

Drug Interaction between Clopidogrel and Proton Pump Inhibitors

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Antiplatelet therapy using both clopidogrel and aspirin has been shown to reduce recurrent cardiac events in patients with acute coronary syndromes or in patients who have undergone coronary artery stent placement. Clopidogrel is a prodrug that is transformed in the liver to an active metabolite by cytochrome P450 enzyme. Due to the concern of bleeding in patients on both clopidogrel and aspirin therapy, concomitant prophylaxis of gastrointestinal ulcer with a proton pump inhibitor (PPI) is occasionally prescribed. Data from recent studies have shown that PPIs, which are extensively metabolized by the cytochrome system, may decrease the antiplatelet activity of clopidogrel. This article reviews the metabolism of various PPIs and existing data regarding the drug-drug interaction between PPIs and clopidogrel.

Key Words: Antiplatelet therapy • Clopidogrel • Proton pump inhibitor

INTRODUCTION

The antiplatelet therapy is beneficial in both primary and secondary treatment strategies for cardiovascular disease.^{1,2} These antiplatelet agents, however, have recognizable risks – in particular, gastrointestinal (GI) complications such as ulceration and related bleeding. These risks may be further compounded by the ancillary use of other adjunctive medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and anticoagulants. Given the high prevalence of antiplatelet therapy in clinical practice, coupled with an increased emphasis on their extended use, especially after implantation of a drug-eluting stent,^{3,4} it is imperative that physicians know the potential benefits and the associated

risks of antiplatelet therapy for primary or secondary prevention of cardiac ischemic events. Clopidogrel, a thienopyridine, is a prodrug that is transformed to an active metabolite, which subsequently blocks platelet activation and aggregation. The active metabolite is formed through the cytochrome P450 (CYP) system after two sequential reactions involving CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4, with CYP2C19 playing a major role.^{5,6}

Proton pump inhibitor (PPI) medications are often prescribed prophylactically with initiation of clopidogrel, with the goal of reducing the risk of gastrointestinal tract bleeding while taking dual-antiplatelet therapy. Recent studies, however, suggest that PPIs may reduce the inhibitory effect of clopidogrel on platelet aggregation.^{7,8} In addition, variations in platelet reactivity have been associated with adverse outcomes following stent implantation.^{9,10} These investigations open the question of whether the efficacy of clopidogrel is influenced by concomitant use of PPIs. Certain PPIs inhibit the CYP2C19 pathway and may interfere with the conversion of clopidogrel to its active form. Due to the fact that individual PPIs differ in their propensity to inhibit CYP450 enzymes, PPIs may vary in the degree to which they re-

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duce the antiplatelet activity of clopidogrel. In 2008, the clinical expert consensus documents from the American College of Cardiology Foundation (ACCF), the American College of Gastroenterology (ACG), and the American Heart Association (AHA) recommended that the use of low-dose ASA for cardioprophylaxis is associated with a 2- to 4-fold increase in upper gastrointestinal event risk. Enteric-coated or buffered preparations do not reduce the risk of bleeding. For patients at risk of adverse events, gastroprotection should be prescribed.¹¹

To date, there remains significant ongoing controversy regarding the clinical outcomes of patients taking clopidogrel and PPIs.¹² The US Food and Drug Administration (FDA) recently released an early communication about a safety review of the potential interaction between these two types of medications.¹³ However, there were insufficient data to make any recommendations, and the FDA highlighted the need for additional studies to evaluate the effectiveness of clopidogrel when used concurrently with PPIs. This report reviewed the relevant articles and provided recommendations on the combined use of clopidogrel and PPIs.

MECHANISM OF INTERACTION

Approximately 15% of an absorbed clopidogrel dose is converted to an active thiol metabolite (R-130964), mainly by the hepatic cytochrome P450 isoenzymes.¹⁴ The CYP2C19 isoform is the key enzyme in the metabolism of many of the PPIs, which are also inhibitors of the CYP2C19 isoenzyme in varying degrees. This is important because the antiplatelet effects of clopidogrel rely upon CYP2C19 activity¹⁵⁻¹⁸ This has led to the assumption that some PPIs have the capability to inhibit metabolic activation of clopidogrel. The PPI's ability to inhibit the CYP2C19 activity would reduce R-130964 generation, which could diminish the antiplatelet effect of clopidogrel.

