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Off-target effects of glycoprotein IIb/IIIa receptor inhibitors

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Abstract

Soon after identification of the platelet membrane glycoprotein (GP) IIb/IIIa, it has become a target of antiplatelet therapy. There are 3 intravenous GP IIb/IIIa receptor inhibitors, namely — eptifibatide, tirofiban and abciximab, used in the contemporary clinical practice, particularly in patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI). The aim of the current review is to summarize available knowledge concerning off-target effects of GP IIb/IIIa receptor inhibitors. All 3 drugs have similar antithrombotic properties, but differ with respect to pharmacodynamics, pharmacokinetics and off-target effects. Eptifibatide and tirofiban are highly specific GP IIb/IIIa receptor inhibitors, while abciximab is unselective and cross-reacts with integrin αvβ3 — a vitronectin receptor and leukocyte-associated integrin Mac-1. As a result of these interactions, abciximab seems to reduce the development of clinical restenosis, decrease infarct size, inhibit adhesion of monocytes to medical steel and modulate the inflammatory response. Intracoronary administration of abciximab provides higher drug concentration in the target area, increasing dose-dependent interactions with other integrins. Off-target effects of small molecule GP IIb/IIIa receptor inhibitors (i.e. eptifibatide and tirofiban) are predominantly connected with their suppressive influence on the inflammatory response. All in all, although GP IIb/IIIa receptor inhibitors are not recommended as a routine therapy during PCI, their antiplatelet properties and potential off-target effects may be beneficial in certain subsets of patients. (Cardiol J 2014; 21, 5: 458–464)

Key words: abciximab, eptifibatide, tirofiban, GP IIb/IIIa receptor inhibitor, off-target effects, pleiotropic effects

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Introduction

The identification of the platelet membrane glycoprotein (GP) IIb/IIIa receptor was a milestone in the understanding of thrombus formation. Because of its key role in platelet aggregation, it has quickly become a target of antiplatelet therapy. In 1994, results of the EPIC trial demonstrated the efficacy of GP IIb/IIIa receptor blockade in reducing thrombotic complications in patients undergoing high risk percutaneous coronary interventions (PCIs) [1]. Within the next 5 years 3 intravenous GP IIb/IIIa receptor inhibitors (GPIs) were approved for clinical practice, particularly in patients treated with PCI due to acute coronary syndrome (ACS) [2–6]. These three drugs possess similar antiplatelet properties, but differ with respect to pharmacodynamics, pharmacokinetics and off-target effects (Table 1). According to the recent European guidelines on ST-segment elevation myocardial infarction, GPIs should be considered for bailout therapy if there is an angiographic evidence of massive thrombus, in case of slow flow or no-reflow or if a thrombotic complication occurs (class of recommendation IIa, level of evidence C) [6].

The aim of the current review is to summarize available knowledge concerning off-target effects of GPI.

A search covering the period from January 1993 to November 2013 was conducted by two independent investigators using MEDLINE, CENTRAL and Google Scholar databases. Proceedings from the Scientific Sessions of the American College of Cardiology (http://www.acc.org), American Heart Association (http://www.heart.org), the European Society of Cardiology (http://www.escardio.org), Transcatheter Cardiovascular Therapeutics (http://www.tctmd.com), and EuroPCR (http://www.europcr.com) were also considered. The following keywords were applied: "abciximab", "eptifibatide", "tirofiban", "GP IIb/IIIa receptor inhibitor", "off--target effects". References of studies retrieved were searched manually for additional studies and reviews. No language restrictions were applied.

