Effect of carvedilol and nebivalol combination on experimental rabbits' blood rheology and platelets' aggregation-adhesion on the background of electrical distress

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ABSTRACT

Nowadays in pharmacotherapy of cardiovascular diseases the β-blockers of third generation – carvedilol and nebivalol (with vasodilatatory effects) are used successfully. In the present work has been shown effect of combined administration of carvedilol and nebivalol (ratio 3:1) on certain indices of blood rheology and platelets' aggregation-adhesion in experimental rabbits on the background of electrical. Has been stated that combination of carvedilol and nebivalol (ratio 3:1) decrease indices of platelets' aggregation-adhesion, and activity of various parameters of coagulation system. This fact is very important in pharmacotherapy of various cardiovascular diseases, especially in case of treatment of ischemic heart disease and patients with manifested coronar syndrome, hypercoagulation and platelets' increased aggregation-adhesion. Combined administration of carvedilol and nebivalol in case of electrical distress (according to the results of previous investigations and present study) efficiently improves blood rheology and effect is much better than in case where the same preparations are used separately.

KEYWORDS: *beta-blocker, carvedilol, nebivalol, prothrombin index, fibrinogen concentration, beta-fibrinogen, platelets' aggregation-adhesion, erythrocytes' osmotic resistance, electrical distress*

Cardiovascular diseases (hypertensive disease, myocardial ischemia, congestive heart insufficiency etc.) still remain as one of the important problems in the modern world. For treatment of the above-mentioned diseases, the third generation β-blockers (with vasodilatatory effct) - cardioselective β-blocker - nebivalol and noncardioselective β-blocker - carvedilol successfully have been used.

It must be mentioned that any preparation, despite of its perfect efficacy, has less therapeutical effect than in combination with other preparations for instance, with preparations of the same or other pharmacological groups, which are similar or not by chemical structure or mechanisms of action [3]. It is generally recognized and proved combined therapy of various infection diseases, malignant tumor growth, arterial hypertension, ischemic heart disease, congestive heart insufficiency etc. There are theoretically reasonable suggestions that combined administration of two or more pharmacological remedies with relatively less doses than usually are used, can potentiate different effects of these two or more remedies despite of their chemical structures or electrophysiological features.

According to the literature data, researchers using combined therapy, compare received results with the results of monotherapy according to the various effects and features. In the last years combined therapy and elaboration of combined therapeutical remedies for treatment of cardiovascular diseases is very promoted and encouraged. Of great and especially importance for the above-mentioned diseases are preparations that have potential for improvement of blood rheological features.

Nowadays, the β-blockers of third generation - carvedilol and nebivalol are successfully used for treatment of arterial hypertension, ischemic heart disease, congestive heart insufficiency etc..

Various international investigations and studies supporte and confirm facts about positive effects of these preparations on blood rheology.

In our previous scientific investigations where we studied effct of carvedilol and nebivalol on experimental rabbits' blood rheology and platelets' aggregation-adhesion on the background of electrical distress revealed that they have anti-aggregative and anti-coagulative features.

According to the literature data and our latest investigations it was interesting to study combined effect of carvedilol and nebivalol on several plasmic factors of hemostasis and platelets' aggregation-adhesion.

We were aimed to study the effect of carvedilol (firm - "Roshe") and nebivalol ("Nebileti", firm-"Berlin-Hem") combination (3:1) on indices of experimental rabbits' (strain of "Shinshila") blood rheology and platelets' aggregation-adhesion on the background of electrical distress [4].

As is known, stress hormones - catecholamines affect and change blood rheological features that are often displayed in case of cardiovascular diseases. Dosage ratio of carvedilol and nebivalol – 3:1 was selected according to the theoretical point of view – proceeding from the mechanisms of their action. It is known that carvedilol is the nonselective β-blocker with features of β-adrenoblocker. and nebivalol cardioselective ?-blocker, resulting induction of NO synthesis in blood vessel endothelium. Because cardioselective β-blockers have relatively less side effects than nonselective β-blockers, for dosage safety, 3 portion of nebivalol (0.075 mg/kg) and 1 portion of carvedilol (0,045 mg/kg) were used.

MATERIAL AND METHODS

Experiments have been carried out on adult rabbits (3-4 kg., n=22). Ddistress was achieved by electrical stimulation [4]. Distress was confirmed by the set of behavior so called – gruming.

Experiment involved 4 series. Have been defined hemostatic factors of plasma - time of blood coagulation, indices of thrombin and prothrombin, fibrinogen concentration, fibrinolytic activity, time of activated thromboplastin, β-fibrinogen, platelets' aggregation-adhesion.

All of the above-mentioned indices were defined by widely used international methods.

In the I series, indices were defined in an intact blood of animals (the control group); In the II series the same indices were defined on the background of electrical distress; In the III series on the 5th day after stress the restitution was proved; In the IV series animals were loaded with nebivalol (0,075 mg/kg.) and carvedilol (0,045 mg/kg) combination every day during 3 days (per os).

Indices were defined on the 3rd day after administration of preparations and distress.

Obtained results were analyzed statistically according to the Student's t criterion.

