

Research Article

Effect of Combination Therapy with Atorvastatin and Ursodeoxycholic Acid on the Course of Ischemic Heart Disease with Co-Existent Non-Alcoholic Fatty Liver Disease and Obesity

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Abstract

Non-alcoholic fatty liver disease is considered as an independent predictor of cardiovascular diseases which plays an important role in the development of ischemic heart disease. The drug most frequently used for treating this comorbidity is atorvastatin which favours better survival outcomes and is essential in the primary and secondary prevention of cardiovascular diseases. Ursodeoxycholic acid is prescribed as an alternative therapy for ischemic heart disease with co-existent non-alcoholic fatty liver disease and obesity to eliminate statin side effects. The use of ursodeoxycholic acid as a hepatoprotector in comprehensive basic treatment contributes to the improvement of the cardiovascular system in patients with ischemic heart disease as well as the increase in treatment efficacy; it improves the functional status of the liver affecting the major pathogenic mechanisms of the disease.

The objective of the research was to study the effect of combined hypolipidemic therapy with atorvastatin and ursodeoxycholic acid on the indices of blood lipids, liver transaminase levels, functional status of the liver and the course of non-alcoholic fatty liver disease in patients with ischemic heart disease and obesity.

Materials and methods. 20 patients with ischemic heart disease, co-existent non-alcoholic fatty liver disease and obesity were examined. They received ursodeoxycholic acid in addition to atorvastatin for four weeks. All the patients underwent clinical tests, visceral ultrasonography, blood lipid test, liver transaminase test and ^{13}C -methacetin breath test.

Results. The study revealed a significant decrease in the level of the pro-atherogenic fractions of blood lipids ($p < 0.01$) as well as an improved functional status of the liver due to a significant increase in metabolic capacity of the liver and cumulative dose on the 40th and 120th minutes after ursodeoxycholic acid administration ($p < 0.01$).

Conclusions. The use of ursodeoxycholic acid in addition to atorvastatin in patients with ischemic heart disease, co-existent non-alcoholic fatty liver disease and obesity makes it possible to avoid the adverse effect of hypolipidemic therapy on the functional status of the liver.

Keywords

ischemic heart disease; non-alcoholic fatty liver disease; atorvastatin; ursodeoxycholic acid; functional status of the liver

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Problem statement and analysis of the recent research

Recently, an increasingly large number of studies have revealed a relationship between non-alcoholic fatty liver disease (NAFLD) and cardiovascular disorders, atherosclerosis, and dyslipoproteinemia [6]. NAFLD is considered as an independent predictor of cardiovascular diseases which plays an important role in the development of ischemic heart disease (IHD) [1, 5]. The cross-over studies show that the number of cardiovascular complications in patients with NAFLD increases due to the increase in the degree of histological changes in the liver tissues [8]. In patients with IHD, NAFLD significantly aggravates ischemic symptoms, increases the occurrence of ventricular arrhythmia, worsens the parameters

of vegetative regulation of cardiac function and slows down their improvement [3].

The drug most frequently used for treatment of this comorbidity is atorvastatin, which increases the patient's life expectancy and plays an important role in the primary and secondary prevention of cardiovascular diseases [9, 10]. Statins have been proven to reduce the risk of unstable angina, cardiac infarction and sudden coronary death by 30-40% (4S, CARE, LIPID, WOSCOPS, ASCOT-LLA) in case of long-term therapies [13]. According to several studies (REVERSAL, 2004; ASTEROID, 2006; SATURN, 2011), statin therapy results in a pronounced decrease in the levels of cholesterol and low-density lipoproteins (LDL), rapid regression of atherosclerotic plaques, cardiac remodeling and remodeling of blood vessels

[12]. At the same time, in case of administering statins to some patients, the phenomenon known as transaminitis is observed; it is caused by the release of increased levels of liver enzymes into the blood flow which may lead to side effect of atorvastatin on the functional status of the liver, especially in case of steatohepatitis [11].

Therefore, to eliminate side effects of statins, ursodeoxycholic acid (UDCA) is prescribed to patients with NAFLD, co-existent IHD and obesity [3].

