androgenic steroids are probably most often abused and studied , especially in terms of maximizing anabolic and minimizing andogenic effects. There is a large amount of various exogenous and endogenous steroids with different ways of administration, which makes their detection to become a difficult task, demanding of authorised institutions great commitment to develop effective tests, and also to educate athletes, coaches and physicians.

Key words: doping, sport, pharmacologicaly active substances

PRIMENA FRAKCIONOG EKSPERIMENTALNOG DIZAJNA U FORMULACIJI TABLETA KARBAMAZEPINA SA TENUTNIM OSLOBAĐANJEM

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U radu je prikazana izrada tableta sa samo-emulgujućim sistemima (SEDDS) granulacijom topljenjem radi povećanja brzine oslobađanja teško rastvorljive lekovite supstance.
Cilj rada bio je ispitivanje uticaja faktora formulacije i procesnih parametara na brzinu rastvaranja karbamazepina iz tableta.
Primenom frakcionog faktorskog eksperimentalnog dizajna (26-2) ispitivan je uticaj šest parametara na brzinu oslobađanja karbamazepina. Varirani faktori su vrsta vezivnog sredstva (Labrafil® 2130CS, Gelucire® 44/14), udeo vezivnog sredstva (20-30%), udeo karbamazepina (20-30%), udeo krospovidona (2-5%), vrsta sredstva za dopunjavanje (mikrokristalna celuloza, Neusilin® UFL2) i sila kompresije (7-8 kN). Ispitivanje brzine rastvaranja izvedeno je u aparaturi sa rotirajućim lopaticama (medijum: prečišćena voda-900 ml, 50 rpm, 37 °C). Vršeno je ispitivanje protočnosti tabletnih smeša i čvrstine tableta. Primenom diferencijalno skenirajuće kalorimetrije (DSC) i difrakcije X-zraka na uzorak u prahu (PXRD) okarakterisana je formulacija tableta iz koje je postignuto najveće povećanje brzine rastvaranja.
Tabletne smeše izrađene upotrebom Neusilin®-a UFL2 pokazale su lošu protočnost, dok su formulacije sa mikrokristalnom celulozom pokazale prihvatljivu i prosečnu protočnost. Veću čvrstinu su imale tablete izrađene upotebom Neusilin®-a UFL2, silom kompresije 8 kN. Najveći uticaj na brzinu rastvaranja su imali vrsta vezivnog sredstva i udeo karbamazepina.

Formulacija F3 (20% Labrafil® 2130CS, 30% karbamazepina, 5% krospovidona, Neusilin® UFL2, sila kompresije 7 kN) je pokazala najveću brzinu oslobađanja karbamazepina iz tableta, 58,67% nakon 30 minuta. Ispitivanjem ove formulacije primenom DSC i PXRD, na osnovu karakterističnih pikova pokazano je da se karbamazepin nalazi u svom farmakološki aktivnom obliku, polimorfnoj formi III.
Primenom frakcionog faktorskog eksperimentalnog dizajna u formulaciji tableta metodom granulacijom topljenjem uz korišćenje lipidnih ekscipijenasa, može se značajno povećati brzina rastvaranja karbamazepina, uz ostanak karbamazepina u polimorfnom obliku III. Nastavak studije bi se mogao sprovesti u smeru ispitivanja stabilnosti izrađenih tableta i optimizacije formulacije u kojoj bi bio dodat nejonski surfaktant, upotrebom odgovarajućeg eksperimentalnog dizajna.

Ključne reči: SEDDS, Neusilin® UFL2, tablete, Gelucire® 44/14, Labrafil® 2130CS

THE APPLICATION OF FRACTIONAL FACTORIAL EXPERIMENTAL DESIGN IN FORMULATION OF TABLETS WITH IMMEDIATE-RELEASE OF CARBAMAZEPINE

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This paper presents the development of self-emulsifying drug delivery systems (SEDDS) tablets, made by using melt granulation technique, with the purpose of increasing drug release rate.
The aim of this study was to examine the influence of formulation constituents and process parameters on carbamazepine release rate from tablets.
The first set of experiments investigated the influence of six parameters on carbamazepine release rate using fractional factorial experimental design (26-2). Varied factors were meltable binder type (Labrafil® 2130CS, Gelucire® 44/14), meltable binder ratio (20-30%), carbamazepine ratio (20-30%), crospovidone ratio (2-5%), constituent type (microcrystalline cellulose, Neusilin® UFL2) and compression force (7-8 kN). In vitro drug release studies were performed in apparatus with rotating paddles (medium: purified water-900 ml, 50 rpm, 37 °C). Flowability of tablet mixtures and tablet hardness were examined. Formulation with greatest release rate of carbamazepine was characterized using differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD).
Tablet mixtures that contained Neusilin® UFL2 had bad flowability, and those with microcrystalline cellulose had acceptable and average flowability. Harder tablets were produced using Neusilin® UFL2 and compression force 8 kN. Type of meltable binder and ratio of carbamazepine had the biggest influence on release rate of carbamazepine. Formulation F3 (20% Labrafil® 2130CS, 30% carbamazepine, 5% Crospovidone, Neusilin® UFL2, compression force 7 kN) showed greatest release rate of carbamazepine, 58,67% after 30 minutes. This formulation was analysed using DSC and PXRD. Based on the characteristic peaks, it was determined that carbamazepine kept pharmacologically active polymorph form III.
Application of fractional factorial experimental design, in formulation of tablets with immediate-release of carbamazepine, can increase the release rate of carbamazepine significantly. In developed tablets carbamazepine kept pharmacologically active polymorph form III. In further

study tablet stability should be examined. Also, optimization of formulation using experimental design with the addition of non-ionic surfactant should be conducted.

Keywords: SEDDS, Neusilin® UFL2, tablets, Gelucire® 44/14, Labrafil® 2130CS

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ISPITIVANJE UTICAJA VISKOZITETA MEDIJUMA NA RASPADLJIVOST TABLETA I BRZINU RASTVARANJA LEKOVITIH SUPSTANCI U BIODIS APARATURI

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Stepen i brzina apsorpcije, biološka raspoživost i efikasnost oralno unetih lekovitih supstanci mogu biti značajno izmenjeni usled istovremenog konzumiranja hrane. Nekoliko studija je pokazalo da je za adekvatnu in vitro simulaciju raspadljivosti tableta i brzine rastvaranja lekovite supstance u stanju sitosti potrebno kontrolisati viskozitet medijuma, kao jedan od ključnih faktora koji utiče na navedene procese.
Cilj ovog rada je bio da se ispita uticaj viskoziteta medijuma na raspadljivost tableta i brzinu rastvaranja izabranih lekovitih supstanci sa različitim biofarmaceutskim karakteristikama primenom BioDis aparature.
Raspadljivost i brzina rastvaranja model supstanci iz tableta sa trenutnim oslobađanjem ispitani su u vodi bez/sa dodatkom 0,5% ili 1,4% hidroksipropilmetil celuloze (HPMC), na 37±0,5 °C. Za poređenje profila brzine rastvaranja korišćene su vrednosti faktora sličnosti (f2). Za procenu odnosa između vremena raspadanja tableta i procenta rastvorene supstance primenjena je regresiona matematička analiza.
Ispitivanjem je pokazano da je povećan viskozitet medijuma u velikoj meri produžio vreme raspadanja tableta i uslovio razlike u profilima brzine rastvaranja ispitivanih lekovitih supstanci. Pri tome je uticaj viskoziteta medijuma na pomenute procese zavisio i od faktora formulacije. Odnos između vremena raspadanja tableta i procenta rastvorene supstance na početku ispitivanja (30 min) najbolje je opisan stepenom funkcijom, dok je odnos između vremena raspadanja tableta i efikasnosti rastvaranja bolje okarakterisan linearnom funkcijom.
Dobijeni rezultati pokazuju da se može uspostaviti određeni nivo korelacije između vremena dezintegracije tableta i brzine rastvaranja lekovitih supstanci u medijumima različitog viskoziteta. Pri tome su vrednosti koeficijenta korelacije dobijene ispitivanjem u BioDis uređaju veće u odnosu na vrednosti dobijene primenom konvencionalnih metoda (aparatura za ispitivanje raspadljivosti i aparatura sa lopaticama za ispitivanje brzine rastvaranja). Međutim, činjenica da je ovaj odnos formulacija-specifičan ukazuje na to da se ne može definisati „univerzalna“ funkcija koja bi ukazivala na zavisnost između raspadljivosti tableta i brzine rastvaranja lekovitih supstanci.

Ključne reči: raspadljivost, brzina rastvaranja, viskozitet, BioDis aparatura

VISCOSITY-MEDIATED TABLET DISINTEGRATION AND DRUG DISSOLUTION IN BIODIS APPARATUS

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Absorption, bioavailability and therapeutic efficacy of orally administered drugs may be significantly altered by concomitant food ingestion. Several studies emphasized that media viscosity is an important factor affecting dosage form disintegration and drug dissolution in the postprandial state, and therefore, should be considered in biorelevant in vitro disintegration and dissolution tests design.
The aim of this study was to estimate the influence of medium viscosity on tablet disintegration time and dissolution rate of the selected model substances with various biopharmaceutical properties using BioDis apparatus.
Tablet disintegration and drug dissolution tests were carried out in aqueous media without/with the addition of 0.5% or 1.4% hydroxypropyl methylcellulose (HPMC), at 37±0.5 °C. Dissolution profiles were compared using similarity factor (f2). Regression analysis was used to assess the relationship between disintegration and dissolution data.
The results showed that increased medium viscosity considerably prolonged tablet disintegration time, and caused differences in drug dissolution rates. However, the magnitude of these effects depended upon formulation factors. The relation between tablet disintegration time and drug dissolution rate at the beginning of dissolution process (30 min) could be described by the power function, while the relationship between tablet disintegration time and dissolution efficiency was better described by the linear function.
The outcomes of this study demonstrated certain level of correlation between tablet disintegration time and drug dissolution rate in media of various viscosity. Furthermore, BioDis test results indicated higher values of coefficient of correlation in comparison to the results obtained using conventional methods (disintegration tester and paddle apparatus for dissolution test). Nevertheless, formulation-dependent viscosity effects signify that there is no “universal” function describing the relationship between viscosity-mediated tablet disintegration and drug dissolution.

Keywords: disintegration, dissolution, viscosity, BioDis apparatus

ODREĐIVANJE SADRŽAJA TEŠKIH METALA U MMR VAKCINAMA

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Vakcina MMR je vakcina protiv malih boginja, zauški i crvenke–rubeole (Measles, Mumps, Rubella). Ona sadrži atenuisane viruse ovih bolesti, koje su visoko kontagiozne. Prva doza

MMR vakcine se daje djeci uzrasta 12-16 mjeseci, a druga doza pred upis u školu (uzrasta 5-6 godina). Neželjena dejstva na komponente vakcine su rijetka ali se mogu javiti: povišena temperatura, osip, malaksalost. Ona se mogu javiti između 5. i 21. dana od primanja injekcije, najčešće 10. dan.
Nakon pojave polemika u javnosti o vezi između pojave autizma kod djece uzrasta do 2 godine i sadržaja metala u MMR vakcini, odlučili smo da ispitamo njihov kvalitet sa aspekta prisustva teških metala. Rađeno je određivanje sadržaja teških metala (žive, olova, arsena, aluminijuma i bakra) u MMR vakcinama pod nazivom Trimovax®, prašak i rastvarač za rastvor za injekciju, i Priorix®, prašak i rastvarač za rastvor za injekciju.
Za određivanje koncentracije teških metala u MMR vakcinama Trimovax® i Priorix® korišćene su instrumentalne tehnike ICP-OES (indukovana kuplovana plazma sa optičkom emisionom spektrometrijom) za određivanje olova, arsena, aluminijuma i bakra, kao i DMA-80 (direktni živin analizator) za određivanje žive.
Na osnovu korišćenih metoda na uzorcima MMR vakcina, sadržaj žive u vakcinama Trimovax® i Priorix® bio je 1 ppb, odnosno 0.2 ppb, dok je sadržaj olova, arsena, aluminijuma i bakra bio ispod limita kvantifikacije (<LoQ).
Naše ispitivanje ide u prilog teoriji da ne postoji direktna veza između sadržaja teških metala u MMR vakcinama i nastanka autizma, uzimajući u obzir da je koncentracija olova, arsena, aluminijuma i bakra ispod limita kvantifikacije. Koncentracija žive je prisutna u tragovima, u onoj količini koja se normalno nalazi u vodi za piće (MDK=5 ppb), a koja ne može ispoljiti negativne fiziološke efekte.

Ključne riječi: MMR vakcina, autizam, teški metali, MDK-maksimalna dozvoljena koncentracija

DETERMINATION OF HEAVY METALS IN THE MMR VACCINE

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The MMR vaccine is an immunization vaccine against measles, mumps, and rubella. It contains the attenuated viruses of these diseases, which are highly contagious. The first MMR vaccine is generally administered to children aged 12-16 months, the second dose is administered before starting school (ages 5-6 years). Side effects of the vaccine components are rare but it may occur: fever, rash, fatigue. It can occur between 5th and the 21st day of receiving the injections, but usually the 10th day.
After the appearance of controversy in the public about the connection between the occurrence of autism in children under the age of 2 years and metal content in the MMR vaccine, we decided to examine their quality in terms of presence of heavy metals. We have made the determination of heavy metals (mercury, lead, arsenic, aluminum and copper) in the MMR vaccine called Trimovax®, powder and solvent for solution for injection, and Priorix®, powder and solvent for solution for injection.
To determine the concentrations of heavy metals in the MMR vaccines Trimovax® and Priorix®, we used instrumental techniques ICP-OES (inductively coupled plasma with optical emission

spectrometry) for the determination of lead, arsenic, aluminum and copper, as well as DMA-80 (Direct mercury analyzer) for determination of mercury.
According to intsrumental methods used on the MMR vaccine samples, the mercury content in Trimovax® and Priorix® vaccine were 1 ppb, i.e. 0.2 ppb, while the content of lead, arsenic, aluminum, and copper were below the limit of quantification (<LoQ).
Our study supports the theory that there is not a direct relationship between the content of heavy metals in the MMR vaccine and autism occurrence, considering the concentration of lead, arsenic, aluminum, and copper below the limit of quantification. The concentration of mercury is present in trace, in the amount that is normally found in drinking water (MAC = 5 ppb), which can't manifest negative physiological_effects.

