

Effect of dilatrend and metoprolol on certain parameters of hemocoagulation system

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ABSTRACT

We were aimed to study effect of the third generation β -blockers - metoprolol and dilatrend (in vitro) on the following parameters of hemocoagulation system in patients with ischemic heart disease: ATIII, time of blood coagulation, time of partial thromboplastin, time of recalcification, prothrombin index, time of thrombin, fibrinogen concentration and fibrinolytic activity of blood. According to the results of investigation dilatrend and metoprolol revealed positive effect on plasma factors of hemostasis compared to the control. Dilatrend was especially efficient that was manifested by increased ATIII activity, time of blood coagulation, recalcification and thrombin. As for fibrinolytic activity of blood and fibrinogen concentration they were decreased that was better expressed 1 month later from beginning of treatment. Reveled Changes were statistically significant. Thus, dilatrend, along with other therapeutical effects revealed positive effect on hemocoagulation system that probably determines its high efficacy in pharmacotherapy of cardiovascular diseases.

KEYWORDS: *newborn dilatrend, metoprolol, antithrombin III (AT III), hemostasis, prothrombin index, time of thrombin, time of activated thromboplastin, fibrinolytic activity*

Treatment of ischemic heart disease, despite results and data obtained after various controlled and randomized studies (Comet, Kopernikus, Senior etc.) recommending group of remedies, which reduce expected complications and mortality, still remains as one of the topical problems in modern medicine.

Nowadays, there are plenty of literature data indicating efficacy of β -blockers in pharmacotherapy of ischemic heart disease (IHD). They also have positive effect on plasma and thrombocytic hemostasis. The main feature of β -blockers is the removal of unfavorable influence of simpatico-adrenal effects on cardio-vascular system. Efficiency (improvement of life quality) of β -blockers is especially expressed in patents with manifested coronary syndrome, hypercoagulation, thrombocytes' increased adhesion-aggregation.

The aim of present work was evaluation of effects of β -blockers - Metoprolol (firm – Egisi, Hungary) and Dilatrend (firm – “Hoffman la Roshe”, Swetzeland) on certain parameters of hemocoagulation system (ATIII, time of blood coagulation, parcial thromboplastin time, thrombin time and recalcification time, prothrombin index, fibrinogen concentration, fibrinolytic activity of blood) in vitro in patients with IHD.

MATERIAL AND METHODS

Simple, open, relative (metoprolol/karvedilol) randomized investigations have been carried out in 2005 from 5 march till 25 October. Have been investigated 60 patients with the age range 46-69 ($60,2 \pm 0,85$) suffering from stenocardia corresponding to the functional class II-III according to the classification of Canada Society of Cardiologists.

Patients with chronic obstructive bronchitis, bronchial asthma, lung, liver and renal diseases, gastrointestinal ulcerations, systemic, joint and endocrine diseases, diabetes mellitus, oncological and hematologic diseases, patients who underwent surgical operations during latest 5 years, patients receiving β -blockers, Ca antagonists, angiotensin converting enzyme inhibitors (ACEI) were excluded from observations.

Investigations involved ECG examination, central hemodynamic testing (end diastolic and systolic volumes of the left ventricle, heart muscle contractility using echocardiography, heart rhythm monitoring with the use of Holter. Have been controlled the following indices: quantity and duration of ischemic episodes, maximal depression of ST segment, lipid specter testing (cholesterol, triglycerides, low density and high density lipoproteins).

Investigations have been carried out before the treatment and month later after treatment.

Patients were subdivided into two major groups: group I (30 patients) involved patients receiving metoprolol (100 mg) and group II (30 patients) involved patients receiving dilatrend (25 mg). The both group patients, along with β -blockers, received cardio-aspirin (100 mg), zoocor (20 mg), prestarium (starting dose was 2 mg and if side effects were not manifested dose was increased to 8 mg).

RESULTS AND DISCUSSION

In both clinical groups central hemodynamic and myocardial contractility were positively changed. The end systolic volume was decreased from $58,5 \pm 11,8$ ml to $55,4 \pm 9,3$ ml (5,3%); end diastolic volume was decreased from $127,9 \pm 10,5$ to $116,2 \pm 8,5$ ml (7,6%), ejection fraction was changed till $59,4 \pm 5,8$ (5,3%).

According to ECG monitoring all patients revealed 1-16 ischemic episodes of heart. Total number of ischemic episodes before treatment consisted 102. Of them, 82 were evaluated as subjectively revealed pain and 20 – as form without pain. All of these episodes were accompanied by depression of ST-segment; duration was not less than 1 minute.

A month later after treatment in clinical group I (on the metoprolol background) total number of ischemic episodes were reduced till 35 and ST-segment depression was short duration, no more than 0,5 mm; In clinical group II (on the dilatrend background) total number of ischemic episodes were reduced till 25 and ST-segment depression was no more than 0,3 mm;

Plasma factors of hemostasis and ATIII were defined before treatment (the control group) and month later after treatment in all clinical groups.

