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PLATELETS: THEIR PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL ROLE AND THERAPEUTIC USE OF ANTIPLATELET DRUGS

TROMBOCITI: FIZIOLOŠKA I PATOFIZIOLOŠKA ULOGA I TERAPIJSKA PRIMENA ANTIAGREGACIONIH LEKOVA

Ivana Mihajlović

Agencija za lekove i medicinska sredstva Republike Srbije

Correspondence to:

Ivana Mihajlović, Dipl. farmaceut
Agencija za lekove i medicinska sredstva Republike Srbije
Vojvode Stepe 458, 11152 Beograd
Tel: 063/ 8480 369
E-mail: ivana.mihajlovic@yahoo.com

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Abstract

Platelets play dual role in our body: physiological (beneficial) and pathophysiological (harmful) one. Physiologically, they prevent bleeding from the vascular wall injury, while pathologically participate in the thrombus formation causing thus very often severe cardiovascular and cerebrovascular events. Platelet activation is initiated by G protein-coupled and the other surface receptors inolved in multistep process ending with recruitment of additional platelets into a growing thrombus causing vascular obstruction. As a consequence, efforts have been successfully made to discover potent antiplatelet agents, which today belong to the most often prescribed drugs. They are used in primary and secondary prevention of cardiovascular and cerebrovascular events. In the later case, they provide protection against possible subsequent events. They are used orally (long-term) or intravenously (short-term acute use) and are in both cases clinically very effective. In primary prevention they are commonly used as monocomponents, but in secondary prevention more often as two-component preparations (e.g. aspirin plus dypiridamole and aspirin plus clopidogrel). Out of 11 antiplatelet preparations marketed world wide, eight (78%) are available in our country. In order to be up-dated, novel parenteral preparations- abciximab and tirofiban- should be added to the existing antiplatelet drugs in our country.

DISCOVERY, ORIGIN AND MORPHOLOGY OF PLATELETS

The first accurate and convincing description of platelets in journal *Archiv für microscopische Anatomie* in 1865. was published by German anatomist Max Schultze, as part of a study devoted mainly to white blood cells. He described "spherules" much smaller than red blood cells that occasionally clump and may participate in collections of fibrous material [(1)].

Platelets are derived from the cytoplasm of megakaryoicytes, primarily located in the bone marrow. They are small, disc-shaped cells without a nucleus, but contain megakaryocyte derived messenger RNA (mRNA) and the translational machinery needed for protein synthesis. Usually measuring 1 to 2 μm in diameter. The mean platelet count in children and adults is about $250x10^9$/L, ranging from 150 to $400x10^9$/L. Normally, a platelets are released to the bloodstream and circulate for about 10 days before their removal, largely by the spleen. They circulate freely without adhesion to the vessel wall or aggregation with other platelets [(2)].

Platelets play a crucial role in hemostasis. In circulation, they are not only the smallest blood cells, but also the lightest. Therefore they are pushed out from the center of flowing blood to the wall of the blood vessel. There they roll along the surface of the vessel wall, endothelium, which prevents anything from sticking to it. However, when there is an injury, platelets are the first to react. Stimulated, platelets become spherical, extend pseudopods, and adhere to vessel walls and to each other [(2)]. They clump onto fiber of the vessel wall, providing the initial seal to prevent bleeding [(3)], fulfilling thus their primary physiological role in our body.

Platelets are composed of three principal components: membrane structures, microtubules, and granules (Fig. 1).

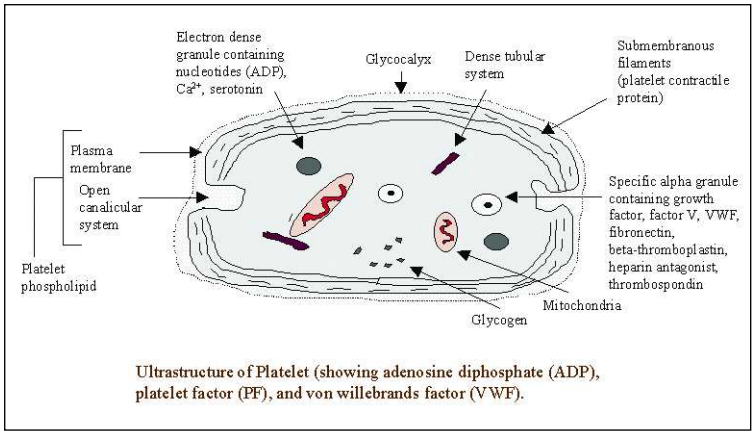

***Fig.1**. Platelet structure available online [2]*

Platelet dysfunction due to congenital and acquired etiologies is one of the most common causes of bleeding encountered in clinical practice.

