

Clopidogrel and Proton Pump Inhibitors: A New Drug Interaction?

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INTRODUCTION

Clopidogrel is a thienopyridine platelet antagonist that irreversibly inhibits the binding of adenosine diphosphate to platelet receptors, ultimately leading to inhibition of platelet aggregation.¹ Clopidogrel is a prodrug requiring hepatic bioactivation via cytochrome P450 isozymes (CYP2C19, CYP3A4, CYP3A5) to its pharmacologically active form. Inhibition of cytochrome P450 may interfere with metabolic activation of clopidogrel, reducing its antiplatelet activity and potentially increasing the risk of thrombosis. More recently, the cytochrome P450 2C19 pathway has been identified as the key pathway in clopidogrel bioactivation.²

Medications and, more recently, genetic mutations have been shown to affect the activity of the cytochrome P450 2C19 pathway.³ Proton pump inhibitors (PPIs), commonly used for prophylaxis and treatment of gastrointestinal bleeding, have been shown to inhibit the cytochrome P450 2C19 pathway to various degrees.⁴ Thus, it is biologically plausible that use of a PPI could impair the metabolic activation of clopidogrel through inhibition of this pathway.

Recent clinical studies have illustrated the potential metabolic interaction between PPIs and clopidogrel, which could result in inhibition of the antiplatelet activity of clopidogrel. The clinical significance of these studies is reviewed below.

METHODS

PubMed and MEDLINE were searched for the period January 1990 to July 2009 using the terms “clopidogrel”, “thienopyridine”, “proton pump inhibitor”, “drug interaction”, “lansoprazole”, “omeprazole”, “pantoprazole”, “esomeprazole”, and “rabeprazole”. Review articles, letters, commentaries, and unpublished abstracts were excluded.

RESULTS

Laboratory studies have demonstrated that PPI interferes with the antiplatelet activity of clopidogrel, because of

inhibition of cytochrome P450 2C19-mediated activation of clopidogrel (Table 1). One of the first studies investigating this phenomenon involved 124 patients taking clopidogrel, who were randomly assigned to receive omeprazole or placebo.⁵ The platelet reactivity index (PRI), a measure of platelet activity for which higher values have been associated with worse adverse cardiac outcomes, was higher in the omeprazole group than the placebo group.⁵ In a prospective cross-over study, Small and others⁶ randomly assigned patients taking clopidogrel to receive lansoprazole or placebo. Relative to placebo, lansoprazole led to a 13% reduction in the area under the curve and a 29% reduction in the maximum serum concentration of metabolites of clopidogrel.⁶ This study demonstrated that concurrent use of a PPI with clopidogrel resulted in fewer clopidogrel metabolites, thus illustrating that less bioactivation of the parent drug, clopidogrel, had occurred. In another prospective cohort study, 300 patients receiving clopidogrel were grouped according to concurrent PPI use (specifically pantoprazole or esomeprazole) or no concurrent PPI.⁷ The 2 groups had similar PRI values, which suggested no metabolic drug interaction between clopidogrel and the PPIs. Thus, laboratory studies have provided conflicting results about the potential interaction between clopidogrel and PPIs. However, the results in the study by Siller-Matula and others⁷ were explained by the fact that omeprazole is a potent inhibitor of the cytochrome P450 2C19 isozyme, which would lead to inhibition of clopidogrel bioactivation. Other PPIs, such as pantoprazole and esomeprazole, have demonstrated less inhibition of the cytochrome P450 2C19 isozyme, which would mean less interference with clopidogrel bioactivation.⁷

More recent observational data have illustrated the clinical impact of a potential interaction between clopidogrel and PPI. Juurlink and others⁸ performed a population-based, nested case-control study of patients discharged from hospital after myocardial infarction with a prescription for clopidogrel. Patients who experienced reinfarction during the 90 days after initial discharge (cases) were matched to patients who were at

Table 1. Studies Investigating Concurrent Use of Clopidogrel and Proton Pump Inhibitors (PPIs)

