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SIDE EFFECTS CORRECTION IN COMBINED LIPID-CORRECTING THERAPY WITH STATINS AND FIBRATES USING LOW-MINERALIZED MINERAL WATER

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The side effects of the combination of statins and fibrates in patients with stable angina and low-mineralized silicon hydrocarbonate calcium-magnesium mineral water in their correction were studied. 64 patients were examined, divided into 2 groups. The first group received atorvastatin (10 mg) and fenofibrate (145 mg), the second group received low-mineralized silicon hydrocarbonate calcium-magnesium mineral water. It was found that use of atorvastatin and fenofibrate does not cause serious side effects, but undesirable effects, levels of alanine aminotransferase and creatine phosphokinase, increase. The positive effect of low-mineralized mineral water on clinical (prevention of symptoms from the digestive and hepatobiliary systems) and biochemical parameters were shown. Levels of creatine phosphokinase, alanine aminotransferase and aspartate aminotransferase decreased, significantly differing from group I ($p<0.05$). This allows us to recommend a low-mineralized silicon hydrocarbonate calcium-magnesium mineral water course for the prevention and treatment of side effects that occur at the beginning of statins and fibrates therapy.

Key words: side effects, statins, fibrates, mineral water, stable angina.

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КОРРЕКЦІЯ ПОБІЧНИХ ЕФЕКТІВ ПРИ КОМБІНОВАНІЙ ЛІПІДО-КОРЕГУЮЧІЙ ТЕРАПІЇ СТАТИНАМИ І ФІБРАТАМИ, ІЗ ЗАСТОСУВАННЯМ МАЛОМІНЕРАЛІЗОВАНОЇ МІНЕРАЛЬНОЇ ВОДИ

Вивчено побічні ефекти комбінації статинів і фібратів у хворих стабільною стенокардією і ефективність маломінералізованої кремнієвої гідрокарбонатної кальцієво-магнієвої мінеральної води в їх корекції. Обстежено 64 хворих, розділених на 2 групи, перша група отримувала аторвастатин (10 мг) і фенофібрат (145 мг), друга–додатково маломінералізовану кремнієву гідрокарбонатну кальцієво-магнієву мінеральну воду. Встановлено, що використання аторвастатину і фенофібрату не викликає серйозних побічних дій, але зростають небажані явища, рівні аланінамінотрансферази та креатинфосфокінази. Показано позитивний вплив маломінералізованої мінеральної води на клінічні (запобігання симптомів з боку травної та гепатобіліарної систем) та біохімічні показники. Знизились рівні креатинфосфокінази, аланінамінотрансферази і аспартатамінотрансферази, що значимо відрізнялось від І групи ($p<0,05$). Це дозволяє рекомендувати курсовий прийом маломінералізованої кремнієвої гідрокарбонатної кальцієво-магнієвої мінеральної води для профілактики і лікування побічних дій, що виникають на початку терапії статинами і фібратами.

Ключові слова: побічні дії, статини, фібрати, мінеральна вода, стабільна стенокардія.

The work is a fragment of the research project "The features of vascular disturbance in the patients of cardioreumatological profile: modern methods of diagnostics and therapy", state registration No. 0119U003576.

Diseases of the circulatory system consistently occupy a leading position in the structure of total mortality [1, 10]. Traditionally, the first place is occupied by coronary heart disease (CHD), whose share in the total mortality structure has increased from 66.6% (2005) to 68.9% (2015 [1].

It is known that one of the key factors in CHD progression is dyslipidemia. First-line hypolipidemic drugs are statins, however, many patients do not receive adequate therapy, due to poor adherence to taking

drugs, about 10% of patients stop taking statins because of subjective complaints [3, 7]. In case of intolerance to the recommended doses of statins, combination therapy is recommended [5].

Besides, additional administration of fibrates is recommended for patients with hypertriglyceridemia (TG>2.3 mmol/l) against the background of statin intake [6]. However, both classes of drugs have similar side effects, and their combined use may increase the frequency and severity of these effects. The common negative effects of statins are an increase in transaminases (0.2–2%), muscle and dyspeptic symptoms [7].

