Clinical Pharmacology of Eptifibatide

David R. Phillips, PhD, and Robert M. Scarborough, PhD

Activation of receptor function of platelet membrane glycoprotein (GP) IIb-IIIa leads to the binding of fibrinogen and is the final common pathway to platelet aggregation. Platelet aggregates provide the structural basis for coronary thrombosis, a major cause of ischemic heart disease. GP IIb-IIIa has a narrow tissue distribution, being found only on platelets and their progenitors, and inhibition of its receptor function has emerged as a promising new therapeutic strategy for management of acute ischemic coronary syndromes and acute ischemic complications of percutaneous coronary interventions. Eptifibatide (INTEGRILIN) is a cyclic heptapeptide inhibitor of GP IIb-IIIa, with an active pharmacophore that is derived from the structure of barbourin, a GP IIb-IIIa inhibitor from the venom of the southeastern pigmy rattlesnake. Like barbourin, eptifibatide is a specific and robust inhibitor of the GP IIb-IIIa receptor function, having a low affinity for other integrins and strongly preventing platelet aggregation. Preclinical pharmacologic studies have established that eptifibatide can inhibit thrombosis effectively, with only modest effects on bleeding time measurements. Pharmacokinetic and pharmacodynamic studies have established that eptifibatide can inhibit thrombosis effectively, with only modest effects on bleeding time measurements. Pharmacokinetic and pharmacodynamic studies in both animal models and humans have shown that the antiplatelet effect of eptifibatide is a rapid onset of action and that the drug has a short plasma half-life. Furthermore, the rapid reversibility of action of eptifibatide, exemplified by an anti-hemostatic effect limited to the period of drug administration, was apparent in both healthy volunteers and patients with ischemic heart disease. In clinical trials, eptifibatide has not been found to be immunogenic or to induce thrombocytopenia. These studies have led to the evaluation of eptifibatide in the pivotal Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT II) trial, which enrolled 4,010 patients undergoing coronary angioplasty. The combination of a bolus plus either of 2 infusion doses of eptifibatide reduced the incidence of ischemic complications without increasing the risk of bleeding or other complications. Recent pharmacodynamic studies have established that more aggressive dosing of eptifibatide provides greater inhibition of ex vivo platelet aggregation and more robust antithrombotic activity. Higher doses of eptifibatide were therefore selected for the Platelet GP IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, which enrolled patients with unstable angina or non-Q-wave myocardial infarction. The available data suggest that eptifibatide may represent a useful clinical alternative to existing antiplatelet therapies. ©1997 by Excerpta Medica, Inc.

Am J Cardiol 1997;80(4A):11B–20B

Platelet aggregation is a pivotal event in coronary artery thrombus formation and a major causative factor in both acute ischemic coronary syndromes (AICS) and acute ischemic complications associated with percutaneous transluminal coronary angioplasty (PTCA).1,2 Important determinants of the onset of AICS include disruption of the atherosclerotic plaque and superimposed formation of a platelet-rich, white thrombus.3 Thrombus formation is triggered by platelet attachment onto subendothelium exposed by plaque rupture and is followed by platelet activation and aggregation.4 The extent of thrombotic occlusion generally determines the clinical presentation of AICS, which can range from unstable angina to acute myocardial infarction to sudden ischemic death. One of the main goals in the management of patients with AICS is the inhibition of the key pathogenic process of thrombus formation, a process mediated primarily by aggregation of platelets.1,2,5–7

Mechanical injury and subsequent formation of platelet-rich, white coronary thrombi result in the clinical manifestation of AICS but are also important contributors to abrupt vessel closure, a major acute complication of PTCA.8,9 Abrupt closure, an occlusion that limits coronary blood flow and results in myocardial ischemia, is the major cause of in-hospital morbidity and mortality related to PTCA, with an incidence ranging from 2–8%.8 Accordingly, one of the goals of adjunct therapy for percutaneous procedures is to prevent early thrombus formation and abrupt closure, which is analogous to the treatment objectives in patients with AICS.8,9

Standard approaches to the prevention of coronary thrombosis include anticoagulation therapy with heparin and antiplatelet therapy with aspirin.10 Whereas these agents are inexpensive and have shown efficacy in advanced clinical trials, recent insights into the pathophysiology of coronary artery thrombus formation point to significant limitations of both drugs. Heparin is an indirect inhibitor of thrombin, but its effect on clot-bound thrombin is significantly weaker than its effect on soluble thrombin.11 Aspirin is an effective inhibitor of the synthesis of prostaglandins, which represents a key step in the production of thromboxane A2, a platelet agonist generated by activated platelets.10 However, thromboxane A2 synthesis is not required for activation and subsequent aggregation of platelets in the presence of potent platelet agonists. In addition, prostaglandin synthesis in endothelial cells is essential for the production of the antiplatelet factor prostaglandin I2 (prostacyclin)12, inhibition of this process also limits the efficacy of aspirin. Furthermore, thrombin and thromboxane A2

From COR Therapeutics, Inc., South San Francisco, California. Address for reprints: David R. Phillips, PhD, COR Therapeutics, Inc., 256 East Grand Avenue, South San Francisco, California 94080.
represent only a fraction of known platelet activators, and platelet activation and aggregation can occur even with optimal heparin and aspirin therapy. Accordingly, neither heparin nor aspirin can be considered strong antiplatelet agents.

