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Clinical Pharmacological Approach To The Use Of Hypolipidemic Drugs In The Treatment Of Atherosclerotic Disease

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Abstract. To evaluate the hypolipidemic effect, the impact on endothelial function, oxidative stress of pitavastatin at a dose of 4 mg in patients with dyslipidemia, arterial hypertension (AH) and chronic obstructive pulmonary disease (COPD) at baseline, in dynamics after 4 weeks and 12 months of treatment. The prospective study included 33 patients (mean age – 60 years) with hypertension, COPD and dyslipidemia. Laboratory examination consisted of determining the lipid spectrum, the level of lipid peroxidation products (LPO). In order to assess the tolerability of the prescribed therapy, creatinine, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) were studied.
Keywords: arterial hypertension, chronic obstructive pulmonary disease, dyslipidemia, low-density lipoprotein cholesterol, total cholesterol.

Introduction

Arterial hypertension (AH) ranks first among cardiovascular pathologies and, according to some authors, in 34% of cases, is combined with chronic obstructive pulmonary disease (COPD)1,2 [1–5]. Extrapulmonary manifestations in COPD are associated with elevated blood levels of proinflammatory cytokines (interleukin-8, interleukin-6, interleukin-1, and tumor necrosis factor α) [1,2]. In turn, systemic inflammation leads to increased vascular wall rigidity, including in large-caliber arteries, which is an important prognostic factor for cardiovascular complications [1, 2]. Persistent systemic inflammation, along with local inflammation in the bronchi, characteristic of patients with COPD, makes a significant contribution to the development of atherosclerosis in this category of patients [1, 2]. Thus, the risk of acute coronary events in patients with COPD is increased, especially during exacerbations [1, 2] due to chronic systemic inflammation, which leads to accelerated growth of atherosclerotic plaques in the coronary arteries, their instability, and also to increased stiffness of the arterial wall.

Materials And Methods

The aim of the study was to evaluate the hypolipidemic effect, as well as the effect on endothelial function and oxidative stress of pitavastatin at a dose of 4 mg in patients with dyslipidemia, hypertension and concomitant COPD at baseline and in dynamics after 4 weeks, and to evaluate the state of atherosclerotic plaques in the carotid arteries after 12 months of treatment. The prospective study included 33 patients with hypertension, COPD and dyslipidemia (Table 1). The average age of patients was 60 [3] years. Inclusion criteria for the study were age over 18 years; essential arterial hypertension; COPD grades 1–3, according to gOLD, outside of exacerbation; laboratory-confirmed dyslipidemia; voluntary informed consent to participate in the study. Exclusion criteria from the study were secondary forms of arterial hypertension; chronic heart failure (CHF) with reduced ejection fraction; CHF III–IV functional class; valvular heart disease with hemodynamically significant disturbances; exacerbation of COPD; oncological diseases; pregnancy, lactation; bronchial asthma; patients who have suffered acute inflammatory diseases within a month before the start of the study.

Results And Discussion

The diagnosis of hypertension was made based on the criteria set out in the clinical guidelines for hypertension (eSC/eCh 2018, RCO 2020) [4, 5]. The degree of hypertension was determined by the level of blood pressure recorded in the patient before the prescription of antihypertensive therapy. The risk of developing cardiovascular complications was calculated using the SCOre scale. The diagnosis of COPD was established in accordance with the criteria of the global COPD initiative (gOLD, 2017, 2020). The criteria for dyslipidemia were determined according to the latest 2019 European clinical guidelines for dyslipidemia

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[4]. The examination of patients included the collection of complaints, anamnestic data, a general examination of organs and systems, as well as additional laboratory and instrumental studies. The laboratory examination included an assessment of the lipid spectrum (total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides (TG)), as well as the level of primary (diene conjugates (DC)), secondary (triene conjugates (TC)) and end products of polyoxyethylene (Schiff bases (SB)) using the method of I.A. Volchegorsky (1989), and an assessment of the intensity of free radical oxidation using the induced biochemiluminescence method of blood serum using the method of E.I. Kuzmina, A.S. Nelyubina, M.K. Shchennikova, 1983 (S, Imax). In order to assess the tolerability of the prescribed therapy, creatinine, bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were studied dynamically.