UDCA therapy has been proven to be efficacious for NAFLD and obesity due to its cytoprotective, immunomodulatory and antiapoptotic action. UDCA prevents damage to the cholangiocyte membranes by hydrophobic bile acids. It contributes to the increase in the antioxidant defence through the suppression of the activity of catalase, glutathione peroxidase, glutathione-S-transferase as well as in the synthesis of glutathione as well. UDCA prevents hepatocyte apoptosis induced by the influence of hydrophobic bile acids, ethanol, etc. Moreover, the drug has anti-inflammatory properties, namely the ability to suppress the secretion of anti-inflammatory cytokines and production of immunoglobulins [7].

The use of UDCA as a hepatoprotective agent during comprehensive basic treatment of IHD improves the state of the cardiovascular system. Hypertrophy regression, left ventricular remodeling, an increased systolic motion of the mitral ring, reduced incidence of ischemic manifestations and ventricular arrhythmia are observed. It is of particular importance during statin therapy allowing us to carry out a long-term hypolipidemic therapy without side effects [2]. UDCA in comprehensive therapy enhances the effectiveness of treatment and improves the functional status of the liver, affecting the main pathogenetic links of the disease [4].

The objective of the research was to study the effect of combined hypolipidemic therapy with atorvastatin and ursodeoxycholic acid on the indices of blood lipids, liver transaminase levels, functional status of the liver and the course of NAFLD in patients with IHD and obesity.

1. Materials and methods

20 patients with NAFLD, co-existent IHD and obesity were examined. They received ursodeoxycholic acid in addition to atorvastatin for four weeks.

There were 12 (60%) males and 8 (40%) females. The average age of patients was 55.6 ± 2.6 years; the average disease duration was 4.8 ± 0.8 years.

All the patients underwent clinical, laboratory and instrumental examinations (anthropometry, blood lipid test, liver transaminase test, electrocardiography, echocardiography, visceral ultrasonography and ^{13}C -methacetin breath test).

Anthropometry involved the measurement of the height and weight of the patient, calculating the body mass index (BMI) by the Quetelet formula: $\text{BMI} = (\text{weight (kg)} / (\text{height (m)}^2))$.

The inclusion criteria were verified IHD (stable angina, post-infarction cardiosclerosis), the level of total cholesterol

exceeding 5 mmol/l, the level of LDL cholesterol exceeding 3 mmol/l and the level of serum triglycerides not exceeding 3.5 mmol/l.

The diagnosis of IHD was made based on the results of coronarography, past myocardial infarction or positive treadmill test.

According to the guidelines of the International Diabetes Federation (2005), to diagnose abdominal obesity, the waist circumference (WC) was measured at the level of the umbilicus and assessed using the criteria for men $\text{WC} > 94$ cm and women $\text{WC} > 80$ cm.

Blood lipids were estimated based on the serum levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). The activity of serum alanine transaminase (ALT) and aspartate aminotransferase (AST) was determined using the Reitman-Frankel transaminase method by means of PLIVA-Lachema kit (the Czech Republic).

Ultrasonography of the hepatobiliary system was performed on an empty stomach using Philips HDI 1500 ultrasound machine with a 3.5 MHz scanning sensor. The following parameters were determined: the size of hepatic lobes, hepatic parenchyma density, the degree of fatty infiltration of the liver, the presence of fibrosis and the diameter of the vena portae (VP). Fatty infiltration of the liver was diagnosed in case of enlarged liver, diffuse homogeneous increase in its echogenicity, distal shadowing and dilated vena portae.

The functional status of the microsomal enzyme systems of hepatocytes was assessed by means of ^{13}C -methacetin breath test (13CMBT) administering 75 g of methacetin labelled with non-radioactive isotope of carbon ^{13}C orally.

The efficacy of prescribed treatment was evaluated after the 4-week therapy using atorvastatin at a dose of 20 mg a day and UDCA at a dose of 10 mg per kilogram of body weight three times a day.

The obtained results were processed in Microsoft Excel using the Student's t-test and the Pearson correlation analysis.

2. Results and Discussion

In all the patients, abdominal visceral adipose tissue deposition was observed. The mean value of the BMI was $32.78 \pm 0.91 \text{ kg/m}^2$.

