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PLATELET FUNCTIONAL ACTIVITY IN EARLY POSTMYOCARDIAL INFARCTION PERIOD

U.Z. Muratova
Tashkent Pediatric Medical Institute, Uzbekistan., ndm2@mail.ru

M.M. Pirnazarov
Tashkent Pediatric Medical Institute, Uzbekistan.

M.M. Shertaev
Tashkent Pediatric Medical Institute, Uzbekistan.

N.R. Muratova
Tashkent Pediatric Medical Institute, Uzbekistan.

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U.Z. Muratova, M.M. Pirnazarov, M.M. Shertaev, N.R.Muratova, I.R.Saidalimova,

The Tashkent pediatric medical instiute.

✓ ***Resume***

The blockade of angiotensin II by specific antagonists in acute period of myocardial infraction reduces content of plasma biomarkers.

The platelets playing key role in development of cardiac infraction and originated from megacariocites also can be subjected to the effect of selective blockers of AT I - receptor. The effect of Valsartan aggregation parameters and activity of platelet phospholipase A_2 of patients with acute myocardial infraction was studied in the work.

Platelet aggregation was studied by Botn technique using adenosinediphosphate as inductor of aggregation in concentration of 0,5 - 5 mcM with step in 0,5 mcM. Activity of phospholipase A_2 was studied using Dole reagent and labeled 14C-phospholipids.

The obtained data show that an acute myocardial infraction is followed by high values of platelet aggregation activity. Activity of platelet phospholipase A_2 increase by the order and more in comparison with the values in donors normal platelets. Preferential hydrolysis of phosphatidylcholine is observed at comparison of two substrates L - 3 phosphatidylcholine and phosphatidylethanolamine.

Early therapy by Valsartan (in dose of 80 mg/day) leads to normalization of platelet aggregative functions and to reduction of activity of platelet phospholipase A_2.

Keywords: valsartan, acute myocardial infraction, platelet, phospholipase A_2

ФУНКЦИОНАЛЬНАЯ АКТИВНОСТЬ ТРОМБОЦИТОВ В РАННЕМ ПОСТИНФАРКТНОМ ПЕРИОДЕ

У.З.Муратова, М.М.Пирназаров, М.М.Шертаев, Н.Р.Муратова, И.Р.Саидалимова,

Ташкентский педиатрический медицинский институт.

✓ ***Резюме***

Блокада ангиотензина II (АТ II) специфическими антагонистами в остром периоде инфаркта миокарда снижает содержание плазменных биомаркеров.

Тромбоциты играют ключевую роль в развитии инфаркта миокарда и следовательно исследование блокаторов АТ I - рецепторов на агрегационные параметры и активность фосфолипазы А2 тромбоцитов является актуальным. В работе изучено действие вальсартана на агрегацию и активность фосфолипазы тромбоцитов в раннем постинфарктном периоде.

Агрегацию изучали методом Born с использованием АДФ в качестве индуктора в концентрации 0,5-5 мкМ. Активность фосфолипазы изучали используя реагент Dole, субстраты - фосфолипиды.

Полученные данные показали, что острый инфаркт миокарда сопровождается высокими значениями агрегационной активности. Увеличивается активность фосфолипазы и изменяется субстратная специфичность фермента к фосфатидилхолину. Ранняя терапия вальсартаном нормализует эти параметры.

Ключевые слова: вальсартан, острое миокардиальное нарушение, пластинка, фосфолипаз A_2.

ИНФАРКТДАН КЕЙИНГИ ИЛК ДАВРДА ТРОМБОЦИТЛАРНИНГ ФУНКЦИОНАЛ ФАОЛЛИГИ

У.З.Муратова, М.М.Пирназаров, М.М.Шертоев, Н.Р.Муратова, И.Р.Саидалимова,

Тошкент педиатрия тиббиёт институти.

✓ ***Резюме***

Миокард инфарктнинг ўткир даврида махсус антагонистлар билан II (АТ II) ангиотензинни блокада қилиш плазмали биомаркерларни камайтиради.

Тромбоцитлар миокард инфарктнинг ривожланишида муҳим роль ўйнайди ва бинобарин, АТ I - рецепторларнинг агрегацион ўлчамларини ҳамда тромбоцитларнинг А2 фосфолипазаси фаоллигини ўрганиш долзарб аҳамият касб этади. Ишда вальсартаннинг агрегацияга таъсири ва инфарктдан кейинги илк даврда тромбоцитлар фосфолипазасининг фаоллиги ўрганилган.

Агрегация Born усулида индуктор сифатида 0,5-5 мкМ концентрациядаги АДФдан фойдаланилган ҳолда ўрганилди. Фосфолипазанинг фаоллиги эса Dole реагентидан, субстратлардан – фосфолипидлардан фойдаланган ҳолда ўрганилди.

