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PROGNOSTIC VALUE OF HYPERURICEMY. ALLOPURINOL AND HEPA-MERZ CORRECTING ACTIVITY IN COMPLEX THERAPY FOR PATIENTS WITH STABLE ANGINA

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Introduction. It has been proved that a nitric oxide (NO) molecule is the main vascular endothelium mediator with vasodilating effect, which decreases platelet and white blood cell adhesion and regulates some of the most important physiological functions of the body [1, 7, 8, 9, 10, 11, 12, 13]. Deficient production or accelerated decay of NO_x result in serious cardiovascular complications, such as hypertensic crisis, stroke or acute coronary syndrome [2, 3, 4, 6]. It was ascertained that hyperuricemy (HU) influences vascular endothelium directly and induces its generalized dysfunction, which explains the mechanism of uric acid (UA) participation in cardiorenal interactions and progression of cardiovascular diseases [5, 14]. The above justifies the inclusion of medicines regulating UA level in a complex therapy for patients with cardiovascular diseases.

Research objective. To detect correlation between clinical presentations in patients with stable angina (SA) and latent HU on the one hand and UA level, some metabolic syndrome indices and NO-system activity on the other hand when including Allopurinol and/or Hepa-Merz in a complex therapy.

Research materials and methods. 73 patients, who were diagnosed coronary disease and I-II functional category SA, participated in the research. 41 (56.2%) of them were men and 32 (43.8%) were women aged 38 to 65 (the average age was 55.6±4.8 years). SA was diagnosed on the basis of the standard criteria: a thoracic attack at rest and during exercise, ECG data.

According to the choice of treatment the patients were divided (by random sampling technique) into three groups: 1st group consisted of 23 (31.5%) patients applied traditional treatment; 2nd and 3rd groups each consisted of 25 (34.2%) patients applied standard therapy plus Hepa-Merz (L-ornithine-L-aspartate by Merz, Germany), 2 – 3 ml (10 – 15 g) a day, diluted with saline, iv, during 7 – 10 days, recommended further administration of granules, 1 sachet three times a day, and/or Allopurinol, 0.1 – 0.2 g a day, up to three months.

The following parameters were recorded in the blood examination report: UA, glomerular filtration rate (GFR), creatinine (CN), NO, nitrate reductase (NR), nitrooxide synthase (NOS), peroxinitrite ($ONOO^-$), total cholesterol (TCS), triglyceride (TG) and glucose. Analysis of the examination results displayed that at the end of a three-month therapy attacks stopped and did not recommence in 6 (26.1%) patients from 1st group and in 23 (92.0%) and 20 (80.0%) patients from 2nd and 3rd groups correspondingly. Attacks remained the same in 5 (21.7%) patients from 1st group.

Research results and discussion of the results. In average 3.7±0.56 episodes of angina pectoris a week were registered and 4.7±0.58 nitroglycerin tablets were used to relieve the symptoms. 14 (19.2%) patients with SA had dyspnea sympthoms, 11 (15.1%) patients had oedema of lower extremities and 5 (6.8%) patients had type II diabetes. 55 (75.3%) patients had been ill for 2 – 5 years and 18 (24.6%) patients had been ill for more than 6 years. ECG initial monitoring displayed 44.3±2.99 min daily duration of ischemia.

Number of episodes of angina pectoris decreased in 9 (39.1%) patients from 1st group, in 2 (8.0%) patients from 2nd group and in 5 (20.0%) patients from 3rd group. 1 (4.3%) patient from 1st group had a SA episode in the form of acute coronary syndrome after three-month treatment and the syndrome was relived.

It should be noticed that according to monthly ECG monitoring general positive dynamics of duration of ischemia was observed in the groups.

The most statistically important decrease of daily duration of ischemia was observed in 2nd group (9.4 min) and 3rd group (10.8 min) ($P<0.001$) as compared with 1st group (15.3 min). Blood examination showed that UA level decreased in every group as against the initial level before the treatment: by 7.5% ($P<0.05$), 45.7% and 36.5% ($P<0.001$) in 1st, 2nd and 3rd groups correspondingly (Table 2).

