The thienopyridine class of antiplatelet drugs

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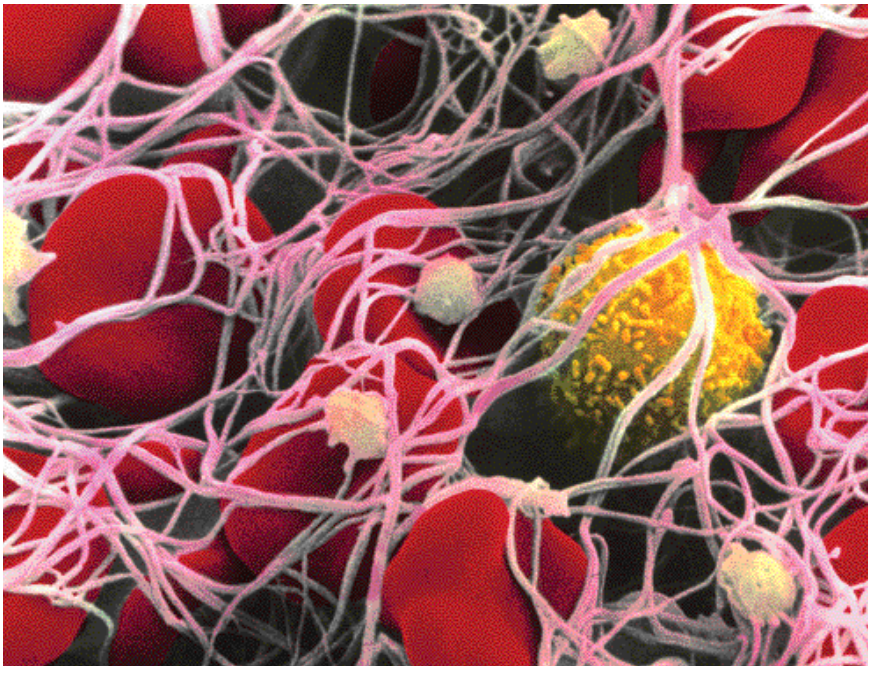
The newer agents of the platelet ADP-receptor blocking class of antiplatelet drugs have greater antiplatelet efficacy and are less prone to cytochrome P450-related drug interactions than clopidogrel but are associated with an increased risk of haemorrhagic complications.



PHOTOLIBRARY

Figure. Coloured scanning electron micrograph of a thrombus, showing erythrocytes trapped in a mesh of fibrin formed by activated platelets.

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Thrombus formation as a result of accumulation of platelets at the site of atherosclerotic plaque rupture is the primary pathology underlying both acute cerebrovascular events and acute coronary syndromes. Cardiovascular disease (CVD) is the most common cause of mortality in Australia. Furthermore, the significant morbidity and effect on a patient's quality of life imposed by CVD imparts considerable psychosocial and global economic pressures. As a consequence, platelets have become a major therapeutic target in the management of patients with CVD.

The current armamentarium of antiplatelet therapies includes aspirin (a cyclo-oxygenase [COX] inhibitor), dipyridamole (a phosphodiesterase inhibitor), glycoprotein IIb-IIIa inhibitors (such as abciximab and tirofiban) and the thienopyridines (ADP-receptor blockers).

The thienopyridines and COX inhibitors exert their effect through inhibition of the amplification loop in platelet activation. When platelets are activated, intracellular ADP is released and binds to its specific receptor on the platelet surface, resulting in a marked amplification of platelet activation and the formation of a stable thrombus. Thienopyridines exert their antiplatelet effect by irreversibly blocking the major platelet ADP receptor, P2Y12. Drugs in this class include clopidogrel, ticlopidine and prasugrel (which

has recently become available under the Pharmaceutical Benefits Scheme [PBS]). Reversible P2Y12-receptor antagonists (inhibitors) are being developed and cangrelor and ticagrelor (both non-thienopyridines) are currently being evaluated in clinical trials.

Both the thienopyridine and the non-thienopyridine P2Y12 antagonists are reviewed in this article.

Ticlopidine

The prototype oral P2Y12 inhibitor ticlopidine was the first drug in this class to demonstrate efficacy in both primary treatment and secondary prevention in acute coronary syndromes as well as in secondary stroke prevention.[1,2] However, because of its propensity to cause life-threatening haematological complications (including agranulocytosis, thrombotic thrombocytopenia purpura and aplastic anaemia) and its potential hepatotoxic side effects, the drug has progressively lost its place and its use has been supplanted by clopidogrel.