Mega and coworkers found evidence strong linking CYP genetic variation to a reduced exposure to the active drug metabolite, less platelet inhibition, and less protection from recurrent ischemic events in persons receiving clopidogrel. Specifically, common polymorphisms in the *CYP2C19* gene, seen in approximately 30% of Caucasians, 40% of Blacks, and more than 55%

of East Asians,¹⁸ significantly diminish both the pharmacokinetic and pharmacodynamic responses to clopidogrel by approximately one quarter to one third. In addition, they demonstrated that among individuals treated with clopidogrel, patients with a reduced-function *CYP2C19* allele tended to have significantly lower levels of the active clopidogrel metabolite, diminished platelet inhibition, and a higher rate of major adverse cardiovascular events, including stent thrombosis.¹⁸

CLINICAL EVIDENCE OF DRUG INTERACTION BETWEEN CLOPIDOGREL AND PPIs

A large epidemiologic study investigated prescription records of the Ontario Public Drug Program.⁵ The investigators isolated 13,636 patients with prescriptions for clopidogrel within three days of an acute MI. Medical records were assessed to establish exposure to PPIs during clopidogrel therapy. A significant association was found between occurrence of MI and the concurrent use of a PPI (adjusted OR 1.27; 95% CI 1.03 to 1.57). A stratified analysis based on the specific PPI used revealed that pantoprazole was not associated with an increased risk of MI in patients taking clopidogrel. In contrast, the other PPIs were associated with a 40% increase in the risk of recurrent MI (OR 1.40; 95% CI 1.10 to 1.77). In fact, the authors calculated that about 14% of all readmissions due to recurrent MI could be attributed to the clopidogrel – PPI interaction. Another report also suggested the preferential use of pantoprazole compared with omeprazole in patients receiving clopidogrel to avoid any potential negative interaction with CYP2C19.¹⁹

Ho et al. performed a retrospective cohort study involving 8205 patients with acute coronary syndrome (ACS) who were taking clopidogrel after discharge from the hospital.²⁰ Using pharmacy refill data, the investigators found that 64% (n = 5244) of the patients were also prescribed a PPI at discharge or during follow-up, while 36% (n = 2961) were not prescribed a PPI. Patients prescribed a PPI tended to have higher rates of diabetes, prior MI, previous coronary artery bypass graft surgery, peripheral vascular disease, and lung and renal disease. Omeprazole was the most frequently prescribed PPI (59.7%, n = 3132). There was a significantly higher rate

of death or rehospitalization for ACS in patients prescribed clopidogrel plus a PPI (adjusted OR 1.25; 95% CI 1.11 to 1.41). However, PPIs were not associated with death or rehospitalization for ACS in patients not prescribed clopidogrel, which supports the theory of an interaction between PPI and clopidogrel. Figure 1 showed the cumulative risk of all-cause mortality and recurrent acute coronary syndrome (ACS) among patients taking clopidogrel after hospital discharge for ACS who were prescribed a proton pump inhibitor (PPI). This figure suggested that patients who had only clopidogrel without PPI had a better prognosis than those who received both clopidogrel and PPI.

The Medco Outcomes Study, reported in an abstract presented at the AHA 2008 Scientific Sessions, analyzed a retrospective cohort of 14,383 patients who were at least 80% adherent to clopidogrel following stent placement during a one-year period.²¹ Patients who had no preceding cardiovascular events prior to receiving their stent showed a 32.5% incidence of major adverse cardiovascular events (hospitalization for stroke, MI, angina,

or coronary artery bypass graft) within a year of stent placement if they were also on PPI therapy compared with a 21.2% incidence in patients not taking PPIs (adjusted OR 1.79; 95% CI 1.62 to 1.97). However, a more pronounced effect was seen among patients with a preceding cardiovascular event prior to receiving their stent (PPI 39.8% vs. no PPI 26.2%; adjusted OR 1.86; 95% CI 1.63 to 2.12).

