Clopidogrel With Proton Pump Inhibitors: Safe or Not?

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ABSTRACT

Gastrointestinal (GI) bleeding is a serious complication associated with use of antiplatelet therapy, and proton pump inhibitors (PPIs) are known to be beneficial in decreasing such risk. Several studies in the recent past have suggested concerns regarding interaction between clopidogrel and PPIs, presumably due to inhibition of clopidogrel activity and thus attenuation of its antiplatelet activity. A web-based literature and guidelines search was done using the keywords “clopidogrel,” “omeprazole,” “proton pump inhibitors” and “interaction.” Of the available results, relevant studies ($n = 11$) were then systematically reviewed and summarized. The studies were categorized based on their retrospective or prospective nature. Most of the retrospective, observational studies suggested a link between the 2; however, recent prospective studies have shown no interaction, as well as a positive influence of PPIs in preventing the GI side effects of antiplatelet therapy. There is currently insufficient clinical evidence to suggest interaction between clopidogrel and PPIs and decision to add PPI therapy to clopidogrel should be guided by its clinical indications rather than as a routine prophylactic measure.

Introduction

Antiplatelet therapy is the cornerstone of management in patients with known coronary artery disease, postpercutaneous coronary intervention (PCI) with stenting, and for reducing incidence of future cardiovascular (CV) events along with mortality.^{1–3} However, there are significant side effects with this therapy, which includes serious bleeding risks, most often gastrointestinal (GI). This can be demonstrated by the fact, that the 1- and 2-year cumulative incidences of GI bleeding among patients on antiplatelet therapy and who were not taking antisecretory drugs were 4.5% and 9.2%, respectively.⁴ To prevent this, the role of PPIs has been well established and is a recommendation of the American College of Cardiology/American Heart Association (ACC/AHA) 2007 Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) guidelines,¹ as well as the American College of Cardiology Foundation/American College of Gastroenterology/American Heart Association (ACCF/ACG/AHA) 2008 expert consensus document,⁵ and its 2010 update.⁶ A testament to this fact is that there are a combined total of more than 100 million prescriptions of both of these generations of drugs in 2009 in North America itself.⁷ This is, however, a conservative number, as many PPIs are now available over the counter and their use can only be estimated.

Clopidogrel is a prodrug, which after absorption gets converted to an active thiol metabolite (R-130964)³

through a complex pathway in the liver, and involves multiple cytochrome P-450 enzymes, mainly CYP2C19 and others like CYP3A, CYP2C9, and CYP1A2. These isoenzymes convert clopidogrel to an active metabolite, which causes irreversible inhibition of platelet P2Y₁₂ adenosine diphosphate (ADP) receptor. This leads to dephosphorylation of intraplatelet vasodilator-stimulated phosphoprotein (VASP). VASP phosphorylation provides platelet reactivity index (PRI), which has been used in studies to determine the response to clopidogrel.

Recent data since the beginning of 2006 suggest that there may be some influence of PPIs on the activity of antiplatelet agents. This was theorized secondary to the fact that all PPIs are hepatically metabolized to an extent via the cytochrome P450 mixed oxidase system. The isoenzymes, CYP3A4 and particularly CYP2C19, are the major isoforms that cause PPI biotransformation *ex vivo*.^{8–10} However, all PPIs have significant variability in the extent of metabolism via this pathway, and competitive inhibition has been a plausible mechanism of interaction between the two. It has been postulated that the interaction between these two genres of drugs may have resulted in attenuated efficacy of clopidogrel. This resulted in the US Food and Drug Administration (FDA) and the European Medicines Agency to recommend avoiding concurrent use of these 2 medications, while emphasizing the need for further research.^{11–13} We summarize our findings from January 2006 to December 2010.