Irrespective of the stimulus used to activate the platelets, the final common pathway to platelet aggregation and coronary thrombosis involves the activation of the receptor function of the platelet glycoprotein (GP) IIb-IIIa complex (also known as αIibβ3). The receptor function of GP IIb-IIIa is highly regulated: on unstimulated platelets, GP IIb-IIIa has a low affinity for soluble adhesive proteins, but after platelet activation, GP IIb-IIIa becomes a receptor for fibrinogen and von Willebrand’s factor. Binding of these ligands to individual GP IIb-IIIa molecules on adjacent platelets leads to the formation of platelet aggregates and coronary thrombi. GP IIb-IIIa thus offers a more rational and, until recently, unexplored therapeutic target.

The synthetic cyclic heptapeptide, eptifibatide (INTEGRILIN; COR Therapeutics, South San Francisco, CA/Schering-Plough, Kenilworth, NJ), is one of the most extensively evaluated GP IIb-IIIa inhibitors, and it has already shown excellent efficacy and safety characteristics in the prevention of ischemic complications of angioplasty. The aim of this review is to: (1) illustrate the role of the GP IIb-IIIa complex in platelet aggregation; (2) review the pharmacologic profile of the GP IIb-IIIa inhibitor eptifibatide in terms of its potency, rapid onset and reversibility of action, and lack of immunogenicity; and (3) provide a rationale for the dosing of eptifibatide in the pivotal Integрин to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT II) and Platelet GP IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrin Therapy (PURSUIT) clinical trials.

PLATELET MEMBRANE GP IIb-IIIa COMPLEX

GP IIb-IIIa belongs to a large family of receptors called integrins, which are heterodimeric cell-surface proteins that play important roles in cell adhesions. Unlike most integrins, GP IIb-IIIa has a narrow tissue distribution, being found only on platelets and cells of the megakaryocytic lineage. GP IIb-IIIa is the most abundant protein on the surface of platelets, with some 80,000 copies per platelet, representing 1–2% of total platelet protein.

As depicted in Figure 1, GP IIb-IIIa is composed of 2 subunits, GP IIb (MW 140,000) and GP IIIa (MW 105,000). In the presence of a physiologic plasma concentration of Ca2+ (1 mM), GP IIb-IIIa binds 5 calcium ions; this binding is required to maintain subunit–subunit interactions. GP IIb-IIIa structure, and the capacity to bind adhesive proteins and mediate platelet aggregation.

GP IIb is a typical integrin α subunit and consists of disulfide-linked heavy and light chains, the former being entirely extracellular and the latter composed of cytoplasmic, transmembrane, and extracellular domains. The heavy chain of GP IIb contains 4 of 5 GP IIb-IIIa Ca2+ binding sites. The GP IIIa subunit is a single-chain polypeptide with a short cytoplasmic tail, a transmembrane region, and a large extracellular domain believed to have one Ca2+ binding site. The GP IIb subunit has so far been found only in complexes with GP IIIa, whereas GP IIIa (also known as β3) can also complex with another α subunit, αv, to form the vitronectin receptor (also known as αvβ3). In contrast to GP IIb-IIIa, αvβ3 is widely distributed and is particularly prominent in motile cells, suggesting that the physiologic effect of highly specific GP IIb-IIIa inhibitors is restricted to platelets.

GP IIb-IIIa on unstimulated platelets does not bind adhesive plasma proteins. Activation of platelets converts GP IIb-IIIa into a ligand-receptive form and leads to platelet aggregation and thrombus formation (Figure 2). Genetic and pharmacologic studies indicate that collagen, adenosine diphosphate (ADP), and thrombin have physiologic roles as platelet activators. Numerous additional agents have also been shown to activate platelets ex vivo, and it is possible that some of these may also have physiologic roles. Activated GP IIb-IIIa is a receptor for soluble fibrinogen, von Willebrand’s factor, vitronectin, and fibronectin, but the binding of fibrinogen and von Willebrand’s factor is most critical for platelet aggregation. These polyvalent adhesive proteins cross-link GP IIb-IIIa on the surfaces of activated platelets to cause platelet aggregation. Activation with strong agonists, such as thrombin or collagen, stimulates the transfer of the GP IIb-IIIa found in the α granules of unstimulated platelets to the platelet surface, thereby increasing de novo expression of the receptors on the platelet surface. A fraction of surface-mobilized GP IIb-IIIa may be expressed with prebound fibrinogen. The activation of the fibrinogen receptor function of GP IIb-IIIa after platelet stimulation, possibly through a conformational change, is referred to as “inside out” GP IIb-IIIa signaling. On the other hand, GP IIb-IIIa on unstimulated platelets is capable of binding fibrinogen molecules immobilized on the vessel wall or on platelet aggregates. This interaction also initiates signal transduction pathways, a process designated “outside in” GP IIb-IIIa signaling, which may facilitate the recruitment of unstimulated platelets to the growing thrombus.