Among the side effects of fibrates, cholestasis and the formation of gallstones are considered to be the most significant [4, 8]. Also, patients may experience gastrointestinal symptoms (up to 5%), rash (up to 2%), muscle symptoms, increased creatinine and transaminase levels [4, 8].

In addition to lipid-lowering therapy, patients should take a number of other medicines, and most patients have comorbidities that require additional therapy. Thus, patients receive at least 3–4 drugs during the day, which significantly increases the risk of drug interactions, side effects, self-cancellation of some drugs, and, as a result, reduces the treatment efficacy. In this respect, it is promising to use such a natural factor as mineral waters, which have the ability to influence both the main pathogenetic mechanisms of CHD–dyslipidemia and oxidative stress, and other regulatory functions of the body, which can help reduce the risk of drug therapy side effects [2, 9, 11, 12]. The most promising is the use of drinking bicarbonate low-mineralized mineral waters (MW), given the already accumulated data on their preventive and therapeutic effects on the gastrointestinal tract, hepato-biliary and cardiovascular system [2, 9, 11, 12].

Low-mineralized silicon hydrocarbonate calcium-magnesium mineral water, produced in Ukraine, with a high content of organic substances is available to patients and presents a particular interest. Being hypotonic, it stimulates diuresis, has lipid-lowering and antioxidant effects, and is capable of reducing chronic inflammation [9].

The purpose of the work was to study the side effects of statins and fibrates when they are used simultaneously in the treatment of patients with stable angina, as well as the possibility of correcting these side effects when using low-mineralized silicon hydrocarbonate calcium-magnesium MW.

Materials and methods. The study group included 62 patients with stable angina of functional classes I–III.

The study was carried out in compliance with the ethical principles of medical research performed with the participation of people set forth in the Helsinki Declaration.

Sampling was formed in accordance with the inclusion criteria: a confirmed diagnosis of stable exertional angina of FC I–III; intolerance to large doses of statins in history; laboratory confirmed dyslipidemia and hypertriglyceridemia (TG>2.3 mmol/l).

The total sample was divided into 2 groups following the randomization procedure using a random number generator (RAND function of Microsoft Excel).

The mean course of treatment was (39.58±0.87) days. The mean age was (57.38±2.13) years for Group I and (61.84±2.24) years for Group II. The groups were representative by gender, age, duration of therapy.

Group I consisted of 32 patients (control group). The treatment included the standard complex of drugs recommended for treatment of stable angina (antiplatelet, beta-blockers, if necessary–nitrates, etc.), and as lipid-lowering therapy–the simultaneous use of statins and fibrates in a reduced daily dose (atorvastatin 10 mg+traikor 145 mg).

Group II comprised 32 patients (main group). The above-described drug complex included taking the low-mineralized silicon hydrocarbonate calcium-magnesium drinking MW “Berezovska” according to the following scheme: 450–600 ml (150 ml for patients weighing less than 70 kg and 200 ml each weighing more than 70 kg), divided into three doses, 30 minutes before meals .

Clinical adverse reactions were studied using a specially designed questionnaire that included the onset or intensification of symptoms described as adverse events of statins and/or fibrates (headaches, dizziness, fainting, memory loss, fears, palpitations, intermissions in cardiac activity, dyspnea, edema, thirst, tremor, abdominal pain, nausea, vomiting, loss of appetite, bitter taste in the mouth, flatulence, constipation, diarrhea, fatigue, muscle weakness, muscle cramps, muscle pain, joint pain, skin itch, skin rashes, sleep disorder, irritability, anxiety).

Biochemical indices reflecting the onset of adverse reactions were determined by standard methods at the beginning and at the end of treatment: aspartate aminotransferase (AST) and alanine aminotransferase (ALT)–using substrate-buffer solutions, the content of bilirubin and its fractions–by the colorimetric method, the concentration of creatinine–by the Popper method based on the Jaffer color reaction, urea–by the diacetyl

monooxime enzymatic-kinetic method, the activity of creatine phosphokinase (CPK)–by enzyme immunoassay.

All data were processed by the method of variation statistics using Student's t-test. Differences between the studied parameters were considered reliable in the range of $p<0.05$. The obtained results were processed using the STATISTICA 6.0 software and are presented in the text as the sample mean and the mean error (M±m).