Structure and role of the GP IIb/IIIa receptor

It is well known that platelet aggregation and thrombus formation play a pivotal role in ACS [7–9]. The rupture of atherosclerotic plaque initiates platelet adhesion, which is followed by platelet activation, including conformational changes in platelet structure, such as activation of the GP IIb/ /IIIa receptors, and finally stimulation of platelet aggregation. The GP IIb/IIIa receptor belongs to the integrin family of adhesion molecules, composed of α and β subunits (Fig. 1) [10]. After platelet activation, the GP IIb/IIIa receptor develops a high affinity for fibrinogen. The fibrinogen molecule has binding sites at both ends, allowing bridging between neighboring platelets, thus leading to thrombus formation [11]. GPI prevents the binding of fibrinogen to the adjacent GP IIb/IIIa receptors [12]. By this mechanism, the final common pathway of platelet aggregation is blocked. There are 3 intravenous GPIs that are used in everyday practice, namely abciximab (large molecule), and 2 small molecule agents — eptifibatide and tirofiban.

Abciximab

Abciximab is a part-murine, part-human chimeric Fab fragment of the monoclonal 7E3 IgG3

Table 1. Characteristics of intravenous glycoprotein IIb/IIIa inhibitors.

	Abciximab	Eptifibatide	Tirofiban
Type	Monoclonal antibody fragment	Cyclic heptapeptide	Non-peptide tyrosine derivative
Inhibition	Noncompetitive	Competitive	Competitive
Platelet affinity	High	Low	Intermediate
Standard dosage:			
Bolus	0.25 mg/kg	180 μg/kg	–
Infusion	0.125 μg/kg/min	2 μg/kg/min	0.4 μg/kg/min over 30 min, next 0.1 μg/kg/min
Plasma half-life	< 10 min	2.5 h	1.5 h
Selectivity	Non-selective	Selective	Selective
Route of elimination	Spleen	Renal	Renal and biliary
Recovery of platelet function	24–48 h	4 h	4 h
Reversibility with platelets infusion	Yes	No	No

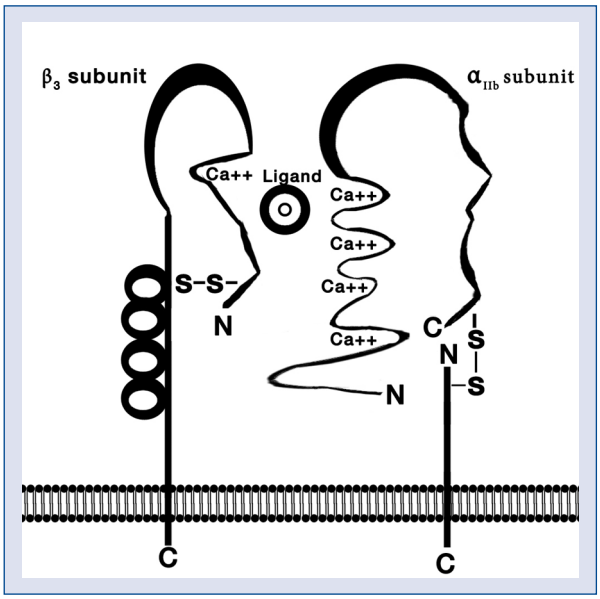

Figure 1. Glycoprotein IIb/IIIa receptor.

antibody against the GP IIb/IIIa receptor. Its structure is based on a murine monoclonal antibody, first described by Coller at al. [13, 14]. Abciximab is a competitive, reversible GP IIb/IIIa receptor inhibitor, which binds to platelets with very high affinity. It is characterized by a short plasma half-life due to its rapid binding to the platelet receptor. The binding site of abciximab is located on the β3 chain of the GP IIb/IIIa receptor [15]. High local concentration of abciximab obtainable with intracoronary administration results in dissolution of existing platelet-rich thrombi and extensive dispersion of platelet aggregates, thus reducing distal microembolization [16–18]. The inhibition of platelet-induced thrombin generation observed with high concentration of abciximab is associated with a decreased release of platelet granules containing inhibitors of fibrinolysis such as plasminogen activator inhibitor-1 and α2-anti-plasmin [19]. The increased porosity of thrombus caused by c7E3 Fab allows penetration of endogenous fibrinolytic agents into the clot, thereby promoting spontaneous thrombolysis [18].