The binding of von Willebrand’s factor, vitronectin, and fibronectin to GP IIb-IIIa on activated platelets may be, in part, mediated by the Arg-Gly-Asp (RGD) sequence, 1 copy of which is found within each of these proteins. Although the RGD motif is present in 2 copies of the fibrinogen α chain, recent data indicate the binding of fibrinogen to GP IIb-IIIa is mediated primarily by the Lys-Gln-Ala-Gly-Asp-Val (KQAGDV) sequence found at the carboxyl terminus of the fibrinogen γ chain. Although the RGD motif does not confer specificity for the GP IIb-IIIa integrin (related integrins also bind peptides containing the RGD sequence), peptides containing this sequence inhibit the binding of fibrinogen to GP IIb-IIIa. Moreover, introduction of the RGD se-
sequence into otherwise nonadhesive proteins allows adherence of the modified proteins to platelets. 38

The pivotal importance of GP IIb-IIIa in platelet aggregation and thrombosis is demonstrated by the fact that the platelets of people who lack this receptor or who have a modified form of it do not aggregate in response to physiologic agonists, a syndrome known as Glanzmann’s thrombasthenia. 39 Patients with this syndrome have a lifelong bleeding diathesis that may manifest in several ways, including recurrent mucocutaneous bleeding. Additional documentation for the pivotal role of GP IIb-IIIa in arterial hemostasis comes from the pioneering work of Coller,13 who demonstrated that the anti–GP IIb-IIIa monoclonal antibody

![FIGURE 1. Model for the structure of the glycoprotein (GP) IIb-IIIa complex embedded into the platelet plasma membrane. Putative Ca²⁺ binding sites are indicated; the 2 depicted by the shaded lines are also implicated in ligand binding. Bound Ca²⁺ regulates GP IIb-IIIa function.](image1)

![FIGURE 2. Schematic illustration of the pivotal role of glycoprotein (GP) IIb-IIIa in platelet aggregation. On unstimulated, discoid platelets, GP IIb-IIIa is unable to bind soluble fibrinogen. When platelets are activated by agents such as collagen, thrombin, or adenosine diphosphate (ADP), they change shape, and the GP IIb-IIIa complex is activated to become a receptor for soluble fibrinogen and von Willebrand’s factor (vWF). Fibrinogen mediates platelet aggregation by bridging the GP IIb-IIIa molecules on the surfaces of adjacent, activated platelets.](image2)
7E3 prevents platelet aggregation and reduces arterial thrombosis in animal models. The realization that GP IIb-IIIa plays a pivotal role in platelet aggregation and coronary thrombosis was the impetus behind the development of GP IIb-IIIa inhibitors as a novel, potent, and more rational therapeutic strategy for management of ischemic heart disease.

DEVELOPMENT OF GP IIb-IIIa INHIBITORS

The first GP IIb-IIIa inhibitor to be developed and extensively evaluated clinically is abciximab (ReoPro, Centocor, Malvern, PA/Eli Lilly, Indianapolis, IN), a human-murine chimeric monoclonal antibody fragment derived from the murine monoclonal antibody 7E3. Abciximab is an effective blocker of GP IIb-IIIa receptor function and has demonstrated antithrombotic efficacy in advanced clinical trials.

The pharmacologic profile of abciximab is reflective of its high affinity for GP IIb-IIIa, its cross-reactivity with other integrins, and its antibody structure. The high-affinity binding of abciximab and its slow dissociation from GP IIb-IIIa cause its effects to persist long after infusion of the antibody is discontinued.

The cross-reactivity of abciximab is evident from its binding not only to GP IIb-IIIa but also to the vitronectin receptor (\(\alpha_v\beta_3\)) and Mac-1 (\(\alpha_m\beta_2\)). Although the results of the Evaluation of c7E3 for Prevention of Ischemic Complications (EPIC) trial suggested that this cross-reactivity may allow abciximab to prevent clinical restenosis following PTCA, this finding was not supported by the follow-up EPISODE (Evaluation of PTCA to Improve Long-term Outcome by c7E3 GP IIb/IIIa Receptor Blockade) trial. In EPISODE, treatment with abciximab did not prevent the need for revascularization in the 6 months following the angioplasty. Accordingly, the clinical implications of the cross-reactivity of abciximab remain unclear. Abciximab has also been shown to be immunogenic, most likely because of its antibody structure. Development of anti-abciximab antibodies may be associated with diminished efficacy or with allergic reactions following the repeat administration of this agent.

