CYCLIC VOLTAMMETRY AS A SENSITIVE APPROACH IN INVESTIGATION OF DOXORUBICIN

M. Pendovska[1,3*], I. Panovska[1], S. Krstevska Balkanov[1],

M. Aleksandrov[2,3], V. Maksimova[3]

[1] PHI University Clinic of Hematology, Ss. Cyril and Methodius University in Skopje, Blvd. Majka Tereza 17, 1000 Skopje, Republic of North Macedonia
[2] Department of production, research and development, TetraHip DOO Kocani, Orizova 9, 2300 Kocani, Republic of North Macedonia
[3] Faculty of Medical Sciences, Goce Delcev University of Stip, Krste Misirkov 10-A, 2000 Stip, Republic of North Macedonia

***Corresponding author e-mail: marija.311156@student.ugd.edu.mk, marija.hemato@gmail.com**

INTRODUCTION AND OBJECTIVE

Doxorubicin is an anthracycline drug. Its chemotherapeutic effect is due to two possible mechanisms, 1)disruption of topoisomerase-II-mediated DNA repair due to its intercalation into DNA helix and 2)generation of free radicals and their damage to cellular membranes, DNA, and proteins. This can be a result of its planar aromatic chromophore which intercalates between two base pairs of DNA [1]. Therefore, its pharmacological/toxicological characteristics are largely dependent on its oxidative properties, and the aim of this study is to summarize the methods and data based on its electrochemical behavior of doxorubicin, obtained by the means of cyclic voltammetry (CV) [2].

METHODS

Cyclic voltammetry is a versatile electrochemical method where the redox reactions occurring at the working electrode result in a flow of current. The potentiostat measures this current and plots it as a function of the applied potential. Each successful forwards and backwards potential sweep produces a a cyclic voltammogram characterized by anodic and cathodic peak currents, peak potentials, and the oxidation and reduction onset potentials.

RESULTS

Our research revealed several studies that feature the electrochemical behavior of doxorubicin. CV in pH~7.4 has shown that doxorubicin undergoes a reversible two-electron reduction with value $E_{1/2}$ = -665 mV(versus Ag/AgCl, saturated KCl). This process was defined as quasi reversible, at low scan rates. Further, the interaction of doxorubicin hydrochloride with calf thymus DNA was studied by measuring cathodic peak current, which gradually decreased as more DNA was added into the cell [3].

The interaction of doxorubicin with calf thymus DNA, was mostly assessed by electrochemical sensors using surface modified working electrodes [4,5,6]. Electrochemical sensor based on multi-walled carbon nanotubes modified platinum electrode (Pt/MWCNTs) [4], electrodeposition of silver nanoparticles and electro-polymerization of alginate layers on the surface of a glassy carbon electrode have been also used in this purpose [5]. CV of doxorubicine on a screen-printed electrodes modified with single-wall carbon nanotubes (SPE/CNT) have shown linear dependence of the intensity of electro reduction/oxidation on the square root of the scan rate which proved that the process is a controlled by diffusion. Moreover, thay imployed differential pulse voltammetry to validate a sensitive method for doxorubicine

quantification. The drug binding processes were examined by DPV via the registration of a decrease in peak current intensity of guanine, adenine, and thymine of DNA in the presence of doxorubicin [6].

CONCLUSION

Cyclic voltammetry can be used as an efffective tool for quantification of doxorubicine and its interactions with DNA or other metals. Reverible oxidation of doxorubicin to semiquinone and back, releases reactive oxygen species that cause DNA damage and lipid peroxidation. The effectivness of the therapeutic effect of doxorubicine depends on its interaction with DNA. These interactions were mostly assessed by using an electrochemical surface modified sensor, in the presence of DNA. These data lead to a conclusion that electrochemical platforms represent a sensitive approach for the investigation of DNA–drug interaction in electrode systems. Examining the electrochemical signals doxorubicin or DNA–doxorubicin complex before and after binding establishes the interaction and helps in mechanism elucidation.

REFERENCES

[1] Thorn CF, Oshiro C, Marsh S, Hernandez-Boussard T, et al. Doxorubicin pathways: pharmacodynamics and adverse effects. Pharmacogenet Genomics. 2011; 21(7): 440–446; doi: 10.1097/FPC.0b013e32833ffb56.