Results of the study and their discussion. Clinical side effects with simultaneous use of atorvastatin and fenofibrate are presented in table. 1 and relate only to those symptoms that patients noted before and/or after treatment in their questionnaire.

Table 1

Incidence of adverse reactions in the studied patients

Adverse reactions	Before treatment, group I, % (n=32)	After treatment, group I, % (n=32)	p1	Before treatment, group II, % (n=32)	After treatment, group II, % (n=32)	p2	p1–2
bitter taste in the mouth	0	3(9.3)	0.08	0	0	1.00	0.08
nausea	0	4(12.5)	0.04	0	0	1.00	0.04
loss of appetite	0	3(9.3)	0.08	1(3.1)	0	0.32	0.05
flatulence	0	2(6.2)	0.16	0	0	1.00	0.15
constipation	1(3.1)	7(21.8)	0.01	4(12)	0	0.04	0.002
skin itch	0	1(3.1)	0.32	0	0	1.00	0.32
skin rashes	0	1(3.1)	0.32	0	0	1.00	0.32
muscle weakness	0	1(3.1)	0.32	0	0	1.00	0.32
muscle pain	0	1(3.1)	0.32	0	0	1.00	0.32

The table shows that out of 9 side effects presented during the course of combination therapy, 5 concerned the digestive system (bitter taste in the mouth, nausea, loss of appetite, flatulence, constipation). Despite the fact that these adverse reactions in patients using statins and fibrates, were not serious, an increase in their frequency should be noted. Thus, in the course of treatment, constipation (only one person was noted before treatment) and nausea (was not observed in a single patient before treatment) increased significantly ($p=0.04$ and $p=0.01$, respectively). The pronounced increase of nausea in this group may be due to bile acid synthesis supression, which is typical for therapy with fibrates.

There was a tendency to an increase in the frequency of bitterness in the mouth and a decrease in appetite ($p=0.08$). It should also be noted that in this group of patients side effects in the skin and muscular system appeared: skin itch and skin rashes appeared in one patient at the same time (3.1% and 3.1%, respectively), and muscle weakness and muscle pain being not observed before treatment, appeared in one patient after the therapy (3.1%).

In contrast to the above stated, the addition of a mineral water to the drug complex permitted to prevent all the above-mentioned side effects, and in some patients it also had a positive effect. Thus, the constipation, the frequency of which occurrence increased in the “atorvastatin+fenofibrate” group ($p=0.01$), was no longer observed when low-mineralized MW was added ($p=0.04$).

Positive changes due to to the low-mineralized MW effect were also confirmed by the intergroup statistical analysis: the difference with the control group in terms of constipation ($p=0.002$), “loss of appetite” ($p=0.05$) and nausea ($p=0.04$) were reliable, permitting to make a conclusion about the positive effect of low-mineralized MW on clinical adverse events on the part of the digestive system.

Since the combined use of statins and fibrates may be accompanied by unfavorable shifts in a number of biochemical parameters, the analysis of the changes degree in their levels during the therapy was one of the main avenues in our study, the average values are presented in table. 2.

As it can be seen from table 2, in the control group in the course of treatment, the levels of ALT and CPK showed a significant increase ($p=0.004$ and $p=0.01$, respectively), and the level of AST showed a pronounced upward tendency ($p=0.07$). The large dynamics of the ALT level, compared to AST in patients of group I, is associated with greater hepatospecificity of ALT. The levels of total, direct and indirect bilirubin, creatinine and urea remained virtually unchanged.

In patients who used mineral water, the mean levels of AST and ALT had a moderate and weak tendency to decrease ($p=0.16$ at $t=1.44$ and $p=0.37$ at $t=0.91$), however, this acquires a special meaning, given

that the levels of ALT and AST in group I tended to increase, resulting in the fact that intergroup differences between these indices were significant (p=0.01 and p=0.03, respectively). The obtained results permit to speak about the hepatoprotective properties of low-mineralized silicon hydrocarbonate calcium-magnesium MW.