Clopidogrel

Clopidogrel, the most widely used of the thienopyridine antiplatelet agents, is a prodrug requiring *in vivo* conversion to the pharmacologically active, thiol-containing metabolite through two sequential oxidative steps dependent on the cytochrome (CYP) P450 system. Only an estimated 2% of ingested clopidogrel ends up bound to platelets.[3]

Indications for use

There is a significant body of evidence supporting the use of clopidogrel in patients with CVD.

The efficacy of clopidogrel was first shown in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial. This study demonstrated a marginal benefit in terms of composite outcome of stroke, myocardial infarction (MI) or vascular death of clopidogrel when compared with aspirin, without a significant increase in bleeding.[4] The efficacy of combining clopidogrel and aspirin in patients undergoing percutaneous coronary intervention (PCI) with stent insertion and in those with acute coronary syndromes is more convincing.[5] It should be noted that this combination therapy does not come without a price, with several studies noting an increased risk of bleeding.[6] Conversely, in the secondary prevention of nonthromboembolic stroke the combination of aspirin and clopidogrel therapy does not provide greater efficacy yet at the same time it substantially increases the risk of bleeding complications.[7]

The aforementioned trial results are reflected in the PBS criteria for prescription of clopidogrel. Under this scheme, clopidogrel is authorised for the indications listed below.

- Secondary stroke or transient ischaemic attack (TIA) prevention:
  - patients with a history of symptomatic cerebrovascular ischaemic episodes while on aspirin therapy
  - if low-dose aspirin poses an unacceptable risk of gastrointestinal bleeding or if there is a history of allergy to aspirin, salicylates or NSAIDs.
- Secondary prevention of MI or unstable angina
  - patients with a history of symptomatic cardiac ischaemic episodes while on aspirin therapy
  - if low-dose aspirin poses an unacceptable risk of gastrointestinal bleeding or if there is a history of allergy to aspirin, salicylates or NSAIDs.
- Acute coronary syndromes (acute MI and unstable angina):
  - treatment of acute coronary syndromes in combination with aspirin
  - treatment in combination with aspirin following cardiac stent insertion and angioplasty.

Dosage

The standard dosage regimen for clopidogrel is a loading dose of 300 to 600 mg followed by 75 mg daily orally. This standardised schedule has recently been challenged by the publication of the OASIS 7 trial (CURRENT-OASIS 7 trial; Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions trial), which demonstrated superior efficacy of double dose clopidogrel for the first week of therapy (600 mg loading dose followed by 150 mg daily) with respect to prevention of further MI and stent thrombosis in patients undergoing PCI.[8]

According to the American College of Cardiology and American Heart Association Guidelines, clopidogrel should be continued for at least one month and up to 12 months in medically treated patients with acute coronary syndromes and patients receiving bare metal stents; patients treated with drug-eluting stents should receive clopidogrel for a minimum of 12 months.[9] Ongoing treatment beyond one year is controversial, but some experts advocate ongoing treatment if it is well tolerated. In this regard it is important to note the 2009 study by Harjai and colleagues that failed to demonstrate any benefit of dual antiplatelet therapy beyond 12 months.[10]

Specific precautions and interactions

Drug interactions

Omeprazole inhibits CYP2C19, the CYP450 enzyme responsible for converting clopidogrel to its active metabolite. Studies have demonstrated a 45% reduction in active metabolite levels in people receiving clopidogrel in conjunction with omeprazole compared with those taking clopidogrel alone. This appears not to be a class effect of proton pump inhibitors.[11] These findings remain controversial and published studies have yielded conflicting results.[12] However, the US Food and Drug Administration (FDA) and the European

Medicines Agency have been prompted to issue warnings on the coadministration of omeprazole and clopidogrel.

Other medications that may exert similar effects on the CYP450 system include esomeprazole, cimetidine, fluconazole, ketoconazole, voriconazole, fluoxetine and fluvoxamine.

Concomitant use of NSAIDs and anticoagulants increases bleeding risk and these combinations should be used judiciously.

Genetic variability

Recent studies have demonstrated that polymorphisms in the gene encoding CYP2C19 that confer reduced enzymatic function are associated with significantly lower levels of the active clopidogrel metabolite, diminished platelet inhibition and a higher rate of major adverse cardiovascular events.[13,14] Although not routine practice in Australia, in the USA the FDA has issued a statement recommending CYP2C19 gene testing for patients receiving this drug. There is emerging evidence that double dose clopidogrel (600 mg loading and 150 mg daily) may prove to be more efficacious in patients who are poor metabolisers of the drug.