Several low-molecular-weight GP IIb-IIIa inhibitors with a pharmacologic profile different from that of abciximab have recently been developed. One of these inhibitors is eptifibatide, a cyclic peptide called barbourin, a constituent of the venom of the southeastern pigmy rattlesnake, Sistrurus m. barbouri. Barbourin belongs to a large family of peptides termed disintegrins, which are found in viper venom and have the unusual property of binding to integrins, thereby inhibiting the binding of their physiologic ligands. Unlike other disintegrins, which bind to several integrins with similar affinities (i.e., GP IIb-IIIa, \(\alpha_v\beta_3\), \(\alpha_s\beta_1\)), barbourin is selective and shows a high affinity only for GP IIb-IIIa. The binding of nonspecific disintegrins to various integrins is mediated by the RGD sequence motif, whereas the high affinity and specificity of barbourin for GP IIb-IIIa is attributed to its unique Lys-Gly-Asp (KGD) amino acid sequence. The substitution of lysine for arginine has been shown to account for the GP IIb-IIIa specificity of barbourin.

The synthetic cyclic heptapeptide GP IIb-IIIa inhibitor eptifibatide, the design of which was based on barbourin, contains a modified KGD sequence. The properties of eptifibatide are listed in Table I. The high affinity of eptifibatide for GP IIb-IIIa enables it to inhibit platelet aggregation rapidly in blood samples containing low nanomolar concentrations of the drug. Similar to barbourin, eptifibatide is a specific inhibitor of GP IIb-IIIa, and since the distribution of this complex is restricted to platelets and their precursors, the pharmacologic action of eptifibatide is limited to these cells, permitting its broad use in the clinic. The rapid dissociation (off rate) of eptifibatide from GP IIb-IIIa and its relatively rapid clearance from plasma allow swift restoration of platelet function and normal hemostasis following the discontinuation of an eptifibatide infusion. The lack of antibody response to eptifibatide, which is most easily explained by the small size of the eptifibatide molecule, may be an important consideration in patients who require repeat administration of a GP IIb-IIIa receptor inhibitor and in those with an unknown history. The cyclic peptide structure makes eptifibatide resistant to plasma proteases and increases its bioavailability. These features have provided the impetus for pharmacologic and therapeutic evaluations of eptifibatide that sought to validate its clinical potential as an alternative to abciximab in the management of AICS.

PHARMACODYNAMICS AND PHARMACOKINETICS OF EPTIFIBATIDE

The main goal of pharmacodynamic and pharmacokinetic studies with eptifibatide has been to correlate the antiplatelet activity of eptifibatide (as measured by its ability to inhibit platelet aggregation and thrombosis) with its plasma levels. On the basis of these studies, several dosing regimens of eptifibatide have been selected, and their effect on bleeding times has been measured in order to evaluate the safety profile of this drug.

Eptifibatide antiplatelet activity: Pharmacodynamic estimates of the in vivo inhibition of platelet aggregation by eptifibatide have been based primarily on its effects on ex vivo platelet aggregation and on bleeding time measurements.

Recent data indicate that ex vivo platelet inhibitory activity of eptifibatide is affected by 2 important variables—the anticoagulant used for blood collection and the agonist used for platelet activation. These parameters were also shown to affect the inhibitory activity of other GP IIb-IIIa receptor antagonists. Ex vivo platelet aggregation analyses are routinely performed in blood anticoagulated with citrate, an agent that prevents in vitro clotting by reducing the ionized calcium concentration from the 1 mM level found in circulating blood to approximately 40–50 \(\mu M\). The low plasma concentration of \(Ca^{2+}\) that
The Properties of Eptifibatide Relevant to Its Use for the Prevention of Thrombosis in Acute Ischemic Coronary Syndromes

- Cyclic heptapeptide
- High affinity for GP IIb-IIIa
- Specific for GP IIb-IIIa
- Rapid on-rate
- Rapid off-rate
- Lack of antibody response