Keywords: MMR vaccine, autism, heavy metals, MAC-maximum allowable concetration

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RACIONALNA UPOTREBA ANTIBIOTIKA MEĐU STUDENTIMA FARMACIJE

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Antibiotici su farmakološki agensi koji mogu imati baktericidno ili bakteriostatsko djelovanje. Glavna prijetnja sa kojom se sada suočavamo je pojava rezistencije pojedinih bakterija na većinu poznatih antibiotika. Pravilna i racionalna upotreba antibiotika može smanjiti i odložiti razvoj rezistencije. To treba postići utvrđivanjem politike upotrebe antibiotika, kontinuiranom edukacijom i sprovođenjem efikasnih aktivnosti i mjera u sprječavanju, prevenciji i kontroli infekcija.
Cilj rada je bio da se izvrši detaljna analiza obima potrošnje propisanih antiinfektiva za sistemsku primjenu među studentima farmacije na području Podgorice.
Sprovedena je studija presjeka (prevalence) i analizirana je upotreba ljekova čiji su troškovi pokriveni sredstvima Fonda zdravstvenog osiguranja Crne Gore. Da bismo dobili reprezentativan uzorak, anketa je sprovedena na cijelom Farmaceutskom fakultetu. Prikupljeni su podaci iz upitnika koji sadrži 12 pitanja i koji je popunio 161 student farmacije.
Na pitanje „Uzimanje antibiotske terapije prekidate čim osjetite poboljšanje simptoma"?, 78,75% studenata starijih studijskih godina je odgovorilo da „nikada ne prekidaju terapiju", dok 42,13% mlađih studenata terapiju „uvijek prekida". Svi studenti četvrte i pete godine znaju da neracionalna upotreba antibiotika dovodi do bakterijske rezistencije, dok 27,6% studenata prve tri godine nijesu sigurni vezano za pojavu rezistencije. 59% studenata prve godine zna da kašalj nije razlog za propisivanje antibiotika, pri čemu se taj procenat studenata povećava, preko 89,16% do 100% među studentima završne godine.
Da bismo se zaštitili od problema širenja bakterijske rezistencije na antibiotike neophodno je racionalizovati njihovu upotrebu. Svako davanje antibiotika treba da posmatramo kao balansirajući čin gdje treba procijeniti koji antibiotik treba dati, a da pri tome neželjena dejstva budu svedena na minimum. To se postiže utvrđivanjem strateškog programa i ciljeva za kontrolu rezistencije bakterija na antibiotike.

Ključne riječi: antibiotici, bakterije, rezistencija, anketa.

THE RATIONAL USE OF ANTIBIOTICS AMONG THE STUDENTS ON FACULTY OF PHARMACY

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Antibiotics are pharmacological agents that can have bactericide or bacteriostatic activity. The main threat we are now facing with, is the emergence of bacterial resistance on most of the antibiotics. Proper and rational use of antibiotics can reduce and delay the development of resistance. This should be achieved by setting the policy of using antibiotics, continuous education and implementation of effective actions and measures to prevent, prevention and control of infection.

The aim of this study is to perform a fundamental analysis of the scope of consumption of prescribed anti-infectives for systemic administration among the students on the Faculty of Pharmacy_in_Podgorica.

We conducted cross-sectional study (prevalence study) and analyzed the use of medicine which expenses were covered by Health Insurance Fund of Montenegro. To obtain a representative sample, the survey was conducted throughout the whole Faculty of Pharmacy. Data were collected from a questionnaire containing 12 questions which was filled by 161 Pharmacy students.

On the question: „Do you stop taking antibiotic therapy when you feel improvement of symptoms"?, 78,75% older students answered „never stop therapy", while 42,13% younger students answered „always do". All of the students from the 4th and 5th year know that irrational use of antibiotics leads to bacterial resistance, while 27,6% students from 1st, 2nd and 3rd year are not sure about resistance. 59% students from the 1st year know that cough is not the reason to prescribe antibiotics, where the percentage of students increases, from 89,16% to 100% among students in their final year.

The usage of antibiotics should be reduced and rationally prescribed in order to protect ourselves from the problem of the bacterial resistance. Each administration of antibiotics should be considered as a balancing act where it has to be estimated which antibiotic is the most appropriate to be given, while adverse effects would be minimized. This could be achieved by establishing strategic program and objectives for the control of bacterial resistance to antibiotics.

Keywords: antibiotics, bacteria, resistance, survey

EFIKASNOST I PODNOŠLJIVOST GABAPENTINA (KATENA) U LIJEČENJU DIJABETIČNE POLINEUROPATIJE

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Dijabetička polineuropatija je najčešća komplikacije šećerne bolesti. Gabapentin je lijek koji pripada prvoj liniji za liječenje neuropatske boli kod neuropatija .
Cilj istraživanja je pratiti efikasnost i podnošenje gabapentina (Katena) u liječenju dijabetičke polineuropatije kod pacijenata sa diabetes mellitusom tip 2.
U ovom prospektivnom istraživanju obrađeno je 56 bolesnika sa DM tip 2 na inzulinskoj terapiji. 34/56 (60,7%) bolesnika su bila muškog spola, a 22/56 (39,3%) bolesnika su bila ženskog spola. Istraživanje je rađeno u periodu od 03.03.2014.-10.10.2014.god. Dužina trajanja bolesti se kretala između 3-36 godina.
Svim pacijentima je urađen EMNG koji je potvrdio prisustvo neuropatije koji je osim anamneze koja je sadržavala simptomatologiju neuropatije bio kriterij za uključivanje u studiju.
Svi pacijenti su evaluirani pomoću upitnika koji je pripremljen za ovo istraživanje i koji sadrži tri dijela: prvi dio je dio sa generalijama i podacima o bolesti, dužina itd., drugi dio sadrži podatke o simptomima neuropatije i treći dio sadrži podatke o podnošenju lijeka koje daje sam pacijent.
Od 56 bolesnika, kod 42 (75%) bolesnika je prijavljeno poboljšanje nakon tromjesečnog uzimanja Gabapentina, dok kod 14/56 pacijenata (25%) nije prijavilo poboljšanje. Simptomi na koje se evidentirao pozitivan učinak lijeka su: smanjenje bola u ekstremitetima, poboljšan san, smanjeno trnjenje i grčevi u nogama. Kod 37 (66 %) bolesnika nije bilo nikakvih nus pojava za vrijeme uzimanja lijeka dok su 19 (34%) bolesnika javili nus pojave: 10/56 (17,9%) pospanost, 3/56 (5,4%) vrtoglavicu, 2/56 (3,5%) umor, 3/56 (5,4 %) konfuzije, 1/56 (1,8 %) promjenu raspoloženja. Simptomi su uglavnom trajali nekoliko dana od početka uzimanja lijeka i potom sami prestali i nisu zahtjevali prekidanje terapije osim u nekim slučajevima postepenije uvođenje. 3 pacijenta koji su imali jaku pospanost i 2 pacijenta koji su imali konfuznost, su samovoljno prekinuli terapiju.
Ovo istraživanje je pokazalo efikasnost gabapentina (Katena) u liječenju neuropatske boli kod dijabetične polineuropatije. Nus pojave koje su se javile su bile uglavnom blage i nije bilo interakcije sa drugim lijekovima što se u ovom istraživanju pokazalo kao sigurnost lijeka u liječenja bolesnika sa hroničnim oboljenjima koji uzimaju veliki broj medikamenata.

Ključne riječi: gabapentin, dijabetična polineuropatija

EFFICACY AND TOLERABILITY OF GABAPENATIN (KATENA) IN THE TREATMENT OF DIABETIC POLYNEUROPATHY

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Diabetic polyneuropathy is the most common complications of diabetes. Gabapentin is a medication that belongs to the first line of neuropathic pain treatment in case of neuropathy.
Goal to follow the effectiveness and tolerability of gabapentin (Katena) in the treatment of diabetic polyneuropathy in patients with diabetes mellitus type 2.
In this prospective study, 56 patients with DM type 2 on insulin therapy were included. From baseline 34/56 (60.7%) patients were male and 22/56 (39.3%) patients were female. The study was conducted over a period from March 3, 2014 - October 10, 2014. The disease duration ranged between 3-36 years.
All patients underwent EMNG which confirmed the presence of neuropathy, which is in addition to a history containing symptoms of neuropathy was the criterion for inclusion in the study.
All patients were evaluated using a questionnaire prepared for this study and which contains three parts: Part I is part on general data and information about the disease, duration etc. The second part contains information about the symptoms of neuropathy and the third part contains information on drug tolerability provided by the patient.
Of 56 patients, in 42 cases (75%) patients reported improvement after three months of taking gabapentin while in 14/56 patients (25%) reported improvement. Symptoms to which were recorded positive effects of the drug are: reduction of pain in the limbs, improved sleep, decreased numbness and cramps in the legs. In 37 (66%) patients there were no side effects while taking the drug, while 19 (34%) patients reported side effects: 10/56 (17.9%) drowsiness, 3/56 (5.4%) dizziness, 2/56 (3.5%) fatigue, 3/56 (5.4%) confusion, 1/56 (1.8%) mood. Symptoms are usually lasted several days from the beginning of the drug use and then stopped themselves and were not demanding the discontinuation of therapy except in some cases more gradual introduction. From baseline 3 patients had severe sleepiness and 2 patients who had confusion, arbitrarily discontinued therapy use.
This study demonstrated the efficacy of gabapentin (Katena) in the treatment of neuropathic pain in diabetic polyneuropathy. Side effects that occurred were mild and there were no interactions with other drugs so this study proved the safety of this drug in the treatment of patients with chronic diseases that use a large number of medications.

Key words: gabapentin, diabetic polyneuropathy

ULOGA FARMACEUTA U SAMOMEDIKACIJI

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Samomedikacija predstavlja izbor i upotrebu ljekova (uključujući i biljne i tradicionalne proizvode) od strane pojedinca, za bolesti i/ili simptome koje sam pojedinac prepozna. Dobra samomedikacija treba da obezbjedi efikasnost, pouzdanost, prihvatljiv rizik, široku dostupnost lijeku i veći izbor liječenja.
Utvrditi koliko je samomedikacija zastupljena na teritoriji Podgorice, za koje indikacije osobe uzimaju lijek samoinicijativno, koje preparate najčešće primjenjuju, šta im pomaže u izboru lijeka, kao i kolika je u tome uloga farmaceuta.
U Podgorici je sprovedena anonimna i dobrovoljna anketa na koju je odgovaralo 110 ispitanika. Ispitanici stariji od 18 godina, oba pola, različitog stepena obrazovanja i različitog socio-ekonomskog statusa, odgovarali su na 11 pitanja koja su se odnosila na to koliko često pribjegavaju samomedikaciji, na koji način biraju lijek i koja je uloga farmaceuta u tome.
Od 110 ispitanika, samo njih 12 (11%) odgovorilo je da nikada ne uzimaju lijek samoinicijativno, od preostalih 98, 8,9% uvijek uzima ljekove bez savjeta sa ljekarom. Kao razlog zbog kojeg se ispitanici odlučuju za samomedikaciju, najveći broj (29%) navodi da bolest ne zahtijeva ljekarsku pomoć, 27% navodi dugo čekanje u bolnicama, a 28% ispitanika smatra da je dovoljan savjet farmaceuta. Najčešće indikacije za samomedikaciju su prehlada (50%) i bolovi (44%). Ispitanici najčešće uzimaju vitamine (37%), biljne preparate (31%) i analgetike (26%). 15% ne čita uputstva priložena uz lijek, a 47% ispitanika uzima ljekove u prevenciji bolesti. 95% ispitanika se pri odabiru lijeka savjetuje sa farmaceutom.
Samomedikacija je u velikoj mjeri zastupljena u Podgorici. Istraživanje je pokazalo da pacijenti nijesu dovoljno informisani o rizicima koje samomedikacija nosi. Farmaceut je jedini zdravstveni profesionalac sa kojim pacijent ostvaruje kontakt pri samomedikaciji, tako da on ima ključnu ulogu u ostvarivanju bezbjedne samomedikacije.

Ključne riječi: samomedikacija, farmaceuti, uloga

THE ROLE OF PHARMACIST IN SELF - MEDICATION

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Self-medication is defined as the selection and use of medicines (including herbal and traditional products) by individuals to treat self-recognized or self-diagnosed conditions or symptoms. Good self-medication should ensure efficiency, reliability, acceptable risk, wide availability of the drug and a greater choice of treatment
To find out how much self-medication is present in the territory of Podgorica, for which indications people are taking the drug on their own initiative, which products are frequently applied, what helps them in the selection of the drugs and what is the role of the pharmacist.

