Prasugrel

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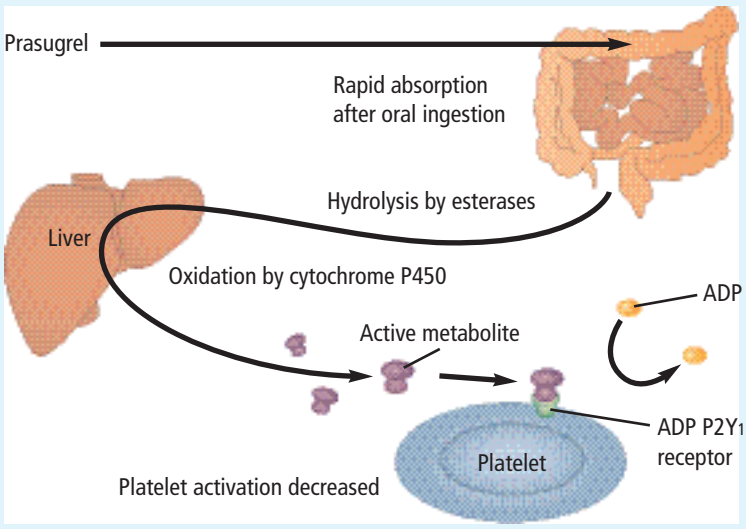

NOTES. Prasugrel is a prodrug metabolised into its active form through hydrolysis by intestinal carboxylesterases and oxidation by intestinal and hepatic cytochrome P450 enzymes. It binds irreversibly to the adenosine diphosphate (ADP) $P2Y_{12}$ receptor on platelets for their lifespan, thereby inhibiting their activation and decreasing subsequent platelet aggregation.

Figure 1. The pharmacological action of prasugrel. (Figure redrawn from: Bhatt DL. Prasugrel in clinical practice. *N Engl J Med* 2009;361:940–2)

Introduction

The benefits of dual antiplatelet therapy with aspirin and clopidogrel in patients with acute coronary syndrome (ACS) are well established, yet many patients continue to have recurrent atherothrombotic events, implying an unmet therapeutic need. Prasugrel, a thienopyridine, like its predecessor clopidogrel, is a recent addition to the current antiplatelet therapy options for atherothrombotic diseases. It is absorbed more rapidly and metabolised more consistently than clopidogrel with less interpatient variability. Following the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38), it was approved for use in patients with ACS undergoing primary or delayed percutaneous coronary intervention.

Pharmacology

Figure 1 outlines the pharmacological action of prasugrel. Like clopidogrel, it is a prodrug.[1] It undergoes complete and rapid absorption after oral ingestion, with mean time to peak plasma concentration of approximately 30 minutes, following which it is hydrolysed to a thiolactone, R-95913. It is then converted into its thiol-containing active metabolite, R-138727, through oxidation by intestinal and hepatic cytochrome P450 enzymes. R-138727 binds irreversibly to the adenosine diphosphate (ADP) $P2Y_{12}$ receptor on platelets for the duration of their lifespan, inhibiting their activation and decreasing subsequent platelet aggregation. Compared to clopidogrel, prasugrel has been shown to inhibit platelet aggregation more rapidly, more potently and more consistently. This is due to a more efficient metabolism, which may be explained by genetic polymorphisms affecting the cytochrome P450 system. Prasugrel metabolism has also been shown to have no significant variability among individuals. There is no evidence that prasugrel has any clinically significant interaction with other drugs, including those metabolised by cytochrome P450 enzymes.

Trials of safety and efficacy

To date, there has been one large randomised controlled trial comparing prasugrel with clopidogrel. In the TRITON-TIMI 38 trial, 13 608 patients undergoing planned percutaneous coronary intervention for unstable angina or myocardial infarction were randomly assigned to receive prasugrel (a 60mg loading dose and a 10mg daily maintenance dose) or clopidogrel (a 300mg loading dose and a 75mg daily maintenance dose) for 6–15 months.[2] The primary endpoint was the composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The key safety endpoints were major bleeding not related to coronary artery bypass grafting (CABG), non-CABG-related life-threatening bleeding, and major or minor bleeding. The trial showed a reduction in the composite endpoint, with 9.9% in the prasugrel group having a primary endpoint compared to 12.1% in the clopidogrel group (hazard ratio [HR] 0.81, p<0.001). This supports the primary hypothesis of superior efficacy. However, the significant difference in rate of endpoints was mainly driven by the reduction in non-fatal myocardial infarction (HR 0.89, p<0.001). There was no significant difference between the two groups in rates of death from cardiovascular causes or non-fatal stroke.