Function of platelets

In a normal physiological state, platelets circulate without adhering to undisturbed vascular endothelium. Upon disruption of the integrity of the vascular endothelium or alteration in the shear stress of the blood flow, platelets are "activated". Platelet activation plays a central role in both benign and pathological responses to vascular injury and thrombus formation. The process of transformation of inactivated platelets into a well-formed platelet plug occurs along a continuum, but may be divided into three steps: (1) adhesion, (2) aggregation, and (3) secretion [4].

The primary function of platelets is to stop blood loss after tissue trauma and exposure of the subendothelial matrix. Hemostasis and pathological thrombus formation are dynamic processes that require a co-ordinated series of events involving platelet membrane receptors, bidirectional intracellular signals, and release of platelet proteins and inflammatory substances [5].

Platelets undergo morphological changes upon activation. Platelet shape changes from a disc to a spiny sphere with multiple pseudopodial extensions. The contents of platelet granules are secreted through the surface-connected canalicular system, with adenosine diphosphate (ADP), fibrinogen, and factor V appearing on the platelet surface and in the milieu immediately surrounding the platelet. Recurrent episodes of platelet activation increases smooth muscle proliferation and may initiate atherosclerosis [6].

As platelets are recruited to the area of blood vessel damage, they become activated by a range of agonists including ADP, thrombin and thromboxanes, which interact with transmembrane receptors. Receptor stimulation results in G protein interactions, which enable activation of enzymes involved in cellular metabolic pathways, in particular, phosphatidylinositol 3-kinase and phpspholipase C. Metabolic pathway activation results in the elevation of cytoplasmic calcium and phosphorylation of substrate proteins, which bring about changes in the cytoskeleton, enabeling platelet shape change and spreading, release of alpha- and dense-granular contents, stimulation of phospholipase A_2 and liberation of thromboxane A_2 (TXA_2), induction of a procoagulant surface, and activation of GPIIb/IIIa receptors [7].

Profile of antiplatelet drugs

Antiplatelet drugs act through a wide range of mechanisms, and they can be classified according to their mechanism of action. Drug classes include: ADP antagonists (thienopyridines), cyclooxygenase (COX-1) inhibitors (the only member of this class is aspirin), phosphodiesterase inhibitors, analogue of prostacyclin and GPIIb/IIIa inhibitors (Table 1):

***Table 1.** Mechanism of action of antiplatelet drugs (8)*

Drug	*Mechanism of action*
Aspirin	**COX inhibitors**
Dipyridamole	**Phosphodiesterase inhibitors**
Treprostinil	**Analogue of prostacyclin**
Clopidogrel Prasugrel Ticagrelor Ticlopidine	**ADP antagonists**
Abciximab Eptifibatide Tirofiban	**GP IIb/IIIa inhibitors**

Antiplatelet drugs protect against myocardial infarction, stroke, cardiovascular death and other serious vascular events in patients with a history of previous events or known risk facctors for cardiovascular disease. They decrease platelet aggregation and may inhibit thrombus formation in the arterial circulation, where anticoagulants have little effect [9, 10].

Aspirin

Aspirin (acetylsalicylic acid) inhibits platelet aggregation and is used in the prevention of arterial and venous thrombosis. It irreversibly inhibits cyclooxygenase in platelets and thereby blocks the formation of thromboxane A_2, a potent vasoconstrictor and platelet aggregant [9, 4].

Since platelets lack the ability to synthesize new proteins, the effects persist for the life of the exposed platelets (7-10 days). Acetylsalicylic acid may also inhibit production of the platelet aggregation inhibitor, prostacyclin (prostaglandin I_2), by blood vessel endothelial cells; however, inhibition of prostacyclin production is not permanent as endothelial cells can produce more cyclooxygenase to replace the non-functional enzyme [11].

Dipyridamole

Dipyridamole inhibits phosphodiesterase, which inactivates cyclic AMP (adenosine monophosphate).

Dipyridamole likely inhibits both adenosine deaminase and phosphodiesterase, preventing the degradation of cAMP, an inhibitor of platelet function. This elevation in cAMP blocks the release of arachidonic acid from membrane phos-

pholipids and reduces thromboxane A_2 activity. Dipyridamole also directly stimulates the release of prostacyclin, which induces adenylate cyclase activity, thereby raising the intraplatelet concentration of cAMP and further inhibiting platelet aggregation. Because the effect is short-lastig, repeated dosing is required to inhibit platelet function for 24 hours [9, 11].