Study	Design	Results	Limitations
Gilard et al. ⁵	Randomized, placebo-controlled trial of 124 patients receiving clopidogrel with either omeprazole 20 mg daily or placebo for 7 days	Platelet reactivity index at 7 days: <ul style="list-style-type: none"> • Omeprazole group: 51.4% • Placebo group: 39.8% • $p < 0.0001$ 	Laboratory end point
Small et al. ⁶	Prospective, 4-period cross-over study of 26 patients Clopidogrel 300 mg load with and without concurrent lansoprazole 30 mg daily* Patients were crossed over to their respective treatment arms	Lansoprazole decreased AUC by 13% and C_{max} of clopidogrel metabolites by 29% relative to clopidogrel alone	Laboratory end point
Siller-Matula et al. ⁷	Prospective cohort study of 300 patients receiving clopidogrel and undergoing PCI for ACS Patients grouped as receiving PPI (pantoprazole or esomeprazole) or not receiving PPI	Platelet reactivity index: <ul style="list-style-type: none"> • PPI group: 51% • No PPI group: 49% • $p = 0.724$ 	Laboratory end point
Juurink et al. ⁸	Population-based nested case-control study of post-MI patients discharged with a prescription for clopidogrel (based on Ontario prescription database) 734 of 13 636 patients were readmitted with recurrent MI within 90 days Cases matched to controls on age, PCI, date of hospital discharge, and predicted short-term mortality Cases (concurrent PPI), $n = 734$ Controls (no concurrent PPI), $n = 2057$	No. of patients taking PPI: <ul style="list-style-type: none"> • Cases: 194/734 • Controls: 424/2057 • OR 1.27 (CI 1.03–1.57) Subgroup analysis showed no association between use of pantoprazole and H_2RA and increased risk of reinfarction	Case-control study Higher background rates of other cardiac risk factors (diabetes, heart failure) among cases than among controls
Ho et al. ⁹	Retrospective cohort study of 8205 patients discharged from hospital after ACS with a prescription for clopidogrel; use of a PPI at discharge or during follow-up was captured through a pharmacy database Clopidogrel and no PPI: 36.1% of sample (2961/8205) Clopidogrel with PPI: 63.9% of sample (5244/8205) PPIs used: 59.7% omeprazole (3132/5244), 2.9% rabeprazole (151/5244), 0.4% lansoprazole (22/5244), 0.2% pantoprazole (15/5244); 36.7% (1924/5244) received more than one PPI	All-cause mortality or readmission to hospital for ACS: <ul style="list-style-type: none"> • Clopidogrel and no PPI group: 615/2961 • Clopidogrel with PPI group: 1561/5244 • Adjusted OR 1.25 (95% CI 1.11–1.41) 	Retrospective cohort study Higher background rates of other cardiac risk factors (diabetes, heart failure, renal disease) in PPI group

ACS = acute coronary syndrome, AUC = area under the curve, CI = confidence interval, C_{max} = maximum serum concentration of drug, H_2RA = histamine₂-receptor antagonist, MI = myocardial infarction, OR = odds ratio, PCI = percutaneous coronary intervention.

*This study also examined therapy with prasugrel 60 mg load with and without concurrent lansoprazole 30 mg daily.

risk but did not experience reinfarction (controls). Patients taking concurrent clopidogrel and PPI therapy had a higher risk of reinfarction than those taking clopidogrel alone (odds ratio [OR] 1.27, 95% confidence interval [CI] 1.03–1.57). Omeprazole was the main PPI used in this retrospective analysis. Subgroup analysis suggested that pantoprazole and histamine₂-receptor antagonists were not associated with the higher risk of reinfarction. In another recent observational study, Ho and others⁹ retrospectively investigated 8205 patients who were discharged from hospital with a prescription for clopidogrel after acute coronary syndrome. Clopidogrel and PPI use were identified through pharmacy databases. Concurrent use of clopidogrel and PPI was associated with a higher rate of death or readmission to hospital for acute coronary syndrome than the use of clopidogrel without concurrent PPI (OR 1.25, 95% CI 1.11–1.41). In subgroup analysis of the cohort receiving clopidogrel and PPI concurrently, the risk of death or readmission to hospital was increased with use of omeprazole and rabeprazole. Other PPIs

were not analyzed, given the small proportion of patients in the concurrent clopidogrel and PPI study cohort who were taking these drugs.

DISCUSSION

Initial studies illustrating the potential of a drug interaction between clopidogrel and PPI used laboratory end points, mainly related to platelet activity. Although platelet activity has been associated with clinical outcomes such as thrombosis and cardiac events, several measures of platelet activity have been reported in the literature (e.g., optical aggregometry, whole-blood aggregometry, measurement of urinary or serum thromboxane, platelet function assays), with no universally adopted standard. As well, the assays employed to assess platelet reactivity are numerous and vary in sensitivity and specificity. Thus, there is no established laboratory standard for the measurement of platelet reactivity, which makes interpretation of the various studies more difficult.

