Editorial

Variability in response to clopidogrel

***Andrew J McLachlan**, Professor of Pharmacy (Aged Care), Faculty of Pharmacy, University of Sydney, and Centre for Education and Research on Ageing, Concord Hospital; and **Terence J Campbell**, Professor of Medicine, University of New South Wales, and Head, University Department of Medicine, St Vincent's Hospital, Sydney*

Key words: pharmacokinetics, platelet antagonists, proton pump inhibitors.

(Aust Prescr 2010;33:62–3)

The antiplatelet drug clopidogrel is effective when used in combination with aspirin for the prevention of coronary events in patients with coronary artery stents and acute coronary syndromes. However, there is growing evidence that despite this dual antiplatelet therapy some patients experience more atherothrombotic events than expected.[1] This therapeutic failure has been called 'clopidogrel resistance'. The possible factors contributing to variability in the response to clopidogrel include poor adherence, variable bioavailability, drug interactions, and genetic polymorphisms in drug metabolising enzymes or in platelet receptors.

Clopidogrel is a prodrug and its active metabolite irreversibly binds to and inhibits the adenosine diphosphate P2Y12 receptor on platelets. Approximately 85% of the dose is metabolised to an inactive metabolite (by plasma esterases) and 15% is activated by hepatic cytochrome P450 (CYP) isoenzymes in a two-step metabolic process involving CYP3A4 and CYP2C19.[2]

The impact of polymorphisms in the genes that control clopidogrel absorption, metabolic activation and pharmacological effect was examined in the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI). This study found that patients who were given clopidogrel after a myocardial infarction were more likely to have a recurrent cardiac event if they had an allelic variation of the CYP2C19 gene that led to reduced enzyme activity.[3] This finding was supported by another study which included healthy volunteers, and patients receiving clopidogrel for acute coronary syndrome (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction, TRITON-TIMI 38). The trial found that people with CYP2C19 variants encoding for reduced metabolic activity had lower concentrations of clopidogrel's active metabolite, reduced platelet inhibition and a higher rate of major adverse cardiovascular events.[4] Taken together these data suggest that the ability to generate adequate concentrations of the active metabolite is central to the variability in response to clopidogrel.

The possible impact of concomitant drug therapy on clopidogrel efficacy (via an effect on concentrations of the active metabolite) has also been investigated. Two retrospective studies, involving 13 000[5] and 8000[6] patients, have suggested a clinically significant reduction of efficacy, in terms of recurrent coronary events, in patients treated with clopidogrel if they were also receiving proton pump inhibitors. The effect was modest (approximately 25% increased risk in both studies) and of only borderline statistical significance, suggesting the need for caution in interpreting these results. Pantoprazole does not appear to attenuate clopidogrel's benefits. This has been attributed to its predominant effect on CYP2C9 inhibition and weaker effect on CYP2C19 activity.[5]

In this issue…

At the time of writing there is a moratorium on the use of seasonal influenza vaccine in children under five years of age. Questions are also being raised about the H1N1 immunisation campaign. It is hoped that these concerns do not detract from the overall benefits of immunisation against infectious diseases.

Preventing bacterial infections is important as antibiotic resistance is increasing. John Turnidge advises how to tackle the multiresistant organisms which are emerging in community practice. Preventing infection is critical in transfusions and Andrew Guirguis and Erica Wood tell us of the methods used to maximise the safety of plasma-derived products.

Prevention is the focus of the article by Jenny Reath and Ngiare Brown on the management of cardiovascular disease in Aboriginal and Torres Strait Islander people. Screening from the age of 18 years should help to reduce the high rates of cardiovascular morbidity and mortality.