In contrast to small-molecule GPIs, abciximab is a non-selective GP IIb/IIIa receptor antagonist. Since the β3 subunit is also present in integrin αvβ3, abciximab also binds to this cellular vitronectin receptor expressed on endothelial and smooth muscle cells, monocytes, polymorphonuclear leukocytes, and T lymphocytes [19–21]. Abciximab also cross-reacts with the leukocyte-associated integrin Mac-1 (αMβ2). Intracoronary administration producing high local concentration of abciximab may also enhance the non-GP IIb/IIIa properties of this agent that are mainly based on complex anti-inflammatory interactions, with off-target effects of abciximab being their consequence.

The endothelial integrin αvβ3 can bind to several molecules such as fibrinogen, vitronectin, thrombospondin and prothrombin. It also causes endothelial adhesion of activated platelets and entrapment of leukocytes in the platelet-fibrin mesh. It is upregulated in case of ischemia, predominantly in small arterioles. As an antagonist of integrin αvβ3, abciximab may influence restenosis, a process of vessel re-narrowing after initially successful PCI. Detailed αvβ3-mediated effects of abciximab, potentially preventing restenosis, include inhibition of smooth muscle cell (SMC) migration and proliferation, thrombin generation and clot retraction. SMC migration and proliferation initiate the process of restenosis [22]. In a study by Baron et al. [23], abciximab inhibited adhesion and migration of human SMC, while Stouffer et al. [24] described hindering influence of abciximab on SMC proliferation in a baboon model. Furthermore, an in vitro study showed abciximab to be a potent inhibitor of human coronary artery SMC migration and invasion [25]. Therefore, αvβ3-mediated effects of abciximab on the development of restenosis may explain the lower incidence of need for long-term recurrent coronary interventions in the EPIC trial [1]. In addition, the EPISTENT and ISAR-SWEET trials suggested a reduction in clinical restenosis in favor of abciximab in diabetic patients [26, 27]. Similar results were observed in a large Danish single-center registry [28]. In a meta-analysis by Wu et al. [29], a decreased 1-year target lesion revascularization risk was the only benefit from abciximab therapy. However, these promising long-term results were not confirmed in the ERASER, EPILOG and CAPTURE trials [2, 3, 30]. Moreover, the beneficial effects on restenosis from abciximab therapy present in diabetic patients receiving coronary bare metal stents were absent in diabetic patients undergoing elective drug-eluting stents implantation [31]. In the STRATEGY trial, the conjunction of tirofiban plus sirolimus-eluting stent was confronted with abciximab plus bare metal stent. The significantly lower occurrence of restenosis and the need for target vessel revascularization observed with tirofiban plus sirolimus-eluting stent [32] suggest that reduction in clinical restenosis is less pronounced in patients treated with abciximab than in those receiving drug-eluting stents. The addition of tirofiban to sirolimus-eluting stent seemed to have no influence on restenosis.

This was further confirmed in the ADVANCE trial, where the administration of high-dose bolus of tirofiban had no significant effect on target vessel revascularization [33].

Referring to an accumulating body of evidence on the influence of abciximab on restenosis, Kim et al. [34, 35] took another step ahead and tested abciximab-coated stents in the setting of stable coronary artery disease, as well as in acute myocardial infarction (AMI), proving abciximab-coated stents to be safe and effective in the prevention of coronary restenosis. Unfortunately, in a 2-year follow-up, abciximab-coated stents did not show superiority over bare metal stents [36]. Hong et al. [37] compared the anti-inflammatory effects of abciximab-coated stents, sirolimus-eluting stents, and paclitaxel-eluting stents in an animal coronary restenosis model. The results were comparable with respect to inhibition of inflammatory cell infiltration and neointimal hyperplasia in abciximab--coated stents and other drug-eluting stents.