An anonymous and voluntary survey was conducted in Podgorica, in which 110 respondents were participating. Respondents aged above 18 years, both sexes, different levels of education and different socio-economic levels, answered 11 questions that were related to how much self-medication is present in patients life, how they choose the medicine and the role of pharmacists in it.
Only 12 (11%) of 110 respondents said they never take the drug on their own initiative, 8,9 % of the remaining 109, always take medicines without the advice of a doctor. As a reason for choosing self-medication, the largest number (29%) said that the disease does not require medical assistance, the reason of a smaller number of respondents (27%) was long waiting in hospitals, and 28% of respondents considered that the advice of the pharmacists is sufficient. The most common indications for self-medication are common cold (50%) and pain (44%). Respondents most often take vitamins (37%), herbal preparations (31%) and analgetics (26%). 15% of respondents never read the instructions provided with medication. 47% of respondents take drugs in disease prevention. 95% of respondents consult with a pharmacist when they choose a medicine.
Self-medication is very common method of treatment in Podgorica. Research has shown that patients are not sufficiently informed about the risks of self-medication. Pharmacist is the only health professional with whom the patient has contact when he decides for self-medication, so pharmacist has a major role in achieving self- medication without the risk.

Key words: selfmedication, pharmacist, role.

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PROCENA UTICAJA UDELA LEKOVITE SUPSTANCE, VELIČINE TABLETA I ODABIRA KOPROCESOVANOG EKSCIPIJENSA NA KARAKTERISTIKE ORALNO DISPERZIBILNIH TABLETA

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Oralno disperzibilne tablete (ODT) predstavljaju neobložene tablete, namenjene za primenu u usnoj duplji, gde treba brzo da se raspadnu, u kontaktu sa salivom. Tokom razvoja ODT, od presudnog je značaja obezbediti brzu dezintegraciju, bez narušavanja mehaničkih karakteristika tableta. Cilj rada je bio procena uticaja udela lekovite supstance, dijametra tableta i odabira koprocesovanog ekscipijensa na karakteristike ODT pripremljenih sa kofeinom, kao model supstancom, uz primenu eksperimentalnog dizajna (DE).
Tabletne mase, pripremljene su mešanjem odgovarajućih količina koprocesovanog ekscipijensa Disintequik™ ODT (Kerry, SAD)/Pharmaburst® 500 (SPI Pharma, Nemačka), sa kofeinom (25 i 50%) i natrijum-stearilfumaratom (Penwest Pharmaceuticals Co, SAD) u koncentraciji od 0,5% i njihovim direktnim komprimovanjem, primenom alata različitog dijametra (6 i 9 mm). Izrađene tablete su ispitivane u pogledu friabilnosti, zatezne čvrstine, raspadljivosti, vremena kvašenja i stepena apsorpcije medijuma. Procena uticaja faktora formulacije na ispitane karakteristike tableta, izvršena je uz primenu 23 faktorijalnog eksperimentalnog dizajna. Statistička značajnost parametara procenjena je na osnovu p vrednosti ($p<0,05$).
U skladu sa dobijenim rezultatima, uočeno je da postoji značajan uticaj dijametra na zateznu

čvrstinu tableta. Udeo kofeina, prečnik tableta, kao i njihova interakcija, utiču na friabilnost. Tablete manjeg dijametra, sa većim udelom kofeina pokazuju bolja mehanička svojstva. Analiza ispitivanih faktora pokazala je da odabir koprocesovanog ekscipijensa, udeo kofeina i njihova interakcija, utiču na raspadljivost i vreme kvašenja tableta. Tablete izrađene sa Pharmaburst® 500, pokazale su neznatnu promenu pomenutih karakteristika sa porastom udela kofeina, dok je znatno izraženija promena u ovim karakteristikama uočena kod tableta izrađenih sa Disintequik™ ODT. Na stepen apsorpcije medijuma značajan uticaj pokazao je odabir koprocesovanog ekscipijensa.
Ispitivani faktori formulacije su pokazali statistički značajan uticaj na karakteristike izrađenih ODT. Primena eksperimentalnog dizajna predstavlja korisnu tehniku za identifikaciju kritičnih faktora formulacije, kao i procenu njihovih efekata, u ranim fazama razvoja leka.

Ključne reči: oralno dipserzibilne tablete, koprocesovan ekscipijens, kofein

AN INVESTIGATION INTO THE EFFECT OF DRUG LOAD, TABLET SIZE AND CO-PROCESSED EXCIPIENTS ON ORODISPERSIBLE TABLET CHARACTERISTICS

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Orodispersible tablets (ODTs) are uncoated tablets intended to be placed in oral cavity, where they should disintegrate fast in contact with small amount of saliva. During ODTs manufacturing, it is of great importance to assure fast disintegration without violating good mechanical properties. The purpose of this work was to assess influence of drug load, tablet diameter and different co-processed excipients on characteristics of ODTs prepared with caffeine, as a model substance, using design of experiments (DoE).
ODT formulations with different drug load (25 and 50% caffeine) were prepared by mixing appropriate amounts of co-processed excipients Disintequik™ ODT (Kerry, USA) or Pharmaburst® 500 (SPI Pharma, Germany) with caffeine and 0,5% Pruv® (Penwest Pharmaceuticals Co, USA) and compressed on a single-punch tablet press, using dies with 6 and 9 mm diameter. Tablets were investigated regarding tensile strength, friability, disintegration time (DT), wetting time (WT) and water absorption ratio (WAR). Influence of different formulation factors on mentioned tablet characteristics was investigated using 23 factorial DoE. Statistical significance of parameters effect was estimated based on the p-values ($p<0,05$).
According to obtained results there is statistically significant influence of tablet diameter on tensile strength. Caffeine load, tablet diameter and their interaction affected tablet friability. Smaller tablet diameter and lower caffeine load lead to the tablets with good mechanical properties. Statistical analysis of factor effects revealed that selection of co-processed excipients and caffeine load, as well as their combined effect, significantly affect tablet disintegration and wetting time. WAR was significantly affected by the type of co-processed excipients used.
Investigated parameters demonstrated statistically significant influence ODT characteristics. DoE is useful tool for the evaluation of the individual and interactive effect of formulation factors and identification of critical quality attributes, in the early stages of drug product development.

Key words: orodispersible tablets, co-processed excipients, caffeine

ORALNE TEČNOSTI ZA DJECU: FORMULACIJA, PREDNOSTI I NEDOSTACI

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Za pedijatrijsku populaciju moraju se koristiti odgovarajuće formulacije. Za odojčad i djecu na intenzivnoj njezi, poželjan je parenteralni način primjene. Školska djeca i adolescenti mogu uzeti lijek u čvrstim oralnim doziranim oblicima. Oralni tečni oblici su formulacija izbora za djecu mlađu od 6 godina.
Dostupna je literatura u kojoj su opisane karakteristike ljekovitih tečnih oblika za djecu. Postoji nekoliko aspekata ovih lijekova koje treba razmatrati: obim apsorpcije, bioraspoloživost, složenost formulacije, problemi stabilnosti i greške u medikaciji.
Bolja brzina apsorpcije tečnih oblika doziranja u odnosu na tablete, rezultira sa više slučajeva predoziranja tečnim oblicima. Formulacija ljekovitih tečnosti je složena i u proizvodu se nalaze različiti ekscipijensi. Neki korastvarači i površinski aktivne supstance pokazali su određenu toksičnost kod novorođenčadi. Djeca eventualno mogu biti više osjetljiva na boje ili arome. Aktivne supstance inkorporirane u tečne oralne oblike su podložne razgradnji.
Glavni izazov je da se osigura sigurnost upotrebe proizvoda kod pedijatrijskih bolesnika. Djeca su više osjetljiva na greške u medikaciji uslijed netačnih mjerenja i neadekvatne isporuke doze lijeka. Izračunavanje koje se mora sprovesti da bi se dobila odgovarajuća doza, temelji se na masi, dobi, tjelesnoj površini i kliničkom stanju pojedinog pacijenta. Korištenje čajne kašike za mjerenje oralnih tečnih ljekovitih preparata u domaćinstvu, umjesto kalibrisanih mjernih kašika, može imati za posljedicu nedovoljnu dozu ili potencijalno opasno predoziranje. Te greške mogu se smanjiti pomoću standardizovanih kašika ili drugih sistema za doziranje.
Upotreba tečnih oblika doziranja u pedijatriji olakšava davanje lijeka, a poboljšava sigurnost pacijenta. Idealnu formulaciju za djecu je teško dobiti, ali za dobrobit pacijenta, potrebno je uložiti dodatne napore, te nastojati formulisati najprikladniji, stabilan i siguran tečni oralni dozni oblik.

Ključne riječi: lijekovi za djecu, oralne tečnosti, greške u medikaciji

ORAL LIQUIDS FOR CHILDREN: FORMULATION, ADVANTAGES AND DISADVANTAGES

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Appropriate formulations must be used for pediatric population. For infants and children in intensive care, parenteral route of administration is preferred. School children and adolescents in general can take medicine in solid oral dosage forms. Oral liquid dosage forms are usually formulation of choice for children under the age of 6.
There is available literature data describing the characteristics of medicinal liquid forms for

children, and there are several aspects of these characteristics that need to be discussed: absorption rate, bioavailability, formulation complexity, stability problems, and medication errors. Better absorption rate of liquid dosage forms compared to tablets results with more cases of overdosing if using liquid dosage forms. Composition of liquid dosage forms is complex and there is great number of incorporated excipients. Some of co-solvents and surface active agents have shown certain toxicity in newborns. Children can possibly be more sensitive to colors of flavors. Active substances incorporated in oral forms are susceptible to degradation.
Major challenge is to ensure safety of product's use in pediatric patients. Children are more susceptible to medication errors because of inaccurate measurement and delivery of drug. Calculation based on weight, age, body surface area, and clinical condition of each individual patient must be done in order to obtain appropriate dose of the medicine. Using the tea spoon at home for liquid dosage form measuring, instead of calibrated measuring spoon, can cause underdose or potentially dangerous overdose. These errors could be reduced by using standardized dosing devices.
The use of liquid dosage forms in pediatrics facilitates the drug administration and improves the security of patient. Ideal formulation for children is difficult to obtain, but for the patient's benefit, it is necessary to make additional efforts, and strive to formulate the most appropriate, stable and safe liquid dosage form.

Keywords: children medication, oral liquids, medication errors

VULVOVAGINALNA KANDIDIJAZA: KARAKTERISTIKE I RIZICI SAMOMEDIKACIJE

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Vulvovaginalna kandidijaza (VVC) predstavlja više od 25% svih slučajeva vaginitisa kod žena reproduktivne dobi. Glavni uzrok VVC su C.albicans sojevi. Žene mogu biti asimptomatski nosioci ili mogu razviti različite nivoe simptomatske infekcije. Iako su mehanizmi ovih infekcija poznati, njihova učestalost se ne smanjuje.
Pregledom literature evidentirani su režimi liječenja za ove infekcije. Antimikotici su dostupni kao over-the-counter proizvodi, i mogu se kupiti i bez odgovarajuće dijagnoze. Ova činjenica je u korelaciji s učestalošću i težinom epizoda kandidijaze, uglavnom kod samomedikacije azolnim antimikoticima.
Osim fluoriranih analoga pirimidina, polienskih i azolnih antimikotika, razvijene su i nove klase lijekova - ekinokandini i derivati levofloksacina. Samoliječenje tim lijekovima najčešće se javlja kod mladih, zaposlenih ljudi. Prednosti samomedikacije su autonomija pacijenta i smanjenje troškova liječenja. Glavni nedostatak je moguća pogrešna autodijagnostika i nepotrebna aplikacija, što dovodi do povećanog morbiditeta (npr., kontaktni dermatitis) i povećanih troškova liječenja. Različiti faktori rizika mogu uzrokovati infekciju ili druga stanja sa simptomima sličnim kandidijazi. Nenormalan vaginalni sekret je često posljedica bakterijske infekcije. Ako nema gljivične infekcije, neprimjereno korištenje topikalnih antimikotika može samo pogoršati stanje pacijenta. Takva upotreba može dovesti do razvoja rezistentnih Candida sojeva. Mehanizmi

rezistencije su nedavno otkriveni. Rezistencija na azolne antimikotike javlja se uglavnom zbog mutacije gena.
Sve ovo može suziti mogućnosti i vrste terapije kod stanja rekurentne kandidijaze. Trebalo bi preporučivati pacijenticama da posjete ljekara, kako bi se uspostavila pravilna dijagnoza vaginalne infekcije, i odgovarajuća terapija.

Ključne riječi: kandidijaza, azolni antimikotici, rezistencija na antimikotike, samomedikacija

VULVOVAGINAL CANDIDIASIS: CHARACTERISTICS AND SELF-MEDICATION RISKS

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Vulvovaginal candidiasis (VVC) represent more than 25% of all vaginitis cases in women of reproductive age. Major cause of VVC are C. albicans strains. Women may be asymptomatic carriers, or may develop different levels of symptomatic infection. Although the mechanisms of these infections are known, their incidence is not reduced.
Therapy regimens for fungal infections are recorded by reviewing the literature. Drugs for this treatment are available as over-the-counter products, and can be purchased without appropriate diagnosis. This is correlated with the frequency and severity of candidiasis episodes, mostly when self-medication includes azole antimycotics.
In addition to the fluorinated pyrimidine analogs, polyenes or azole antimycotics, there are new classes of drugs developed – echinocandins and levofloxacin derivatives. Self-medication with these drugs is most common in young, employed people. The benefits of self-medication are the autonomy of the patient and reduced costs. The main drawback is the possible wrong self-diagnosis and unnecessary application, leading to increased morbidity (eg.,contact dermatitis) and increased treatment costs. Various risk factors can cause the infection or other conditions with symptoms similar to candidiasis symptoms, and can mislead patient. Abnormal vaginal discharge is often a consequence of bacterial infection. If there is no fungal infection, inappropriate use of topical antimycotic drugs can only worsen the patient's condition. Such use may also lead to development of resistant Candida strains. Mechanisms of resistance have been discovered recently. Azole resistance occurs mainly due to gene mutation.
Consequently, this can narrow the treatment possibilities for recurrent candidiasis. It should be recommended to patients to visit the physician , in order to establish a proper diagnosis of vaginal infection, and adequate therapy.