According to anamnestic data, during outpatient examination, 17 (85.0%) patients complained of a feeling of heaviness in the left hypochondrium, 16 (80%) patients reported general weakness, 15 (75.0%) patients suffered from fatigue, 18 (90.0%) patients had bloating, 12 (60.0%) patients complained of nausea and 16 (80.0%) patients reported bitter taste in the mouth. The examination revealed that in 18 (90%) cases, the lower edge of the liver extended beyond the costal arch. Visceral ultrasonography revealed different stages of hepatomegaly in 18 (90%) cases and hyperechogenicity of hepatic parenchyma in 85.0% of cases. An important feature was the detection of bend neck of the gallbladder with biliary

retention in 60% of patients. Thus, according to the anamnesis, physical examination and visceral ultrasonography, in patients of this group the symptoms of fatty infiltration of the liver were observed.

The four-week combination therapy with atorvastatin and UDCA for patients with IHD and co-existent NAFLD resulted in a significant reduction of the level of the pro-atherogenic fractions of blood lipids ($p < 0.01$) (Table 1).

In 30% of patients increased AST level was observed and 20% had increased ALT level. At the same time, there were no significant differences between the levels of liver transaminases, although there was a tendency towards reduction in the mean concentration of ALT from 0.61 ± 0.06 to 0.53 ± 0.03 $\mu\text{mol/l}$ and AST from 0.50 ± 0.04 to 0.46 ± 0.02 $\mu\text{mol/l}$ ($p > 0.05$).

When assessing the functional status of the microsomal enzyme systems of hepatocytes using ^{13}C -methacetin breath test in patients with comorbidity, a significant increase in metabolic capacity of the liver and cumulative dose on the 40th and 120th minutes after administering UDCA was found ($p < 0.01$) (Table 2). The results of the study showed that the use of combination therapy with atorvastatin and UDCA in patients with the given comorbidity contributed to the improvement of general condition of patients. On the one hand, UDCA reduced biliary retention; on the other hand, atorvastatin decreased the concentration of the pro-atherogenic fractions of blood lipids. Combination therapy with atorvastatin and UDCA was more effective in reducing the levels of triglycerides compared to the use of atorvastatin only [13].

However, significant positive changes in the indicators of ^{13}C -methacetin breath test which were manifested as the increase in hepatic metabolism and cumulative doses on the 40th and 120th minutes were the most important.

Thus, the use of UDCA with atorvastatin in patients with IHD, co-existent NAFLD, and obesity makes it possible to reduce the adverse effects of hypolipidemic therapy in case of disturbed functional status of the liver.

3. Conclusions

1. The use of UDCA in combination with atorvastatin results in a significant reduction in the concentration of the pro-atherogenic fractions of blood lipids in patients with NAFLD, co-existent IHD and obesity.
2. Combination therapy with atorvastatin and UDCA in patients with comorbid pathology results in significant improvement of functional status of the liver due to the increase in metabolic capacity of the liver and metabolic rate on the 40th and 120th minutes.

4. Prospects for further research

Prospects for further research consist in developing the criteria for selecting patients with IHD, co-existent NAFLD and obesity for protracted treatment with statins.

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Table 1. Lipid profile and liver transaminase level in patients with NAFLD, co-existent IHD and obesity before and after combination therapy

Lipid profile	Before treatment (n=20)	After treatment (n=20)	Statistical significance, p
TC, mmol/l	6.28 ± 0.23	5.32 ± 0.31	<0.01
HDL-C, mmol/l	1.22 ± 0.07	1.23 ± 0.08	>0.05
LDL-C, mmol/l	4.31 ± 0.21	3.48 ± 0.27	<0.01
TG, mmol/l	2.22 ± 0.28	1.85 ± 0.21	<0.01
ALT, umol/l	0.61 ± 0.06	0.53 ± 0.03	>0.05
AST, umol/l	0.50 ± 0.04	0.46 ± 0.02	>0.05

Note.

n – the number of patients in the group.

Table 2. Results of ¹³C-methacetin breath test in patients with IHD, co-existent NAFLD and obesity before and after combination therapy

¹³ C-methacetin breath test results	Before treatment (n=20)	After treatment (n=20)	Statistical significance, p
Hepatic metabolism rate (% ¹³ C/g/hr)	15.81 ± 0.84	21.36 ± 1.48*	<0.01
Cumulative dose on the 40th minute (% ¹³ C)	7.33 ± 0.50	9.55 ± 0.56*	<0.01
Cumulative dose on the 120th minute (% ¹³ C)	13.57 ± 1.03	17.61 ± 1.22**	<0.01

Note.

n – the number of patients in the group.

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