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NSW tag New South Wales Therapeutic Advisory Group Inc.

Clopidogrel – Proton Pump Inhibitor Drug Interaction
Discussion paper
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Introduction

Concern about a possible interaction between clopidogrel and proton pump inhibitors (PPI) arose following publication of data in 2006 that showed an association between PPI treatment and a diminished biological action of clopidogrel.[1] Since publication of these data, considerable debate has developed regarding the clinical significance and importance of this interaction. This paper will briefly review the available data regarding the interaction, platelet inhibition and potential clinical importance.

What is the basis of the interaction?

Clopidogrel and PPIs are both metabolised by the hepatic cytochrome P450 (CYP) enzyme system. The original paper raising the interaction proposed the mechanism of the interaction was a competitive effect of PPIs on CYP2C19.[1]

Clopidogrel is a specific and potent inhibitor of platelet aggregation. Clopidogrel is a prodrug that is metabolised to its active form in sequential oxidative steps. CYP isoenzymes that have been reported to be involved in the metabolism/activation of clopidogrel include CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP3A5,[2-4] with indications that CYP2C19 plays a key role.[5, 6]

PPI metabolism (except rabeprazole) is undertaken by CYP2C19 and CYP3A4.[7, 8] Most PPIs inhibit CYP2C19 (omeprazole, esomeprazole, lansoprazole) but each PPI inhibits individual CYP isoenzymes to a different extent. For example, pantoprazole is a more potent inhibitor of CYP3A4 than the other PPIs and is the most potent inhibitor of CYP2C9.[7] Rabeprazole is metabolised to rabeprazole thioether primarily by a non-enzymatic process with only a small contribution by CYP2C19 and CYP3A4 to its metabolism.[9] However, rabeprazole thioether has been shown to inhibit CYP2C9, CYP2C19 and CYP3A4 activity.[7]

Concern regarding the clinical significance of a pharmacokinetic interaction between clopidogrel and PPIs is supported by a number of pharmacogenetic studies. These studies show clopidogrel response is diminished in people who carry a reduced-function CYP2C19 variant allele and have confirmed they have less of the clopidogrel active metabolite than those with the normal-function CYP2C19 allele.[3, 6, 10-13] Some studies have also demonstrated higher rates of subsequent cardiovascular events in those taking clopidogrel who have the reduced-function CYP2C19 variant allele.[10-12] These pharmacogenetic differences may explain the 15–20% of individuals who do not respond to clopidogrel.

The interaction between clopidogrel, PPIs and the CYP isoenzymes is complicated and there is no conclusive evidence indicating which PPIs are more likely or less likely to interact with clopidogrel than others.

Regarding H_2 antagonists as an alternative to PPIs, one study suggests there is no significant pharmacokinetic or pharmacodynamic interaction between ranitidine and clopidogrel,[14] whilst cimetidine is a known inhibitor of many CYP isoenzymes.[15]

Platelet inhibition

A number of studies (including two prospective randomised controlled trials (RCTs)) have shown that co-administration of PPIs attenuate the platelet response to clopidogrel to various degrees. These studies are summarised in Table 1.

Clinical significance of the interaction

A number of studies have been conducted assessing the clinical significance of the interaction but there have been no completed or published prospective RCTs assessing clinical outcomes. Study types conducted include retrospective database studies, post-hoc analyses of RCTs, case-control and retrospective cohort studies.

There is no conclusive evidence about the clinical significance of the interaction with findings varying between studies showing no effect of concomitant clopidogrel and PPI on outcomes and studies showing increased rates on acute coronary syndrome, death or other unfavourable outcomes in patients on both medications. The reasons for the differences in the results of these studies are unclear but some of the variability may be due to different rates of clopidogrel non-responders and effects of pharmacogenetic differences in other CYP enzymes such as CYP3A5. These studies are summarised in Table 2.

Recommendations by regulatory agencies and professional bodies
A number of regulatory agencies and professional bodies around the world have made statements regarding this. There is a spectrum of advice ranging from the cautious (do not co-prescribe unless absolutely necessary) to more relaxed approaches (evidence does not justify a change in practice). Recommendations are summarised in Table 3.