Keywords: Candidiasis, azole antimycotics, resistance to antifungal drugs, self-medication

PRIMJENA NEOPIOIDNIH ANALGETIKA U CRNOJ GORI

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Neopioidni analgetici (aspirin, paracetamol, pirazoloni i NSAIL) služe za suzbijanje blagih i umjerenih bolova kao što su: glavobolja, zubobolja, artralgije i mialgije. Analgetici se ubrajaju u najčešće korištene ljekove, često se koriste bez nadzora ljekara/farmaceuta i zloupotrebljavaju se.
Ispitati u kojoj mjeri stanovništvo Crne Gore poznaje neopioidne analgetike, koliko često ih koristi i da li se konsultuju sa farmaceutima prije konzumiranja analgetika.
Naše pilot istraživanje rađeno je u martu 2015. U anonimnoj i dobrovoljnoj anketi (15 pitanja) je učestvovalo 160 stanovnika Crne Gore starosti 20-60 godina, različitog stepena obrazovanja i socioekonomskog statusa, iz nekoliko crnogorskih gradova (Herceg Novi, Bijelo Polje, Kotor, Podgorica, Nikšić, Budva).
Od 162 ispitanika, više od polovine (66,7%) rijetko koristi neopioidne analgetike, dok ih često koristi 19,8% ispitanika. Samoinicijativno ih koristi 35,2% a onih koji se redovno konsultuju sa ljekarom/farmaceutom je 29,0%. Ne čita uputstva ili ih rijetko čita čak 45,7% ispitanika. Najčešće koriste ovu vrstu ljekova za suzbijanje glavobolje. Među ispitanicima, najviše upotrebljavan neopioidni analgetik je ibuprofen (20,4%), zatim paracetamol (17%).
Prema istraživanju sprovedenom u Americi u periodu 2006-2008, čak 20% odraslih Amerikanaca koristi neopioidne analgetike skoro svakodnevno, a u Finskoj 8,5%. U Velikoj Britaniji na listi najviše korištenih ljekova, neopioidni analgetici su na trećem mjestu. Prema našoj anketi, može se zaključiti da je i u Crnoj Gori veliki procenat onih koji ove ljekove uzimaju vrlo često (čak 19,8%).
Veliki broj ljudi u Crnoj Gori često koriste neopioidne analgetike i to samoinicijativno i bez prethodnog čitanja uputstva. Kako bi ih racionalnije primjenjivali i njihov izbor bio pravi, potrebno je više konsultacije sa farmaceutima.

Ključne riječi: nesteroidni analgetik, primjena, Crna Gora

USE OF NON-OPIOID ANALGESICS IN MONTENEGRO

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Non-opioid analgesics (aspirin, paracetamol, pyrazolones and NSAID) serve for repression mild and moderatelyh pain such as : headache, toothache, arthralgia and myalgia. Analgesics are among the most widely used drugs , often they are used without supervision of a doctor or pharmacist and they are abused.
Research the extent which the population of Montenegro knows about non-opioid analgesics, how often it is used and whether to consult with the pharmacist before consuming analgesics.
Our pilot research was carried out in March 2015. In voluntary anonymous survey (15 questions) took part 160 citizens of Montenegro aged 20 to 60 years, varying degrees of education and

socioeconomical status , from several Montenegrian towns (Heceg Novi, Bijelo Polje, Kotor, Podgorica, Niksic, Budva).
Of 162 respondents, more than half (66,7%) rarely used non-opioid analgesics, while often used by 19,8% of respondents. Used them on their own initiative 35,2% and those who regularly consult a doctor/pharmacist is 29,0%. Do not read the instructions or rarely read even 45.7% of respondents. They are most frequently used to control headaches. Among respondents, most widely used painkiller is ibuprofen (20,4%), and then paracetamol (17%).
Acording to research conducted in USA in period 2006-2008, even 20% of adult Americans use non-opioid analgesics almoust every day, in Finland 8,5%. In United Kingdom on list the most used drugs, non opioid analgesics are in third place. Acording to our questionnaire it can bi concluded that in Montenegro is large percentage of those who this medicaments use very often (even 19,8%).
A large number of people in Montenegro very often use non-opioid analgesics, on their own initiative and without reading the instructions. In order to make them more rationally applied, and their choice was the right one, it needs more consultation with pharmacists.

Key words: non-opioid analgesics, use, Montenegro

PROBLEMI NAKON SAMOMEDIKACIJE

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Samomedikacija predstavlja sve ono što čovjek sam čini za sebe u cilju dostizanja i očuvanja zdravlja, prevencije ili liječenja. Međutim, baš zbog široke zastupljenosti, jedan je od problema loših terapijskih ishoda liječenja. Zadnjih godina samomedikacija zauzima sve značajnije mjesto u društvu i sistemu zdravstvene zaštite zahvaljujući sve većoj dostupnosti informacija o bolestima i njihovom liječenju i velikom broju OTC preparata.
Cilj rada je da se identifikuje prisustvo prakse samomedikacije i da se odrede potencijalni faktori koji mogu da utiču na učestalost samomedikacije, kako bi se pacijentima pružila kvalitetnija usluga i unaprijedilo njihovo zdravstveno stanje.
Istraživanje je sprovedeno korišćenjem anonimne ankete namijenjene pacijentima Doma zdravlja Pljevlja i pacijentima koji su posjetili nekoliko privatnih apoteka u Nikšiću. U anketi je učestvovalo 200 pacijenata različitih starosnih dobi. Zabilježeni su razlozi i uzroci zbog kojih se konzumiraju ljekovi, kao i najčešće grupe ljekova koje pacijenti primjenjuju ,,na svoju ruku".
Od ukupnog broja ispitanih pacijenata njih 178(89%) je potvrdilo postojanje samomedikacije kao oblika samonjege. Samomedikacija je značajno više zastupljena kod žena u odnosu na muškarce (93,2% : 85,3%). Najviše je zastupljena kod pacijenata starosne dobi preko 60 godina, dok je nešto manje izražena kod pacijenata starosne dobi 45-60 godina i mlađih. Uzroci pojave samomedikacije iz ugla pacijenata su sledeći: lakoća pristupa lijeku-pozajmljivanje od članova porodice, prijatelja, rođaka(28,2%); to što se propisani lijek mora kupiti(25,8%); ušteda vremena koja se ostvaruje izbjegavanjem ljekarske usluge(23%); povjerenje u sopstveno ili tuđe pozitivno terapijsko iskustvo sa određenim lijekom(17,3%) i nesvjesnost o ozbiljnosti nekontrolisanog uzimanja ljekova(5,7%). Kao najčešće zdravstvene probleme zbog kojih sami uzimaju ljekove

ispitanici su naveli glavobolju, slab imunitet, slabu koncentraciju, uznemirenost, umor i bol u grlu, a najčešće korišćeni ljekovi pripadaju grupi analgetika, antibiotika, psihofarmaceutika, antihipertenziva i različitih fitopreparata.
Samomedikacija je veliki problem. Kako bi doprinijeli uspješnijem terapijskom ishodu liječenja tokom samomedikacije, farmaceuti moraju savladati i vještinu komunikacije sa pacijentom, edukovati se, unaprijediti saradnju sa svim zdravstvenim radnicima, strukovnim organizacijama i regulatornim tijelima u cilju razmjene iskustava i podataka, treba da učestvuju u kampanjama za promociju zdravlja i da pružaju savjete u cilju donošenja ispravnih odluka o sopstvenom zdravlju.

Ključne riječi: samomedikacija, razlozi za samomedikaciju, liječenje, prevencija bolesti, uloga farmaceuta

PROBLEMS AFTER SELF-MEDICATION

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Self-medication represents what the man does for himself in order to achieve and preserve health, as well as to prevent or treat diseases. However , because of the wide distribution, it is one of the leading problems of bad therapeutic treatments. In recent years, self-medication has occupied more significant place in society and the health care system due to the increasing availability of information about diseases and their treatment, and a large number of registered OTC products.
The aim is to identify the presence of self- medication practice and to determine potential factors that may affect the incidence of self-medication, in order to provide more quality service for patients and improve their health.
The research was conducted using anonymous survey designed for Pljevlja Health Center patients and patients who visited a few private pharmacies in Nikšić. Two hundred patients of various age participated in the survey. Reasons and causes for using medicines as well as the most common groups of medicines that patients ,,apply on their own" have been recorded. Of the total number of tested patients 178 of them (89 %) confirmed the existence of self-medication as a form of self-care. Self-medication is significantly more common in women than in men (93.2 % : 85.3 %). Self-medication was highest in patients aged over 60 years, while it was somewhat less pronounced in patients aged 45-60 years and younger. Causes for self-medication from the patients' perspective were as follows: the ease of access to medicines - borrowing from family members, friends, relatives (28,2 %); the fact that prescribed medication must be bought (25,8 %); saving time, which is achieved by avoiding medical services (23 %); confidence in their own or other people's positive therapeutic experience with a particular drug (17,3 %) and unawareness of the seriousness of uncontrolled use of medications (5,7 %).
As the most common health problems for taking medications on their own respondents stated headache, weak immune system, poor concentration, anxiety, fatigue and pain in the throat and the most commonly used drugs belong to the group of analgesics, antibiotics, psycho-pharmaceuticals, anti-hypertensive and different phytopreparations.

Self-medication is a major problem. In order to fulfill its role in the system of self-medication, in addition to the innovation of drugs knowledge, the pharmacist has to posses communication skills with patients, educating skills, as well as to collaborate with other health care professionals, professional organizations and regulatory bodies in order to exchange experiences and information, participate in health promoting campaigns and provide advice for making correct decisions about their own health.

Keywords: self-medication, reasons for self-medication, treatment, disease prevention, the role of pharmacists.

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UTICAJ OKSITOCINA NA PONAŠANJE I KONCENTRACIJU SEROTONINA U PLAZMI WISTAR PACOVA NAKON DUGOTRAJNOG TRETMANA KORTIKOSTERONOM

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Kortikosteron (CORT) je glavni glukokortikoidni hormon glodara, dok je poznato da neuropeptid oksitocin (OXY) značajno menja odgovor organizma na stres. Cilj ove studije je ispitivanje uticaja hroničnog tretmana oksitocinom na ponašanje i koncentraciju serotonina u plazmi Wistar pacova tretiranih kortikosteronom tokom tri nedelje.
40 mužijaka Wistar pacova podeljeno je u 4 grupe na osnovu tretmana: CORT (100mg/L rastvoren u vodi za piće, 21 dan), OXY (100IU/400µl, s.c., 14 dana), CORT/OXY (oksitocin je aplikovan poslednjih 14 dana tretmana kortikosteronom) i odgovarajuća kontrolna grupa. Počev od 20-og dana eksperimenta, ponašanje životinja testirano je izvođenjem uzdignutog plus lavirinta (eng. Elevated-plus maze, EPM) i testa forsiranog plivanja (eng. Forced Swim Test, FST). Nakon FST testa, životinje su žrtvovane i uzorkovana je krv za kvantitativnu analizu serotonina.
Rezultati EPM testa su pokazali veći procenat ulazaka u otvorene krake životinja tretiranih OXY i CORT/OXY u odnosu na kontrolnu grupu ($p<0.05$ i $p<0.01$, redom), kao i u odnosu na životinje CORT grupe ($p<0.05$ i $p<0.01$, redom). Imobilnost životinja u FST testu značajno se povećala kod CORT grupe u poređenju sa kontrolom ($p<0.01$), dok je kod CORT/OXY grupe ovaj parametar bio značajno kraći, a period od početka testa do prve imobilne epizode (latentno vreme) značajno duži u poređenju sa CORT grupom ($p<0.01$ i $p<0.01$, redom). Tretman kortikosteronom značajno je smanjio koncentraciju serotonina u plazmi ($p<0.05$), dok je kod životinja CORT/OXY grupe primećen značajan porast koncentracije ovog hormona u plazmi u poređenju sa CORT grupom i kontrolom ($p<0.001$ i $p<0.05$, redom).
Rezultati ove studije ukazuju da tretman oksitocinom smanjuje anksiozno i depresivno ponašanje Wistar pacova, indukovano dugotrajnom primenom kortikosterona. Takođe, koncentracija serotonina u plazmi koja je snižena kod pacova tretiranih kortikosteronom, značajno se povećava nakon dodatnog tretmana oksitocinom.

Ključne reči: Oksitocin, depresija, serotonin, kortikosteron.