Aspirin, dipyridamole

Dipyridamole alone has little antiplatelet effect. It is currently used in combination with aspirin in the prophylaxis of thromboembolic disorders [12] approved in our Country [13] as Aggrenox® .

Clopidigrel, aspirin (DuoPlavin®)

It has been recently shown that the combination therapy with clopidogrel and aspirin provided greater protection against subsequent stroke than aspirin alone [14].

Treprostinil

Treprostinil is a synthetic analogue of prostacyclin, used to treat pulmonary hypertension. The major pharmacological actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation [11].

Thienopyridine derivatives

Clopidrogel, ticlopidine and prasugrel

Clopidrogel and ticlopidine are thienopyridine derivatives and metabolised in the liver to active compounds which covalently bind to the adenosine diphosphate (ADP) receptor on platelets and dramatically reduce platelet activation [9,12,15].

The active metabolite of clopidogrel prevents binding of adenosine diphosphate (ADP) to its platelet receptor, impairing the ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. It is proposed that the inhibition involves a defect in the mobilization from the storage sites of the platelet granules to the outer membrane. The drug specifically and irreversibly inhibits the P2Y12 subtype of ADP receptor, which is important in aggregation of platelets and cross-linking by the protein fibrin. No direct interference occurs with the GPIIb/IIIa receptor. As the glycoprotein GPIIb/IIIa complex is the major receptor for fibrinogen, its impaired activation prevents fibrinogen binding to platelets and inhibits platelet aggregation. By blocking the amplification of platelet activation by released ADP, platelet aggregation induced by agonists other than ADP is also inhibited by the active metabolite of clopidogrel [11].

The active metabolite of ticlopidine prevents binding of adenosine diphosphate (ADP) to its platelet receptor, impairing the ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. It is proposed that the inhibition involves a defect in the mobilization from the storage sites of the platelet granules to the outer membrane. No direct interference occurs with the GPIIb/IIIa receptor. As the glycoprotein GPIIb/IIIa complex is the major receptor for fibrinogen, its impaired activation prevents fibrinogen binding to platelets and inhibits platelet aggregation. By blocking the amplification of platelet activation by released ADP, platelet aggregation induced by agonists other than ADP is also inhibited by the active metabolite of ticlopidine. Ticlopidine is the oldest thienopyridine currently available [11, 16].

Prasugrel

Prasugrel is an thienopyridine which inhibits ADP receptors by irreversibly acting on the P2Y12 receptor on platelets. The active metabolite of prasugrel prevents binding of adenosine diphosphate (ADP) to its platelet receptor, impairing the ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Prasugrel is proposed to have a similar mechanism of action to clopidogrel. Prasugrel is more effective than ticlopidine and clopidogrel at inhibiting the ADP receptor. Prasugrel is a novel platelet inhibitor [11, 17].

Glycoprotein IIb/IIIa receptor blockers: abciximab, eptifibatide and tirofiban

The glycoprotein IIb/IIIa inhibitors are used parenterally in patients with acute coronary syndromes by specialists. This class of drugs is not used in an outpatient setting by non-specialists. Platelet membrane GPIIb/IIa receptors constitute the final common pathway of platelet aggregation; the integrin GPIIb/IIIa antagonists prevent cross-linking of platelets. Their action is independent of the aggregation-inducing stimulus [12].

Abciximab

Abciximab is a humanised mouse antibody fragment (Fab fragment of the chimeric human-murine monoclonal antibody 7E3) with a high binding affinity for the glycoprotein IIb/IIIa receptor, binds to the glycoprotein (GP) IIb/IIIa receptor of human platelets and inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor and other adhesive molecules [9,11,15].

Eptifibatide

Eptifibatide mimics part of the structure of fibrinogen that interacts with the glycoprotein IIb/IIIa receptor and thus compete with ligand binding of fibrinogen to the glycoprotein IIb/IIIa receptor. The drug is always used combined with aspirin or clopidogrel. Synthetic cyclic hexapeptide that binds to platelet receptor glycoprotein [9,11,15,18].

Tirofiban

Tirofiban is a reversible antagonist of fibrinogen binding to the GP IIb/IIIa receptor, the major platelet surface receptor involved in platelet aggregation. Platelet aggregation inhibition is reversible following cessation of the infusion of tirofiban. It is a non-peptide reversible antagonist of the platelet glycoprotein (GP) IIb/IIIa receptor [11,15].

Ticagrelor

Ticagrelor, cyclopentyltriazolopyrimidine, is a inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP-receptor [19].

THERAPEUTIC USE OF ANTIPLATELET DRUGS, CLINICAL EFFICACY

Antiplatelet drugs can inhibit platelet adhesion, aggregation, release and activation of platelets and with different mechanisms may be important in antithrombotic treatment.