**TABLE I**

The collection of blood in citrate is expected to reduce the amount of Ca$^{2+}$ bound to GP IIb-IIIa and, as illustrated in Figure 3, to enhance the apparent inhibitory activity of eptifibatide on platelet aggregation. In plasma anticoagulated with citrate, the concentration of eptifibatide required to achieve 50% inhibition of ADP-induced platelet aggregation (IC$_{50}$) is 140 nM. In contrast, when physiologic concentrations of Ca$^{2+}$ are maintained, as when blood is anticoagulated by the direct thrombin inhibitor PPACK (D-phenylalanyl-L-propyl-L-arginyl-chloromethyl ketone), the IC$_{50}$ of eptifibatide is 570 nM. Eptifibatide IC$_{50}$ values similar to those obtained with PPACK are observed when blood is anticoagulated with hirudin or heparin, which also maintain physiologic Ca$^{2+}$ levels (1 mM). Measurements of the quantity of GP IIb-IIIa molecules occupied by eptifibatide at these 2 calcium ion concentrations show that the low Ca$^{2+}$ concentration in citrate-anticoagulated blood enhances the binding of eptifibatide. In contrast, the binding of fibrinogen to GP IIb-IIIa is less effective at lower Ca$^{2+}$ concentrations. These considerations suggest that in the ex vivo platelet aggregation assay that uses citrate as the anticoagulant, Ca$^{2+}$ levels are significantly lower than in vivo, leading to increased binding of eptifibatide and decreased binding of fibrinogen to the GP IIb-IIIa receptor. As a result, this assay may overestimate the level of in vivo GP IIb-IIIa inhibition by eptifibatide that occurs in the presence of a significantly higher Ca$^{2+}$ concentration.

Thrombin receptor agonist peptide (TRAP), a mimic of the amino terminal fragment of thrombin receptor that is generated when thrombin acts on the thrombin receptor (also known as PAR-1, or protease-activated receptor-1), is another useful tool for the ex vivo analysis of platelet aggregation, since it stimulates platelets through the thrombin receptor without affecting fibrin clot formation. Stimulation of platelets with either TRAP or ADP activates the GP IIb-IIIa molecules expressed on the platelet surface. However, TRAP (but not ADP) is capable of inducing the de novo expression of GP IIb-IIIa from the intracellular pool of $\alpha$ granules to the platelet surface, and is therefore a more potent agonist. In blood anticoagulated with PPACK, the concentration of eptifibatide required to inhibit platelet aggregation is significantly higher when platelets are activated by TRAP (IC$_{50}$ = 1,190 nM) than it would be if the agonist were ADP (IC$_{50}$ = 570 nM; Figure 3). Inhibition of platelet aggregation induced by TRAP requires increased concentrations of other GP IIb-IIIa antagonists as well. However, since TRAP is not a physiologic platelet agonist and its stimulatory effect may be greater than that of the environment found within the circulation, in vivo antithrombotic activity of GP IIb-IIIa inhibitors continues to be routinely estimated from the ex vivo platelet aggregation assays that employ ADP as an agonist.

**Preclinical pharmacodynamics of eptifibatide:** Both preclinical and clinical studies have established that eptifibatide is a potent inhibitor of platelet aggregation, with a rapid onset of action and only modest effects on bleeding time measurements. Additionally, the antithrombotic effect of eptifibatide is readily reversible. Although the doses of eptifibatide studied in animals cannot be directly compared with those used in humans because of the differences in GP IIb-IIIa reactivity and in pharmacokinetics, the results of these studies do indicate features of the drug that appear to be of value for treatment of acute thrombotic coronary syndromes.

In one preclinical study, performed in a baboon model of thrombosis, complete inhibition of ex vivo ADP-induced platelet aggregation in citrate-anticoagulated blood was obtained 25 minutes after the initiation of eptifibatide infusion (5 or 10 $\mu$g/kg per min), demonstrating a rapid onset of inhibitory activity. Inhibition of ADP-induced platelet aggregation in PPACK-anticoagulated blood was less pronounced. Although a modest, dose-dependent prolongation of simple bleeding times caused by platelet inhibition was observed, spontaneous bleeding was not induced by either eptifibatide dose. Rapid reversibility of GP IIb-IIIa inhibition was apparent from the normalization of platelet aggregation within 15–30 minutes of the cessation of infusion. Bleeding times, if ele-
vated, normalized more rapidly than did platelet aggregation measurements and were within the normal range if their measurements were initiated on cessation of the eptifibatide infusion.

In another study, performed in dogs, ADP-induced ex vivo platelet aggregation in citrate-anticoagulated blood was found to be inhibited by infusion of eptifibatide at 4 μg/kg per min, without any evidence of prolongation of the buccal bleeding time. In yet another canine study, the rapidly reversible antihemostatic effect of eptifibatide was associated with preservation of platelets and their function during cardiopulmonary bypass and with paradoxical minimization of postoperative bleeding.64

Clinical pharmacokinetics and pharmacodynamics of eptifibatide: Potent and rapidly reversible GP IIb-IIIa inhibition by eptifibatide was also demonstrated in healthy volunteers and in a variety of clinical settings. In the volunteers, plasma concentrations of eptifibatide were shown to be proportional to the dose and rate of eptifibatide administration for infusions of 0.2–1.5 μg/kg per min, with a half-life of 50–60 minutes.65