In relation to the safety endpoints, there was an excess of major bleeding among patients on prasugrel. In the prasugrel group, 2.4% of patients had at least one major haemorrhage not related to CABG, as compared to 1.8% in the clopidogrel group (HR 1.32, p=0.03). There was also a higher rate of life-threatening bleeding (fatal and non-fatal) in the prasugrel group (1.4% vs 0.9% in the clopidogrel group, HR 1.52, p=0.01). The rate of fatal major bleeding was higher in the prasugrel group (0.4% vs 0.1% in the clopidogrel group, HR 4.19, p=0.002), but there was no significant difference in the rate of non-fatal life-threatening bleeding. A higher rate of major and minor bleeding was also observed in the prasugrel group (5.0% vs 3.8% in the clopidogrel group, HR 1.31, p=0.002).

The TRITON-TIMI 38 trial showed that across the full spectrum of acute coronary syndromes, treatment with prasugrel, as compared with clopidogrel, resulted in a significant 2.2% absolute reduction and a 19% relative reduction in the rate of the primary efficacy endpoint. However, this was associated with a significant increase in the rate of bleeding – the relative rate of major haemorrhage was increased by 32%. Following post-hoc analyses, the authors suggested that prasugrel should be avoided in certain subgroups of patients as it may result in less net clinical benefit or net clinical harm. These are patients with a history of stroke or transient ischaemic attack, the elderly (age ≥75 years), and those with a body weight of <60kg.

Specific evidence for use in diabetes

A pre-specified analysis of TRITON-TIMI 38 was conducted evaluating the effects of prasugrel in patients with diabetes mellitus (DM).[3] The subject population consisted of 3146 patients with a pre-existing history of DM, including 776 receiving insulin. While the primary endpoint was significantly reduced with prasugrel among subjects without DM (9.2% vs 10.6% in the clopidogrel group, HR 0.86, p=0.02), the effect was greater in patients with DM (12.2% vs 17.0% in the clopidogrel group, HR 0.70, p<0.001, $p_{interaction}$=0.09), especially for those taking insulin (14.3% vs 22.2% in the clopidogrel group, HR 0.63, p=0.009). Diabetic patients not on insulin also experienced a benefit with prasugrel (11.5% vs 15.3% in the clopidogrel group, HR 0.74, p=0.009). There was no difference in the rates of major haemorrhage in both groups (2.6% in the prasugrel group vs 2.5% in the clopidogrel group, HR 1.06, p=0.81, $p_{interaction}$=0.29). This is in contrast to the increased rate of major haemorrhage among subjects without DM on prasugrel (1.6% vs 2.4% in the clopidogrel group, HR 1.42, p=0.02). This subanalysis showed that the net clinical benefit with prasugrel was greater for subjects with DM than for subjects without DM – there is a greater reduction in ischaemic events without an observed increase in major bleeding.

Discussion

The primary analysis of the TRITON-TIMI 38 trial showed that, in the overall subject population, the reduced rates of ischaemic events from prasugrel are associated with an increased risk of major bleeding. Due to the associated risk of bleeding, clinicians should weigh the benefits and risks when considering the choice of antiplatelet regimens for patients with acute coronary syndromes. However, the study also showed that more intensive oral antiplatelet therapy in the form of prasugrel is of particular benefit to patients with DM. This suggests that, for this subgroup of patients, the degree of platelet inhibition may be an important marker of outcome. This is in keeping with previous studies that showed DM to be a proinflammatory and a prothrombotic state. Those with DM may not just be a high risk group – they may be fundamentally different from other patients with ACS.[4] The diabetic substudy of TRITON-TIMI 38 identified a subgroup of patients who may benefit to a greater extent from a more potent antiplatelet regimen. Larger cohort studies of individuals with DM are needed to address the issue of a variable response to therapy between individuals.

Key points

- Prasugrel is a more potent antiplatelet agent than clopidogrel
- Prasugrel is associated with an increased risk of bleeding compared to clopidogrel
- Overall, the net clinical benefit with prasugrel is greater for patients with diabetes

Declaration of interests

Dr Sidik and Dr McKay have no conflict of interest to declare. Professor Fisher has served on advisory boards for Daiichi Sankyo and Eli Lilly.

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