Table 2. Antiplatelet drugs - clinical use [11,15,16,19,20]

Agent	Route of administration	Clinical use	Absorbtion	Biotransformation	Half life	Protein binding	Volumen of distribution	Side effects
Abciximab	Solution intravenous	As an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications in patients undergoing percutaneous coronary intervention and in patients with unstable angina not responding to conventional medical therapy when percutaneous coronary intervention is planned within 24 hours.	Rapidly. Platelet function recovers over about 48 hours although abciximab may remain in the circulation for 15 days or more in a platelet-bound state.	Most likely removed by opsonization via the reticuloendothelial system when bound to platelets, or by human antimurine antibody production.	10-30 min			Bleeding, hypoesthesia, nausea, hypotension, atrial fibrilation, pleural effusion or pleurisy.
Acetylsalicylic acid	Oral	In the prevention of arterial and venous thrombosis	Rapid and complete following oral administration but may vary according to specific salicylate used, dosage form, and other factors such as tablet dissolution rate and gastric or intraluminal pH.	Rapidly hydrolyzed primarily in the liver to salicylic acid, which is conjugated with glycine (forming salicyluric acid) and glucuronic acid and excreted largely in the urine.	Approximately 15 minutes	High (99.5%) to albumin		Tinnitus, abdominal pain, hypokalemia, hypoglycemia, pyrexia, hyperventilation, dysrhythmia, hypotension, hallucination, renal failure, confusion, seizure, coma, and death
Clopidrogel	Oral	Reduce atherosclerotic events such as myocardial infarction, stroke, and vascular death in patients who have had a recent stroke, recent MI, or have established peripheral vascular disease.	At least 50% based on urinary excretion of clopidogrel-related metabolites.	Hepatic, extensive and rapid, by hydrolysis to the main circulating metabolite, a carboxylic acid derivative, which accounts for approximately 85% of the circulating drug-related compounds. A glucuronic acid derivative of the carboxylic acid derivative has also been found in plasma and urine. Neither the parent compound nor the carboxylic acid derivative has a platelet inhibiting effect.	Carboxylic acid derivative: 8 hours (after single and multiple doses). Covalent binding to platelets has accounted for 2% of radiolabeled clopidogrel with a half-life of 11 days.	98%		Vomiting (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage.

Agent	Route of administration	Clinical use	Absorbtion	Biotransformation	Half life	Protein binding	Volumen of distribution	Side effects
Dipyridamole	Oral	Combined with other anticoagulant drugs, such as warfarin, to prevent thrombosis in patients with valvular or vascular disorders. Dipyridamole is also used in myocardial perfusion imaging, as an antiplatelet agent, and in combination with aspirin for stroke prophylaxis.	70%	Hepatic	40 minutes	99%	1 to 2.5 L/kg	Hypotension, if it occurs, is likely to be of short duration, but a vasopressor drug may be used if necessary.
Eptifibatide	Solution intravenous	Unstable angina and non-ST-segment-elevation myocardial infarction. Acute ischemic Complications of PCI	Antiplatelet effects persist for about 4 hours after stopping a continuous infusion.	The drug appears to undergo rapid and nonmetabolic degradation in the urinary bladder after its elimination from plasma	2.5-2.8 hours	25% bound to plasma proteins	185-260 mL/kg	Bleeding, decrease in platelet count or thrombocytopenia, hypotension.
Prasugrel		Acute coronary syndromes planned for percutaneous coronary intervention (PCI).		Prasugrel is a prodrug and is rapidly metabolized to a pharmacologically active metabolite and inactive metabolites.	The active metabolite has an elimination half-life of about 7 hours (range 2-15 hours).			
Ticlopidine	Oral	To reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke.	Greater than 80%. Food increases absorption.	Metabolized extensively by the liver; only trace amounts of intact drug are detected in the urine. At least 20 metabolites have been identified. It has been proposed that 1 or more active metabolites may account for ticlopidine's activity, because ticlopidine itself is an extremely weak platelet aggregation inhibitor in vitro at the concentrations achieved in vivo.	Half-life following a single 250-mg dose is approximately 7.9 hours in subjects 20 to 43 years of age and 12.6 hours in subjects 65 to 76 years of age. With repeated dosing (250 mg twice a day), half-life is about 4 days in subjects 20 to 43 years of age and about 5 days in subjects 65 to 76 years of age.	Reversibly (98%) to plasma proteins, mainly to serum albumin and lipoproteins.		GI hemorrhage, convulsions, hypothermia, dyspnea, loss of equilibrium and abnormal gait.