[2] Doma I, Negm EA, Shrif AY. Cyclic voltammetry of bulk materials system (BMS) and nano manganese sulfate (NMS) with Doxorubicin using glassy Carbon electrode. Int. J. Nano Dimens. 2017; 8(1): 89-96; DOI: 10.22034/ijnd.2017.24380.

[3] Guin PS, and Das S. Exploration of Electrochemical Intermediates of the Anticancer Drug Doxorubicin Hydrochloride Using Cyclic Voltammetry and Simulation Studies with an Evaluation for Its Interaction with DNA. International Journal of Electrochemistry. 2014; (Article ID 517371): 8 pages; DOI:10.1155/2014/517371.

[4] Hajian R, Tayebi Z, Shams N. Fabrication of an electrochemical sensor for determination of doxorubicin in human plasma and its interaction with DNA. Journal of Pharmaceutical Analysis. 2017; 7(1): 27-33; https://doi.org/10.1016/j.jpha.2016.07.005.

[5] Lulek E, Soleymani J, Molaparast M, Ertas YN. Electrochemical sensing of doxorubicin hydrochloride under sodium alginate antifouling conditions using silver nanoparticles modified glassy carbon electrodes. Talanta. 2023; Volume 265, 124846; https://doi.org/10.1016/j.talanta.2023.124846.

[6] Pronina VV, Kostryukova LV, Bulko TV, Shumyantseva VV. Interaction of Doxorubicin Embedded into Phospholipid Nanoparticles and Targeted Peptide-Modified Phospholipid Nanoparticles with DNA. Molecules. 2023; 28(14), 5317; https://doi.org/10.3390/molecules28145317.

KEY WORDS: cyclic voltammetry, doxorubicin, oxidation, reduction.

PRESENTATION FORMAT : POSTER

CIKLIČKA VOLTAMMETRIJA KAO OSJETLJIV PRISTUP U ISTRAŽIVANJU DOKSORUBICINA

M. Pendovska[1,3*], I. Panovska[1], S. Krstevska Balkanov[1],

M. Aleksandrov[2,3], V. Maksimova[3]

[1] JZU Univerzitetska hematološka klinika, Univerzitet Sv. Ćirila i Metodija u Skoplju, Bul. Majka Tereza 17, 1000 Skoplje, Republika Severna Makedonija
[2] Odeljenje za proizvodnju, istraživanje i razvoj, TetraHip DOO Kočani, Orizova 9, 2300 Kočani, Republika Severna Makedonija
[3] Fakultet medicinskih nauka, Univerzitet Goce Delčev u Štipu, Krste Misirkov 10-A, 2000 Štip, Republika Severna Makedonija
***E-mail autora za dopisivanje: marija.311156@student.ugd.edu.mk , marija.hemato@gmail.com**

UVOD I CILJ

Doksorubicin je antraciklinski lijek. Njegov kemoterapeutski učinak je posljedica dva moguća mehanizma, 1) poremećaja popravke DNK posredovane topoizomerazom-II zbog njene interkalacije u spiralu DNK i 2) stvaranja slobodnih radikala i njihovog oštećenja ćelijskih membrana, DNK i proteina. Ovo može biti rezultat njegovog planarnog aromatičnog hromofora koji se interkalira između dva bazna para DNK [1]. Stoga, njegove farmakološke/toksikološke karakteristike u velikoj mjeri zavise od njegovih oksidativnih svojstava, a cilj ovog istraživanja je sumiranje metoda i podataka zasnovanih na njegovom elektrohemijskom ponašanju doksorubicina, dobijenog cikličkom voltametrijom (CV) [2].

METODE

Ciklična voltametrija je svestrana elektrohemijska metoda gdje redoks reakcije koje se javljaju na radnoj elektrodi rezultiraju protokom struje. Potenciostat mjeri ovu struju i prikazuje je kao funkciju primijenjenog potencijala. Svaki uspješan potez potencijala naprijed i nazad proizvodi ciklički voltamogram koji karakteriziraju anodne i katodne vršne struje, vršni potencijali i potencijali početka oksidacije i redukcije.

REZULTATI

Naše istraživanje je otkrilo nekoliko studija koje pokazuju elektrohemijsko ponašanje doksorubicina. CV u pH~7,4 je pokazao da doksorubicin prolazi kroz reverzibilnu redukciju od dva elektrona sa vrijednošću E1/2 = -665 mV (u odnosu na Ag/AgCl, zasićeni KCl). Ovaj proces je definiran kao kvazi reverzibilan, pri niskim brzinama skeniranja. Nadalje, interakcija doksorubicin hidrohlorida sa DNK timusa teleta je proučavana mjerenjem katodne vršne struje, koja se postepeno smanjivala kako je više DNK dodavano u ćeliju [3].

