HEPATOTOXICITY AS AN ADVERSE DRUG REACTION TO STATINS

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ANNOTATION

This article describes a clinical study conducted among patients on an outpatient basis on the basis of the agmi " Andijan State Medical Institute ". Features of hepatotoxicity as an undesirable drug reaction of statin use were revealed.

Keywords : HMG-CoA reductases , echocardiography , hepatotoxic effect, mevalonic acid.

Introduction

Statins , or HMG-CoA reductase inhibitors , are currently the most studied group of lipid -lowering drugs, firmly established in clinical practice and giving a pronounced clinical effect.

HMG-CoA reductase inhibitors have radically changed the approach to the prevention of coronary heart disease and other atherosclerotic vascular lesions, pushing traditional lipid -lowering substances (nicotinic acid, fibrates , anion-exchange resins) into the background in their time.

The mechanism of action of statins is associated with inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase and, as a result, inhibition of the conversion of HMG-CoA to mevalonic acid, which is an intermediate product of cholesterol synthesis in hepatocytes . Reducing the synthesis of cholesterol and reducing its content in the liver increases the activity of low-density lipoprotein (LDL) receptors (LDL) of hepatocytes , which promotes the capture of circulating LDL from the bloodstream, as well as, to a lesser extent, very low density lipoproteins (VLDL) and intermediate (LDL) densities. As a consequence of the capture of LDL circulating blood by hepatocytes , there is a moderate decrease in LDL, cholesterol and, to some extent, VLDL, serum triglycerides . Inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase also leads to a decrease in the synthesis of certain biologically active substances, such as isoprenoids . A decrease in the synthesis of these substances of

this group underlies the pleiotropic effects of statins (anti-inflammatory, antiproliferative).

The effect of statins develops rather slowly, at least a month after the start of treatment, and is lost after discontinuation of drugs, as a result of which lifelong therapy with this group of drugs is necessary.

HMG-CoA reductase inhibitors are the drugs of choice in patients with hyperlipidemia of any origin and are second only to fibrates in their effect on triglycerides .

HMG-CoA reductase inhibitors reduce the overall risk of death from all cardiovascular diseases, are used for secondary prevention in patients with existing coronary heart disease, obliterating peripheral vascular disease, and stroke.

The main absolute contraindications to the use of statins are active liver disease against the background of a persistent increase in liver enzymes, pregnancy (there is evidence of a teratogenic effect of drugs in the form of a developmental disorder of the central nervous system, anomalies in the development of the lips in the first trimester of pregnancy), lactation and breastfeeding. The use of HMG-CoA reductase inhibitors should be carried out with caution in patients with a history of liver disease, as well as in alcohol abusers.

The most significant and common adverse reaction following HMG-CoA reductase therapy is elevated liver enzymes (aspartate aminotransferases and alanine aminotransferase).

The hepatotoxic effect and its mechanisms differ depending on the drug, among the mechanisms are: the effect on the cytochrome-450 system, the deterioration of bile acid transport, the immune inflammatory process on the administration of the drug or its metabolites, oxidative stress and intracellular damage. The hepatotoxic effect of statins has a predominantly hepatocellular element, while the picture of an isolated cholestasis is extremely rare. There is also an opinion that the hepatotoxicity of HMG -CoA reductase inhibitors is associated with drug interactions (there is evidence of liver damage with the combined use of simvastatin and amiodarone , flutamide , troglitazone , diltiazem).

Methods for monitoring the safety of treatment include assessing the activity of aspartate and alanine aminotransferase , which is carried out before treatment, after 2-3 weeks, after 2-3 months and then every six months to a year . If the activity of liver enzymes exceeds the upper limit of the norm by more than 3 times, then a review of lipid -lowering therapy is necessary.

Purpose of the study

To determine the frequency of occurrence of elevated liver transaminases in patients after the first 3 months of lipid -lowering therapy (atorvastatin)

Research materials
The data of 22 patients who had no history of liver diseases and whose serum aminotransferase values were within the reference values before the start of therapy, namely the values of liver enzymes in a biochemical blood test, after 3 months after the start of lipid -lowering therapy, were analyzed.

Results and discussions
The following values were taken as reference values: 10-48 IU/L for aspartate aminotransferase and 10-69 IU/l for alanine aminotransferases .

As a result of the analysis of case histories of patients treated with HMG-CoA reductase inhibitors in order to reduce the level of atherogenic lipids, the following data were obtained:

Table 1.
Aspartate values aminotransferases (AST) and alanine serum aminotransferase (ALT) in the study group of patients

A patient	AST value	ALT value	A patient	AST value	ALT value
one	65.1	89.1	12	32.9	33.9
2	15.5	36.1	13	30.7	45.4
3	109.8	120.1	fourteen	119.5	134.3
four	24.8	18.0	fifteen	21.2	32.4
5	28.4	33.3	16	68.0	99.8
6	15.4	31.2	17	15.3	13.2
7	22.7	14.6	eighteen	19.8	36.8
eight	23.1	56.2	19	165.1	227.8
9	14.7	25.9	twenty	17.5	19.4
ten	42.6	68.0	21	32.2	25.7
eleven	28.3	44.1	22	91.2	112.7

As can be seen from the table, 5 out of 22 people had an increase in hepatic enzymes in the blood serum, in addition, in one of the patients, aspartate values aminotransferases and alanine aminotransferases were more than 3 times higher than

the upper limit of the reference norm (165.1 and 227.8), which is an indication for correction of therapy (specifically, in this case, the use of drugs from another group), while in 4 other patients with increased level of aminotransferases , there are no indications for discontinuation of therapy.

It is also worth noting the fact that in all patients the increase in liver enzymes was not accompanied by any symptoms of liver damage.

Conclusion

An increase in aminotransferases was observed in 5 patients out of 22 (22.7%), while an increase above the reference values more than 3 times in 1 of them (4.5%), and all of them had asymptomatic hyperenzymemia .

There are studies showing that liver damage from statins , including liver failure, is extremely rare. In the United States between 1990 and 2002, among 51,741 liver transplant patients due to acute liver failure, only 3 cases were recorded when liver damage was associated with statin use .

Thus, the issue of hepatotoxicity of HMG -CoA reductase inhibitors is still open.

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