What it means in practice
Until prospective RCTs are published no definitive advice regarding this the clopidogrel-PPI drug interaction will be possible beyond the general principles of quality use of medicines (QUM) i.e. judicious selection of treatment options (including choice between drug or non-drug treatment and no treatment), appropriate choice of medicines when they are required, and safe and efficacious use of medicines.[16]

Therefore the following practice points based on QUM principles are recommended:

1. Reviewing the need for all medications on a routine basis is a principle of QUM. Therefore, reviewing the need for a PPI in patients prescribed clopidogrel, particularly in those who have had a cardiac event while taking clopidogrel, is supported.
2. Decisions to cease or continue dual clopidogrel-PPI therapy should be made on an individual basis balancing the risks and benefits for each patient.
3. There is no rational basis to swap PPIs in individual patients.
4. If a decision to cease the PPI is made and gastroprotection is still desired then an H_2 antagonist (except cimetidine) may be considered. However, the relative efficacy of H_2 antagonists compared to PPIs should be taken into account.
5. Patients should be advised not to stop taking clopidogrel unless recommended to do so by their medical practitioner.
6. Patients should be advised to seek urgent medical attention if they suffer chest pain (or other symptoms of cardiac disease) or experience bleeding while taking these medications.

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Table 1: Summary of studies assessing platelet function during concomitant clopidogrel and PPI therapy

Year Author	Study type	Industry Sponsorship	Platelet function test	PPI tested	Finding
2009 Siller-Matula et al[17]	Compared responsiveness to clopidogrel with or without PPI in 300 patients with coronary artery disease – do not describe method of randomisation if any	Nil declared	VASP assay* ADP aggregometry**	Pantoprazole Esomeprazole	"The intake of pantoprazole or esomeprazole was not associated with a reduced platelet inhibition by clopidogrel as compared to patients without PPI"
2009 Cuisset et al[18]	RCT	Nil declared	VASP assay* ADP aggregometry**	Omeprazole Pantoprazole	Use of omeprazole significantly reduced the antiplatelet activity of clopidogrel compared with pantoprazole.
2009 Sibbing et al[19]	Cross-sectional observational study	Dynabyte provided material for analysis of platelet function free of charge	ADP aggregometry**	Omeprazole Esomeprazole Pantoprazole	"Attenuating effects of concomitant PPI treatment on platelet response to clopidogrel were restricted to use of omeprazole." Due to power of study attenuating effects of esomeprazole cannot be excluded
2008 Gilard et al[20]	RCT	Nil declared	VASP assay*	Omeprazole	Patients with omeprazole plus clopidogrel had less platelet inhibition than patients with clopidogrel alone: "The clinical impact of these results must be assessed by further investigation, but we recommend not adding systematically a PPI treatment to the antiplatelet dual therapy without formal indication."
2008 Small et al[21]	Open-label 4 period crossover study	Eli Lilly	Turbidimetric aggregometry	Lansoprazole	Inhibition of platelet aggregation was lower in patients on lansoprazole and clopidogrel than patients on lansoprazole and prasugrel

*VASP assay = vasodilator-stimulated phosphoprotein phosphorylation assay
**ADP aggregometry = adenosine diphosphate aggregometry

Table 2: Summary of Studies assessing clinical outcomes in people receiving concomitant clopidogrel and PPI therapy

Year Author	Study type	Industry Sponsorship	Primary endpoints	Adjustment for confounders	Finding
2009 Rassen et al[22]	Retrospective study of 3 healthcare databases in North America	Nil	ACS* hospitalisation, revascularisation, death	Yes	No conclusive evidence of a clopidogrel-PPI interaction of major clinical relevance. Data suggests that if this effect exists, it is unlikely to exceed a 20% risk increase.
2009 O'Donoghue et al[23]	Post-hoc analysis of two previously conducted RCTs (PRINCIPLE-TIMI and TRITON-TIMI) - in both trials PPI use at discretion of treating doctor and not concealed	Nil declared for this analysis. Industry sponsorship for original trials	Cardiovascular death Nonfatal ACS* Nonfatal stroke	Yes	PPI modestly attenuated the pharmacodynamic effects of clopidogrel but did not affect the clinical outcome of patients given clopidogrel.
2009 Juurlink et al[24]	Population-based nested case-control study. Cases were those readmitted within 90 days after discharge	Nil declared	Recurrent ACS* Death	Yes	Current use of PPIs was associated with an increased risk of infarction. But pantoprazole had no association with readmission for ACS
2009 Ho et al[25]	Retrospective cohort study looking at all-cause mortality or rehospitalisation for acute coronary syndrome	Nil declared	All cause mortality Rehospitalisation for acute coronary syndrome	Yes	Clopidogrel and PPI after ACS* was associated with an increased risk of adverse outcomes compared to clopidogrel without PPI.
2008 Pezalla et al[26]	Claims database analysis	Nil	ACS*	Limited	One year acute ACS* rates were 1.38% in controls, 3.08% in the low PPI exposure, and 5.03% in the high PPI exposure group.
2008 Dunn et al[27]	Abstract – post-hoc analysis of CREDO trial	Unknown	Death, ACS*, stroke	Yes	Clopidogrel reduced adverse events at 1 year to similar degree whether or not patients were on a PPI
2008 Aubert et al[28]	Abstract – retrospective cohort study using the national Medco Integrated Database file	Unknown	Stroke, angina, ACS*, CABG†	Not reported	Patients taking PPIs with clopidogrel had a 32.5% incidence of a major cardiovascular event within one year vs 21.2% of patients not taking PPIs (adjusted OR 1.79, CI 1.62-1.97)
2009 Bhatt et al[29]	Abstract presented at Transcatheter Cardiovascular Therapeutics 2009. RCT of a phase 3 study testing a combination product containing 75 mg clopidogrel with 20 mg of omeprazole.	Cogentus	Gastrointestinal bleeding and other events, ACS*, CABG†, stroke	Yes	There was no increase in cardiovascular event in patients taking concomitant medications compared to placebo (HR 1.02; 95% CI 0.70-1.51). Gastrointestinal events were significantly higher in patients randomized to placebo (HR 0.55; 95% CI 0.36-0.85). Note: Trial stopped early due to sponsor bankruptcy and enrolled fewer patients than planned and followed for a shorter time.