INFLUENCE OF OXYTOCIN ON BEHAVIOR AND SEROTONIN PLASMA LEVEL AFTER LONG-TERM CORTICOSTERONE TREATMENT OF WISTAR RATS

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Corticosterone (CORT) is the main stress hormone in rodents, while neuropeptide oxytocin (OXY) significantly modulates stress response. In this study, we examined if chronic OXY treatment affected behavior and serotonin levels after long-term corticosterone treatment.
40 male Wistar rats were divided into 4 groups: CORT (100mg/L via drinking water, 21 day), OXY (100IU/400µl/day, s.c., 14 days), CORT/OXY (oxytocin was administered last 14 days of corticosterone treatment) and respective controls. From day 20, animals were tested in elevated-plus maze (EPM) and forced swim test (FST). After FST test, rats were sacrificed and blood samples were taken for serotonin determination.
Testing in EPM showed that OXY and CORT/OXY group had higher percentage of entries in open arms compared to control ($p<0.05$ and $p<0.01$ respectively) and CORT groups ($p<0.05$ and $p<0.01$ respectively). FST revealed that CORT group displayed increased immobility compared to controls ($p<0.01$), while in CORT/OXY group this parameter was significantly lower, and latency to first immobile period significantly higher than in CORT group ($p<0.01$ and $p<0.01$ respectively). CORT treatment significantly lowered plasma serotonin level ($p<0.05$), in animals treated with CORT/OXY where significant increase in serotonin was observed compared to both CORT and control groups ($p<0.001$ and $p<0.05$ respectively).
This results suggest that oxytocin treatment reduced anxiety and depression-like behavior induced by long-term corticosterone treatment, while it restores plasma serotonine level that was diminished in corticosterone-treated Wistar rats.

Keywords: Oxytocin, depression, serotonin, corticosterone.

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EFEKTI HRONIČNE PRIMENE MAGNEZIJUMA NA PONAŠANJE PACOVA TRETIRANIH ADRENOKORTIKOTROPNIM HORMONOM

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Disregulacija hipotalamo-hipofizno-adrenalne osovine (HPA) i poremećaj u serotonergičkoj transmisiji predstavljaju patološke mehanizme za koje se smatra da su uključeni u razvoj depresije. Cilj studije je da se ispitaju efekti hronične primene magnezijuma (Mg) na promene u ponašanju koju su uzrokovane tretmanom adrenokortikotropnim hormonom (ACTH) i da se utvrdi korelacija između nivoa magnezijuma u organizmu i aktivnosti serotonergičkog sistema.
Pacovi Wistar soja su podeljeni u 4 grupe: Mg (300 mg/L, per os, 28 dana), ACTH (10 µg/ 400 µl

s.c., 21 dan), ACTH/Mg i kontrolnu grupu i praćeno im je ponašanje primenom testa otvorenog polja (OFT) i forsiranog plivanja (FST). Pored toga, određivan je nivo serotonina u plazmi.
Nije bilo statistički značajne razlike u ukupnom pređenom putu u OFT ($F(3.24)= 1.029$; $p=0.397$), ali pacovi koji su dobijali ACTH su proveli manje vremena u centralnoj zoni u poređenju sa kontrolnom grupom ($p=0.013$). Mg je anulirao anksiogeni efekat ACTH, tako da je ACTH/Mg grupa životinja provela više vremena u centralnoj zoni u poređenju sa ACTH grupom ($p=0.047$) i nije bilo razlike između ACTH/Mg i Mg i kontrolne grupe.
Tokom FST-a vreme imobilnosti je bilo produženo kod životinja koje su dobijale ACTH u poređenju sa kontrolnim ($p=0.009$). Mg je poništio ovaj efekat, tako da su pacovi iz ACTH/Mg grupe imali značajno kraće vreme imobilnosti od ACTH grupe ($p=0.031$) i nisu se razlikovale vrednosti ovog parametra između ACTH/Mg i Mg i kontrolne grupe.
Nivo serotonina je bio značajno povišen kod životinja koje su primale Mg u poređenju sa kontrolnom, ACTH i ACTH/Mg grupom ($p<0.001$, $p=0.001$ i $p=0.001$ redom).
Rezultati upućuju da hronična primena magnezijuma redukuje simptome depresije i anksioznosti izazvane tretmanom adrenokortikotropnim hormonom. Međutim, predstoje dalja istraživanja u cilju potvrde da li je porast nivoa serotonina direktna posledica primene magnezijuma.

Ključne reči: depresija magnezijum, ACTH, HPA osa.

EFFECTS OF CHRONIC MAGNESIUM ADMINISTRATION ON BEHAVIOR OF ADRENOCORTICOTROPIC HORMONE TREATED RATS

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Pathological mechanisms that are commonly involved in development of depression include dysregulation of hypothalamic-pituitary-adrenal (HPA) axis and modulation of serotonergic transmission.. This study was designed to determine the effects of chronic magnesium (Mg) supplementation on behavioral changes induced by adrenocorticotropic hormone (ACTH) treatment and to examine correlaton of Mg level and serotonergic system activity.
Wistar rats assigned into four treatment groups: Mg (300 mg/L, per os, 28 days), ACTH (10 μg/ 400 μl s.c., 21 days), ACTH/Mg combined treatment and controls; were tested in open field (OFT) and forced swim test (FST). Lastly, plasma serotonin levels were determined.
Distance travelled in the OFT did not differ statistically ($F(3.24)=1.029$; $p=0.397$), but ACTH rats spent less time in the central zone compared to controls ($p=0.013$) while Mg diminished anxiogenic effect of ACTH so ACTH/Mg group spent more time in the central zone compared to ACTH group ($p=0.047$), and equally to control and Mg group.
ACTH-treated animals in the FST spent more time being immobile compared to controls ($p=0.009$), but magnesium abolished this effect and ACTH/Mg rats were significantly less immobile compared to ACTH rats ($p=0.031$), and there was no difference in this parameter between ACTH/Mg and Mg and control group.
Serotonin level was significantly increased in Mg group compared to controls, ACTH and ACTH/Mg group ($p<0.001$, $p=0.001$ and $p=0.001$ respectively).

Results suggest that chronic magnesium administration reduces ACTH ensuing depression- and anxiety-like behavior, but weather the elevation of serotonin level is directly induced by magnesium supplementation remains to be confirmed.

Keywords: depression, magnesium, ACTH, HPA axis

UPOTREBA DIJETETSKIH SUPLEMENATA ZA SMANJENJE TJELESNE MASE

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Gojaznost je hronična bolest koja dovodi do značajnog povećanja morbiditeta (dijabetes tip 2 ,srčane bolesti, kancer, osteoartritis..) i mortaliteta,uz smanjenje kvaliteta života. Svako povećanje 10% od idealne težine smatra se gojaznošću. Česta je u svakoj dobi,u pubertetu je jednaka među polovima,a kasnije češće se javlja kod žena nego kod muškaraca.
Cilj ove prezentacije je bio da se utvrdi na koji način su ispitanici regulisali tjelesnu masu, u kojoj mjeri su koristili suplemente za smanjenje tjelesne mase i da li su zadovoljni njihovom efikasnošću.
Istraživanjem je obuhvaćeno 115 osoba (65 ženskog i 50 muškog pola), starijih od 15 godina. Istraživanje je rađeno u toku februara i marta 2015 na teritoriji Podgorice.
Od ukupnog broja ispitanika 53,9%, koristi/koristilo je dijetetske suplemente za smanjenje tjelesne mase (DSTM). Najveći broj ispitanika koji su koristili DSTM, koristili su ove proizvode iz estetskih razloga (40,9%), nešto manje zbog prevencije bolesti koju boluju (2,6%). Ispitanici oba pola najčešće su koristili medije (TV, novine) kao izvor informacija o DSTM (52,2%), savjete od zdrastvenih radnika je potražilo njih 15,7%, a njih 13% informacije su dobili iz flajera iz apoteka.
Veći broj ispitanika (42,6%) regulisali su tjelesnu masu fizičkom aktivnošću, dijetom (33%), smanjenim unosom hrane (14,8%), a povećanim unosom tečnosti (8,7%). Veliki broj ispitanika kupuje DSTM isključivo u apoteci (48,7%), a nešto manje u prodavnicama zdrave hrane (13%), u super marketima (5,2%), na internetu 4,3%.
Prema mišljenju ispitanika, veći broj je rekao da su DSTM skupi (47,8%), a nešto manje (33%) da su pristupačni.Ispitanici su, takođe, upoznati sa indikacijama i neželjenim dejstvima (70,4%), dok manji broj (12,2%) je reklo da nije upoznato.
S obzirom da veliki broj ispitanika kupuje preparate DSTM u apotekama, farmaceuti bi trebalo da imaju značajniju ulogu u davanju detaljnijih informacija o indikacijama i neželjenim dejstvima.

Ključne riječi: gojaznost, dijetetski suplemeni za smanjenje tjelesne mase, upotreba

USE OF DIETARY SUPPLEMENTS FOR WEIGHT LOSS

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Obesity is a chronic disease that leads to a significant increase in morbidity (type 2 diabetes, heart disease, cancer, osteoarthritis ...) and mortality, with a reduction of the quality of life. Every increase of 10% from the ideal weight is considered as obesity. It is common in every age group, during the puberty is equal between the genders, and after it, is more common among women than among men.
The objective of this presentation was to determine the method for regulating body weight of the respondents, the extent to which they used supplements for weight reduction and whether they were satisfied with the effectiveness.
The research included 115 individuals (65 females and 50 males), over 15 years old. The survey was conducted during February and March 2015 in Podgorica.
53.9% of the total respondents used / have used dietary supplements for weight loss (DSTM). The largest number of respondents, who have used DSTM, used these products for aesthetic reasons (40.9%), slightly fewer used them for the prevention of disease from which they suffered (2.6%). Both genders have mostly used media (TV, newspapers) as a source of information on DSTM (52.2%), 15.7% of them have sought advice from health care workers and 13% of them have received information from the pamphlets from the pharmacy.
The greater number of respondents (42.6%) regulates the body mass with physical activity, diet (33%), decreased food intake (14.8%), and increased fluid intake (8.7%). A large number of respondents exclusively buy DSTM in pharmacies (48.7%), and slightly fewer of them buy in health food stores (13%), in supermarkets (5.2%), on the Internet 4.3%.
According to the respondents, the greater number of them confirmed that DSTM are expensive (47.8%), and slightly fewer (33%) that these are affordable. Respondents were also familiar with the indications and adverse effects (70.4%), while fewer (12.2%) said they were not aware of that.
According to the fact that a large number of respondents buys DSTM medicines in pharmacies, pharmacists should have a significant role in providing detailed information on indications and adverse effects.

Keywords: obesity, dietary supplements for weight loss, usage

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NAJNOVIJA SAZNANJA O FARMAKODINAMSKIM EFEKTIMA MASLINE I MASLINOVOG ULJA

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Plod masline i maslinovo ulje su tipični mediteranski proizvodi čiji pozitivni uticaj na zdravlje je dobro poznat od davnina. Brojne farmakološki aktivne supstance izolovane iz ovih proizvoda i

danas su predmet opsežnih naučnih istraživanja na različitim nivoima.
Cilj ovog rada je bio da se na jednom mjestu sakupe prilično rasute informacije o ljekovitim sastojcima masline i maslinovog ulja, kao i raspoloživi podaci o njihovom farmakodinamskom djelovanju.
Za ovu analizu smo pretražili radove iz "PubMed" baze objavljene u periodu 2005-2015 koji su se odnosili na farmakodinamska djelovanja masline i maslinovog ulja. Uzete su u obzir studije izvedene na ćelijskim linijama, eksperimentalnim životinjama, ali i klinička ispitivanja na ljudima. Iz ove analize su isključene studije u kojima farmakodinamski efekti navedenih sastojaka nijesu mogli da budu precizno izdvojeni i opisani.
Oleinska kiselina (OK) smanjuje koncentraciju i oksidaciju LDL-a i rizik od razvoja kardiovaskularnih bolesti, a posjeduje i antitumorsko dejstvo. Osnovni mehanizam kojim OK smanjuje koncentraciju LDL-a jeste povećanje njegovog klirensa preko LDL-receptora u jetri. Mehanizmi antitumorskog dejstva još nijesu do kraja razjašnjeni, a u opticaju je nekoliko teorija vezanih za inhibiciju proliferacije i indukciju apoptoze tumorskih ćelija. Oleuropein ispoljava neuro-, hepato- i kardioprotektivno dejstvo, ima hipotenzivno i antiinflamatorno djelovanje i moćan potencijal u prevenciji razvoja tumora kolona i dojke. Hidroksitirozol posjeduje izrazita antioksidantna svojstva, a djeluje i antiinflamatorno, antiagregaciono i antitumorski. Tirozol posjeduje antioksidantna svojstva koja su slabije izražena nego kod hidroksitirozola.
Maslina ima višestruko povoljne efekte na očuvanje ljudskog zdravlja, prevenciju i liječenje bolesti. Obzirom na to da Crna Gora ima veliki potencijal za uzgajanje masline, moraju se što je moguće prije preduzeti mjere u cilju stimulisanja proizvodnje i upotrebe proizvoda od masline, uz istovremenu edukaciju stručne i laičke javnosti o njihovom povoljnom farmakodinamskom djelovanju.