Dose monitoring

There is no consensus in the literature pertaining to the best test of adequate platelet function blockade by clopidogrel. Further, there is conflicting evidence as to the utility of such testing. A recently published study by Breet and colleagues found that following cardiac stent insertion, atherothrombotic events only weakly correlated with results obtained using aggregometry, VerifyNow and Plateletworks assays.[15] Conversely, Bonello and colleagues used vasodilator-associated stimulated phosphoprotein testing to adjust clopidogrel dosages and were able to significantly improve outcome in patients undergoing PCI compared with those treated with a standard dosing regimen.[16]

At the present time there is insufficient evidence to make firm recommendations regarding the best test for assessing response and how to apply any results to patient management. Therefore, dosing currently is empirical, and platelet testing should be confined to research centres and for patients enrolled in clinical trials.

Surgery and invasive procedures

When possible, nonelective surgery requiring cessation of clopidogrel should be postponed for six weeks and 12 months after bare-metal and drug-eluting stent insertion, respectively. There are no definite consensus guidelines pertaining to the required period for clopidogrel cessation before an invasive procedure. However, empirically many surgeons and anaesthetists will not operate or perform neuraxial anaesthesia within five to seven days of cessation of the drug.

In situations where immediate action is required, platelet transfusions may be given to abrogate the effect of clopidogrel. However, this must be balanced against the risk of stent thrombosis and decisions must be made in consultation with a patient's cardiologist.

Prasugrel

Prasugrel, like clopidogrel, is a prodrug requiring the CYP450 system for conversion to its active metabolite. Prasugrel, however, inhibits ADP-induced platelet aggregation more rapidly and with greater efficacy than clopidogrel. The TRITON trial (TRITON–TIMI 38; Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) demonstrated the superiority of prasugrel in the prevention of MI and stent thrombosis in patients undergoing PCI, particularly in the diabetic cohort.[17] This was counterbalanced by an increased risk of bleeding observed in patients with a history of cerebrovascular accident, those who were 75 years of age or older and those whose weight was less than 60 kg.[17] As a result, the FDA has issued a 'black box' warning regarding these patient cohorts. Prasugrel has recently gained authority PBS approval for patients with acute coronary syndromes managed by PCI in combination with aspirin.

Given prasugrel's more efficient metabolism and antiplatelet effects, CYP450 drug interactions and genetic variability are less of an issue with this drug than with clopidogrel. With regards to invasive procedures in patients taking prasugrel, similar approaches to those used for patients taking clopidogrel should be implemented.

Cangrelor

Cangrelor, a nonthienopyridine ATP analogue, is a competitive inhibitor with a high affinity for the P2Y12 receptor. It is given intravenously and has a short half-life of three to six minutes. Due to its pharmacokinetic profile it may have a role in the treatment of patients who require rapid but reversible platelet inhibition. It is currently not licensed for clinical use but is being extensively investigated in clinical trials.[18,19]

Ticagrelor

Ticagrelor, a cyclopentyl triazolopyrimidine, is a direct acting, reversible and selective P2Y12 inhibitor. It has a rapid onset of action following oral administration and demonstrates less variability in terms of its pharmacodynamics when compared with clopidogrel. A dose of 90 to 180 mg twice daily results in significant inhibition of ADP-induced platelet aggregation.

Ticagrelor has undergone extensive evaluation culminating in a phase three study that has recently been published (the Platelet Inhibition and Patient Outcomes [PLATO) study].[20] In this study, more than 18,000 patients with acute coronary syndromes were randomised to receive ticagrelor (loading dose of 180 mg followed by 90 mg twice daily) or

clopidogrel (at a loading dose of 300 mg and a maintenance dose of 75 mg). At 12 months, ticagrelor was clearly superior when compared with clopidogrel, with the primary endpoint (the composite of death from vascular causes, MI or stroke) observed in 9.8% of patients receiving ticagrelor compared with 11.7% in patients on clopidogrel. Interestingly and for the first time, this improved outcome was not associated with an increased risk of bleeding, with a 1.04 hazard ratio for major bleeding for ticagrelor as compared with clopidogrel. These results are encouraging, particularly in view of the size of the cohort studied. If the drug continues to be well tolerated then it may be a significant advance and a major addition to the currently available antiplatelet therapies.

Conclusion

The P2Y12-blocking class of antiplatelet drugs are a vital component in the armamentarium against CVD. Although clopidogrel is currently the most widely used drug in this class, there are issues associated with dosing and also with CYP450-related drug interactions and genetic variability in its metabolism. Therefore, the emerging drugs in this class, which may be able to be better tailored to certain clinical scenarios, may supplant its use.

Despite well over a decade of experience with this class of drugs, several unanswered questions remain. These include the optimal dosing regimen, duration of therapy and optimal reversal strategy for patients requiring surgery or who present with major bleeding. MT

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