

Advances in Peripheral Arterial Combination Thrombolytic Therapy with Platelet Antagonists

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Introduction

Platelet adhesion, activation, and aggregation (1-4)

Circulating platelets are inactive. When arterial injury occurs, either spontaneously or as result of a percutaneous intervention, sub-endothelial adhesive glycoproteins are exposed at the luminal surface. These glycoproteins (which include collagen, fibrinogen, vWF, fibronectin, and vitronectin) bind with high affinity to surface receptors on platelets within the boundary layer of the bloodstream. This results in the *adhesion* of a monolayer of platelets onto the injured surface. A hemostatic or occlusive thrombus forms when this layer of platelets is *activated* and platelet aggregation is initiated. Adhesion alone, as well as the local secretion or release of pro-aggregatory agents, lead to the expression of platelet receptor sites that play a key role in platelet *aggregation*. The more important of these agonists are adenosine diphosphate (ADP), epinephrine, and thrombin. ADP is contained in intracellular granules that are released when the platelets are activated. ADP, like the other agonists, binds to specific receptors on circulating platelets and induces intracellular pathways, such as the release of arachidonic acid (AA) and formation of thromboxane A₂ (TxA₂), that activate the GP IIb/IIIa receptor. The GP IIb/IIIa receptors, which are specific to platelets, represent the final common pathway for aggregation that occurs when these receptors bind to fibrinogen and cross-link adjacent platelets. There are approximately 80,000 GP IIb/IIIa receptors per platelet. These

receptors recognize the Arg-Gly-Asp (RGD) amino acid sequence, which is the adhesive motif of circulating fibrinogen and other adhesive proteins.

Mechanisms of action of available antiplatelet agents

Oral agent (2,4-6)

Aspirin (Acetylsalicylic acid, ASA) irreversibly acylates cyclooxygenase and blocks the metabolism of arachidonic acid into TxA₂, a proaggregant vasoconstrictor. Since platelets are unable to regenerate cyclooxygenase, this effect lasts for their lifetime of 7-10 days. ASA also inhibits the formation of endothelial prostacyclin, an antiaggregant vasodilator. However, this effect can only be sustained at high doses, since endothelial cells are able to regenerate cyclooxygenase. The mechanism of action of persantine (Dipyridamole) is less well understood and may be related to several of the above factors. Both drugs prolong bleeding time, and may cause gastrointestinal problems. For peripheral interventions, ASA (80 or 325 mg PO QD) is usually started at least a day prior to the procedure and continued indefinitely, since most of these patients are at risk for other cardiovascular events.

Plavix® (Clopidogrel) (5) and Ticlid® (Ticlopidine HCl) (6) are chemically related oral antiplatelet agents. Both are thienopyridine derivatives that inhibit the binding of ADP to its platelet receptor, thereby blocking the ADP-mediated activation of the GP IIb/IIIa complex. Both drugs irreversibly modify the platelet ADP receptor for the lifetime of the platelet. Repeated dosing (Plavix 75 mg QD or Ticlid 250mg BID) inhibits platelet aggregation on the first day, reaching a steady state effect in 3-7 days. Plavix is about six times more potent than Ticlid in inhibiting human platelet aggregation.

When Plavix is discontinued, platelet aggregation and bleeding time return to baseline values within about 5 days. Plavix should be discontinued about 7 days prior to elective surgery, but platelet

transfusions are useful when more rapid recovery of platelet function is desired. On the other hand, it is generally advised that Ticlid be discontinued 10-14 days prior to elective surgery, although when necessary prolonged bleeding time can be normalized within 2 hours by the intravenous administration of 20mg of methylprednisolone. Platelet transfusions may also be useful.

Plavix has a lower incidence of GI hemorrhage than ASA, and unlike Ticlid, it is not associated with neutropenia or thrombocytopenia. No dosage adjustment of Plavix is required for renal impairment, but caution is advised in the setting of severe hepatic dysfunction and bleeding diatheses. Clopidogrel was shown to provide a greater benefit than aspirin in preventing both fatal and non-fatal cardiovascular events in high-risk patients (CAPRIE) (7).

Ticlid is associated with neutropenia, reported in 2.4% of patients, and noted to occur within 3 months of initiation of treatment. Also, about 1 in 2000-4000 patients exposed to Ticlid develop thrombotic thrombocytopenic purpura (TTP). Therefore, both white blood cell and platelet counts should be monitored every two weeks for the first three months of therapy, and corrective actions taken as necessary. Ticlid is not recommended for patients with severe hepatic dysfunction and doses must be adjusted for renal impairment. Ticlid may potentiate the effects of ASA and so co-administration is generally not recommended. However, such combination antiplatelet therapy has been reported to be superior to long-term oral anticoagulation therapy in terms of clinical outcomes following coronary stenting (8). Nevertheless, in light of the aforementioned complexities with Ticlid, this drug should be reserved for patients who have either failed ASA therapy, or are intolerant or allergic to it.