Ključni riječi: maslina, maslinovo ulje, farmakodinamski efekti

THE LATEST FINDINGS ON THE PHARMACODYNAMIC EFFECTS OF OLIVE FRUIT AND OLIVE OIL

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Olive fruit and olive oil are typical Mediterranean products, whose positive influence on health has been well-recognized since ancient times. Numerous pharmacologically active substances isolated from these products are still the subject of extensive scientific research at different levels.
The objective of this work was to bring together quite scattered information on useful components of olive fruit and olive oil, as well as available data on their pharmacodynamic actions.
For this analysis, we searched studies published on the PubMed in the years of 2005-2015, in which the pharmacodynamic actions of olive fruit and olive oil were investigated. We considered studies conducted on cell lines and experimental animals, as well as human clinical trials. We excluded studies, in which the pharmacodynamic actions of the mentioned substances could not be precisely distinguished and described, from our analysis.
Oleic acid (OA) decreases concentrations and oxidation of LDL, reduces the risk of development

of cardiovascular diseases, as well as possesses some antitumor effects. The major mechanism by which OA decreases LDL concentrations involves increased clearance of LDL via hepatic LDL-receptors. The mechanisms of antitumor effects have not been fully clarified yet. Still, there are some theories related to inhibition of proliferation and induction of apoptosis of tumor cells. Oleuropein exhibits neuro-, hepato- and cardioprotective activities, possesses hypotensive and anti-inflammatory effects, as well as strong potential in prevention of development of colon and breast cancer. Hydroxytyrosol possesses pronounced anti-oxidant properties, as well as anti-inflammatory, antiplatelet and antitumor activities. Tyrosol exhibits anti-oxidant properties that are less pronounced than those of hydroxytyrosol.
Olives have multiple beneficial impacts on human health, as well as help to prevent and even treat different diseases. Considering the fact that Montenegro has a great potential to grow olives, actions to encourage production and use of olive wood products and to teach the professional and general public about their favorable pharmacodynamic effects should be taken as soon as possible.

Key words: olive fruit, olive oil, pharmacodynamic effects

UTICAJ FARMAKOKINETIKE NA FARMAKOTERAPIJU GERIJATRIJSKE POPULACIJE SA POSEBNIM OSVRTOM NA ULOGU KLINIČKOG FARMACEUTA U SISTEMU FARMAKOLOŠKOG NADZORA

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Za racionalan pristup terapiji lijekovima kod starih neophodno je razumijevanje farmakokinetskih promjena (sporija apsorpcija, redukovan volumen distribucije, redukovani metabolizam u jetri, opadanje renalnog protoka, glomerularne filtracije i tubularne sekrecije), usljed kojih su koncentracije lijekova u plazmi i tkivima obično povišene pa je često potrebno prilagoditi dozu.
Cilj rada je da se utvrdi uloga kliničkog farmaceuta u optimizaciji terapije starijih pacijenata, kao i efekat farmakokinetičkih faktora na ishod primijenjene medikamentozne terapije.
Ispitivanje je vršeno u domu za stare “Duga” koji se nalazi u Martinićima. Smještajni kapacitet ovog doma obuhvata 36.lica koji su i obuhvaćeni ispitivanjem.
Sprovedena je anketa koja se temelji na sljedećim parametrima: funkcionalna sposobnost, redovnost u uzimanju terapije, najčešće primjenjivani lijekovi u terapiji i primijećene neželjene reakcije koje se povezuju sa primijenjenom terapijom.
Kao što se očekivalo, kod starih lica su prisutna hronična oboljenja. Mentalno zdravlje ovih lica, kao značajna komponenta zdravlja i kvaliteta života, je ugroženo čestim prisustvom usamljenosti.
Lijekovi se ponekada primjenjuju u pogrešno vrijeme, dozama koje nisu optimalne, neodgovarajućem trajanju. Zabrinjavajuća je praksa u vezi sa propisivanjem lijekova kao što su: antipsihotici, anksiolitici, sedativi, antidepresivi itd.
Kao rezultat neadekvatnog propisivanja, načina primjene ili monitoringa medikamentozne terapije kod pacijenata se javljaju brojne neželjene reakcije koje uključuju najčešće: opstipaciju, padove, delirijum, depresiju i urinarnu inkontinenciju.

Klinički farmaceuti imaju važnu ulogu počev od praćenja propisivanja lijekova, primjene propisane terapije, uočavanja grešaka u propisivanju i neželjenih reakcija usljed neadekvatne terapije ili nepridržavanja terapiji.
Angažovanjem kliničkog farmaceuta, bezbjednost terapije bi bila veća, a samim tim i zadovoljstvo korisnika terapije.

Ključne riječi: Farmakokinetika, gerijatrijska populacija, Klinička farmacija

THE IMPACT ON THE PHARMACOKINETICS OF PHARMACOTHERAPY IN GERIATRIC POPULATION WITH SPECIAL EMPHASIS ON THE ROLE OF CLINICAL PHARMACISTS IN THE PHARMACOLOGICAL CONTROL SYSTEM

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Understanding changes in pharmacokinetic in the elderly population is necessary for a rational approach to drug therapy (slower absorption, reduced volume of distribution, reduced hepatic metabolism, a decrease in renal blood flow, glomerular filtration and tubular secretion), because they are followed with changes in drug concentrations within plasma and tissues. For this reason it is often necessary to adjust the dose of medication in elderly patients.
The aim of this study was to determine the role of clinical pharmacists in optimizing therapy in the elderly population, as well as the effect of pharmacokinetic factors on the outcome of applied medical therapy.
The test was performed in a nursing home " Duga" which is located in Martinići. The capacity of this home includes 36.persons. They are all examinated. A survey was based on the following parameters: functional ability, regularity in taking treatment, most frequently used drugs in the treatment and observed adverse reactions associated with the applied treatment.
As expected, in the elderly are present chronic diseases. Mental health of these individuals, as well as an important component of health and quality of life is threatened by the frequent presence of loneliness.
Medicines are sometimes applied at the wrong time, doses that are not optimal or inappropriate period. Regarding disturbing practice in prescribing drugs such as antipsychotics, anxiolytic, sedatives, antidepressants, etc. present concern among doctors is not surprising.
As a result of inappropriate prescribing, administration form or monitoring of drug therapy, there are a lot of adverse reactions involving the most common: constipation, falls, delirium, depression and urinary incontinence.
Clinical pharmacists have an important role from the monitoring of prescribed therapy until identifying medication errors and adverse reactions due to inadequate treatment or non-compliance with therapy.
Engaging clinical pharmacists, security of applied treatment would be higher, and thus the satisfaction of patients.

Key words: Pharmacokinetics, geriatric population, Clinical pharmacy

FIZIČKOHEMIJSKA, BIOFARMACEUTSKA I IN VIVO PROCENA IRITACIONOG POTENCIJALA MIKROEMULZIJA NA BAZI ŠEĆERNIH ESTARA: UTICAJ HIDROKSIPROPIL-B-CIKLODEKSTRINA

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Saharozni estri (SE) su nejonski surfaktanti sa niskim iritacionim potencijalom. U cilju poboljšanja transporta aceklofenaka kroz kožu, ispitivane su mikroemulzije na bazi SE, kao vehikulumi koji čine kožu permeabilnijom. Dodatno, u cilju povećanja penetracije/permeacije aceklofenaka, izvršeno je inkorporiranje ciklodekstrina u odabrane mikroemulzije. Stoga, cilj rada je procena uticaja hidroksipropil-β-ciklodekstrina na karakteristike mikroemulzija na bazi SE (visokoprečišćena voda/surfaktant-izopropanol/izopropilmiristat), koristeći kao surfaktant saharozu laurat (SL) i saharozu miristat (SM).
Izvršena je fizičkohemijska (merenje električne provodljivosti i pH) i biofarmaceutska (uređaj za dissolution test sa mini-lopaticama uz primenu VanKel Enhancer® ćelija) karakterizacija mikroemulzija bez ciklodekstrina, kao i sa masenim udelom ciklodekstrina 1% i 2%. Dodatno, izvršena je i procena in vivo iritacionog potencijala, primenom tehnika bioinženjeringa kože (transepidermalni gubitak vode (TEGV), stepen hidratisanosti stratum corneum-a (SCH) i eritema indeks (EI)).
Dodatak ciklodekstrina u ispitivane sisteme doveo je do povećanja električne provodljivosti, i nije doveo do promene pH vrednosti. Brzina oslobađanja aceklofenaka iz mikroemulzija na bazi SL je veća u odnosu na mikroemulzije sa SM. Odsustvo statistički značajne razlike između ukupne količine oslobođenog aceklofenaka ukazuje da je efekat ciklodekstrina na povećanu isporuku lekova kroz kožu verovatno posledica interakcije sa lipidima kože. SCH je statistički značajno smanjena kod svih mikroemulzija u odnosu na bazalne vrednosti, netretiranu kontrolu sa okluzijom i bez okluzije. TEGV je statistički značajno povećan kod svih ispitivanih formulacija u odnosu na bazalne vrednosti, izuzev u slučaju FL sa 2% ciklodekstrina, iako postoji trend povećanja TEGV.
Smanjenje SCH i povećanje TEGV, i odsustvo promena u EI, ukazuju na moguću fluidizaciju i solubilizaciju lipida SC-a, što ukazuje da ispitivane mikroemulzije mogu biti efikasne u (trans)dermalnoj isporuci aceklofenaka. Kako bi se potvrdile pretpostavke da dodatak CD u mikroemulzije povećava penetraciju i/ili resorpciju, neophodno je sprovesti procenu dermalne raspoloživosti aceklofenaka iz odabranih formulacija i/ili farmakokinetička ispitivanja na eksperimentalnim životinjama.

Ključne reči: mikroemulzije, saharozni estri, hidroksipropil-β-ciklodekstrin, aceklofenak

PHYSICOCHEMICAL, BIOPHARMACEUTICAL CHARACTERIZATION AND IN VIVO SKIN IRRITATION STUDY OF SUCROSE ESTER-BASED MICROEMULSIONS: THE INFLUENCE OF HYDROXYPROPYL-B-CYCLODEXTRIN

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Sucrose esters (SE) are non-ionic surfactants with low skin irritation potential. To improve the transport of aceclofenac across the skin, SE-based microemulsions have been studied as drug delivery vehicles prospectively making the skin more permeable. Additionally, we incorporated cyclodextrins into selected microemulsions, as they may have significant influence on skin permeation rate of drugs. The main objective of the study is to investigate the effect of hydroxypropyl-β-cyclodextrin on properties of SE-based microemulsions (ultra-purified water/ surfactant-isopropyl alcohol/isopropyl myristate), using as surfactant: sucrose laurate (SL) and myristate (SM).
We performed physicochemical (conductivity and pH measurements) and biopharmaceutical (mini-rotating paddle apparatus, modified by addition of VanKel Enhancer® cell) characterization of microemulsions without and with cyclodextrins (1 and 2% w/w). Additionally, we assessed their in vivo irritation potential, employing methods of skin bioengineering (transepidermal water loss (TEWL), stratum corneum hydration (SCH) and erythema index (EI)).
Addition of cyclodextrins caused increase in conductivity and did not cause changes in pH values of the formulations. SL-based microemulsions showed higher quantity of released aceclofenac in comparison to SM-based microemulsions. The lack of statistical significance in total amount of released aceclofenac suggested that cyclodextrins increase transport of drugs through extraction of skin lipids. SCH was significantly decreased in all formulations, compared to basal values, non-treated control under and without occlusion. TEWL was significantly increased in all formulations compared to basal values, except in case of FL with 2% cyclodextrin, although the trend of TEWL increase could be observed.
Lower SCH values, increase in TEWL, and the absence of changes in EI, could be related to potential of formulations to fluidize and solubilize SC lipids, probably contributing to more pronounced transport of aceclofenac through the skin. To confirm this hypothesis, it would be important to perform skin penetration study and/or pharmacokinetic study on animal models.

Key words: microemulsions, sucrose esters, hydroxypropyl- β-cyclodextrin, aceclofenac

LIOFILIZACIJA: PRINCIPI I FARMACEUTSKA APLIKACIJA

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Liofilizacija (sušenje smrzavanjem,kriodesikacija) je proces sušenja koji se koristi za prevođenje rastvora labilnih materijala u čvrsto stanje sa dovoljnom stabilnošću za distribuciju i čuvanje. Sušenje smrzavanjem je metod izbora za proizvodnju parenteralnih rastvora. Uglavnom se o liofilizaciji u farmaceutskoj tehnologiji govori u kontekstu sušenja proteina. Danas se ispituje i mogućnost upotrebe ove metode u druge svrhe u farmaciji. Proces liofilizacije određen u koracima: predsmrzavanje, primarno i sekundarno sušenje.
Ekscipijensi, imaju specifične funkcije, obično povezane sa stabilnošću ili procesom, i mogu činiti većinsku frakciju osušene čvrste supstance. Efikasan proces je onaj koji se odvija na što višoj temperaturi, ali ne prevelikoj kako ne bi uticala na kvalitet proizvoda. Danas, istraživači pokušavaju što više doprinijeti razumijevanju svih koraka ovog procesa. Poznavanje načina na koji se može kontrolisati i manipulisati fazom smrzavanja će omogućiti efikasniji proces liofilizacije kao i razvoj biofarmaceutskih proizvoda sa poboljšanom stabilnošću. Temperatura prelaska u staklasto stanje multikomponentnog amorfnog sistema može se procijeniti iz istih temperatura individualnih amorfnih komponenti. Strategija stabilizacije se fokusira na tri glavna faktora: specifične hemijske zahtijeve, fizičko stanje čvrste supstance i strukture proteina. Liofilizacija je danas našla svoje mjesto u različitim vidovima farmaceutske primjene što ukazuje na značaj ove metode. Unapređenjem ove metode na različite načine olakšan je razvoj novih, poboljšanih formulacija i procesa što rezultuje boljim kvalitetom proizvoda.