*ACS = Acute coronary syndrome
† CABG = coronary artery bypass grafting

Table 3: Recommendations by regulatory authorities and professional bodies about concomitant clopidogrel and PPI therapy

Date	Agency	Recommendations
Nov 2009	Food and Drug Administration (US)	• The concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel's active metabolite levels and anti-clotting activity. Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction. • At this time FDA does not have sufficient information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to make specific recommendations about their co-administration. Healthcare professionals and patients should consider all treatment options carefully before beginning therapy. • There is no evidence that other drugs that reduce stomach acid, such as most H2 blockers ranitidine (Zantac), famotidine (Pepcid), nizatidine (Axid), except cimetidine (Tagamet and Tagamet HB - a CYP2C19 inhibitor) or antacids interfere with the anti-clotting activity of clopidogrel. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190787.htm
Aug 2009	New Zealand Medicines and Medical Devices Safety Authority	• Medsafe recommends that healthcare professionals continue their current prescribing practices for clopidogrel. However patients requiring concomitant treatment with a proton pump inhibitor should have their treatment reviewed. If possible an H2-receptor blocker and/ or antacid should be considered instead of a proton pump inhibitor in these patients. http://www.medsafe.govt.nz/profs/PUArticles/Clopidogrel%20and%20proton%20pump%20inhibitors%20-%20possible%20interaction%20Aug%2009.htm
July 2009	Medicines and Healthcare Products Regulatory Agency (MHRA) UK	• The need for PPI therapy in patients who are also taking clopidogrel should be reviewed at their next appointment: avoid concomitant use of these medicines unless considered essential • Prescribe PPIs in line with their licensed indications where possible • Check whether patients who are taking clopidogrel are buying over-the-counter omeprazole and consider whether another gastrointestinal therapy would be more suitable http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON051770
May 2009	European Medicines Agency	• The new concern relates to several recently published studies examining clinical outcomes of clopidogrel users. Taken together, these studies suggest that a significant interaction might occur between clopidogrel and members of the PPI class of medicines, making clopidogrel less effective when given with these medicines • Taking all the data into account, the Agency's Committee for Medicinal Products for Human Use (CHMP) and its Pharmacovigilance Working Party (PhVWP) have recommended that the product information for all clopidogrel-containing medicines should be amended to discourage concomitant use of PPI and clopidogrel-containing medicines unless absolutely necessary. http://www.ema.europa.eu/humandocs/PDFs/EPAR/Plavix/32895609en.pdf
Nov 2008	The Society for Cardiovascular Angiography and Interventions (US)	• Conflicting data from two studies presented at the 2008 American Heart Association Scientific Sessions concerning possible interaction between clopidogrel and a type of heartburn medication called proton pump inhibitors (PPI; common brands include Prilosec, Prevacid, and Nexium) do not provide sufficient evidence to change clinical practice…Based on these conflicting findings and the previously published literature, SCAI recommends physicians continue prescribing dual antiplatelet therapy after stent implantation according to the guidelines and prescribe a PPI medication when there is a clinical indication for it. http://www.scai.org/pr.aspx?PAGE_ID=5763
Nov 2008	American College of Cardiology / American College of Gastroenterology / American Heart Association	• Neither of the studies presented today provides sufficient evidence to change clinical practice. In the interest of patient safety, the AHA/ACC and the American College of Gastroenterology (ACG) advise that patients who are currently taking these medications should not change their medication regimen unless advised by their healthcare provider. http://americanheart.mediaroom.com/index.php?s=43&item=611

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