After 4 weeks of treatment with pitavastatin at a starting dose of 4 mg, there was a reliable decrease in all parameters characterizing the lipid spectrum, namely, total cholesterol decreased by 26% from the initial level, LDL by 33%, TG by 19%, while HDL increased by 18% from the initial level. Initially, the primary products of POI, namely DK and TK, as well as the final products of POI in the form of osh, exceeded the norm. The analysis performed using the nonparametric Kruskal-Wallis method showed that the accumulation of POI products and the level of ET-1 increases both as the severity of obstructive disorders of COPD and cardiovascular risk increases. It should be noted that among the studied ED indicators, only for the ET-1 level a dependence on the degree of broncho-obstruction (Kruskal-Wallis criterion = 14.7; $p < 0.001$) and cardiovascular risk (Kruskal-Wallis criterion = 34.76; $p < 0.001$) was revealed. Against the background of treatment with pitavastatin, after 4 weeks of treatment, an improvement in ED indicators and lipid peroxidation processes was observed. Statistically significant results were obtained for DK, TK, OS, S, Imax. A reliable increase in the OS/ (DK + TK) ratio after 4 weeks of treatment is associated with a decrease in primary products (DK) and accumulation of end products of PO (OS). When assessing the indicators of the antioxidant defense system (Imax), their normalization was noted. Initially, when conducting a test with espv, patients showed a decrease in the diameter and blood flow velocity in the brachial artery, with espv being 4.9 [5]%. After 4 weeks of treatment, a statistically significant increase in espv to 6.6 [2]% was noted.

Ultrasound duplex scanning of the carotid arteries, as one of the pools of subclinical atherosclerosis, most accessible for visualization using ultrasound, was performed after 12 months of treatment. A limitation of this stage of the present study was the lack of data on the state of the lipid spectrum and other indicators in the majority of patients, performed in dynamics after 4 weeks of observation, which did not allow them to be analyzed after 12 months of treatment. However, the value of the information, allowing us to assess the state of the identified atherosclerotic plaques in the carotid arteries, which would be illogical to do after 4 weeks or another shorter period of time due to the lack of rapid dynamics of these data, prompted us to analyze the ultrasound data of the carotid arteries initially and after 12 months of treatment with pitavastatin at a dose of 4 mg. Available and generally accepted indices of atherosclerotic plaque assessment, such as sumstca and maxstca, were analyzed. In 29 (87%) patients included in the study, ab were detected during ultrasound examination of the carotid arteries. After 12 months of treatment with pitavastatin at a dose of 4 mg, sumstca decreased by 7.5% (from 40.2% to 37.2%), and maxstca decreased by 4.6% (from 49.5% to 47.2%).

concomitant COPD in patients with cardiovascular pathology can rightfully be considered an additional factor of cardiovascular risk regardless of smoking status. in COPD, activation of proinflammatory cytokines triggers a cascade of pathological reactions leading to an imbalance in the oxidant-antioxidant system, dysfunction of the endothelium and early aggressive course of atherosclerosis.

in our study, patients with hypertension in combination with COPD showed significant disturbances in the vascular, vascular and lipid spectrum, which required high-intensity lipid-lowering therapy. Pitavastatin was prescribed at a starting dose of 4 mg immediately. Our study showed that the administration of pitavastatin at a high starting dose of 4 mg after only 4 weeks of treatment allows for a decrease in lipid peroxidation processes, activation of the antioxidant defense system and improvement of endothelial function, which will certainly prevent further development of atherosclerosis. After 4 weeks of treatment, lipid spectrum parameters significantly improved, however, target LDL parameters were not achieved, which is quite common in clinical practice, especially in patients with high and very high cardiovascular risk according to SCOre, and which, according to the latest recommendations on dyslipidemia [4], requires the addition of a second lipid-lowering drug. It should be especially noted that, despite the high dose of pitavastatin 4 mg, no

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adverse reactions were registered, and there was no deterioration in renal and hepatic biochemical parameters.

The effect of pitavastatin on atherosclerosis by stabilizing and regressing AB has been demonstrated in a number of studies (the Japan Assessment of pitavastatin and Atorvastatin in Acute Coronary Syndrome study, TOgeThAr trial), in which intravascular ultrasound was used for analysis, which allows us to speak about the high accuracy of the results obtained. A limitation of our study was that we used ultrasound of the carotid arteries, which is less accurate, but is often used in clinical practice, and therefore may be of interest to practicing physicians. Among the mechanisms of AB regression against the background of pitavastatin intake, one can distinguish an increase in the production of apoA1, an increase in the expression of scavenger receptors b1 of macrophages, and stimulation of cholesterol metabolism between cells and HDL [3]. After 12 months of treatment with pitavastatin at a dose of 4 mg, we observed regression of AB in the carotid arteries, which suggests the ability of pitavastatin to reduce the rate of progression of atherosclerosis, cause regression of the atherosclerotic process, and therefore indirectly reduce the risk of cardiovascular complications.

Conclusion

Correction of lipid metabolism disorders in patients with hypertension and concomitant COPD by prescribing pitavastatin at a starting dose of 4 mg allows for a rapid reduction in total cholesterol, LDL and TG, while positively influencing endothelial function and oxidative stress. Pitavastatin therapy at a starting dose of 4 mg in patients with dyslipidemia, hypertension and COPD is safe. After 12 months of regular administration of pitavastatin at a dose of 4 mg, regression of the volume of ab.

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