UA renal excretion increased by 9.4% ($P<0.05$), 20.0% and 18.4% ($P<0.001$), CN level in blood decreased by 15.8% ($P<0.05$), 27.7% and 26.1% ($P<0.01$) and glucose level in blood decreased by 19.5% ($P<0.05$), 30.4% and 22.4% ($P<0.01$) against relative increase of GFR by 1.2% ($P<0.1$), 4.3% ($P>0.05$) and 7.7% ($P>0.01$) correspondingly. At the same time the number of TCS atherogenic fractions in blood decreased by 10.4% ($P<0.05$), 22.5% ($P<0.05$) and 17.6% ($P<0.01$) and the number of TG atherogenic fractions decreased by 6.0% ($P<0.1$), 25.3% ($P<0.05$) and 18.9% ($P<0.01$). Positive changes in NO-system metabolism in red cell membranes were observed against the improvement of purine, nitrogen and lipid metabolism.

Analysis of the research results shows that NO-system functional activity in red cell membranes increased at the end of the three-month treatment. It was characterized by considerable increase in NO major stable metabolites in red cell membranes: by 12.1% ($P<0.05$) in 1st group, 42.4% in 2nd group and 34.6% ($P<0.001$) in 3rd group. Increase of NO and NOS levels was accompanied by simultaneous decrease in $ONOO^-$ in red cell membranes (by 15.4% ($P<0.05$), 47.1% and 28.8% ($P<0.001$)) and NADPH-dependent NR (by 24.5% ($P<0.01$), 40.3% and 27.6% ($P<0.001$)) correspondingly. We can suppose that the decrease in $ONOO^-$ was related with the increase of activity of an antioxidant system enzyme – superoxide dismutase: by 16.3% ($P<0.01$) in 1st group, 30.0% in 2nd group and 26.4% ($P<0.001$) in 3rd group at the end of the three-month therapy. High initial levels of glucose, cholesterol and TG in blood of patients with SA decreased after appropriate treatment, which evidences significance of the elements in metabolic syndrome progression.

At the same time the increase of both GFR and UA excretion and the decrease of CN level in blood after three-month treatment applied to 1st, 2nd and 3rd groups of patients with SA indicate that renal function does not suffer sufficiently and detected HU and creatinemia were caused by other mechanisms before the treatment.

To substantiate the significance of HU in the onset mechanisms of endothelial dysfunction in patients with SA, we made correlation analysis of UA level in blood and indices describing the state of NO-system in red cell membranes. Before the treatment high UA level correlated with decrease of NO ($r = -0.73$, $P<0.001$) and eNOS ($r = -0.84$, $P<0.001$), NR high activity ($r = +0.96$, $P<0.001$) and content of $ONOO^-$ ($r = +0.98$, $P<0.001$). Therefore, high UA level in blood is a significant factor of endothelial dysfunction and the onset of SA. Restoration of UA and creatinine balance was accompanied by substantial increase of both NO level in red cell membranes and eNOS activity and decrease of NR activity expression and $ONOO^-$ level as well as by renewal of glucose reference content in blood. Improvement of metabolic systems that define renal functional activity, UA and CN expression in blood and indices describing the state of NO-system were higher in 2nd group of patients with SA, who were administered Hepa-Merz, than in patients, who were administered Allopurinol. It is important to emphasize that patients from 1st group still had sound correlation between UA level in blood and NO / eNOS / NR / $ONOO^-$: $r = -0.58$, -0.61, $+0.70$ and 0.83 ($P<0.001$) correspondingly when such correlation in 2nd and 3rd groups abated: $r = -0.29/-0.19$, $-0.30/-0.16$, $0.25/-0.17$ and $+0.31/-0.16$ correspondingly at the end of 10th day of the treatment.

Specificity and susceptibility in 1st group were the lowest: 57.0 and 58.8 correspondingly. Obviously, the low indices of specificity and susceptibility in patients from 1st group were influenced by a large number of negative results (4 (17.4%)), the onset of angina pectoris episode in the form of acute coronary syndrome (1 (4.3%)) and quite a large number of false-positive results (6 (26.1%)).

In view of the low indices of specificity and susceptibility in 1st group, factor-positive patients had high predictable outcome OP (8.0), other outcomes OP (8.8) and low asymmetry parameter (2.2) as compared with such data in 3rd and 2nd groups. At the same time, percentage of correct prognoses and AB-correctness of diagnoses were rather high in all the three groups: 71.9 / 0.72 in 1st group, 92.3 / 0.90 in 2nd group and 84.0 / 0.85 in 3rd group. When considering the question of clinical effectiveness of treatment applied to the groups, we found that additional administration of Allopurinol (3rd group) or Hepa-Merz (2nd group) increased the effectiveness by 50.8% and 55.0% correspondingly as compared with standard treatment applied to 1st group. Therefore, Hepa-Merz increased clinical effectiveness of traditional therapy by extra 4.2% as compared with Allopurinol.

