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mentary mechanisms of action - has been proposed not only as a means of improving lipid-modifying efficacy but also with some other potential anti-atherothrombotic effects, including the modification of hemostatic factors, as well as the inhibition of inflammatory mediators involved in atherogenesis (6). Animal studies have demonstrated that inhibition of Lp-PLA2 may be anti-atherogenic and thus, inhibitors of this enzyme may represent novel therapies that specifically target the atherosclerotic processes in the arterial wall (1, 4). Anyhow, the human clinical implications of these potential positive therapeutic effects remain to be established.

AIM OF THE STUDY

The main aim of the present study was to elucidate the separated and joint effects of the long-term (12 months) treatment with statins and/or fibrates on various athero-thrombotic risk factors in a prospective, randomised, open and intention-to-treat study in high-risk patients with various types of CAD.

MATERIALS AND METHODS

109 consecutive CAD patients (mean age 59,5 (±10,4) years were randomly allo-cated into two treatment groups, receiving either fenofibrate (250 mg/day) or simvastatin (20 mg/per day). At the first follow-up visit (at 12 weeks) the groups were further halved randomly - till the end of the study (52nd week) patients received either fenofibrate (250-500 mg/d) (group F), fenofibrate (250 mg/d) + simvastatin (10 mg/d) (group F+S), simvastatin (20 mg/d) (group S) or simvastatin (10 mg/d) + fenofibrate (250 mg/d) (group S+F). Plasma lipid and fibrinogen levels were measured by standard methods , and PLA_2 by a colorimetric assay using sPhospholipase A Assay Kit (IBL, Immuno-Biological Laboratories, Hamburg, Germany).

RESULTS

Simvastatin alone decreased total cholesterol (TC) significantly more than fenofibrate (-18,3 % vs. -8,9 %), while it was decreased by -20,9% and -21,2 % in combined therapy groups. Fenofibrate increased HDL-C significantly more than simvastatin (by +9,6% vs. +1,7%), while in statin-fibrate group it increased by +7,7 – 8,3%. The mean baseline fibrinogen levels (4,85±1.34 mg/l) decreased on average significantly more by fenofibrate alone, -34 % (group F), while there were no significant differences betwen the rest of the three treatment groups, -23,7% (group S), -25,4% (group F+S), and -22% (group S+F). During 12 months of therapy the serum PLA_2 activity decreased significantly more using the statin therapy alone (-16,6%), while significant increases were established in patients treated with fibrates alone (+12,1%) or combination of statins and fibrates (+17,1%) ($p<0,005$). Significant correlations of serum PLA_2 were observed with decreased TC, total triglyceride, and LDL-C. The absence of a correlation with HDL-C suggests that the PLA_2 activity of HDL is not related to its total concentration, but rather to an as yet undetermined functional or structural property of HDL particles, possibly associated with TC or triglyceride levels.

CONCLUSIONS

The simvastatin-fenofibrate lipid lowering combination has a highly beneficial and more prominent effect than monotherapy on all lipid parameters by which it significantly improves overall patient's risk status. From the results of the present study it can also be concluded that besides its effects on blood lipids, the benefical alterations in other atherothrombotic / proinflammatory atherosclerotic markers were exerted by combined statin-fibrate treatment. The trend of increasing activity of serum PLA_2 during one year of combined lipolytic therapy could be explained as a manifestation of antiatherogenic role of $sPLA_2$ (6). If its changes induced with lipid lowering drugs are related to the reduction in clinically manifest events observed in clinical trials, then it can be defined as the novel target for therapy to reduce cardiovascular risk (7). Future studies should determine whether selective inhibition of PLA_2 reduces ischemic cardiovascular events and whether statins and/or fibrates are more effective for their prevention in patients with elevated levels of PLA_2(8).

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PERFORMANCE EVALUATION OF DIFFERENT HPLC COLUMNS IN SILDENAFIL AND TADALAFIL ANALYSIS

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INTRODUCTION

Sildenafil and tadalafil are oral drugs used to treat male sexual function problems (impotence or erectile dysfunction) by blocking an enzyme 5-phosphodiesterase in the body. However, there is no analytical method for determination of these two active compounds in pharmaceutical preparations in the current European and US Pharmacopoeia. The aim of this study was to evaluate performance of the various HPLC columns in sildenafil and tadalafil analysis using validated HPLC method.

MATERIALS AND METHODS

The following columns were compared: LiChrospher® 100 RP-18 (250 x 4 mm i.d., 5 µm); Hypersil BDS-C18 (125 x 4 mm i.d., 5 µm) and Chromolith® Performance RP-18e (100 x 4.6 mm i.d., monolithic rod). The performance evaluation was done by comparison of the following parameters: resolution (*Rs*), back-pressure (ΔP, bar), and theoretical plate height (ΔH, µm) in correlation with flow-rate (*u*, mL/min).

HPLC analyses were performed using a Schimadzu LC-2010 chromatographic system (Schimadzu, Kyoto, Japan) consisting of a LC-20AT Prominence liquid chromatograph pump with DGU-20A5 Prominence degasser, a SPD-M20A Prominence Diode Array Detector, RF 10AXl fluorescence detector and a SIL-20 AC Prominence auto sampler. Data analyses were done using Class VP 7.3 Software. The mobile phase consisted of a phosphate buffer (20 mM, pH 2.8)-acetonitrile (71:29, *V/V*) at controlled temperature (25°C) and autosamler temperature at 4 °C. Detection of sildenafil and tadalafil was carried out at 285 nm.