Phase I investigation of 63 healthy volunteers demonstrated a complete inhibition of ADP-stimulated platelet aggregation (in citrate-anticoagulated blood) by a constant infusion of eptifibatide (1.0–1.5 μg/kg per min), which could be reversed 2–4 hours after the infusion was terminated.65 Although simple bleeder times were slightly prolonged during the infusion period, they returned to normal within 30 minutes of the cessation of infusion. No clinical bleeding events were observed.65

Two studies have assessed the pharmacodynamic properties of eptifibatide in patients with unstable angina. In one study, 3 different combinations of bolus and 12–72-hour infusions of eptifibatide were evaluated: a 120-μg/kg bolus with a 1.0-μg/kg per min infusion; a 135-μg/kg bolus with a 1.0-μg/kg per min infusion; and a 150-μg/kg bolus with a 1.25-μg/kg per min infusion.17 These eptifibatide regimens reduced ADP-stimulated ex vivo platelet aggregation in citrate-anticoagulated blood by 70–80%. A second study of 227 patients with unstable angina compared the efficacy of aspirin with the efficacy of 2 eptifibatide regimens: a 45-μg/kg bolus with a 0.5-μg/kg per min infusion and a 90-μg/kg bolus with a 1.0-μg/kg per min infusion.66 Infusions were administered for 24–72 hours, and inhibition of platelet aggregation was monitored. Rapid and significant inhibition of platelet aggregation was evident within 1 hour of initiation of infusion with both doses of eptifibatide and was maintained throughout the infusion. The inhibition was dose-dependent, and platelet aggregation returned to 60% of baseline levels within 4 hours of the cessation of infusion. Clinical events were rare in each of the treatment arms, and the incidence of bleeding events did not significantly differ between patients receiving aspirin and those treated with eptifibatide.

Rapid reversibility of inhibition of platelet aggregation by eptifibatide was also demonstrated in patients with acute myocardial infarction.67 A bolus of 135 μg/kg followed by an infusion of 0.75 μg/kg per min of eptifibatide inhibited ADP-induced platelet aggregation by >70%. Platelet aggregation returned to near-normal levels within 4 hours of the cessation of infusion, and the incidence of clinical events and serious bleeding episodes in patients treated with eptifibatide was similar to that observed in patients assigned to placebo.

Pharmacodynamic evaluations of eptifibatide in patients scheduled to undergo elective PTCA were instrumental in the selection of doses of eptifibatide for the pivotal IMPACT II trial. In a study of 150 such patients, a 90-μg/kg bolus of eptifibatide was found to inhibit ex vivo ADP-induced platelet aggregation in citrate-anticoagulated blood by 86%.18 Continuous infusion of eptifibatide (1.0 μg/kg per min) following the bolus dose maintained this level of platelet inhibition. Rapid reversibility of the antihemostatic effect of eptifibatide was evident from the return of platelet aggregation to baseline levels 15 minutes after the infusion was terminated. Another study, summarized in Figure 4, monitored platelet aggregation and bleeding times after the administration of several dosing regimens of eptifibatide in patients undergoing elective PTCA.19 Bolus doses ranging from 90–180 μg/kg established a rapid and significant (85–100%) inhibition of ADP-induced platelet aggregation in citrate-anticoagulated blood. The 0.5-μg/kg per min infusion of eptifibatide maintained the level of inhibition at >70%, whereas the 0.75-μg/kg per min infusion dose sustained the inhibition achieved with a bolus dose (>85%). The infusion doses used in this study had only a modest effect on the simple bleeding times. The 0.5-μg/kg per min and 0.75-μg/kg per min infusion doses were associated with prolongations of the bleeding time from 7 minutes at baseline to 12 and 17 minutes, respectively, during the eptifibatide infusion. The potent antiplatelet effect of eptifibatide was significantly reversed within 2 hours of the cessation of infusion (Figure 4). Rapid restoration of platelet aggregation was accompanied by the return of simple bleeding times to near-normal levels within 1 hour of infusion termination. The rapid reversibility of the antiplatelet effect of eptifibatide may be of particular importance for patients with bleeding events and for those at bleeding risk because of the need for emergency or urgent repeat revascularization caused by abrupt vessel closure.

DOSE SELECTION OF EPTIFIBATIDE IN THE IMPACT II AND PURSUIT TRIALS

The dosing regimens of eptifibatide in the pivotal IMPACT II trial were selected to achieve effective antithrombotic activity safely during the procedure and in the critical hours after PTCA. IMPACT II randomized 4,010 low- and high-risk patients scheduled to undergo percutaneous intervention to receive either a placebo or 1 of the 2 eptifibatide doses.20 All patients in the eptifibatide arms received the same 135-μg/kg bolus, which was selected because it provided a robust and rapid inhibition of ADP-induced ex
vivo platelet aggregation. Patients in both eptifibatide groups, thus, had a comparable level of inhibition of platelet aggregation during the most acute thrombogenic period after coronary intervention. The bolus was followed by a continuous infusion of either 0.5 \( \mu g/kg \) per min or 0.75 \( \mu g/kg \) per min of eptifibatide, which was administered for 20–24 hours and which had been shown\(^{19} \) to maintain a dose-dependent inhibition of ADP-induced platelet aggregation.