Ključne riječi: liofilizacija, sušenje smrzavanjem, farmaceutska aplikacija

LYOPHILIZATION: PRINCIPLES AND PHARMACEUTICAL APPLICATION

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Lyophilization (freeze-drying; cryodessication) is a drying process used for conversion of solutions of labile materials into solids of sufficient stability for distribution and storage. This process has a long history in the pharmaceutical industry as a technique for stabilization of labile drugs and it improves drug's stability and long term storage. Lyophilization allows water removal from a product by sublimation. After the water is frozen and placed under a vacuum, ice changes directly from solid to vapor without passing through a liquid phase. The process comprises three steps: freezing, primary drying and secondary drying.
Available literature data in the field of pharmaceutical lyophilization used to describe mostly drying of proteins. Nowadays, use of this method in other pharmaceutical applications is investigated. New chemical entities very often suffer from poor solubility and bioavailability. Lyophilization

represents possible way of overcoming this challenge. It is method of choice for production of parenteral preparations. About 50% of the currently biopharmaceuticals are lyophilized. Lyophilization is today important for the preservation of nucleic acid based pharmaceuticals. Lyophilization is a multistage operation in which, each step is critical. Researchers are trying to understand every single step of the process. Thorough understanding of each step of this complex process and how to manipulate with it as well as knowledge of how these steps affect product's quality is obligatory. Knowing how to control or manipulate the freezing step will enable researchers to come up with more efficient lyophilization process what will lead to development of biopharmaceutical products with improved stability. Method improvement leads to development of new, improved formulations and processes and to the better product's quality.

Key words: Lyophilization, freeze-drying, pharmaceutical application

PROMOTIVNA PREDAVANJA

STARA LJUBAV ZABORAVA NEMA

Tatjana Milošević

Nesteroidni antiinflamatorni lekovi (NSAIL), a medju njima i ibuprofen spadaju među najviše korišćene lekove kod nas i u svetu. Čine važnu grupu lekova koje propisuju lekari, ali koje izdaju i farmaceuti u apoteci, što ovoj grupi lekova daje veliki značaj sa aspekta farmaceuta. Ovi lekovi se koriste za suzbijanje blagih do umerenih akutnih bolova kao što su glavobolja, zubobolja, artralgije i mijalgije, kao I jakih akutnih, pa i hroničnih bolova. Pored analgetičkog, NSAIL I ibuprofen ispoljavaju antipiretičko i antiinflamatorno dejstvo. Kako glavne razlike između neopioidnih analgetika nisu toliko u efikasnosti, već u bezbednosti primene, pri izboru neopioidnog analgetika prvenstveno se vodi računa o neželjenim dejstvima koja se javljaju pri terapijskim dozama (npr. gastrointestinalni, renalni i kardiovaskularni neželjeni efekti).
Ibuprofen predstavlja prvi propionski nesteroidni antiinflamatorni lek u svetu, otkriven 1961. godine od strane dr Stewarta Adamsa I saradnika. Tokom višegodišnje upotrebe I postojanja na tržištu, dokazao je svoju efikasnost, a brojne studije pokazuju povoljan bezbednosni profil i nizak rizik za izazivanje neželjenih efekata u gastrointestinalnom I u kardiovaskularnom sistemu.
Bezbedna i efikasna kontrola bola, povećane telesne temperature i inflamacije u dece je važna komponenta savremene medicinske prakse. Opsežne kliničke i opservacione studije su pokazale veću antipiretičku i analgetičku efikasnost ibuprofena u poređenju sa paracetamolom.

LOVE FOR A LIFE!

Tatjana Milošević

Nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen are among the most used drugs in the world and our country. They constitute an important group of drugs prescribed by doctors, but also recommended by pharmacists, which gives this group of drugs important place in daily work of pharmacists. These drugs are used for relieving mild to moderate acute pain such as headache, toothache, arthralgia and myalgia, as well as severe acute pain and chronic pain. Beside analgesic, NSAID's and ibuprofen have antipyretic and anti-inflammatory effects. As the main difference between the non-opioid analgesics is not so much in efficiency, but in the safety of administration and side effects that occur at therapeutic doses (eg, gastrointestinal, renal and cardiovascular side effects), which should be the main characteristics in choosing and recommending NSAID's.

Ibuprofen is the first propionic non-steroidal anti-inflammatory drug in the world, discovered in 1961 by Dr. Stewart Adams and associates. During many years of use and existence in the market, Ibuprofen has proved its effectiveness and safety profile. Numerous studies have shown a favorable safety profile and low risk of causing adverse effects in the gastrointestinal and the cardiovascular system.

Safe and effective pain relief, fever and inflammation in children are an important components of modern medical practice. Extensive clinical and observational studies showed greater antipyretic and analgesic efficacy of ibuprofen as compared to acetaminophen.

PREPARATI UREE I POVRŠINSKA ZAŠTITA KOŽE ŠAKA I STOPALA

Katarina Milošević Kostadinović

Apoteka Medicor Kotor

Koža šake i stopala je svakodnevno izložena spoljnim uticajima i podložna je narušavanju njene osnovne barijerne funkcije. Zbog svoje jedinstvene uloge i većem kontaktu sa iritantima koža šake i stopala sklona je razvoju preosjetljivosti i različitim dermatozama.
Koža šaka i stopala je različita u strukturi u poređenju sa kožom na drugim dijelovima tijela. Koža na šakama i stopalima je jače inervirana, čvršća i ima veću gustinu ekrinih znojnih žljezda, a manju apoktinih.
Zaštitna, regenerativna i vlažeća njega kože šaka i stopala je osnova svakog tretmana suve kože kao i tretmana poremećaja i oboljenja udružena sa simptomom suve kože. Simptomatski tretman suvoće kože sa odgovarajućim zaštitnim i hidratantnim preparatima može da reducira upotrebu potentnijih odn. medikamentoznih tretmana.
Zaštitna, regenerativna i hidratantna njega kože je osnova za zaštitu i prevenciju suve kože i smanjuje razvoj bolesti i poremećaja povezanih sa ovim simptomom.
Cilj ovog rada i prezentacije je prikaz primjene uree, kao prirodnog vlažećeg faktora, u farmaceutskim proizvodima i njihovo djelovanje na stanje stratum corneuma.
Primjena hidratantnih kremova koji sadrže ureu povećava njenu koncentraciju u stratum corneumu i dovodi do promjena u njegovoj strukturi, hidrira i pomaže u očuvanju barijerne funkcije kože.

Ključne riječi: urea, suva koža, njega kože, stopala, šake.

UREA FORMULATIONS AND PROTECTION OF HAND AND FEET SKIN

Katarina Milošević Kostadinović

Pharmacy Medicor Kotor

Hand and feet skin is hihgly exposed to environmental influence and is highly prone to disruption of basic barrier function. Because of their unique role and more often in contact with irritnants, this part of skin is more prone to sensitivity and dermatosis.
Palm and feet skin is difrent in structure from other body sites. It is highly innervated, thicker and has a high density of eccrine sweat glands and lack of apocrine glands.
Protective, regenerative and moisturizing skin care of hand and feet skin is base of every treatment of dry skin, also as treatment of diseases and disorders with simptoms of dry skin.Simptomatic tratment of dry skin with protectiv and moisturizing preparation may reduce use of more potent and medical tratmants.
Protective, regenerative and moisturizing skin care is basic treatment for protection and prevention of dry skin and decrease appearance and development of some illneses and disorders contected with simptom of dry skin.
Aim of this article and presentation is representation of urea as natural moisturising factor and use in pharmaceutical products and their activity on stratum corneum.
Aplication of moisturizers containing urea is shown to increase its contcentration in stratum corneum and exert changes in its structure, moisturizing and helping to keep a barier function of the skin.

Keywords: urea, dry skin, skin care, feet, hand.

FARMACEUTI I KOMPRESIVNA TERAPIJA

Katarina Milošević Kostadinović

Apoteka Medicor Kotor

Kompresivna terapija kao zlatni standard indikovana je u svim stanjuma hronične venske bolesti, limfedema, kod nekih povreda, nakon operacija vena, skleroterapija, rana, kao i kod nekih fizioloških stanja gdje venski sistem trpi dodatana opterećenja i gde kompresivna terapija ima preventivno dejstvo, kao kod trudnoće, opterečenja, dugih staticnih položaja bez kretanja - kod dugih putovanja, nekih medicinskih procedura gdje je pacijent podložan pojavi tromboze i sl.
Uobičajeno farmaceuti ne ucestvuju u propisivanju i odredjivanju kompresivne terapije, ali pacijenti su upućeni na farmaceute kod odabira i primjene komresivne terapije.
Primjena kompresivne terapije i kod zdravih ljudi u cilju prevencije bolesti, kao i sve veći broj proizvoda koji se nalaze u apoteci povećava potrebu za edukacijom farmaceuta u vezi sa kompresivnom terapijom.
Cilj ovog rada i prezentacije je prikaz kompresivnih terapija iz ugla farmaceuta.
Farmaceut je stručnjak koji je najdostupniji pacijentu i koji u saradnji sa ljekarom omogućava uspješnu i djelotvornu primjenu terapije.
Način odabira, uzimanje mjera, ispravno odredjivanje veličine i adekvatnog sastava, uputstva o primjeni i odrzavanju kao i kontrola ispravnog postavljanja kompresivne terapije zadaci su ali i izazovi u svakodnevnoj praksi u apoteci.

Ključne riječi: kompresivna terapija, hronična venska bolest, limfedem, rane, trudnoća.

PHARMACISTS AND COMPRESSION THERAPY

Katarina Milošević Kostadinović

Pharmacy Medicor Kotor

Compression therapy as golden standard is used in all conditions of chronic venous disease, lymphedema, injuries, aftercare following surgery, scerotherapy, leg ulcers and in some physiological states where venous systems is compromised, where compression therapy have preventive effect-during pregnancy, heavy load positions, static positions without
proper moving-long distance travel, some medical procedures where patient is in danger of developing thrombosis , etc.
Usually pharmacists do not participate in prescribing of compression therapy, but patients are directed to them for choosing and way of application.
Applying of compression in heathy people in preventive care and great number of different products in pharmacies rises a need for education of pharmacists in this topic.
Aim of this article and presentation is displaying compression therapy from pharmacists view.
Pharmacist is a medical expert most accessible to the patient, who together with the doctor provide adequate successful and effective therapy.
Choosing, taking of measurements, correct selection of size and composition, instruction of wearing and utilization, cleaning and adequate control of proper wearing of compression therapy are assignments but also a challenge in everyday practice in pharmacy.

Keywords: comression therapy, chronic venous disease, lymphedema, leg ulcers, pregnancy.

LIRAGLUTID U LEČENJU DIJABETES MELITUSA TIP 2

Branislava Miljković

Univerzitet u Beogradu - Farmaceutski fakultet

Relativno nov terapijski pristup u lečenju pacijenata sa dijabetes melitusom tip 2 zasnovan je na delovanju glikoregulatornog peptida iz familije inkretina. Glukagonu sličan peptid 1 (glucagon like peptide 1, GLP-1) se sekretuje u L-ćelijama gastrointestinalnog trakta kao odgovor na unos hrane. GLP-1 ima višestruke efekte na fiziološke procese. Najznačajniji je direktan efekat GLP-1 na alfa, beta i delta ćelije pankreasa. Podstiče sintezu i sekreciju insulina u beta ćelijama i snižava sekreciju glukagona delimično preko povećanja sekrecije somatostatina i direktnim efektom na alfa ćelije. Značajno je istaći da GLP-1 ispoljava svoje efekte na glukozno-zavisan način. Rezultati istraživanja u animalnim modelima su dokumentovali da GLP-1 povećava masu beta ćelija preko stimulacije neogeneze i priliferacije beta ćelija kao i smanjenja njihove apoptoze. Mogućnost da se očuva funkcija beta ćelija pankreasa je od posebnog interesa u terapiji dijabetes melitusa tip 2 koji nepovratno i progresivno iscrpljuje njihovu funkciju. Rezultati sprovedenih ispitivanja pokazuju da GLP-1 smanjuje brzinu pražnjenja želuca i odlaže resorpciju hrane što utiče na povećanje osećaja sitosti. GLP-1 receptori se nalaze i u centralnom nervnom sistemu i na taj način doprinose povećanju osećaja sitosti i smanjenoj potrebi za unosom hrane. U toku su i ispitivanja kardioprotektivnog delovanja GLP-1.

Egzogeno primenjen GLP-1 brzo podleže metabolizmu pod dejstvom dipeptidil peptidaze-4 i zbog veoma kratkog poluvremena eliminacije ne ispoljava duži klinički efekat. U cilju prevazilaženja ovog nedostatka razvijen je analog GLP-1, liraglutid, čija je sličnost u strukturi sa GLP-1 97%. Male strukturne izmene u molekuli GLP-1 omogućile su samoasocijaciju molekula u heptamere i na taj način odloženu resorpciju sa mesta primene kao i izmenjene farmakokinetičke karakteristike koje se odnose na veći afinitet vezivanja za albumine plazme i otpornost na dipeptidil peptidazu-4. Rezultat izmena u farmakokinetičkim karakteristikama bio je značajno duže poluvreme eliminacije (oko 12h). Odložena resorpcija (vreme postizanja maksimalnih koncentracija 11-13h posle s.c. primene) i produžena eliminacija omogućavaju primenu liraglutida s.c. jednom dnevno.

Višestruki farmakološki efekti koji su glukozno zavisni, potencijal za očuvanje funkcije beta ćelija i povoljan farmakokinetički profil čine liraglutid unapređenom terapijskom opcijom za pacijente sa dijabetes melitusom tip 2.