Intravenous Agents (2-4,9-13)

Currently, three intravenous agents are approved by the FDA: abciximab (ReoPro®), eptifibatide (Integrilin®), and tirofiban hydrochloride (Aggrastat®). All three are direct GP IIb/IIIa receptor antagonists that prevent fibrinogen-mediated platelet aggregation.

Aciximab is the Fab fragment of the chimeric human-murine monoclonal antibody 7E3 that binds to the GP IIb/IIIa receptor. Abciximab binds with similar affinity to the vitronectin receptor ($\alpha_v\beta_3$). Integrilin is a synthetic heptapeptide that reversibly blocks the GP IIb/IIIa receptor. Aggrastat is a reversible nonpeptide blocker of the GP IIb/IIIa receptor. All three drugs are approved as adjunctive therapy for the prevention of cardiac ischemic events during percutaneous coronary interventions (PCI), with concomitant PO ASA and IV heparin administration. The latter two agents have shorter biological half-lives than abciximab. Since excess bleeding is a concern with all of these agents manufacturer guidelines and contraindications, which are similar to those for thrombolytic agents, should be followed.

The recommended dose for ReoPro is a bolus of 0.25 mg/kg given within an hour prior to PCI, followed by an infusion of 0.125 $\mu\text{g}/\text{kg}/\text{hr}$ (for a maximum of 10 $\mu\text{g}/\text{min}$) for 12 hours. This has been the dose used for peripheral interventions as well (12). Low dose heparin and PO ASA are recommended. Following this bolus and infusion dose, abciximab blocks 80% of the GP IIb/IIIa receptors. Upon discontinuation, platelet function gradually returns over about 48 hours. Although plasma levels fall rapidly upon termination of infusion, abciximab remains platelet-bound in the circulation for about 15 days. When used with low dose heparin, there is less than a 1% incidence of severe thrombocytopenia, which generally occurs within the first 24 hours of treatment. Thus, monitoring should include platelet counts at baseline, 2-4 hours after initiation, and at 24 hours. If there is a need to restore platelet function, abciximab should be discontinued, and platelets may be transfused. With transfusion, abciximab restores platelet function partially by redistributing itself over the entire population of platelets, leading to a lower level of receptor blockade. Generally, prior to the initiation of the agent, baseline ACT, PT, and aPTT levels are also recommended. Early sheath removal is encouraged, but an aPTT \leq 50 seconds and an ACT \leq 175 seconds must be first achieved. Although, neither excess anaphylactic nor hypersensitivity reactions have been reported with

primary administration or re-administration of this agent, the potential for this does exist.

The dosing of Integrilin has been modified (ESPRIT) from the original coronary trials to include an initial double-bolus (180mcg/kg x 2 - 10 minutes apart) followed by a continuous infusion (2mcg/kg/min) for 24 hours (13). A similar dose regimen will be used for the planned ULTIMATE trial. Doses must be adjusted for severely compromised renal function. Low dose heparin and PO ASA are recommended. Upon dosing, inhibition of platelet aggregation (> 80%) is rapid and bleeding time increases 2- to 4- fold, but platelet function and bleeding time return to normal within 4 - 8 hours of termination.

Aggrastat is given for PCI at an initial rate of 0.4 µg/kg/min over 30 minutes, followed by a continuous infusion of 0.1 µg/kg/min for 12-24 hours. This dose must be adjusted for severe renal insufficiency. Greater than 90% inhibition of platelet aggregation is attained within 30 minutes of dosing, and this is promptly reversed by stopping the infusion. For PCI, concomitant heparin is recommended because of the risk of excessive mortality with Aggrastat alone. For peripheral interventions, low dose heparin is probably appropriate.