Олинган маълумотлар ўткир миокард инфаркти агрегацион фаоллик юқори бўлганда юз беришини кўрсатди. Фосфолипазанинг фаоллиги кучаяди ва ферментнинг фосфатидилхолинга субстрат ўзига хослиги ўзгаради. Вальсартан билан эрта даволаш бу кўрсаткичларни меъёрга солади.

Калит сўзлар: вальсартан, ўткир миокардиал бузилиш, пластинка, фосфолипаз A_2.

The retrospective analysis of the clinic data shows that increase of platelet activity accompanied by high level of plasma biomarkers is observed at patients with an acute myocardial infraction (1). Local endocardiac components of rennin-angiotensin system makes considerable contribution in development of cardiac infraction and in its complications. The blockade of angiotensin II (All) in acute period of cardiac infraction leads to expressed reduction of content

of plasma biomarkers and to less enduring episodes of ventricular disturbance of heart rhythm. Therefore at the present the effects of antagonists All (valsartan, losortan) and captopril on forecast and mortality at acute myocardial infraction is estimated in study of VALIANT and OPTIMAAL (2-4). The platelets playing key role in development of cardiac infraction and originated from megacardiocites also can be subjected to the effect of selective blockers of ATI - receptor. Notwithstanding that the blockers of AT 1-receptors are more effective at tissue level and platelets play role of the causal factor in development of cardiac infraction we have not found out the data about effects of selective antagonists on functional properties of plates in early postmyocardial infraction period In this connection the purpose of the present research was to study effects of valsartan VL - nonpeptide antagonist with molecular weight of 435,5 on aggregative activity (AAT) and activity of platelet phospholipase A_2 at patients in early postmyocardial infraction period.

Materials and methods

32 men (aged 54,3 ± 3,6 years) hospitalized in clinic within first two days of AM I without serious accompanying diseases (Diabetum among them) have been included to the study. The diagnosis "cardiac infraction" was determined in accordance with criteria of World Health Organization (5). The patients were treated by standard therapy for AMI. Valsartan was administered on 2d-3d day of AMI after stabilization of hemodynamics in a starting doze of 40 mg/day, arterial pressure 120/80 mm Hg. After 4-5 days of administration a doze of valsartan was brought to 80 mg/day in case of good acceptability. 9 healthy men (aged 51,5 ± 2,3 years) composed the control group. General clinic physical examinations - electrical and echocardiography, the biochemical analysis of blood have been done for all patients. Platelet aggregation was studied by Born (6). Blood in plastic test tubes was stabilized with 0,13 M sodium citrate in the ratio 9:1 Plasma rich in platelet was obtained by centrifugation (200xg) within 7 minutes. Study was carried out during 2h since the moment of taking of blood. ADP (Sigma, USA) in concetration - 0,5-5 mcM with step of 0,5 mcM was used as inductor. The maximal amplitud was determined on the third minute after addition of ADP at concentration - 0,5 mcM and 5mcM.

Studies of platelet aggregation were out at healthy donors and patients before introduction of anticoagulant or in 6 hours after reperfussion therapies in day of hospitalization and after 3 weeks of hospitalization. Then studies of effect of valsartan (5·10 mol/1) on aggregative parameters of 5 10 mol/l healthy subjects and patients were carried out. At statistical processing of the results t - Student criterion have been used. Platelet activity was normally determined in 6 hours after the basic infusion. Activity of PLA2 in platelets was determined by the work (7).

Results and discussion

Study of A AT at patients with AMI has shown that 14 (44%) patients had low plates activity. Reduction of functional platelet activity can be connected both with administration of preparations (for example inhibitors of cyclooxygenase) and with insufficiency, an exhaustion of platelet functions in the given population of cells. The other patients - 18 (56%) had high functional platelet activity in comparison with normal parameters. In this connection a group of patients with high parameters of platelet aggregation was included to the study. Results represented in the table show that 3 week therapy by diovan causes improvement of plates functions which was shown in reduction of velocity of aggregation, amplitudes and in increase of AAT parameter.