Sakuma et al. [38] compared the effect of the combined blockade of the GP IIb/IIIa receptor and integrin $\alpha v\beta 3$ with the blockade of GP IIb/IIIa receptor alone, using a highly specific inhibitor — tirofiban, relating the results to a control group receiving saline. They found that out of these 3, simultaneous inhibition of GP IIb/IIIa and integrin $\alpha v\beta 3$ cause a marked reduction in infarct size, in a model of acute coronary thrombosis and primary PCI, which is associated with reduced myocardial microthrombi and inflammation, as well as improved myocardial blood flow and regional function [38]. Abciximab was not used in the study, but as far as we know, abciximab inhibits both — the GP IIb/IIIa receptor and integrin $\alpha v\beta 3$, so we may assume that the effect would be similar.

The leukocyte $\beta 2$ integrin Mac-1 is a pivotal adhesion molecule, involved in the interaction of neutrophils and monocytes with the microvasculature, limiting reperfusion in AMI [39–42]. In a study by Neumann et al. [43], increased platelet--leukocyte interaction in patients with AMI was observed. Importantly, the authors demonstrated that binding of activated platelets induces the release of interleukin-1β, interleukin-8, and monocyte chemoattractant protein-1 in leukocytes. The study findings suggest that leukocyte-platelet adhesion contributes to the regulation of inflammatory responses in AMI. In another research, Neumann et al. [44] demonstrated that abciximab reduces Mac-1 surface expression and platelet--leukocyte interaction, by decreasing the platelet mass in platelet-monocyte aggregates.

According to Schuler et al. [45], the monocyte integrin receptor Mac-1 is a central mediator of monocyte adhesion to medical steel, for example metal stents. Since cell adhesion could be blocked by anti-Mac-1-antibodies, the cross-reacting anti-GP IIb/IIIa antibody fragment — abciximab — may potentially inhibit monocyte adhesion to stents.

Schwarz et al. [46] found that abciximab not only binds to the leukocyte integrin Mac-1, but also inhibits binding of several distinct ligands and thereby may modulate inflammation, cell proliferation, and coagulation. The binding of fibrinogen, the inactivated complement factor 3b and the coagulation factor X to Mac-1 was inhibited by abciximab in vitro. As a functional consequence, the conversion of factor X to factor Xa mediated by Mac-1 was impaired by abciximab. The adhesion of monocytic cell line to immobilized intercellular adhesion molecule 1 and to fibrinogen, ligands abundant in the injured vessel wall, was reduced significantly by abciximab [47]. Fibrinogen-mediated cell aggregation was also impaired. Overall, the inhibition of Mac-1 can provide additional clinical benefits of abciximab beyond the well-described blockade of GP IIb/IIIa.

Inflammation plays an important role in the progression of atherosclerosis [48]. Systemic markers of inflammation are increased in patients with ACS and usually rise within 24 h to 48 h after PCI [49, 50]. Cross-reactions of abciximab with integrins $\alpha v\beta 3$ and Mac-1 are assumed to decrease the endothelial inflammatory reaction. In their study, Lincoff et al. [51] measured the concentration of C-reactive protein (CRP), interleukin-6 and tumor necrosis factor α before and 24–48 h after PCI. They observed, that in patients receiving periprocedural abciximab, the magnitude of rise of the measured inflammatory markers was diminished, compared with patients receiving placebo [51].

Recently the topic of intracoronary use of abciximab has been extensively discussed in the literature [52–56]. This administration route seems to provide a much higher concentration of abciximab in the target area and possibly allow direct influence not only on the platelet GP IIb/IIIa receptor, but also on vitronectin and Mac-1 receptors, enhancing dose-dependent off-target effects of abciximab. Two independent small randomized trials showed intracoronary administration of abciximab to be associated with improved myocardial perfusion and smaller infarct size [57, 58].