ATIII-activity was defined by the Abildgaard's method; Plasma factors of hemostasis (time of blood coagulation, time of partial thromboplastin, time of recalcification, prothrombin index, time of thrombin, fibrinogen concentration and fibrinolytic activity of blood) were studied with the use of hemocoagulometer – ГК-2110 (firm - "solari", Belarus).

As is known from literature data [1,3,4], decreased activity of ATIII and increased activity of certain parameters of hemocoagulation system is common for patients with IHD.

During statistical analysis of control group (before treatment, in an intact patients) have been compared data of group I (treated with metoprolol) and group II (treated with dilatrend) patients.

Obtained data were analyzed using the Student's t-criterion. Statistically significant was $p < 0,05$.

As it has shown in Tab.1, both preparations revealed positive influence on hemocoagulation system compared to the control group that has been manifested (clinically and according to the above-mentioned indices) month later after treatment

Increase in ATIII-activity was better expressed in patients treated with dilatrend (Group II $80,3 \pm 1,23\%$; $p < 0,05$) than in patients treated with metoprolol (Group I $78,6 \pm 1,46\%$; $p < 0,05$); time of blood coagulation, partial thromboplastin, recalcification and thrombin were increased in II clinical group ($p < 0,05$) than in group I.

Prothrombin index was more reduced in patients treated with dilatrend ($92 \pm 3,6\%$; $p < 0,001$) than in patients treated with metoprolol ($100 \pm 8,9\%$; $p < 0,1$ compared to the control group. Fibrinogen concentration ($2,92 \pm 0,08 \text{ mg/l}$; $p < 0,001$) and fibrinolytic activity of blood were more decreased ($14,6 \pm 2,2\%$; $p < 0,05$) on the background of dilatrend compared to control.

As is known, dilatrend is nonselective β -blocker with additional vasodilatory effect [2]. Unlike with other β -blockers, it is characterized by various positive effects on hemocoagulation system (according to our investigations), which is especially important in pharmacotherapy of patients with IHD [5,6]. Noteworthy that it caused increase in activity of endothelial ATIII, which is probably related with stimulation of release of endothelial NO, since ATIII and NO are released from vascular endothelial cells after influence of activated C-protein [7,8]; Proceeding from the aforesaid we can explain the positive effect of dilatrend on anticoagulation mechanisms that lesser was expressed in case of nonselective β -blocker – metoprolol.

Indices	Control group n=60	I group (metoprolol background) n=30	II group (dilatrend background) n=30
AT III (%)	$68,2 \pm 1,2$	$70,6 \pm 4,46$ $p < 0,01$	$80,3 \pm 1,23$ $p < 0,001$
Time of blood coagulation (sec)	$300 \pm 15,0$	$32,0 \pm 11,2$ $p < 0,05$	$360 \pm 5,25$ $p < 0,05$
Time of plasma recalcification (sec)	$86 \pm 2,0$	$110 \pm 2,7$ $p < 0,05$	$120 \pm 2,5$ $p < 0,001$
Prothrombin index (%)	$105 \pm 7,2$	$100 \pm 8,9$ $p < 0,1$	$92 \pm 3,6$ $p < 0,001$
Time of thrombin (sec)	$14 \pm 0,4$	$15 \pm 2,6$ $p < 0,1$	$18 \pm 1,4$ $p < 0,05$
Fibrinogen concentration (mg/l)	$4,2 \pm 0,7$	$3,8 \pm 1,08$ $p < 0,1$	$2,92 \pm 0,58$ $p < 0,05$
Fibrinolytic activity (%)	$15,8 \pm 3,2$	$15,5 \pm 4,6$ $p < 0,2$	$14,6 \pm 2,2$ $p < 0,05$
Time of parcial thromboplastin (sec)	$24 \pm 2,8$	$26 \pm 4,8$ $p < 0,2$	$30 \pm 2,1$ $p < 0,05$

Note: Control group present indices that have been defined before treatment in intact patients. Group I indices on the metoprolol background; Group II _ on the dilatrend background.

Tab.1 Effect of metoprolol and dilatrend on certain plasma factors of hemostasis before treatment and month later after treatment.

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Сравнительное влияние дилатренда и метопролола на некоторые параметры гемокоагуляционной системы организма

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Р Е З Ю М Е

Целью исследования являлось изучение влияния метопролола и дилатренда на некоторые параметры гемокоагуляционной системы организма (антитромбин III - АТIII, время свертывания, активированное частичное тромбопластиновое время - АЧТВ, время рекальцификации, время тромбина, протромбиновый индекс, концентрация фибриногена, фибринолитическая активность крови) у больных, страдающих ишемической болезнью сердца. Установлено, что метопролол и дилатренд вызывают улучшение параметров гемокоагуляционной системы. Особенно это касается дилатренда. По сравнению с контрольными группами достигнуты следующие результаты: увеличились - активность АТIII, время свертывания, время рекальцификации, время тромбина и активированное частичное тромбопластиновое время; понизились - фибринолитическая активность крови и концентрация фибриногена. Полученные результаты позволяют рекомендовать применение этих препаратов в фармакотерапии сердечно-сосудистых заболеваний.

Ключевые слова: *дилатренд, метопролол, АТIII, гемостаз, индекс протромбина, время тромбина, АЧТВ, фибринолитическая активность*