Proton pump inhibitors are often prescribed to patients taking dual antiplatelet therapy to try and reduce the risk of gastrointestinal bleeding, so it is particularly relevant to know if they do reduce the efficacy of clopidogrel. A recent prospective randomised comparison of clopidogrel with prasugrel, a new thienopyridine antiplatelet drug, in which one-third of 14 000 patients were taking a proton pump inhibitor at study entry,[7] failed to confirm any clinically significant interaction during a 400-day follow-up period. There was no difference in the efficacy of either clopidogrel or prasugrel in preventing vascular events, between those patients who were taking proton pump inhibitors and those who were not. This appears to have been confirmed by the only randomised trial of omeprazole versus placebo in 3627 patients taking clopidogrel, the COGENT study, which was presented in September 2009 (21st annual Transcatheter Cardiovascular Therapeutics scientific symposium, California), but is not yet published. There were a total of 136 cardiovascular events over a mean follow-up of 133 days, and the Kaplan-Meier curves for the two groups were absolutely superimposed. While possibly not powered to detect very small differences, this result does seem to rule out any major reduction in the efficacy of clopidogrel caused by omeprazole. This is a reassuring finding as it has not been clear what could be done to avoid this problem. The use of H_2 antagonists (such as ranitidine) has been suggested, but there are doubts about their equivalent efficacy to proton pump inhibitors (and few data to support this recommendation).

In November 2009, however, the US Food and Drug Administration (FDA) announced changes to the product information, based on studies suggesting reduced efficacy in terms of platelet function. The new recommendations are to avoid prescribing omeprazole or esomeprazole concurrently with clopidogrel. The FDA states that there are insufficient data to make a recommendation regarding other proton pump inhibitors, but it also recommends that patients on clopidogrel avoid cimetidine (but not other H_2 antagonists), fluconazole, ketoconazole, voriconazole, etravirine, fluoxetine, fluvoxamine and ticlopidine.[8] Understandably this recommendation has caused confusion in the cardiological community, who believe that clinical outcomes are more important than platelet function studies.

Suggestions to overcome so-called clopidogrel resistance include the assessment of adherence to clopidogrel therapy, increasing the clopidogrel dose (to increase the amount of active metabolite), screening patients to identify CYP2C19 variants, and avoiding drug interactions with proton pump inhibitors. Well-designed trials to evaluate the effectiveness of these strategies are lacking, but a recent case series suggested minimal benefits from increasing the clopidogrel dose to as high as 300 mg daily.[9] Routine testing of CYP2C19 allelic variations is not common practice and the risk of adverse effects from increasing the clopidogrel dose requires further investigation. Assessing patient adherence to clopidogrel therapy and avoiding possible drug interactions currently appear to be the most practical strategies. Lastly, it remains unclear whether the interaction between proton pump inhibitors and clopidogrel is of clinical significance.

References

1. Angiolillo DJ. Variability in responsiveness to oral antiplatelet therapy. Am J Cardiol 2009;103(Suppl):27A-34A.
2. Kim KA, Park PW, Hong SJ, Park JY. The effect of CYP2C19 polymorphism on the pharmacokinetics and pharmacodynamics of clopidogrel: a possible mechanism for clopidogrel resistance. Clin Pharmacol Ther 2008;84:236-42.
3. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Meneveau N, et al; French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med 2009;360:363-75.
4. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354-62.
5. Juurlink DN, Gomes T, Ko DT, Szmitko PE, Austin PC, Tu JV, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009;180:713-8.
6. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009;301:937-44.
7. O'Donohue ML, Braunwald E, Antman EM, Murphy SA, Bates ER, Rosenman Y, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. Lancet 2009;374:989-97.
8. US Food and Drug Administration. Information for healthcare professionals: Update to the labeling of clopidogrel bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC). 2009 Nov 17. www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190787.htm [cited 2010 May 7]
9. Pena A, Collet JP, Hulot JS, Silvain J, Barthelemy O, Beygui F, et al. Can we override clopidogrel resistance? Circulation 2009;119:2854-7.

Further reading

Acute Coronary Syndrome Guidelines Working Group. Guidelines for the management of acute coronary syndromes 2006. Med J Aust 2006;184(8 Suppl):S9-29.

Professor McLachlan was a member of a clopidogrel advisory board sponsored by Sanofi Aventis in 2008.

Professor Campbell: none declared