Analysis of the data from IMPACT II, however, demonstrated considerable standard deviations about the mean plasma levels of eptifibatide during the infusion period, resulting in a significant overlap between the 2 experimental groups. Platelet aggregation inhibition achieved by the infusion doses of eptifibatide used in IMPACT II (0.5 and 0.75 \( \mu g/kg \) per min) had previously been shown to achieve effective inhibition of arterial thrombosis in both the dog and the baboon models.\(^{68} \) In dogs, these infusion regimens maintained inhibition of ADP-induced platelet aggregation (in citrate-anticoagulated blood) at 10–20% of the baseline level.\(^{68} \) As a result, the cyclic flow variations—which are attributed to coronary artery occlusions by platelet-rich thrombi, interspersed with episodes of increased blood flow caused by thrombus dislodgement—were effectively prevented. In a well-characterized model of thrombosis in baboons,\(^{63} \) the platelet aggregation inhibition achieved by these doses significantly inhibited platelet deposition on a Dacron graft inserted in a femoral arteriovenous shunt, and higher doses were more effective.\(^{68} \)

The preclinical and clinical studies discussed above involved measurements of platelet aggregation in blood anticoagulated with citrate, an agent now known to reduce the plasma concentration of calcium ions and thereby to enhance the apparent inhibitory activity of eptifibatide. To evaluate the clinical effects of infusion doses of eptifibatide used in IMPACT II, it
is important to understand how these regimens inhibit platelet aggregation reactions in the presence of physiologic levels of Ca\(^{2+}\). Additionally, it is of significant interest to determine how the infusion doses of eptifibatide affect platelet aggregation reactions induced by the potent platelet agonist TRAP. Figure 4 illustrates the effect of various eptifibatide concentrations in normal human platelet-rich plasma on ADP-induced aggregation in citrate and PPACK and on TRAP-induced aggregation in PPACK. Blood levels of eptifibatide achieved at steady state by the infusion doses of eptifibatide used in IMPACT II and the resulting degrees of platelet aggregation inhibition are indicated in the figure. The plasma levels of eptifibatide following the infusion of either dose from IMPACT II (0.5 or 0.75 \(\mu g/kg\) per min) are similar and would be expected to inhibit ADP-induced platelet aggregation in citrate-anticoagulated blood by 70–100%. However, in PPACK-anticoagulated blood, the degree of inhibition of ADP-induced platelet aggregation by these infusion doses of eptifibatide is significantly lower (35–50%). Furthermore, these doses would be expected to inhibit TRAP-induced platelet aggregation in PPACK-anticoagulated blood by <20%. On the other hand, a bolus of 135 \(\mu g/kg\) used in IMPACT II achieved plasma levels of >600 nM eptifibatide, a concentration expected to provide robust inhibition of platelet aggregation even in PPACK-anticoagulated blood. Therefore, although the bolus dose of eptifibatide used in IMPACT II established a rapid and significant inhibition of platelet aggregation in vivo, the infusion doses were associated with a more modest antiplatelet effect.

Although it is now apparent that the infusion doses of eptifibatide used in IMPACT II were potentially at the low end of the dose–response curve, both of them nevertheless demonstrated a sustained benefit during and after the angioplasty, without increasing the bleeding risk. Both eptifibatide doses significantly reduced the incidence of the composite endpoint of death, myocardial infarction, or secondary revascularization at 24 hours\(^{69}\) and their beneficial effect was sustained for 6 months following termination of treatment.\(^{20}\)

The success of IMPACT II, along with the knowledge that more aggressive dosing of eptifibatide produces greater inhibition of platelet aggregation and more robust antithrombotic activity, has led to the selection of higher doses of eptifibatide for the PURSUIT trial.\(^{70}\) PURSUIT, a worldwide phase III evaluation of eptifibatide in the setting of unstable angina and non–\(Q\)-wave myocardial infarction, completed the enrollment of 10,948 patients in January 1997 and is the largest clinical evaluation of a GP IIb-IIIa inhibitor to date. Patients were initially randomized to receive placebo or 1 of 2 eptifibatide dosing regimens. A bolus of 180 \(\mu g/kg\) was administered to both eptifibatide groups, while the infusion doses, 1.3 \(\mu g/kg\) per min or 2.0 \(\mu g/kg\) per min, were administered for 72 hours (or 96 hours if the patient had a PTCA). These doses are 3-fold to 4-fold higher than the ones used in IMPACT II and are estimated to provide a minimum of 80% of inhibition of ADP-induced platelet aggregation in PPACK-anticoagulated blood. Following an interim analysis, the Data and Safety Monitoring Committee recommended discontinuation of the 1.3-\(\mu g/kg\) per min infusion dose and continuation of the 2.0-\(\mu g/kg\) per min infusion regimen for the remainder of the trial. Patients enrolled in PURSUIT after this recommendation were randomized to receive either placebo or a 180-\(\mu g/kg\) bolus followed by a 2.0-\(\mu g/kg\) per min infusion of eptifibatide.