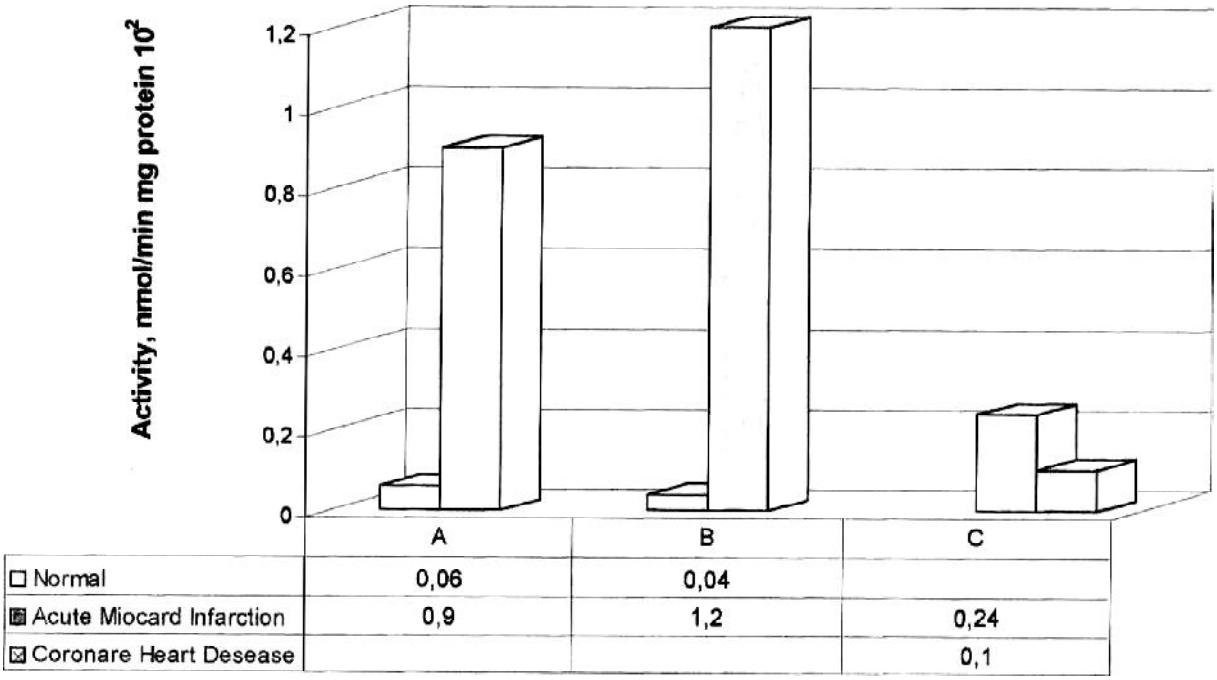
Various antagonists of AA I - receptors inhibit platelet activity by antagonism (TxA2)/Pg H_2- receptors and it is established that antiplatelet effect of AT I - antagonists does not depend on presence of not condensed imidasol in their chemical structure. Only high dozes of of valsartan (more than 5·10-6 mol/1) had ingibiting effect on platelet activity at donors in ours in vitro study. Other studies also have shown low efficiency of valsartan at studying of Tromboxan A2 depended platelet activation (8-9). Nevertheless as it is seen from our data early valsartan therapy suppresses ADP - induced platelet aggregation.

As it is know high platelet aggregation condition is accompanied by the cascade of events where the basic place occupies increase of endocellular concentration of Ca(10-11).Multiphase increase of calevel in platelets causes activation of some enzymes and first of all those which participate in transduction an external signal.One of such enzymes is endocellular PLA_2 producing arachidonic acid - the predecessor of prostaglandins, leukotriens and the platelet activation factor. The increase in enzyme activity for the order (fig. 1) was revealed at study of PLA_2 activity in platelets of patients with AMI. Valsartan therapy has allowed to reduce values of PL A_2 activity in platelets of patients with AMI. Valsartan therapy has allowed to reduce values of PLA_2 activity to a level observable at ischemic heart disease. PLA_2 possesses high sensitivity to Ca and hence a level of cAMP, work of potential dependent Ca - channels and calmodulin make the contribution to increase of enzyme activity. As it follows from the received data (fig. 1) phosphatidylcholine fraction is preferentially hydrolysed at AMI, whereas phosphatidylethanolamines were mainly decomposed in norm at platelet activation. Changes ol platelet functional condition at AMI as strengthening of aggregation are accompanied by increase in content of endocellular Ca, by infringement of regulation an a - aarenoreceptors, by increase of sensitivity to ADP, arachidonic.

Efficiency of valsartan on platelet aggregation activity parameters in patients with AMI.

Variable	Donors	Patients with AMI		
		Before treatment	After treatment	P
V 0,5com.unit./min	0,67±0,07	2,11± 0,18	1,56± 0,15	P<0,05
A 0,5max. com. unit	0,97±0,09 2,3±4	2,48 ±0,24	1,39± 0,15	P< 0,05
A 5 max.com.unit AAT	0,22 2,27±0,24	2,98 ±0,32	2,49± 0,27	
		1,1± 0,09	2,04± 0,19	P< 0,001

Activity of PLA2 of platelets in a normal condition and in case of AMI



A. Substrate - L-3-phosphatidilethanolamine, 1- acil -2(1-^{14}C)-linoline acid.
B, C. Substrate - L - 3 - phosphatidylcholine, 1 - palmitoile - 2 (1 -^{14}C) - oleine acid.

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