Editorial

Oral Platelet Glycoprotein IIb/IIIa Receptor Antagonists: The Present Challenge Is Safety

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An indisputable body of angiographic, angioscopich, pathological, and biochemical evidence supports the role of thrombus in the pathogenesis of acute myocardial infarction, unstable angina, and percutaneous coronary intervention. Compelling data from large-scale trials and analyses have established the role of platelet inhibitors in reducing coronary events in patients with the acute coronary syndromes and in maintaining patency of vascular grafts in the long-term. Persistent reports of high clinical event rates in the modern era of acute coronary syndromes despite aggressive medical therapy have spurred the development of more effective antiplatelet agents. Despite its efficacy, aspirin is a relatively weak antiplatelet agent, inhibiting only thromboxane A2–mediated platelet aggregation. The final common pathway of platelet aggregation involves activation of the platelet glycoprotein IIb/IIIa (GP IIb/IIIa) receptor to allow fibrinogen binding. Studies involving a number of intravenous inhibitors of GP IIb/IIIa receptors have demonstrated efficacy in reducing ischemic complications after percutaneous angioplasty and in the acute coronary syndromes. 

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In patients who have survived an episode of unstable angina or myocardial infarction, activation of the hemostatic system may persist for several months after the acute event. Studies with GP IIb/IIIa inhibitors and with specific antithrombins have demonstrated efficacy of these agents during the short-term period coinciding with intravenous administration, with subsequent decay in clinical benefit after cessation of parenteral treatment so that no demonstrable clinical benefit is evident at late (1 month) follow-up. Hence, there exists a compelling rationale for long-term antiplatelet treatment, including GP IIb/IIIa inhibition. More than one dozen oral GP IIb/IIIa inhibitors are in clinical trials, and early reports from several phase II studies are appearing.

The Present Study

In the present issue of Circulation, Cannon et al conducted a dose-ranging study of sibrafiban, an orally active peptidomimetic GP IIb/IIIa antagonist. In the pharmacokinetic/pharmacodynamic study, seven dosing regimens of sibrafiban were assessed with serial evaluations of platelet aggregation; four doses that achieved at least minimum-grade platelet inhibition (defined as >50% inhibition of ADP-induced platelet aggregation for >75% of the day) were then chosen for evaluation in the safety study, and aspirin served as control. In the safety cohort, 223 patients with documented coronary artery disease after an acute coronary syndrome (unstable angina, non-Q-wave myocardial infarction [MI], Q-wave MI) were studied for 28 days.

High levels of platelet inhibition were achieved (mean peak values, 47% to 97% inhibition of 20 μmol/L ADP-induced platelet aggregation on day 28). Good correlations between blood level and degree of platelet inhibition were noted. Major hemorrhage occurred in 1.5% of sibrafiban-treated and 1.9% of aspirin-treated patients. Protocol-defined minor bleeding occurred in 0% to 32% of the sibrafiban groups and in no patient treated with aspirin alone. Between 6% and 10% of patients experienced a clinically significant major or minor hemorrhage at the doses that achieved <70% to 80% platelet inhibition. One patient (0.3%) developed severe thrombocytopenia (nadir platelet count, 6000 per μL) that required cessation of study drug. The overall cardiac event rate was low (1.8% death, 1.4% recurrent MI, 4.0% recurrent ischemia), and the study was not statistically powered to detect differences in clinical events among the treatment groups.