RESULTS AND DISCUSSION

Chromatographic peak resolution data (*Rs*) obtained are acceptable for all three tested columns with values higher then the limit given in Ph.Eur. (>1.5) (Fig. 1). The best peak resolution data showed the longest column, as it was expected.

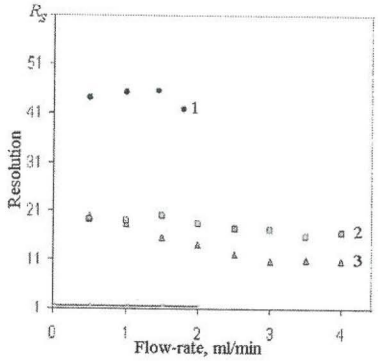

Fig. 1: Correlation between flow-rate and resolution: LiChrospher® 100 RP-18 (1); Hypersil BDS-C18 (2) and Chromolith® Performance RP-18e (3).

There is a significant difference between column back-pressure using different flow-rate. Thus, the longest column was tested only at flow-rate up to 2 ml/min because its high back-pressure induced by increasing flow-rate. The other two columns were tested up to flow-rate of 4 ml/min. The monolithic rod column generates fourfold lower back-pressure in comparison with the longest column, and nearly twice lower back-pressure then the other column.

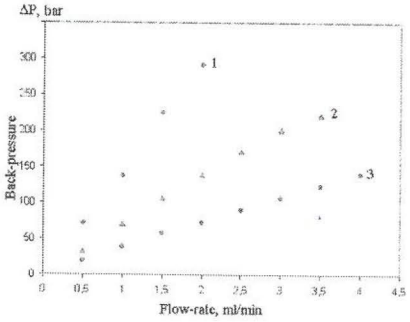

Fig. 2: Correlation between flow-rate and back-pressure: LiChrospher® 100 RP-18 (1); Hypersil BDS-C18 (2) and Chromolith® Performance RP-18e (3).

The efficiency of the columns is presented by the van Deemter plots. According to the results, the most efficient column is the longest column packed with particles, but the flow-rate which might be used is limited at maximum 2 ml/min. The shorter column packed with particles showed the worst efficiency in comparison with other tested columns. This column has acceptable efficiency only up to flow-rate of 1 ml/min. With increasing flow-rate its efficiency dramatically decreases. The van Deemter plot of the monolithic rod column demonstrates clearly that separation efficiency does not decrease significantly when the flow-rate is increased, as it is the case with particulate columns. Therefore it is possible to operate with this type of columns at higher flow-rate without loss of peak resolution. The same conclusion for efficiency of the columns is obtained for the both tested compounds, but the results obtained for tadalafil are better in comparison with those for sildenafil.

CONCLUSIONS

According to all experimental results obtained, the monolithic rod column is a column of choice for tadalafil and sildenafil analysis. Using this column means shorter analysis time (for factor 3.6) in comparison with the longest column. Additionally, it is important to be mentioned that decreased consumption of organic solvent considerably reduces the laboratory expenses.

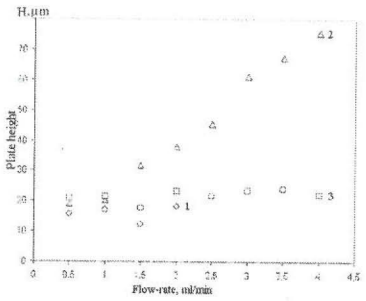

Fig. 3: Correlation between flow-rate and plate height obtained for sildenafil: LiChrospher® 100 RP-18 (1); Hypersil BDS-C18 (2) and Chromolith® Performance RP-18e (3).

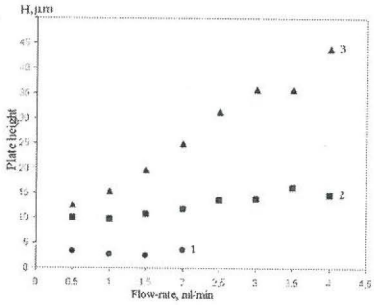

Fig. 4: Correlation between flow-rate and plate height obtained for tadalafil: LiChrospher® 100 RP-18 (1); Hypersil BDS-C18 (2) and Chromolith® Performance RP-18e (3).

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OPTIMATION OF AIR VOLUME IN TABLET COATING PROCESS WITH SCALE DOWN METHOD

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INTRODUCTION

In the pharmaceutical industry the coating process of the solid preparations needs almost the highest energy and cost. One of the main aim of the formulators, to prepare the best preparation with a most economic way. To ensure the clear and filtered air during coating is very expensive because of the length of the coating procedure. The applied volume of the air depends on the size and the geometric parameters of the coating pan. The coater manufacturers develop different equipment with a different drum size and geometry, which causes a difficulty in the process adoption from one to another equipment. If the process conditions including the equipment parameters are well known the procedure transfer or scaling up or down is most simple and cost effective.