Table 2

Dynamics of biochemical blood parameters in patients of the studied groups

Parameter	Before treatment, group I (n=32)	After treatment, group I (n=32)	p1	Before treatment, group II (n=32)	After treatment, group II (n=32)	p2	p1–2
Creatinine, mmol/l	0.069±0.003	0.068±0.003	0.96	0.070±0.004	0.069±0.003	0.90	0.95
Urea, mmol/l	6.45±0.32	6.20±0.35	0.60	6.36±0.35	6.31±0.32	0.89	0.74
Glucose, mmol/l	5.15±0.14	4.93±0.14	0.21	5.26±0.16	4.87±0.10	0.01	0.42
Total bilirubin, μmol/l	12.79±0.57	12.86±0.50	0.93	13.16±0.82	12.96±0.90	0.84	0.83
Direct bilirubin, μmol/l	1.61±0.23	1.44±0.17	0.59	1.56±0.27	1.78±0.53	0.63	0.49
Indirect bilirubin, μmol/l	11.19±0.36	11.43±0.37	0.66	11.50±0.57	11.18±0.48	0.66	0.54
ALT, U/L	8.48±0.64	12.11±0.96	0.004	9.69±0.98	8.76±0.69	0.37	0.01
AST, U/L	6.51±0.54	8.13±0.79	0.07	6.85±0.69	5.95±0.33	0.16	0.03
CPK, U/L	83.78±8.40	111.00±7.77	0.01	113.03±8.80	94.69±7.07	0.03	0.002

In patients, who received mineral water, absolutely all the mean levels of indices changed downward. So, the level of CPK showed a significant (p=0.03) decrease. Intergroup difference in this index after treatment was also statistically significant (p=0.002). Considering that in the control group, CPK increased (p=0.02 and p=0.01), a decrease in its level in patients of group II can be explained by the positive effect of MW on muscle metabolism, tissue respiration processes, electrolyte and protein metabolism. This is particularly relevant, given that muscle symptoms and myopathies are one of the reasons for cessation of lipid-lowering therapy.

Indices of nitrogen metabolism (creatinine, urea) and bilirubin with its fractions almost did not change in both groups by the end of the treatment, which resulted in the absence of significant intergroup differences by the end of the therapy course. However, it should be emphasized that in patients with these indices exceeding the norm normalization occurred, which indicates the corrective effect of low-mineralized silicon hydrocarbonate calcium-magnesium MW on these indices.

It should be noted that there was no significant change in the blood glucose level in the control group (p=0.21), while in patients taking mineral water, glucose content decreased significantly (p=0.01). The absence of intergroup difference (p=0.42) for this index is explained by the unidirectionality of changes in each group.

Considering that the mean levels of indices presented above only carry information about the degree of their increase, but do not carry information about the number of patients in whom it was observed, we analyzed the frequency of biochemical adverse reactions manifestations in combination therapy, the results of which are presented in table 3.

Table 3

Encounter rates of patients with biochemical parameters exceeding the norm

Parameter	Before treatment, group I (n=32)	After treatment, group I (n=32)	p1	Before treatment, group II n=32))	After treatment, group I I =32)	p2	p1–2
Creatinine	2(6.2)	2(6.2)	1.00	3(9.3)	1(3.1)	0.32	0.49
Urea	3(9.3)	4(12.5)	0.71	8(25.0)	5(15.6)	0.32	0.33
Glucose	2(6.2)	1(3.1)	0.32	2(6.2)	0	0.16	0.56
Total bilirubin	0	0	1.00	1(3.1)	1(3.1)	1.00	1.00
Direct bilirubin	0	0	1.00	2(6.2)	2(6.2)	1.00	1.00
Indirect bilirubin	0	0	1.00	1(3.1)	0	0.32	0.32
ALT	4(12.5)	11(34.3)	0.03	3(25.0)	5(15.6)	0.26	0.02
AST	5(15.6)	10(31.2)	0.13	7(21.8)	7(21.8)	1.00	0.26
CPK	3(9.3)	5(15.6)	0.32	5(15.6)	1(3.1)	0.04	0.04

As it can be seen from the table, the obtained data show an increase in the biochemical manifestations frequency of adverse reactions by four parameters: ALT, AST, CPK and urea in patients receiving a combination of statin and fibrate.