Interakcija doksorubicina sa DNK timusa teleta, uglavnom je procenjivana elektrohemijskim senzorima korišćenjem površinski modifikovanih radnih elektroda [4,5,6]. U tu svrhu korišteni su i elektrohemijski senzor baziran na višeslojnim ugljičnim nanocijevima modificirane platinske elektrode (Pt/MWCNT) [4], elektrodepozicija srebrnih nanočestica i elektropolimerizacija alginatnih slojeva na površini staklaste ugljične elektrode [5]. CV

doksorubicina na sitoštampanim elektrodama modificiranim jednoslojnim ugljičnim nanocjevčicama (SPE/CNT) pokazale su linearnu ovisnost intenziteta elektroredukcije/oksidacije od kvadratnog korijena brzine skeniranja što je dokazalo da je proces kontroliran od strane difuzije. Štaviše, koristili su diferencijalnu pulsnu voltametriju kako bi potvrdili osjetljivu metodu za kvantifikaciju doksorubicina. Procesi vezivanja lijeka ispitivani su DPV-om putem registracije smanjenja vršnog intenziteta struje gvanina, adenina i timina DNK u prisustvu doksorubicina [6].

ZAKLJUČAK

Ciklična voltametrija se može koristiti kao efikasan alat za kvantifikaciju doksorubicina i njegovih interakcija sa DNK ili drugim metalima. Reverzibilna oksidacija doksorubicina u semikinon i natrag, oslobađa reaktivne vrste kisika koje uzrokuju oštećenje DNK i peroksidaciju lipida. Efikasnost terapijskog efekta doksorubicina ovisi o njegovoj interakciji s DNK. Ove interakcije su uglavnom procjenjivane korištenjem elektrohemijskog površinski modificiranog senzora, u prisustvu DNK. Ovi podaci upućuju na zaključak da elektrohemijske platforme predstavljaju osjetljiv pristup za istraživanje interakcije DNK-lijek u elektrodnim sistemima. Ispitivanje elektrohemijskih signala doksorubicin ili kompleks DNK-doksorubicin prije i nakon vezivanja uspostavlja interakciju i pomaže u razjašnjavanju mehanizma.

LITERATURA

[1] Thorn CF, Oshiro C, Marsh S, Hernandez-Boussard T, et al. Doxorubicin pathways: pharmacodynamics and adverse effects. Pharmacogenet Genomics. 2011; 21(7): 440–446; doi: 10.1097/FPC.0b013e32833ffb56.

[2] Doma I, Negm EA, Shrif AY. Cyclic voltammetry of bulk materials system (BMS) and nano manganese sulfate (NMS) with Doxorubicin using glassy Carbon electrode. Int. J. Nano Dimens. 2017; 8(1): 89-96; DOI: 10.22034/ijnd.2017.24380.

[3] Guin PS, and Das S. Exploration of Electrochemical Intermediates of the Anticancer Drug Doxorubicin Hydrochloride Using Cyclic Voltammetry and Simulation Studies with an Evaluation for Its Interaction with DNA. International Journal of Electrochemistry. 2014; (Article ID 517371): 8 pages; DOI:10.1155/2014/517371.

[4] Hajian R, Tayebi Z, Shams N. Fabrication of an electrochemical sensor for determination of doxorubicin in human plasma and its interaction with DNA. Journal of Pharmaceutical Analysis. 2017; 7(1): 27-33; https://doi.org/10.1016/j.jpha.2016.07.005.

[5] Lulek E, Soleymani J, Molaparast M, Ertas YN. Electrochemical sensing of doxorubicin hydrochloride under sodium alginate antifouling conditions using silver nanoparticles modified glassy carbon electrodes. Talanta. 2023; Volume 265, 124846; https://doi.org/10.1016/j.talanta.2023.124846.

[6] Pronina VV, Kostryukova LV, Bulko TV, Shumyantseva VV. Interaction of Doxorubicin Embedded into Phospholipid Nanoparticles and Targeted Peptide-Modified Phospholipid Nanoparticles with DNA. Molecules. 2023; 28(14), 5317; https://doi.org/10.3390/molecules28145317.

KLJUČNE REČI: ciklična voltametrija, doksorubicin, oksidacija, redukcija.

NAČIN IZLAGANJA : POSTER