So diagnostic and prognostic testing was the most reasonable in groups that were administered Allopurinol or Hepa-Merz. It was ascertained that in such groups testing, which determined susceptibility and specificity of diagnostics and prognosis for a disease, was the most effective and it helped to estimate probability of a disease more exactly, to determine significance of HU in the onset and progression of SA and to justify the administration of purine metabolic correctors – Allopurinol and Hepa-Merz – to the patients.

To summarize, we assert that Allopurinol and even greater Hepa-Merz decrease UA level in blood – the main reason of apparent endothelial dysfunction and the onset of SA. Besides, Allopurinol and Hepa-Merz increase GFR and UA excretion and help to decrease glucose level in blood, which is a matter of principle when curing patients with metabolic syndrome.

Conclusion.

1. Patients with stable angina have latent hyperuricemy, which is accompanied by metabolic disorders in tissues and endothelial dysfunction.

2. Allopurinol and even greater Hepa-Merz decrease uric acid level in blood and increase glomerular filtration rate and uric acid renal excretion.

3. Allopurinol and Hepa-Merz potentiate standard treatment applied to patients with stable angina, which manifests itself through more substantial balance of NO-system in red cell membranes and is accompanied by decrease of correlation dependence between its main indices (NO / eNOS / NR / $ONOO^-$) and uric acid level in blood.

4. Allopurinol and Hepa-Merz increase the effectiveness of standard therapy by 50.8% and 55.0% ($P<0.001$) correspondingly.

Outlook for further research. The outlook for further research within the area consists in study of pathogenetic significance of hyperuricemy in generation of metabolic syndrome and cardiovascular complications, and development of diagnostic,

prophylactic and predicting criteria and adequate therapeutic approaches.

LIST OF LITERATURE

1. Абакумов М. М. Оксид азота и свертывающая система крови в клинике / М. М. Абакумов, П. П. Голиков // Вестник РАМН.–2005.–№10.–С. 53-56.
2. Аметов А. С. Новые стратегии ангиопротективной терапии у больных сахарным диабетом 2 типа и артериальной гипертензии / А. С. Аметов, Т.Ю. Демидова, С. А. Косых // Российский кардиологический журнал–2005.–№1(51).–С. 47-54.
3. Аметов А. С. Синтез оксида азота в эндотелии сосудов у больных сахарным диабетом 2-го типа / А.С. Аметов, Т.Ю. Демидова, С.А. Косых // Клиническая медицина–2005.–№8.–С. 62-68.
4. Балаболкин М. И. Роль дисфункции эндотелия и окислительного стресса в механизмах развития ангиопатии при сахарном диабете 2-го типа / М.И. Балаболкин, В.М. Каминская, Е.М. Клебанова // Кардиология–2004.–№7.–С. 90-97.
5. Джанашия П. Х. Является ли гиперурикемия компонентом метаболического синдрома? / П. Х. Джанашия, В. А. Диденко // Российский кардиологический журнал.–2001.–№1.–С. 12-16.
6. Кузнецова Т. Ю. Влияние полиморфизмов генов эндотелиальной NO-синтазы и НАДФН-оксидазы на развитие осложнений артериальной гипертензии / Т.Ю. Кузнецова, Д. В. Гаврилов, И.П. Дуданов [и др]. // Кардиология.–2008.–№3. -С. 27-33.
7. Кургалюк Н. Н. Оксид азота как фактор адаптационной защиты при гипоксии / Н. Н. Кургалюк // Успехи физиологических наук.–2002.–№33(4).–С. 65-79.
8. Лукъянова Л. Д. Роль биоэнергетических нарушений в патогенезе гипоксии / Л. Д. Лукъянова // Патологическая физиология и экспериментальная терапия.–2004.–№2.–С. 2-11.
9. Мазур Н. А. Дисфункция эндотелия, монооксид азота и ишемическая болезнь сердца / Н. А. Мазур // Терапевтический архив.–2003.–№3.–С. 84-86.
10. Малышев И. Ю. Введение в биохимию оксида азота. Роль оксида азота в регуляции основных систем организма / И. Ю. Малышев // Российский журнал гастроэнтерологии, гепатологии, колопроктологии. – 1997.–№1.–С. 49-55.
11. Марков Х. М. Молекулярные механизмы дисфункции сосудистого эндотелия / Х. М. Марков // Кардиология.–2005.–№12.–С. 62-72.
12. Покровский В. И., Виноградов Н. А. Оксид азота, его физиологические и патофизиологические свойства / В.И. Покровский, Н.А. Виноградов // Терапевтический архив.–2005.–№1.–С. 82-87.
13. Пушкарева Т. А. Критерии оценки дисфункции эндотелия артерий и пути ее коррекции / Т. А. Пушкарева, Л.Б. Корякина, А. А. Рунович [и др]. // Клиническая лабораторная диагностика.–2008.–№5.–С. 3-7.
14. Филиппов М. Е. Дисфункция эндотелия и факторы риска при ишемической болезни сердца / М. Е. Филиппов, А. М. Ханджян, К.А. Солодухин [и др]. // Клиническая медицина. -2008.–№2.–С. 28-33.