In Group I, increase in the number of patients with elevated ALT levels was significant (p=0.03), and that of the AST level was characterized as a tendency (p=0.13). It should be noted that the degree of ALT exceeding the norm before treatment was insignificant–no more than 36%, whereas after treatment the maximum excess over the norm was observed more than by 2 times. The opposite tendency, although not statistically significant, was characteristic of the frequency of elevated ALT level in patients of group II (p=0.26). The difference with group I, where the growth of such patients number was noted, was only significant in respect of ALT (p=0.02). The reduction in the number of patients with elevated AST levels was not observed, which is explained by its lower hepato-specificity.

A number of patients in the statin+fibrate group showed an increase in the level of CPK after treatment, although the growth in the number of patients with CPK exceeding the norm was not statistically significant (p=0.32). Thus, in some patients it has grown by 2–3 times from the initial level. In patients of group II, the opposite changes were observed; the number of patients with CPK exceeding the norm decreased (p=0.04), which indicates a favorable effect of low-mineralized silicon hydrocarbonate calcium-magnesium MW.

In the control group, the number of patients with elevated levels of urea and creatinine did not grow, which coincides with the literature data, while in Group II, these indices were even normalized in a number of patients, there was no intergroup difference.

The frequency of other studied parameters, in particular glucose, did not change in patients of group II and there was no intergroup difference with the control group (p=0.56), however, in all patients receiving MW this parameter's level was normalized. The study of this effect requires further research with a large number of observations.

Summarizing the data obtained, it should be noted that there are no serious side effects, which indicates the safety of using reduced doses in this combination. At the same time, the results indicate an increase in side effects in patients with this combination therapy, particularly from the skin and muscular system, as well as the hepatobiliary and digestive systems (nausea, constipation, bitterness in the mouth, loss of appetite, flatulence), last may be due to the lithogenic effect of fibrate therapy [7].

We did not register a significant increase in the number of kidney-related adverse events, whereas Choi HD et al. noticed [4]. We registered an increase in the biochemical manifestations frequency of adverse reactions by ALT, AST, CPK in patients receiving a combination of statin and fibrate. The results of the study correlate with the detailed summary reports of Okopien B. et al. and Choi HD et al. [4, 8].

It should be noted the positive effect of low-mineralized silicon hydrocarbonate calcium-magnesium MW on clinical side effects, to prevent the development of all complaints from the digestive and hepatobiliary systems, constipation, decrease in appetite and nausea were not observed in this group. This can be explained by the increased production of bile, as shown in the study by Aslanabadi N. et al and Zunnunov Z. [2, 12].

A similar positive effect of this mineral water was recorded in the biochemical manifestations of side effects observed in the control group. This was manifested in a decrease in the number of patients with biochemical parameters exceeding the norm, and in relation to CPK, this dynamics was reliable. The same tendency was typical for all other biochemical parameters: a significant decrease in glucose and CPK, a pronounced tendency to a decrease in AST and ALT, and the change in these parameters was significantly different from group I, which coincides with the opinion of other authors. Zunnunov Z. in his study showed the positive effect of mineral waters in patients with hepatitis [12]. A significant decrease in glucose levels under the influence of low-mineralized silicon hydrocarbonate calcium-magnesium MW has been shown by many authors [2, 9].

All of the above confirms the ability of low-mineralized silicon hydrocarbonate calcium-magnesium mineral water to reduce the incidence of adverse events against the background of combined lipid-correcting therapy and allows recommending its course for the prevention and treatment of side effects that often arise at the beginning of statin and fibrate therapy. The data obtained suggest that the use of this MW may be effective in preventing such side effects caused by taking other drugs.

Conclusion

The use of atorvastatin and fenofibrate by the standard scheme in patients with stable angina does not cause serious side effects that require cessation of therapy, but is accompanied by a number of adverse reactions, particularly in the hepatobiliary system and the digestive tract. These reactions often serve patients as an unsound reason to discontinue the therapy.

Low-mineralized silicon hydrocarbonate calcium-magnesium mineral water has a high efficacy in prevention of the side effects of the combined therapy, and its course administration permits leveling all clinical and biochemical adverse events caused by the use of atorvastatin with fenofibrate.

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