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Sibrafiban

A Viewpoint by Christopher P. Cannon

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The initiating event of acute coronary syndromes is atherosclerotic plaque rupture followed by local thrombosis. Antithrombotic therapy, most notable with aspirin, leads to a 25 to 50% reduction in death and/or myocardial infarction (MI) across the spectrum of acute coronary syndromes.[1] These dramatic clinical effects have focused attention on the platelet as a target for more potent therapies, notably with inhibitors of the platelet glycoprotein (GP) IIb/IIIa receptor which mediates platelet aggregation.

The mechanisms of action of currently available oral antiplatelet agents and GP IIb/IIIa inhibitors are quite distinct. Aspirin permanently acetylates cyclo-oxygenase, thereby blocking the synthesis of thromboxane A2 by the platelet, which in turn produces less activation of other platelets. Ticlopidine and clopidogrel act by blocking the ADP receptor; thus they also decrease platelet activation.[2] GP IIb/IIIa receptor blockers are a new potent class of platelet inhibitors. In contrast, GP IIb/IIIa receptor antagonists block the binding of fibrinogen to specific platelet GP IIb/IIIa receptors, thus preventing platelet aggregation. Whereas platelet activation is produced by a wide variety of stimuli, the final common step to platelet aggregation is fibrinogen binding. Therefore, no matter what physiological stimuli are present, blockade of the GP IIb/IIIa receptor can prevent formation and/or propagation of platelet thrombus.

Sibrafiban is one of several GP IIb/IIIa inhibitors currently being tested in phase III trials. Sibrafiban was first tested in patients with stabilised acute coronary syndromes in the TIMI 12 trial, a phase II, double-blind, dose-ranging trial designed to evaluate the pharmacokinetics, pharmacodynamics, safety and tolerability of sibrafiban in 329 patients after acute coronary syndromes.[3] As reviewed by Dooley and Goa in this issue of *Drugs*, sibrafiban achieved high levels of platelet inhibition: mean peak values ranged from 47 to 97% inhibition of 20 μmol/L ADP-induced platelet aggregation on day 28 across the 7 doses. Major haemorrhage was rare in patients treated with sibrafiban (1.5%) or aspirin (1.9%). However, protocol-defined 'minor' bleeding, usually mucocutaneous, occurred in 0 to 32% of patients in the various sibrafiban groups compared with none of the aspirin-treated patients. The mucocutaneous bleeds appeared to be related to the degree of platelet inhibition and plasma drug concentration, as well as total daily dose, and to once daily versus twice daily dosages – with higher drug levels relating to higher rates of minor bleeding. In addition, patient factors such as bodyweight and renal function were important determinants of minor bleeding. Thus, the oral GP IIb/IIIa antagonist sibrafiban achieved effective, long term platelet inhibition with a clear dose-response effect, but at the expense of a relatively high incidence of minor bleeding. With the results of TIMI 12, sibrafiban is now being tested in the 9000 patient SYMPHONY trial, using bodyweight- and renal function-adjusted dosages.

Thus, oral GP IIb/IIIa inhibitors are a promising class of drugs for the treatment of acute coronary syndromes, percutaneous coronary interventions and stroke,[4] for either early treatment or secondary prevention. To date, data are available only on the pharmacokinetic and pharmacodynamic effects of these agents. Numerous questions remain, most notably the primary hypothesis that long term GP IIb/IIIa inhibition will be beneficial in patients with coronary disease. Other questions include: what level of platelet inhibition is optimal, how efficacy and safety can be best balanced, whether other adjunctive agents are needed and whether monitoring of platelet function will assist in the use of these agents. Ongoing large-scale clinical trials will assess many of these issues and the clinical effects of this promising class of agents.

References

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