Prospective Studies

Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) trial,¹⁴ is the only multicenter, international, randomized, double-blinded, placebo-controlled, parallel group, phase 3 efficacy and safety study between CGT-2168, which was a fixed-dose combination of clopidogrel (75 mg) and omeprazole (20 mg) as compared with clopidogrel only. The incidence of GI events on dual antiplatelet therapy with PPIs and any interaction between clopidogrel and PPIs were studied. Primary endpoints were upper GI bleeding or bleeding of presumed GI origin with decrease in hemoglobin of ≥ 2 g/dL or hematocrit $\geq 10\%$, and a composite of CV death, nonfatal myocardial infarction (MI), coronary artery bypass graft/postpercutaneous coronary intervention, or ischemic stroke. A total of 3761 patients were enrolled against an anticipated total of 5000, as the sponsor declared bankruptcy. The median follow-up was 106 days, with 109 adjudicated CV events (hazard ratio [HR]: 0.99; 95% confidence interval [CI]: 0.68–1.44; $P = 0.96$) and 55 adjudicated GI events (HR: 0.34; 95% CI: 0.18–0.63; $P < 0.001$). The results indicated no clinically adverse CV interaction between clopidogrel and PPIs, but a statistically significant decrease in the incidence of GI events.

O'Donoghue et al¹⁵ performed a subanalysis of the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44), and Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) data to assess the association between PPI use, measure of platelet functioning, and clinical outcomes in patients receiving clopidogrel or prasugrel. The PRINCIPLE-TIMI 44 trial was a double-blind, 2-phase, crossover study randomizing individuals undergoing planned PCI, to prasugrel (60 mg loading, 10 mg maintenance dose, $n = 102$) or high dose of clopidogrel (600 mg loading, 150 mg maintenance dose, $n = 99$). Crossover to the alternate treatment arm was done at 15 days of randomization. Measurement of platelet activity performed at 18 to 24 hours and day 15 prior to crossover, were included in the subanalysis of interaction due to PPIs. Mean inhibition of platelet aggregation in patients receiving a high dose of clopidogrel was significantly lower in those on PPIs at 2, 6, and 18 to 24 hours after administration of the loading dose. This trend continued with the 150 mg maintenance dose until the 15th day ($29.4\% \pm 23.7\%$ vs $48.8\% \pm 17.6\%$, $P = 0.06$). Thienopyridine hyporesponsiveness, defined as $<20\%$ inhibition of platelet aggregation with $20 \mu\text{M}$ ADP, was significantly higher in patients on PPIs as well (50% vs 7.9% , $P = 0.012$). However, only a few patients had a hypo or inadequate response to prasugrel irrespective of the use of PPIs. The TRITON TIMI 38 trial¹⁵ was a randomized, double-blind, phase 3 trial involving 13,608 patients with acute coronary syndrome (ACS) undergoing planned PCI assigned to prasugrel ($n = 6813$, 60 mg loading, 10 mg/day maintenance dose) or clopidogrel ($n = 6795$, 300 mg loading, 75 mg/day maintenance dose). The primary endpoint of the trial was a composite of CV death, nonfatal MI, or nonfatal stroke. Reduced CYP2C19 enzyme activity would theoretically be more susceptible to additional CYP2C19 inhibition by a PPI, thereby having a higher risk

of CV events. Analysis was also done to determine whether there was an increased risk of adverse outcomes in patients having a single reduced function CYP2C19 allele and taking PPI with either clopidogrel or prasugrel. Multivariate Cox proportional hazards analysis showed no significant association between use of PPIs and risk of a primary endpoint, both for clopidogrel (adjusted hazard ratio [AHR]: 0.94; CI: 0.80–1.11; $P = 0.46$) and for prasugrel (AHR: 1.0; CI: 0.84–1.2; $P = 0.97$). For those with the single reduced-function CYP2C19 allele who were on clopidogrel, primary endpoint occurred in 10.2% on PPIs compared to 13.2% not on PPIs. However, this difference was not significant after adjusting for the propensity to be treated with a PPI. Similarly, no statistically significant difference was noted in patients randomized to clopidogrel and having wild type carriers of CYP2C19 allele. O'Donoghue et al concluded that their current findings did not support the need to avoid PPIs in patients receiving clopidogrel or prasugrel when clinically indicated.

The PACA (Proton pump inhibitors And Clopidogrel Association) trial¹⁶ was a prospective, randomized study comparing the effects of omeprazole vs pantoprazole on platelet reactivity to clopidogrel. Patients ($n = 104$) undergoing PCI following non-ST-segment elevation myocardial infarction and receiving 75 mg aspirin with 150 mg clopidogrel were randomized 1:1 to 20 mg omeprazole or 20 mg pantoprazole daily. The primary endpoint was clopidogrel response 1 month after discharge as determined by PRI-VASP, whereas the secondary endpoint was platelet reactivity assessed with adenosine diphosphate-induced platelet aggregation (ADP-Ag). Baseline values of PRI-VASP and ADP-Ag were not significantly different in the two groups. At the end of 1 month, when compared using the PRI-VASP measurement, pantoprazole had a significantly better platelet response to clopidogrel compared to omeprazole ($36 \pm 20\%$ vs $48 \pm 17\%$; $P = 0.007$). However, no statistically significant difference in platelet reactivity was noted between the two using ADP-Ag ($52 \pm 15\%$ vs $50 \pm 18\%$; $P = 0.29$). The study limitations were its small sample size, lack of comparison to placebo, and laboratory endpoints rather than clinical.