Efficacy

Major questions must be resolved before oral agents enter routine clinical practice. In this study and in other dose-ranging studies, a clear-dose response relationship was seen, with higher drug levels correlating with higher levels of platelet inhibition and higher levels of bleeding complications. In trials of intravenous GP IIb/IIIa receptor antagonists, agents with effective (ie, >80%) receptor blockade are more effective than those with more limited receptor blockade in reducing clinical events. It is unknown what degree of receptor inhibition is needed in the long-term setting to prevent recurrent ischemic cardiac events, without the hazard of hemorrhagic complications. Although the development of reliable bedside assays for measurement of degree of platelet inhibition may ultimately prove helpful in optimizing the safety of GP IIb/IIIa therapy, an effective and safe level of receptor blockade must first be established. Similarly, it is unknown whether the degree of platelet inhibition required changes over time after the acute coronary syndrome. It is interesting to note that in the present study, in patients who underwent complete pharmacokinetic evaluation, the drug concentration required to give 50% inhibition was similar on days 1 and 28, suggesting that the patients’ platelets did not change over time with respect to platelet surface GP IIb/IIIa receptor number or activation state.

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The role of concomitant aspirin treatment has not been studied prospectively; some trials have added an oral GP IIb/IIIa inhibitor to background aspirin treatment, and others, including the present study, compared the oral GP IIb/IIIa receptor antagonist to aspirin.

Safety

The safety of prolonged GP IIb/IIIa inhibition is similarly unknown. Patients with Glanzmann thrombasthenia lack GP IIb/IIIa function on the basis of a genetic defect. Although the generally favorable clinical outcome of Glanzmann patients (largely mucocutaneous bleeding with rare spontaneous central nervous system bleeding) has served as the theoretical model for the development of pharmacologic interruption of the GP IIb/IIIa receptor, the long-term outcome of patients with pharmacologically mediated inhibition of GP IIb/IIIa is unknown. Moreover, the optimal duration of treatment after an acute coronary syndrome is also unknown.

A major concern with the long-term use of oral GP IIb/IIIa antagonists is bleeding. Thus, in the present study of Cannon et al., 6% of patients experienced gastrointestinal bleeding with sibrafiban; whether this effect can be reduced or eliminated with concomitant antacid or H2 blocker is also unknown. Although patients with creatinine >1.5 mg/dL were excluded from the present study, a higher rate of major or minor hemorrhage was observed in patients with even moderate impairment of renal function (creatinine clearance <67 mL/min) in multivariate analysis. In regard to low platelet count, acute profound thrombocytopenia has been reported with abciximab. However, the observation that elevated reactivity to human antichimeric antibody before the first dose of abciximab was not associated with an increased incidence of thrombocytopenia, and the consistent finding of thrombocytopenia with other nonantibody GP IIb/IIIa receptor antagonists suggests the existence of mechanisms other than direct reticuloendothelial binding of the platelet/drug complex. For example, binding of a number of molecules to the GP IIb/IIIa receptor produces a conformational change in the receptor resulting in the expression of new epitopes, known as ligand-induced binding sites. A preexisting IgG type antibody that binds to the GP IIb/IIIa receptor in the presence of an experimental GP IIb/IIIa receptor antagonist causes profound thrombocytopenia. This antibody was detected in about 1% of human samples.

Ultimately, it would be presumed that a rapid acting intravenous agent would be administered acutely during the hospitalization for the acute coronary syndrome or revascularization procedure, with outpatient conversion to an orally active preparation of the same compound; indeed, several such products are in development. However, it has been shown that the pharmacodynamic response to an oral GP IIb/IIIa receptor antagonist is potentiated by antecedent treatment with abciximab. Whether this finding will be observed with other combinations of oral and parenteral GP IIb/IIIa receptor antagonists is unknown. This observation may have important implications regarding safety of sequential GP IIb/IIIa blocker therapy, particularly considering that in the present study by Cannon et al., patients had not received prior treatment with an intravenous preparation.

Conclusions

For cardiologists at the dawn of a new century, antiplatelet therapy is at a crossroads. Aspirin celebrated its centenary this past summer and remains the mainstay of the therapeutic arsenal due to its efficacy, safety profile, and cost effectiveness. Although some degree of optimism should prevail about future potential efficacy for chronic oral GP IIb/IIIa inhibitors, the major challenge to be pursued at this time is safety.

References


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