The GP IIb/IIIa Inhibitor Coronary Trials

The EPIC trial (**E**valuation of 7E3 in **P**reventing **I**schemic **C**omplications) was the first large-scale study to establish the clinical efficacy of a GPIIb/IIIa inhibitor, in this case abciximab, as adjunctive therapy for reducing complications among high-risk patients undergoing coronary PTA or directional atherectomy (14). At 30-day follow-up, the patients who received abciximab (bolus + infusion) had a 35% relative reduction compared with placebo in the primary composite clinical endpoints (death, MI, and urgent revascularization). This relative reduction remained significant at 23% at 6-month follow-up, and it had a durable impact at three-year follow-up (13% reduction rate). Unfortunately, the abciximab group had an incidence of major bleeding events of 14%, double that of the

placebo group. The EPILOG trial (**E**valuation in **P**TCA to **I**mprove **L**ong-term **O**utcome with **A**bciximab **G**PIIb/IIIa blockade) extended the benefits of adjunct abciximab therapy to all patients undergoing PCI, while minimizing the risk of bleeding by employing low-dose heparin and early sheath removal, together with the elimination of post-procedural heparin(15). The CAPTURE (**c**7E3 Fab **A**ntiplatelet **T**herapy in **U**nstable **R**efractory Angina) showed that pretreatment with abciximab (for 24 hours) in patients with medically refractory unstable angina scheduled to undergo PCI reduces the risk of ischemic complications, possibly as a result of plaque passivation (16). The combined data of these three trials revealed no increased risk for stroke with abciximab therapy (11).

For the purposes of this brief discussion, the clinical efficacy of Integrilin (eptifibatide) in similar coronary artery disease settings was established by the IMPACT-II (**I**ntegrilin to **M**inimize **P**latelet **A**ggregation and **C**oronary **T**hrombosis) (17) and PURSUIT (**P**latelet **G**P IIB/IIIa in **U**nstable Angina: **R**eceptor **S**uppression **U**sing **I**ntegrilin) trials (18). Early sheath removal and low-dose heparin were again found to minimize bleeding complications. More recently, the ESPRIT trial used a modified dosing regimen demonstrating reduced ischemic complications when Eptifibatide is used prior to planned coronary stenting (13). Aggrastat (tirofiban hydrochloride), with concomitant ASA and IV heparin, was found to be useful for similar indications in the RESTORE (**R**andomized **E**fficacy **S**tudy of **T**irofiban for **O**utcomes and **R**estenosis) (19), PRISM (**P**latelet **R**eceptor **I**nhibition in **I**schemic **S**yndrome **M**anagement) (20), and PRISM-PLUS (**P**atients **L**imited to **U**nstable **S**igns and **S**ymptoms) trials (21).

Peripheral Arterial Thrombolytic Therapy

The primary goal of using GP IIB/IIIa inhibitors in PVD would be to prevent rethrombosis during thrombolytic therapy (22,23,24) and to passivate the vessel wall after angioplasty or stenting with view towards preventing acute thrombosis and restenosis. At the time

of this writing there is little documented evidence of such benefit from using these agents in the peripheral arteries. Nevertheless, the combined results of the coronary intervention trials discussed above and some preliminary reports of applications in the peripheral vessels lend some support for extending the use of these drugs for peripheral vascular interventions.

Early anecdotal reports of spontaneous resolution of coronary thrombi with either IV or local IC abciximab infusions were published in abstract form. Platelet disaggregation has been shown to occur in vitro. The observation of spontaneous disruption of acute IC thrombi by abciximab therapy is probably due to the combined effects of platelet disaggregation and endogenous lysis.

The TAMI-8 trial (Thrombolysis and Angioplasty in Acute Myocardial Infarction-8) (25,26) studied a small group of patients to assess the activity and safety of combining rtPA and abciximab (n=60) compared to controls (rtPA only, n=10). Ninety percent of the treated patients had angiographically patent infarct-related arteries, versus only 5 of the 9 controls. Eighty-seven percent of the treated patients were free of recurrent ischemia, and there were no excess bleeding complications due to abciximab. Similarly, the multi-center PARADIGM (**P**latelet **A**ggregation **R**eceptor **A**ntagonist **D**ose **I**nvestigation for **R**eperfusion **G**ain in **M**yocardial **I**nfarction) trial studied various doses of lamifiban in combination with either rtPA or streptokinase for patients with acute onset (<12 hours) MI. Of the patients treated with lamifiban, about seventy five percent (vs 63% control) had angiographically patent infarct-related vessels at 90 minutes. Lamifiban also reduced the time to steady-state reperfusion by 28%. However, 30-day clinical outcomes were not different between the study and control groups, and the incidence of major bleeding was higher in the lamifiban patients (3% vs 1.7%). Another study combined eptifibatide (with ASA and heparin) with rtPA to treat AMI patients (28). The results showed that the incidence and speed of reperfusion was significantly enhanced by such a strategy, but there were no significant differences between the study group and controls with respect to clinical outcomes or severe bleeding. Thus,

the combination of platelet inhibitors with fibrinolytic agents appears to accelerate thrombolysis.