OCLA (Omeprazole CLopidogrel Aspirin) Study⁸ was a double-blind, placebo-controlled trial, in which consecutive patients ($n = 140$) undergoing PCI and receiving aspirin (75 mg/day) with clopidogrel (loading, followed by 75 mg/day) were randomized to receive either omeprazole (20 mg/day) or placebo for 7 days. Clopidogrel effect was tested using platelet VASP expressed as PRI. Blood samples for analysis were drawn on day 1 prior to clopidogrel intake and day 7. A good response to clopidogrel was a PRI $<50\%$, and a poor response was otherwise. Baseline values of PRI in both groups were not statistically different (mean $83.2 \pm 5.6\%$ and $83.9 \pm 4.6\%$; $P = \text{not significant}$). However, on day 7, there was a significant difference in the mean PRI between the 2 groups ($39.8 \pm 15.4\%$ vs $51.4 \pm 16.4\%$; $P < 0.0001$), thus indicating that omeprazole significantly decreased clopidogrel inhibitory effect on platelet P2Y₁₂ as assessed by VASP phosphorylation test.

In January 2010, Yun et al¹⁷ presented a single-blinded, prospective, crossover study in which 20 young, healthy volunteers were randomized to receive clopidogrel (loading

dose of 300 mg once, followed by 75 mg daily) and 20 mg omeprazole or placebo for 14 days with a crossover after 3 weeks. Significant reduction in platelet reactivity was reported in patients receiving placebo compared to omeprazole. This crossover design ensured that genetic determinant of clopidogrel response was minimized. However, this study was limited by its small sample size and being conducted in healthy volunteers.

Retrospective Studies

Juurlink et al¹⁸ conducted a population-based case control study involving 13 636 patients, 66 years or older, who started taking clopidogrel between April 2002 and December 2007 after having received treatment for an acute MI. The cases included in this study were those who got readmitted with an acute MI within 90 days following discharge ($n = 734$). These cases were matched with 2057 controls for age and predicted probability of short-term mortality. Multivariate analysis revealed that current use of PPIs was associated with an increased risk of reinfarction (95% CI: 1.03–1.57). A stratified analysis showed that pantoprazole was not associated with readmission for MI (95% CI: 0.7–1.47). The authors also concluded that pantoprazole was not associated with loss of beneficial effects of clopidogrel when compared to other PPIs.

Ho et al¹⁹ conducted a retrospective study, which included 8205 patients with ACS taking clopidogrel after discharge from 127 veterans affairs hospitals from October 2003 to January 2006. Of these, 63.9% were prescribed a PPI either at discharge or during a follow-up period, whereas 36.1% were not. A multivariate analysis showed that the use of clopidogrel along with PPIs was associated with an increase in the risk of death or rehospitalization for ACS compared with the use of clopidogrel without PPIs. Further analysis of secondary outcomes showed a higher risk of hospitalization for recurrent ACS, but no difference in the all-cause mortality when compared to patients taking clopidogrel without a PPI. Review of medication use as a time-varying covariate noted that the period of use of clopidogrel without a PPI was associated with a significantly lower risk of adverse events. In this study, patients were prescribed either omeprazole (59.7%), rabeprazole (2.9%), lansoprazole (0.4%), or pantoprazole (0.2%), and 36.7% were prescribed more than 1 type of PPI in the follow-up period. This allowed evaluation of interaction of individual PPIs with clopidogrel, which showed a consistent association of omeprazole and rabeprazole with adverse outcomes. They concluded that longer duration of treatment was associated with higher incidence of adverse outcomes, suggesting that time receiving the combination treatment is important, and that PPIs should be prescribed for clear indications such as history of GI bleeding rather than as routine prophylaxis.