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ПРОГНОСТИЧЕСКАЯ ЗНАЧИМОСТЬ ГИПЕРУРЕКЕМИИ И КОРРИГИРУЮЩАЯ АКТИВНОСТЬ АЛЛОПУРИНОЛА И ГЕПА-МЕРЦ В КОМПЛЕКСНОЙ ТЕРАПИИ У БОЛЬНЫХ СТАБИЛЬНОЙ СТЕНОКАРДИЕЙ

Ташкенбаева Э.Н.

Резюме. В исследованиях на 73 больных в возрасте 38 до 65 лет (средний возраст 55, 6± 4, 8 года) с диагнозом ишемическая болезнь сердца со стабильной стенокардией I-II функционального класса, установлено, что аллопуринол и в большей степени Гепа-Мерц при их назначении в общепринятую стандартную терапию снижают уровень в крови мочевой кислоты, повышают скорость клубочковой фильтрации и экскреции с мочой мочевой кислоты. Гепа-Мерц в большей степени способствует увеличению в мембранах эритроцитов уровня основных, стабильных метаболитов оксида азота (NO_x), активность эндотелиальной NO-синтетазы, снижает экспрессию НАДФН-зависимой нитратредуктазы, уровня пероксинитрита, чем препарат аллопуринол. Выявлена четкая корреляционная зависимость между снижением в крови мочевой кислоты и позитивными изменениями в мембранах эритроцитов показателей, характеризующих состояние в них NO–системы. На основании полученных данных делается вывод о необходимости включения в комплекс традиционной терапии, для коррекции гиперурикемии назначать аллопуринол и/или Гепа-Мерц.

Ключевые слова: Аллопуринол, Гепа-Мерц, гиперурикемия, метаболический синдром, ишемическая болезнь сердца.

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ПРОГНОСТИЧНА ЗНАЧУЩІСТЬ ГИПЕРУРЕКЕМІЇ ТА КОРИГУЮЧА АКТИВНІСТЬ АЛОПУРИНОЛУ І ГЕПА-МЕРЦ В КОМПЛЕКСНІЙ ТЕРАПІЇ ХВОРИХ СТАБІЛЬНОЮ СТЕНОКАРДІЄЮ

Ташкенбаєва Е.Н.

Резюме. У дослідженнях на 73 хворих віком 38-65 років (середній вік 55, 6±4, 8 року) з діагнозом ішемічна хвороба серця із стабільною стенокардією I-II функціонального класу, встановлено, що Алопуринол і більшою мірою Гепа-мерц при їх включенні в загальноприйняту стандартну терапію знижують рівень в крові сечової кислоти, підвищують швидкість клубочкової фільтрації і екскреції з сечею сечової кислоти. Гепа-мерц більшою мірою сприяє збільшенню в мембранах еритроцитів рівня основних, стабільних метаболітів оксиду азоту ($NOx_{,}$, активність ендотеліальної NO-синтетази, знижує експресію НАДФН-залежної нітратредуктази, рівня пероксінітриту, чим препарат Алопуринол. Виявлена чітка кореляційна залежність між зниженням в крові сечової кислоти і позитивними змінами в мембранах еритроцитів показників, що характеризують стан в них NO-системи. На підставі отриманих даних робиться висновок про необхідність включення в комплекс традиційної терапії, для корекції гіперурикемії Алопуринолу або Гепа-Мерцу.

Ключові слова: Алопуринол, Гепа-Мерц, гіперурикемія, метаболічний синдром, ішемічна хвороба серця.

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