Ključne reči: liraglutit, dijabetes melitus tip 2, GLP-1, farmakokinetika

SMERNICE ZA FARMACEUTE: FARMACEUTSKA ZDRAVSTVENA ZAŠTITA U TERAPIJI GASTROEZOFAGEALNOG REFLUKSA

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Gastroezofagealni refluks predstavlja kretanje gastričnog sadržaja u ezofagus i kada su simptomi učestali i utiču na kvalitet života pacijenta razmatra se kao gastroezofagealna refluksna bolest (GERB). GERB je jedna od najčešćih bolesti digestivnog sistema a najčešći simptomi su gorušica, osećaj pečenja u grlu i grudima. Veoma često se javlja i nadutost stomaka, posebno nakon obroka, dok su nešto ređe zastupljeni mučnina, slabost i osećaj rane sitosti.
Istraživanja su pokazala da se više od 70 posto pacijenata sa simptomima GERB-a leči bez prethodnog saveta sa lekarom. Stručnost i dostupnost farmaceuta su otuda od ključnog značaja u savetovanju pacijenata, preporuci terapije, prepoznavanju alarmnih simptoma (hematemeza, melena, disfagija, odinofagija) i faktora rizika (osobe starije od 55 godina, pozitivna porodična istorija na kancer želuca i/ili jednjaka, česti relapsi) za upućivanje pacijenta lekaru.
U okviru prezentacije biće predstavljene smernice za farmaceutsku zdravstvenu zaštitu u terapiji GERB-a kao podrška farmaceutima u svakodnevnoj praksi. Koraci zbrinjavanja pacijenata sa GERB-om su predstavljeni u algoritmu koji farmaceuta upućuje na pružanje aktivnosti ili intervencija. Značajno je istaći i aspekt prepoznavanja alarmnih simptoma i faktora rizika zbog kojih je potrebno pacijente uputiti lekaru. Poseban aspekt je savetovanje pacijenata o prestanku pušenja, smanjenju telesne mase i pravilnoj ishrani. Pored nefarmakoloških mera, smernice predstavljaju terapijske opcije, značaj primene inhibitora protonske pumpe kao i mesto blokatora H2 receptora i antacida u terapiji GERB-a. Takođe, biće predstavljen i način praćenja ishoda terapije.

Ključne reči: Farmaceutska zdravstvena zaštita, gastroezofagealni refluks, savetovanje, smernice, terapija

DOBRA ISHRANA- DOBAR POČETAK

Tatjana Nikolić

Poslednjih godina je postalo već sasvim jasno da adekvatna ishrana u veoma ranom periodu života, počevši već od samog začeća, značajno utiče ne samo na kratkoročni morbiditet, već i dugoročni razvoj novorođenog deteta. Znamo da su morfološke i funkcionalne karakteristike sisara uslovljene njegovim genonom. Međutim, sve je više epidemioloških studija, kao i kontrolisanih eksperimentalnih studija na životinjama, koje ukazuju na to da vrsta hranjivih materija koje fetus i novorođenče dobijaju tokom intrauterusnog i novorođenačkog života, mogu značajno menjati genom. Epigenetski mehanizmi, trigerovani ishranom tokom ranog razvoja, mogu uticati na metaboličke procese i povećati predispoziciju ka razvoju hroničnih bolesti tokom celog života individue.

Ishrana novorođenčeta majčinim mlekom je zlatni standard i ima, ne samo nutritivnih prednosti, već i značajne efekte u smanjenju morbiditeta, podsticanju maturacije gastrointestinalnog trakta, uspostavljanju adekvatnih metaboličkih funkcija, kao i ulogu u dugoročnom neurosenzornom razvoju.

Nažalost, uz hipogalaktiju, postoje i stanja majke koja predstavljaju kontraindikaciju za ishranu novorođenčeta njenim mlekom. U ovim situacijama u ishranu novorođenčeta se uvode adaptirane mlečne formule. Sastav mlečne formule treba uskladiti sa potrebama uslovljenim uzrastom i zrelošću novorođenčeta , a često i sa nekom od dodatnih potreba ili faktora rizika novorođenčeta.

Mlečne formule se uopšteno mogu klasifikovati u odnosu na tri osnovna kriterijuma: kalorijska vrednost, izvor ugljenih hidrata i proteinski sastav. Tragajući za optimalnim sastavom, koji će zadovoljiti ne samo nutritivne potrebe već imati i uticaj na dugoročni rast, razvoj i zdravlje dece, poslednjih decenija sprovedene su brojne studije. Među njima je i BEMIM (Belgrade-Munich Infant Milk trial) randomizirana, dvostruko slepa studija, koja je ispitivala optimalnu količinu i sastav priteina u mečnoj formuli za terminsko novorođenče. Ono čemu su brojni istraživači poklanjali pažnju je i značaj dodavanja dugolančanih masnih kiselina mlečnim formulama.

Znajući koliko je zdrava ishrana majke važna za kvalitet njenog mleka, ne smeju se zanemariti ni ekološki uslovi na farmama sa kojih se dobija kravlje mleko.

GOOD NUTRITION - GOOD START

Tatjana Nikolic

During the last years it has become clear that adequate nutrition in the vey early period of life, beginning from the very conception, significantly influence not only short-term morbidity but also long-term development of a new-born child. We know that morphological and functional characteristics of mammals are conditioned by their genome. However, there are more and more epidemiologic studies, as well as controlled experimental studies on the animals, which show that the kind of nutrients that fetus and new-born baby get during intrauterine period and a very beginning of life can significantly change the genome. Genetic mechanisms triggered by nutrition during early development can influence metabolic processes and increase predisposition to development of chronic illnesses during the whole life of an individual.

Feeding a new-born baby on mother's milk is a golden standard and it has not only nutritional advantages, but also significant effects on reducing morbidity, stimulating maturation of gastrointestinal tract establishing adequate metabolic functions, as well as it has a role in a long-term neuro-sensory development.

Unfortunately, apart from hyper-lactation, there are some conditions of the mother that represent contraindication for feeding a new-born baby on her milk. In these situations, adapted milk formulas are introduced. The structure of the formula should be coordinated with the needs conditioned by the age and maturity of a new-born baby, and often with some extra needs or factors of risks.

Milk formulas can generally be classified according to three criteria: caloric value, source of carbon-dioxide and protein content. Searching for optimal content which will meet not only nutritive requirements, but will have an impact on long-term growth, development and health of children, numerous studies have been carried out during the last decades. Among them, the one called BEMIM (Belgrade Munich Infant Milk Trial) is randomized; a doubly blind study, which examined the optimal quantity and content of proteins in the formula for a baby born in term. The issue that numerous researchers paid attention to is importance of adding long-chained amino acids to formulas.

Knowing how much healthy food that mother takes is important for the quality of her milk, you mustn't neglect ecological conditions on the farms from where you get the cow milk.

PEGILOVANI INTERFERON-A2A – NAŠA ISKUSTVA U LIJEČENJU HCV INFEKCIJA

Dragica Terzic

Klinika za infektivne bolesti KCCG

Hronični hepatitis C je glavni uzrok hroničnih bolesti jetre na globalnom nivou, a prirodni tok progresije može dovesti do ciroze sa zatajenjem jetre, hepatocelularnog karcinoma i prerane smrti. Dosadašnji podaci pokazuju da je interferon-osnovna terapija za hepatitis C hroničnu infekciju.
Predstaviti dosadašnja iskustva u liječenju pacijenata sa HCV infekcijom u Crnoj Gori Pegilovanim interferonom-α2a u kombinaciji sa lijekom Ribavirin.
U svakodnevnoj rutinskoj praksi na klinici za Infektivne bolesti KCCG u proteklih 10 godina ukupno je 260 pacijenata primilo pomenutu terapiju. Isti su liječeni, u zavisnosti od njihove tjelesne težine i genotipa HCV, tokom 48 ili 24 nedelje, lijekom Pegilovani interferon-α2a, jednom nedeljno subkutano 180 ili 135 mikrograma i lijekom Ribavirin 1000 ili 1200 mg/dan. Praćeni su 24 nedelje nakon tretmana. Svim pacijentima su kontrolisani funkcionalni testovi jetre i radjena je kontrola viremije.
Imali smo negativan HCV RNA (PCR) kod 71% pacijenata na kraju liječenja a šest mjeseci nakon sprovedene terapije. Negativni HCV RNA, odnosno stabilan viruloški odgovor (SVR) naden je kod 69,5% pacijenata. SVR u grupi je potvrdjen kod 85% korisnika narkotika, nezavisno od vrste genotipa. Za jednu ili dvije godine nakon završenog liječenja otkriveno je 3,5% pacijenata sa relapsom i 2,7% pacijenata sa reinfekcijom nekim drugim genotipom HCV. Najčešće prijavljena neželjena dejstva su: sindrom sličan gripu(48%), neutropenija(41%) i hipothireoza(5%).
Kombinacija terapije ljekova Pegilovanog interferona-α2a i Ribavirina dovodi do SVR u većini liječenih pacijenata(69,5%) posebno u pomenutoj grupi korisnika narkotika(85%). Datu antivirusnu terapiju pacijenti su dobro podnosili. Neželjena dejstva antivirusnog tretmana su rijetko(1,5%) dovodila do prekida terapije.

Ključne riječi: Pegilovani interferon-α2a, Ribavirin, hronični hepatitis C

PEGYLATED INTERFERON-A2A – OUR EXPERIENCE IN HCV INFECTION TREATMENT

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Chronic hepatitis C is the major cause of chronic liver disease globally, and the natural history of progression may lead to cirrhosis with liver failure, hepatocellular carcinoma, and premature death. Current data shows that interferon is the basic therapy for Hepatitis chronic C infection.
To present our experiences in the treatment of patients with HCV infection in Montenegro with Pegylated interferon-α2a in combination with the drug Ribavirin.
In daily routine practice at the Clinic for Infectious diseases of the Clinical Center of Montenegro in the past 10 years 260 patients received mentioned treatment. Depending on their body weight and genotypes, patients received 180 μg or 135 μg of Pegylated interferon-α2a subcutaneously, once a week, along with either 1000 or 1200 mg/day of Ribavirin, for 48 weeks or 24 weeks depending on the type of genotype. Patients were followed up for 24 weeks. Liver function tests and control of viremia were made for all patients.
We had negative HCV RNA (PCR) with 71% of patients at the end of treatment, whilst six months after the completed therapy, negative HCV RNA i.e. stable virologic response (SVR) was assessed with 69.5% of patients. SVR in narcotic users group was assessed in 85%, regardless of the type of genotype. In one or two years after the completed treatment, 3,5% of patients with relapse and 2,7% of patients with re-infection from another genotype of HCV have been discovered. The most common side effects were flu-like syndrome (48%), neutropenia (41%) and hypothyroidism (5%).
Combined therapy of Pegylated interferon-α2a with Ribavirin results to SVR with the majority of treated patients (69,5%), especially in the group of users of narcotics (85%). The side effects of antiviral treatment have rarely resulted in termination of therapy (1.5%)

Keywords: Pegylated interferon-α2a, Ribavirin, chronic hepatitis C

TIROTRICIN – ČUDESNI ANTIBIOTIK

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Tirotricin je antimikrobni lijek za lokalnu primjenu, iz grupe polipeptidnih antibiotika. Sastoji se iz dvije aktivne komponente: tirocidina i gramicidina. Djeluje prvenstveno na gram pozitivne, kao i na neke gram negativne bakterije, koje su najčešći uzročnici površinskih infekcija. Efikasan je i protiv bakterija i gljivica koje su rezistentne na standardnu terapiju.
Definisanje primjene tirotricina, u obliku praška ili gela, u zavisnosti od tipa površinske povrede. Podaci iz literature i vlastito iskustvo.
Tirotricin se ne apsorbuje preko kože ili mukoznih membrana, a razara se u digestivnom traktu, pa nema bojazni od sistemskih neželjenih efekata. Posjeduje odličnu lokalnu podnošljivost, uz minimalni rizik od senzibilizacije. Zbog specifičnog mehanizma djelovanja ne izaziva ukrštenu rezistenciju sa drugim antibioticima. Posle višedecenijske upotrebe nije registrovano smanjivanje efikasnosti, ili povećanje bakterijske rezistencije. Iz navedenih razloga (visoko povoljan odnos korist/rizik) tirotricin je jedini antibiotik za lokalnu primjenu koji se može izdavati bez ljekarskog recepta.
Tirotricin je dostupan u obliku Tyrosur® praška i gela. Koristi se u terapiji površinskih rana, od ogrebotina do razderotina, sa superinfekcijama izazvanim mikrobima osetljivim na tirotricin.

Ključne reči: tirotricin, lokalni antibiotik, povrede kože, Tyrosur®

TYROTHRICIN – A MIRACULOUS ANTIBIOTIC

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Tyrothricin is an antimicrobial drug for topical application, from the group of polypeptide antibiotics. It consists of two active components: tirocidin and gramicidin. It acts primarily against the gram positive and some gram negative bacteria, which are the most common causes of surface infections. It is effective against bacteria and fungi that are resistant to standard therapy. To define the application tyrothricin, in the form of powder or gel, depending on the type of superficial injuries.
Data from the literature and own experience.
Tyrothricin is not absorbed through the skin or mucous membranes and destroys in the digestive tract, so there is no risk of systemic adverse effects. It has excellent local tolerance, with minimal risk of sensitization. Because of the specific mechanism of action, it does not cause cross-resistance with other antibiotics. After decades of using tyrothricin, reduced efficiency or increasing bacterial resistance is not registered. For the stated reasons (highly favorable benefit / risk ratio) tyrothricin is the only antibiotic for topical application which can be dispensed without a prescription.
Tyrothricin is available in the form of Tyrosur® powder and gel. It is used in the treatment of superficial wounds, scratches to lacerations, with superinfections caused by microbes sensitive to tyrothricin.

Keywords: tyrothricin, local antibiotics, skin injury, Tyrosur®