A retrospective cohort study by Gupta et al was conducted in patients who underwent PCI from January 2003 to August 2004 and received clopidogrel following discharge.²⁰ They reviewed the risk of adverse clinical outcomes with concomitant use of clopidogrel and PPIs following PCI. The primary outcome was a major adverse CV event (MACE), which was defined as a composite of death (cardiac and noncardiac), MI (Q wave and non-Q wave), and target vessel

failure. Target vessel failure was defined as a composite of cardiac death, clinically driven target lesion, or target vessel revascularization. A total of 315 post-PCI patients were discharged on clopidogrel, including 72 who were discharged on PPI as well. The follow-up period lasted for 50 months with no differences in baseline characteristics of both groups. It is important to note that the use of bare metal stents was higher in patients in the concomitant clopidogrel and PPI group. Also, 78% of the 72 patients in this group received rabeprazole, 15% received omeprazole, and 7% lansoprazole. The results showed that patients discharged on clopidogrel and PPIs had a MACE rate of 56% compared to those on clopidogrel alone having a MACE rate of 38%. The study was limited by its retrospective nature and small sample size.

In a cross-sectional observational study by Sibbing et al²¹ involving 1000 consecutive patients on clopidogrel, ADP-Ag was measured with multiple electrode platelet aggregometry. Platelet aggregation was significantly higher in patients with omeprazole treatment compared to patients without PPI treatment ($P = 0.001$). It was, however, similar in patients on pantoprazole or esomeprazole compared with patients without PPIs. The results were stratified and pantoprazole use was associated with no increase in risk of death/MI (odds ratio [OR]: 1.02; 95% CI: 0.70–1.47), whereas other PPIs were associated with an increased risk of death/MI (OR: 1.40; 95% CI: 1.10–1.77).

In March 2010, a large observational study was presented by Ray et al.²² This was a retrospective cohort study of 20,596 patients hospitalized for CV causes, such as MI, PCI, or UA and receiving clopidogrel from January 1999 through December 2005. Concomitant PPI use and subsequent risk for hospitalizations due to GI bleeding and serious CV disease were studied. It was noted that PPI use in patients at high risk of bleeding resulted in a 3-fold decrease in rates of admission for gastroduodenal bleeding. However, it was not associated with a statistically significant increased risk for serious CV disease (acute myocardial infarction, sudden cardiac death, stroke, or other CV death) (HR: 0.99; 95% CI: 0.82–1.19), either for the entire cohort or for patients having a PCI with stenting. However, the upper bounds of the CIs for these estimates were compatible with a possible increased CV risk associated with concurrent PPI use. Serious CV events were similar in both the low as well as high-dose PPI group.

In April 2010, Kwok et al²³ presented a meta-analysis pooling together 23 studies, covering 93,278 patients, which were either randomized control trials ($n = 3$ studies) or controlled observational studies ($n = 20$ studies), and reported CV adverse events and death in patients who received clopidogrel with or without PPI exposure. Although there were multiple flaws and biases in the studies used for the analysis, resulting in inconsistent and conflicting results, the authors concluded that there is no effect on overall mortality.

A major limitation to the retrospective studies was their inability to address issues related to medication adherence, misclassification of both medication exposure, as well as unmeasured confounding, as over the counter medication use could not be evaluated.

Recently, the FDA issued a black box warning²⁴ to clopidogrel stating that certain subgroups of patients, who have variability in the CYP2C19 enzyme, have lower conversion of clopidogrel to its active metabolite²⁵ and may thus have subtherapeutic activity. This variation in the enzyme is present in 2% to 14% of the adult US population and could have been a potential confounder in the above-mentioned retrospective and prospective studies.

Conclusion

In summary, we can see that there is little concrete evidence regarding interaction between PPIs and clopidogrel. A large, randomized, placebo-controlled trial is needed to further evaluate the interaction between these 2 classes of drugs. Also, routine use of PPIs should be avoided and patients should be screened for the need for PPI therapy. This has been endorsed in the recent ACCF/ACG/AHA 2010 Expert Consensus Document released in December 2010.⁶ A potential method to avoid any possible interaction would be maintaining a time gap between the dosing of PPI and clopidogrel. In such a scenario, the PPI could be administered in the morning, with clopidogrel being dosed at evening, or vice versa. Alternatively, other classes of PPIs other than omeprazole can be used.

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