The results of experimental and early clinical studies using combination platelet inhibitor and thrombolytic therapy in peripheral arteries are encouraging. A recent experimental study showed that treatment with reteplase (Retavase™) and abciximab of peripheral arterial thrombi in primates significantly reduces the time to sustained reperfusion of the limb (29). Haas et al reported that the addition of abciximab therapy restored patency in 8 of 8 patients in whom lytic therapy with urokinase alone had failed (30). There were three minor bleeds. Tepe et al. reported a 100% technical success rate during their early clinical experience with combining abciximab and urokinase in fourteen patients peripheral arterial occlusions (< 6 months duration) (12). Treatment times ranged from 50 minutes to 8 hours. There were only two minor early bleeds and one intermediate-term reocclusion (at 8 months; follow-up range 1-15 months). They have recently reported treatment times below 4 hours, high technical success, and 2 major and 2 minor bleeds in a total of 38 patients. Yoon et al reported their preliminary experience with treating a small group (n=7 in each arm) of PAO patients with a combination of eptifibatide, rtPA, and heparin or rtPA and heparin only (31). Although treatment times were dramatically longer than reported by Tepe et al, the time to treatment was nearly double in the control group in comparison with the treated group (40 vs 22 hours). However, more recently, in a larger trial, the same group failed to show a reduction in treatment time, but did show a significant reduction in the rt-PA dose necessary for achieving thrombolysis, without loss of efficacy or safety, when Eptifibatide is used concomitantly (32). Recently, Schweizer et al. (33) reported on their experience with 84 patients who were randomized to two equal groups receiving either IV ASA or abciximab during thrombolytic therapy with rtPA. Interestingly, they used an aggressive short-term thrombolysis protocol in which they combined suction thrombectomy with rapid 5 mg infusions of rtPA until the thrombus was cleared. This was followed by angioplasty as needed. Sub-therapeutic doses of IV heparin were used during

treatment and all patients were anticoagulated for six months. There were no major complications and the few minor complications occurred with equal frequency in both groups. Lysis times were significantly shorter in the abciximab group and a composite clinical outcome at six months significantly favored the use of this agent. Most interestingly, claudication distance was not only significantly higher in the abciximab group, but it also showed a gradual improvement over the six-month period of observation, whereas the ASA group showed some deterioration. Duda et al have recently published the results of the PROMPT study (34). In a randomized comparison of patients with acute lower extremity PAO treated either with urokinase alone or urokinase plus abciximab, they showed that the combination group had faster dissolution of thrombus and a significantly improved amputation-free survival rate at 90 days. These early studies have stimulated enough interest that there are at least two industry sponsored multi-center national trials currently being designed for treatment of PAO with combination therapy (R&R, ULTIMATE).

Many patients who receive GPIIb/IIIa inhibitor therapy during peripheral vascular interventions will need elective, and at times emergent, surgery. Abciximab, for instance, is associated with higher incidence mortality and bleeding following major surgery (e.g., CABG) (9). Thus, the problem of rapid reversal of the antiaggregation effects of these drugs becomes important. Eptifibatide and tirofiban are rapidly reversed when treatment is terminated and platelets are transfused. Abciximab is less easily reversed, but the degree of blockade can be reduced with platelet transfusion. These should be considerations when choosing these agents for specific situations.

Maintaining Patency

The role of oral antiplatelet agents for maintenance of long-term patency is also evolving. There is accumulating evidence that antiplatelet therapy is of early and long-term benefit to patients

undergoing peripheral vascular surgery. The Antiplatelet Trialists' Collaboration concluded that ASA was superior to placebo in preventing peripheral vascular occlusion in PVD patients, whether or not they had had a peripheral artery procedure (35). Antiplatelet therapy prevents reocclusion and avoids future major vascular events in PVD patients. This is also true for patients with AVF or shunts for hemodialysis. A meta-analysis of studies on patients with peripheral revascularization procedures showed that clinical outcomes were improved with ASA or Ticlid antiplatelet therapy (36). For patients with intermittent claudication, Ticlid (250 BID) was shown to reduce the need for vascular reconstructive surgery. In the CAPRIE trial, clopidogrel significantly reduced the risk of ischemic stroke, MI, or vascular death when compared to aspirin.). Nevertheless, based on cost considerations and side effects, ASA continues to be the drug of choice, except when patients are sensitive or intolerant of it.

Conclusions

Newer antiplatelet agents have improved acute and long-term clinical outcomes following coronary artery interventions. From our understanding of platelet biology and the mechanisms of action of these agents, they should benefit peripheral vascular procedures as well. Early evidence is encouraging demonstrating shortening of treatment times and perhaps long-term clinical benefit as well. However, larger and longer-term results are needed for solidly establishing these benefits. Even so, cost-benefit analyses will be the ultimate determinants of whether these agents find widespread application.

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