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Pharmacodynamics and pharmacokinetics of the platelet GPIIb/IIIa inhibitor tirofiban in patients undergoing percutaneous coronary intervention: implications for adjustment of tirofiban and clopidogrel dosage

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Abstract

Introduction: Despite extensive data supporting the use of platelet glycoprotein (GP) IIb/IIIa (GPIIb/IIIa) inhibitors in the therapy of patients with acute coronary syndromes (ACS), there is considerable debate as to the optimal choice of antiplatelet regimen. The objective of this study was to conduct a detailed time-resolved analysis of the effects of the GPIIb/IIIa inhibitor tirofiban with concomitant clopidogrel in ACS patients undergoing percutaneous coronary intervention (PCI) to improve the dosing regimen of these two commonly used antiplatelet drugs.
Methods: The study was performed in 14 patients with non-ST-segment elevation (NSTE) ACS who underwent PCI while being treated with the current typically utilized regimen of tirofiban (10 μg/kg bolus, 0.15 μg/kg/min infusion) and clopidogrel (300 mg). Platelet function was assessed before, during, and after

Abbreviations: GPIIb/IIIa, platelet glycoprotein (GP) IIb/IIIa; PCI, percutaneous coronary intervention; ACS, acute coronary syndromes; NSTE, non-ST-segment elevation; MI, myocardial infarction; PRP, platelet-rich-plasma; PPP, platelet-poor plasma.

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tirofiban infusion using a panel of agonists for ADP receptors, PAR1 and PAR4 thrombin receptors, and collagen receptors.
Results: Measurements of circulating tirofiban levels demonstrated a trough, which paralleled a reduction in platelet inhibition for all platelet agonists during the time when PCI was being performed. Interestingly, younger ACS patients (<55 years) exhibited less inhibition of platelet function both during the PCI procedure and after termination of the tirofiban infusion. These apparent age differences were primarily attributed to a decreased responsiveness of the younger patients to clopidogrel.
Conclusions: This study shows that the currently utilized tirofiban dosage is suboptimal and suggests that patients may benefit from a higher dose regimen.

Introduction

Percutaneous interventions that target the culprit coronary lesion invariably lead to intimal disruption. Such iatrogenic disruptions expose subendothelial and subintimal components leading to activation of platelets and the potential for thrombus formation. Platelet activation and aggregation have been shown to be heightened in the setting of angioplasty and stenting, which may cause clinical complications of the procedure, including acute myocardial infarction (MI) and death [1,2]. Blocking platelet aggregation with inhibitors of the integrin platelet glycoprotein (GP) IIb/IIIa (GPIIb/IIIa) as adjunctive therapy during percutaneous coronary intervention (PCI) has been demonstrated to be of unequivocal benefit in broad populations of patients [3,4]. The platelet GPIIb/IIIa is an effective drug target because it plays a central role in the final common pathway of formation of platelet—fibrinogen—platelet aggregates [5].

Three parenteral GPIIb/IIIa inhibitors, abciximab, tirofiban and eptifibatide, are approved for clinical use in the United States. A large body of data has documented the efficacy of the antibody abciximab during PCI in heterogeneous populations of patients, including those with stable and unstable coronary syndromes [6—8]. Likewise, the small molecule GPIIb/IIIa inhibitors, tirofiban and eptifibatide, improve important clinical endpoints such as MI or death in non-ST-segment elevation (NSTE) acute coronary syndromes (ACS), including the subset of these patients undergoing PCI [9—11]. The American College of Cardiology/American Heart Association guidelines for the management of patients with unstable angina and non-ST-segment elevation MI note that the safety of PCI in patients with NSTE-ACS is "enhanced by the addition of intravenous GP IIb/IIIa inhibitors to the standard regimen of aspirin, heparin, and antiischemic medications" [12].

To date, the TARGET study [13] is the only randomized trial that has compared clinical outcomes utilizing two different GPIIb/IIIa inhibitors. This study randomized patients undergoing nonemergent PCI to either tirofiban or abciximab and examined the incidence of the composite endpoint of death, MI, or urgent revascularization as well as safety outcomes at 30 days. Part of the rationale for this trial was the cost differential between the two agents—abciximab is approximately four times the cost of tirofiban. In addition, the biologic half-life of abciximab is much longer than that of tirofiban, raising concerns of bleeding risks in patients that may require urgent surgical intervention in the event of failed PCI. The TARGET study reported a small (1.6%) but significant reduction in the incidence of the primary composite endpoint in the abciximab group primarily due to a reduction in MI. However, the abciximab-treated patients had a significantly greater incidence of minor bleeding as well as thrombocytopenia.

We and others [14,15] have posited that the differences in outcomes between abciximab and tirofiban in TARGET may have been due to inadequate dosing of tirofiban. A similar issue was encountered with the other small molecule GPIIb/IIIa inhibitor, eptifibatide [16,17]. This is despite the fact that the 10/0.15 tirofiban dose routinely employed during PCI (10 μg/kg bolus followed by 0.15 μg/kg/min maintenance infusion) is higher than that approved for the treatment of unstable angina (0.4 μg/kg/min×30 min loading infusion followed by 0.1 μg/kg/min maintenance infusion) [9,13,18]. The currently used dosage of tirofiban for medical treatment of unstable angina is based primarily on findings from the PRISM Plus study [9]. The dose used during PCI has previously been utilized in the RESTORE [18] and TARGET [13] trials and by trials assessing the association of clinical outcomes following PCI with point of care platelet testing during PCI [19].