RESULTS AND DISCUSSION

As it has shown from the *Tab.1*, in the control group in intact animals indices of platelets' aggregation-adhesion, hemostatic factors of plasma corresponds to the norm. On the background of distress (*Tab.1*, II series) concentration of platelets increases and increase is statistically significant ($p<0,05$); Increase both, aggregation and adhesion; As for hemostatic factors of plasma, distress revealed the following changes of investigated indices: time of blood coagulation (*Tab.2*, II series) was decreased approximately 1,6-times ($p<0,02$); Index of prothrombin was increased 1,12-times ($p<0,01$); Concentration of fibrinogen was increased approximately 1,8-times ($p<0,01$); Fibrinolytic activity of blood was increased 1,4-times ($p<0,02$); β-fibrinogen was positive (+++); Time of thrombin was reduced 1,25-times ($p<0,05$).

In the III series, on the 5th day after electrical stress, the restitution was detected. It is known that in case of stress in the chromaffin cells of the adrenal gland production of epinephrine and other catecholamines are exaggerated. The increased production of so called stress hormones affects on blood coagulation system, platelet aggregation-adhesion.

The similar changes are detected in case of cardiovascular diseases such arterial hypertension, ischemic heart disease, congestive heart insufficiency etc.

In the IV series, after distress changes in blood of rabbits loaded with combination of carvedilol and nebivalol were different compared to the results of the II series. Concentration of platelets, indices of aggregation-adhesion were reduced ($p<0,05$); Changes of hemostatic factors of plasma after electrical distress on the background of combination of preparations were normalized at the expense of blood rheology. The time of blood coagulation was increased statistically ($p<0,05$) compared to the results of the II series; Index of prothrombin was reduced 1,2-times; The time of thrombin was prolonged 1,5-times and concentration of fibrinogen was reduced 1,8-times; Fibrinolytic activity was decresed 1,5-times as well. β-fibrinogen that was sharply positive on the background of electrical distress, after administration of carvedilol and nebivalol was not detected.

Thus, combination of carvedilol and nebivalol (dosage ratio 3:1) decrease indices of platelets' aggregation-adhesion, and activity of various parameters of endogenous coagulation system. This fact is very important in pharmacotherapy of various cardiovascular diseases, especially in case of treatment of ischemic heart disease and patients with manifested coronar syndrome, hypercoagulation and platelets' increased aggregation-adhesion.

According to the results carried out by us revealed that anti-aggregative effect was better expressed in case of treatment with nebivalol than in case of carvedilol. The latter was more effective on blood coagulation system in case of electrical distress.

Proceeding from the aforesaid, combined administration of carvedilol and nebivalol (dosage ratio 3:1) in case of experimental distress was much more efficient and improved blood rheology than the same preparations when they were used separately. This fact suggest idea and encourages us to elaborate combined preparations that probably will be much more efficient preparation with lesser side effects.

Indices	1	2	3	4
Platelets' concentration	512±28,6	580±35,7 p<0,05	520±18, Pp<0,05	500±17,4 p<0,05
Adhesión %	86,2±1,28	100,2±7,1 p<0,01	90,1±5,6 p<0,02	70,2±1,6 p<0,01
Aggregation %	90,5±1,9	100,3±4,2 p<0,02	92,7±1,7 p<0,01	80,8±2,43 p<0,01

Tab.1 *Changes of indices of platelets' aggregation-adhesion in rabbits.*

Indices	1	2	3	4
Time of blood coagulation (sec)	330±0,64	200±0,6 p<0,02	340±5,7 p<0,01	350±3,4 p<0,05
Time of activated thromboplastin (sec)	22±1,5	19±1,1 p<0,02	22±1,6 p<0,05	26±0,7 p<0,01
Prothrombin index (%)	94±3,6	106±2,43 p<0,01	96±2,3 p<0,05	90±3,6 p<0,01
Time of thrombin (sec)	20±1,3	16±1,7 p<0,05	21±0,9 p<0,01	24±1,89 p<0,01
Fibrinogen concentration (mg/l)	3,1±0,24	5,6±0,57 p<0,01	3,2±0,85 p<0,01	3,0±0,28 p<0,01
Fibrinolytic activity	10,08±0,6	15,6±0,73 p<0,02	10,4±0,38 p<0,02	10,0±0,61 p<0,01
β-fibrinogen	-	+++	-	-

Tab.2 *Canges of hemostatic factors of plasma in rabbits.*

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Влияние небивалола и карведилола на реологию крови, агрегацию - адгезию тромбоцитов у экспериментальных кроликов в условиях электрического дистреса

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Р Е З Ю М Е

В фармакотерапии сердечно-сосудистых заболеваний в настоящее время весьма эффективно применяются бета-адреноблокаторы 3-его поколения – карведилол и небивалол. Исследовано влияние комбинации небивалола и карведилола (в соотношении 3:1) на некоторые реологические показатели и агрегацию-адгезию тромбоцитов у экспериментальных кроликов на фоне электричекого дистреса. Результаты исследования показали, что при комбинированном применении небивалола и карведилола снижаются показатели агрегации-адгезии, активности параметров коагуляционной системы крови, что особенно важно при лечении заболеваний сердечно-сосудистой системы, особенно пациентов с манифестированным коронарным синдромом, гиперкоагуляцией, повышением агрегации-адгезии тромбоцитов. Этот эффект обнаруживается более отчетливо, нежели при раздельном применении этих препаратов.

Ключевые слова: *бета-блокатор, карведилол, небивалол, протромбиновый индекс, концентрация фибриногена, бета-фибриноген, агрегация-адгезия тромбоцитов, осмотическая резистентность эритроцитов, электрический дистрес*