Agent	Route of administration	Clinical use	Absorbtion	Biotransformation	Half life	Protein binding	Volumen of distribution	Side effects
Tirofiban	Solution intravenous	For treatment, in combination with heparin, of acute coronary syndrome, including patients who are to be managed medically and those undergoing PTCA or atherectomy.	After stopping an infusion, the antiplatelet effect persists for about 4 to 8 hours.	Metabolism appears to be limited	2 hours	65%	22 to 42 L	Bleeding, decrease in platelet count or thrombocytopenia occurs occasionally, bradycardia, edema/swelling or vasovagal reactions, pelvic pain, leg pain and dizziness.
Treprostinil	Solution intravenous	For use as a continuous subcutaneous infusion or intravenous infusion (for those not able to tolerate a subcutaneous infusion) for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise.	Relatively rapid and complete after subcutaneous infusion. Absolute bioavailability approximately 100%.	Substantially metabolized by the liver, but the precise enzymes responsible are unknown.	Terminal elimination half-life is approximately 2 to 4 hours. Plasma half-life is 34 and 85 minutes for intravenous and subcutaneous infusion of the drug, respectively.	Approximately 91% in in vitro concentrations ranging from 330 to 10,000 μ/L.	14 L/70 kg	Flushing, headache, hypotension, nausea, vomiting, and diarrhea.
Ticagrelor	Oral	To reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ASC) unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction	tmax of 1.5 h	CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite.	The mean t½ is approximately 7 hours for ticagrelor and 9 hours for the active metabolite		88 L	Bleeding

Antiplatelet drugs approved for use in Serbia compared with some other countries

In our country 8 medicines (two in combination with aspirin) according to their International Nonproprietary Names (INNs) are approved for use (Table 3).

Table 3 shows that the number of antiplatelet drugs approved for the use in our country is less compared with the rest of the world [20], USA (7, 21) and Great Britain [10, 22] (being 11 and nine: eight, amounted to 78% in relation to world-wide and USA). This lag in the first place relates to abciximab and tirofiban, two important antiplatelet drugs used intravenously blocking GP IIb/IIIa receptor. They decrease the incidence of thrombotic complications associated with acute coronary syndromes. Therefore, they might be considered as the useful supplements to the existing antiplatelet drugs in our country.

***Table 3**: Antiplatelet drugs registered for the use world-wide [20], USA [7,21], Great Britain [10,22] and in Serbia [13]*

Agent	USA	Great Britain	Serbia	MD[1]
Abciximab	+	+	-	+
Aspirin	+	+	+	+
Aspirin, dipyridamole	+	+	+	+
Clopidrogel	+	+	+	+
Clopidogrel, aspirin Dipyridamole	- +	- +	+ -	- +
Eptifibatide	+	+	+	+
Prasugrel	+	+	-	+
Ticlopidine	+	-	+	+
Ticagrelor	++	+	+	+
Tirofiban	+	+	-	+
Treprostinil	+	-	+	+
Total	11	9	8	11

1 Sweetman, Martindale [20]

Sažetak

Trombociti imaju dvostruku ulogu u našem organizmu: fiziološku (korisnu) i patološku (štetnu). Fiziološka se ispoljava u sprečavanju krvarenja iz oštećenog zida krvnog suda, dok se patološka ogleda u njihovom učešću u formiranju tromba koji često predstavlja uzrok teških kardiovaskularnih i cerebrovaskularnih događaja. Aktivacija trombocita inicirana je udruživanjem G proteina i drugih receptora na površini membrane trombocita. Ovaj proces završava se dodatnim nagomilavanjem trombocita u rastući tromb, koji izaziva vaskularnu opstrukciju. Iz tog razloga, radilo se na iznalaženju moćnih antiagregacionih lekova, koji se danas nalaze u grupi najčešće propisivanih lekova. Oni se koriste u primarnoj i sekundarnoj prevenciji kardiovaskularnih i cerebrovaskularnih događaja, i na taj način sprečavaju moguće komplikacije. Upotrebljavaju se oralno (dugotrajna upotreba) ili intravenozno (kratkotrajna akutna upotreba), i u oba slučaja su klinički veoma efikasni. U primarnoj prevenciji se najčešće koriste kao monokomponentni, ali u sekundarnoj češće kao dvokomponentni preparati (npr. aspirin plus dipiridamol i aspirin plus klopidogrel). Od 11 antitrombocitnih lekova koji se nalaze na tržištu širom sveta, osam (78%) je dostupno u našoj zemlji. Da bi se postigla savremenost asortimana u našoj zemlji, postojećim antitrombocitnim lekovima treba dodati još i parenteralne preparate abciksimaba i tirofibana.

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