A bolus of abciximab is usually administered through the guiding catheter into the infarct--related artery. This method does not assure an

optimal effect of abciximab, with the rapid wash out by the coronary flow. Prati et al. [59] tested the effectiveness of local abciximab delivery to the site of IC thrombus vs. IC bolus infusion in patients with ACS undergoing PCI. For local IC delivery of abciximab a dedicated perfusion catheter was applied. This catheter enables local drug delivery to reach approximately a 500-fold higher drug concentration vs. systemic delivery. Significantly lower rates of procedure-related AMI and major adverse cardiac events at 1 year were observed in the local intracoronary infusion group. These results strongly suggest that the use of the dedicated perfusion catheter leads to higher concentrations of abciximab within the thrombus, allowing for an additional antiplatelet, antithrombotic, and anti--inflammatory effect [59].

Further efforts should be undertaken to define the benefits of super-selective local delivery of abciximab.

Small molecular weight GPIs: Eptifibatide and tirofiban

Eptifibatide is a cyclic heptapeptide modeled on the structure of barbourin — a disintegrin that contains a KGD aminoacid sequence, which provides this molecule with high specificity for binding to the GP IIb/IIIa receptor. Eptifibatide acts specifically on the αIIb chain of the GP IIb/ /IIIa receptor, which is a RGD binding site. It is a selective molecule for the GP IIb/IIIa receptor with very rapid association and dissociation kinetics concerning this receptor, while it shows no reactivity with other integrins. Eptifibatide is eliminated by the kidneys, with the most of it excreted as the unchanged drug in the urine.

Tirofiban is a non-peptide tyrosine derivative. Like eptifibatide, it is an antagonist against the RGD binding site on the αIIb chain of the GP IIb/ /IIIa receptor [60]. It is also highly specific for the GP IIb/IIIa receptor and does not interact with other integrins. Tirofiban's affinity for the GP IIb/ /IIIa receptor is intermediate between abciximab and epitfibatide. It has also very rapid association and dissociation with the GP IIb/IIIa receptor. Tirofiban is removed by both renal and biliary excretion.

Both tirofiban and eptifibatide may exert anti-inflammatory effects. In a study by Azar et al. [61], in high risk patients undergoing PCI, tirofiban significantly suppressed the rise of high sensitivity CRP. In a paper by Walters et al. [62], the combination of high dose tirofiban with enoxaparin resulted in an attenuated inflammatory response compared with the combination of high dose tirofiban with unfractionated heparin. Ercan et al. [63] explain the anti-inflammatory effect of tirofiban with platelet inhibition, since products of activated platelets may aid neutrophil accumulation and enhance inflammation. Activated leukocytes and platelets mutually potentiate each others' effects. Tirofiban strongly inhibits the platelet aggregation. The decreased platelet aggregation can suppress the inflammatory proteins, chemokines, and the expression of adhesion molecules. In their study, CRP elevation was attenuated in patients with non-ST segment elevation myocardial infarction (NSTEMI) treated with tirofiban infusion. Ueland et al. [64] confirmed the potential of eptifibatide as anti-inflammatory drug able to down-regulate platelet-mediated inflammation. On the other hand, Mazaev et al. [65] failed to find any anti-inflammatory effects of eptifibatide in patients with unstable angina and NSTEMI.

Summary

All the 3 agents discussed are effective inhibitors of the GP IIb/IIIa receptor. However, the exact binding site of each agent is different, causing potentially different functional responses in platelets. In addition, these agents have different specificities for other integrins. Tirofiban and eptifibatide have been designed to inhibit the platelet GP IIb/IIIa receptor without cross-reacting with other integrins. In contrast, abciximab is non-specific, because it also blocks integrin $\alpha v\beta 3$ and leukocyte-associated integrin Mac-1. As a result of these interactions, some of the clinical effects of abciximab, such as anti-inflammatory effects, reduction of clinical restenosis and infarct size, go beyond the consequences of its plain binding to the GP IIb/IIIa receptor. All in all, although GPIs are not recommended as a routine therapy during PCI, their antiplatelet properties and potential off-target effects may be beneficial in certain subsets of patients.

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