Two recent retrospective studies have illustrated the clinical implications of the apparent interaction between clopidogrel and PPI.^{8,9} Because these studies were retrospective, they established only an association and not a causal relationship between concomitant use of clopidogrel and PPI and adverse clinical outcomes. Furthermore, they were subject to the flaws inherent in all retrospective observational studies, namely biases and multiple confounding factors. Both studies established that the concurrent use of clopidogrel and PPI was associated with higher rates of reinfarction and readmission to hospital than use of clopidogrel alone. This phenomenon is thought to be a result of inhibition by PPI of clopidogrel bioactivation by the cytochrome P450 2C19 isozyme. Mechanistically, in vitro interaction between omeprazole and clopidogrel has been demonstrated,⁵ an interaction that was confirmed by the 2 recent retrospective studies. Omeprazole is metabolized by the cytochrome P450 2C19 isozyme to a greater extent than other PPIs, which may make this PPI more likely to interfere with clopidogrel bioactivation. Other PPIs (e.g., pantoprazole) are metabolized by different metabolic pathways and demonstrate less inhibition of CYP2C19; use of these PPIs may avoid or limit the potential for an interaction with clopidogrel.

Although omeprazole was the most common PPI used in the 2 recent studies, there are insufficient clinical data to suggest that another PPI (pantoprazole) would be devoid of this effect on clopidogrel. The subgroup analysis of the PPI cohort in the study by Juurlink and others⁸ suggested that pantoprazole lacks this interaction with clopidogrel. The danger with drawing this conclusion is that the main study was a retrospective, nested case-control study; as such, performing subgroup analysis is fraught with potential biases and errors. The study by Ho and others⁹ had insufficient patients taking pantoprazole to allow a subgroup analysis to determine if that PPI lacked the interaction. The suggestion that there is a specific PPI that does not exhibit this drug interaction is based on subgroup analysis of retrospective data and must therefore be interpreted with caution.

The evidence that one PPI might be safer than another for patients also taking clopidogrel is evolving and controversial. An analysis of the Clopidogrel for the Reduction of Events During Observation (CREDO) study illustrated that use of a PPI increased cardiovascular events regardless of whether patients were receiving clopidogrel.¹⁰ A preliminary presentation on the Medco Outcomes study, the largest study of this topic to date (with 16 690 patients), showed that concurrent use of clopidogrel and a PPI led to more cardiovascular events than use of clopidogrel alone.¹¹ The increased risk of cardiovascular events was similar among all PPIs studied (omeprazole, esomeprazole, pantoprazole, and lansoprazole), with the highest rate of cardiovascular events occurring among patients taking pantoprazole. Thus, there are conflicting data about whether one particular PPI is safe for use by patients taking clopidogrel.

The US Food and Drug Administration is reviewing the data on interactions between clopidogrel and PPIs, but firm recommendations have yet to be made.¹² The latest guidelines from the American College of Cardiology and the American College of Gastroenterology recommend that PPIs should be prescribed when there is a clinical indication for them.¹³

CONCLUSIONS

Evidence is emerging of an association between concurrent use of clopidogrel and PPIs and adverse cardiac outcomes, which supports the mechanistic hypothesis that PPI inhibits the bioactivation of clopidogrel. However, the data are conflicting, and it is not clear if there is one PPI that is safer than the others.

On the basis of the data available, use of PPIs should be avoided by patients who are already taking clopidogrel. Histamine₂ receptor antagonists should be considered, if appropriate, in lieu of a PPI. If a PPI is absolutely necessary, omeprazole should be avoided, given laboratory and clinical studies that have consistently demonstrated an interaction. Pantoprazole is preferred if a PPI is strongly indicated, based solely on laboratory and mechanistic data. The benefit of spacing the administration of clopidogrel and PPI over time, to minimize the impact of this potential drug interaction, is unclear.

Other review articles that have recently been published on this drug-drug interaction^{14,15} confirm that the literature about this particular interaction is constantly evolving. These review articles reached a similar overall conclusion as did the authors of the current review: that concomitant administration of clopidogrel and PPIs should be avoided because of a purported drug-drug interaction. The reviews differed slightly in their recommendation as to whether one particular PPI is safe for use with clopidogrel, because of differing interpretations of subgroup analyses of the published studies included in the reviews and differing relative emphasis on laboratory and clinical results. Interestingly, more recent evidence from prospective randomized trials suggests no clinically significant drug-drug interaction between clopidogrel and PPIs at all.^{16,17} The results of these 2 prospective studies are not covered in the current review, because the current article was already in production at the time these 2 trials were published. The evidence for the drug interaction between clopidogrel and PPIs continues to evolve, and health care professionals must remain alert to further evidence as it arises.

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