**CONCLUSIONS AND PROSPECTS**

The conventional approaches to the management of coronary thrombosis underlying AICS and the ischemic complications of percutaneous coronary interventions have been anticoagulation with heparin and antiplatelet therapy with aspirin. The efficacy of each of these agents, however, is limited by their relatively weak effect on platelet aggregation, a key event in the pathophysiology of ischemic heart disease. The platelet GP IIb-IIIa complex involved in the final common pathway to platelet aggregation is now recognized as a rational target of antithrombotic therapy. A significant and growing body of evidence demonstrates the clinical utility of GP IIb-IIIa inhibition for the prevention of the ischemic complications of angioplasty.

Eptifibatide is a highly specific peptide inhibitor of GP IIb-IIIa. The active domain of this synthetic cyclic heptapeptide is derived from that of the disintegrin barbourin, a peptide component of pit viper venom whose specific binding to GP IIb-IIIa is mediated by the KGD sequence. Pharmacologic evaluations of eptifibatide in animal models and in humans have demonstrated a rapid onset of action, short plasma half-life, and rapid clearance from plasma. Elimination is both renal and extrarenal, and it is directly proportional to weight and inversely correlated with age. Robust inhibition of platelet aggregation is rapidly established after a bolus of eptifibatide and can be maintained at a desired level by infusion of the drug. The antihemostatic effect of eptifibatide is reversed rapidly after the cessation of infusion. Preclinical and clinical studies have also demonstrated that eptifibatide is not immunogenic, most likely because of its low molecular weight. Clinically, these pharmacologic properties translate into a solid efficacy and safety profile for eptifibatide. The potent antithrombotic effect that is dose-dependent and related to the period of drug administration suggests that bleeding events, if any, can be managed easily. The lack of immune response to eptifibatide indicates its repeat use is highly unlikely to be compromised by adverse reactions due to antibody response. These characteristics suggest eptifibatide may represent a useful clinical alternative to abciximab, currently the only GP IIb-IIIa receptor inhibitor approved in the United States for the treatment of high-risk patients scheduled to undergo angioplasty.

Bolus and infusion doses of eptifibatide chosen for the pivotal IMPACT II trial have been found to be both efficacious and safe. Pharmacokinetic and phar-
macromolecular structures and functions in an attempt to achieve the best possible therapeutic efficacy. The selection of these agents as a standard therapy for the full range of ischemic heart disease.
plasma.

sex difference in the aggregation of human platelets in citrated platelet-rich

membrane glycoprotein IIb-IIIa complex.


Marguerie GA, Edgington TS, Plow EF. Interaction of fibrinogen with its
platelet receptor as part of a multistep reaction in ADP-induced platelet aggrega-

Scarborough RM, Naughton MA, Teng W, Hung DT, Rose J, Yu T-K H,
Wheaton VL, Turch CW, Coughlin SR. Tethered ligand agonist peptides: struc-
tural requirements for thrombin receptor activation reveal mechanism of proteo-


Uthoff K, Zehr KJ, Geerling R, Herskowitz A, Cameron DE, Reitz BA.
Inhibition of platelet adhesion during cardiopulmonary bypass reduces postoper-

Charo IF, Scarborough RM, du Mee CP, Wolf D, Phillips DR, Swift RL.

Schulman SP, Goldschmidt-Clermont PJ, Topol EJ, Califf RM, Navetta FL,
Willerson JT, Chandra NC, Guerci AD, Ferguson JI, Harrington RA, Lincoff AM, Yakubov SJ, Bray PF, Bahr RD, Wolfe CL, Yock PG, Anderson HV,

Ohman EM, Kleiman NS, Gacioch G, Worley SJ, Navetta FI, Talley JD,
Anderson HV, Ellis SG, Cohen MD, Spriggs D, Miller M, Kereakes D, Yakubov S, Kitt MM, Sigmon KN, Califf RM, Krucoff MW, Topol EJ, for the IMPACT-
AMI Investigators. Combined accelerated tissue-plasminogen activator and plate-
let glycoprotein IIb/IIIa integrin receptor blockade with Integrin in acute myo-

Strongy J, Hanson S. Personal communication.

Tcheng JE. Glycoprotein IIb/IIIa receptor inhibitors: putting the EPIC,
IMPACT II, RESTORE, and EPILOG trials into perspective. Am J Cardiol

Harrington RA. Design and methodology of the PURSUIT Trial: Evaluating epifibatide for acute ischemic coronary syndromes. Am J Cardiol 1997;80(3B):
34B–38B.