A similar study, the Clopidogrel Medco Outcomes Study, was presented at the Society of Cardiovascular Angiography and Interventions (SCAI) 2009 Scientific Sessions.²² Researchers analyzed integrated data on pharmacy and medical claims from more than 10 million patients, including 16,690 patients taking clopidogrel for a full year following coronary stents. The study found that the risk of major adverse cardiovascular events was raised from 17.9% to 25.1% in patients also taking PPIs (HR 1.51; 95% CI 1.39 to 1.64; $p < 0.0001$). The overall risk of major cardiac events was 51% higher among patients taking any PPIs. This included a 70% increase in the risk of myocardial infarction or unstable angina, a

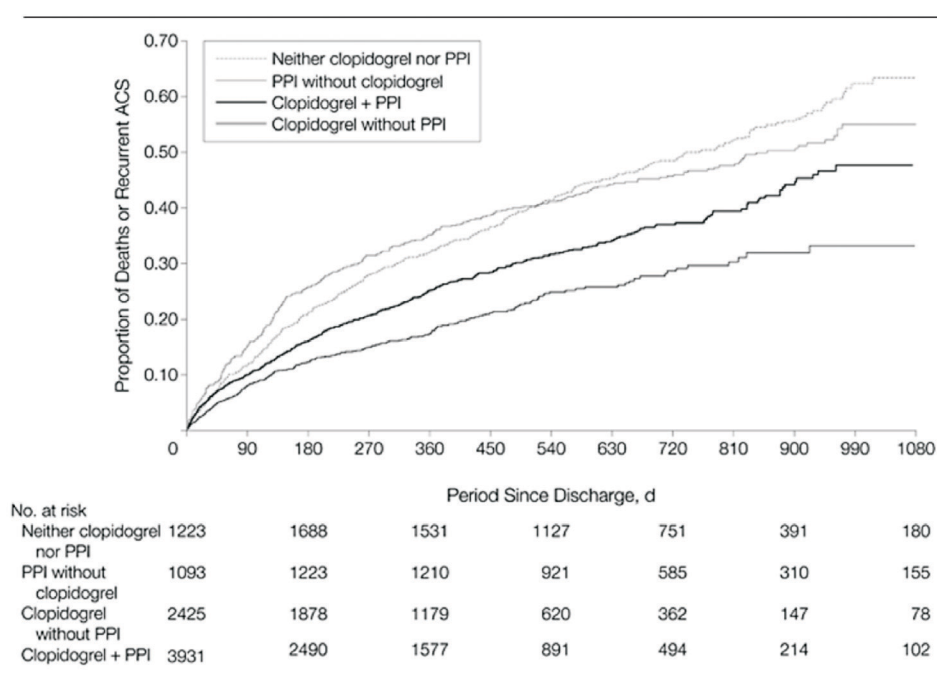


Figure 1. The cumulative risk of all-cause mortality and recurrent acute coronary syndrome (ACS) among patients taking clopidogrel after hospital discharge for ACS prescribed a proton pump inhibitor (PPI). The number at risk indicates the number of individuals at risk for each period during the 90-day interval, with medication use as the time-varying covariate. This figure demonstrates that patients who only had clopidogrel without PPI had a better prognosis than those receiving both clopidogrel and PPI.

From: Ho PM, Maddox TM, Wang L, 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. Reproduced with permission from the American Medical Association, Copyright 2009.

48% increase in the risk of stroke or TIA, and a 35% increase in the need for an urgent target vessel revascularization. The findings were equally concerning when the effects of individual PPIs were analyzed. Omeprazole correlated with a 39% increased risk, esomeprazole with a 57% increased risk, pantoprazole with a 61% increased risk, and lansoprazole with a 39% increased risk. All of the associations were highly statistically significant.²² In summary, these reports found that concomitant use of PPIs and clopidogrel was associated with an increased risk of recurrent myocardial infarction. This effect is not only observed for omeprazole but may also be seen in all PPIs.^{5,20,22} A recent report also found that there was a slightly increased risk (less than 20%) of myocardial infarction hospitalization or death in older patients initiating both clopidogrel and a PPI.²³

CLASS EFFECT?

An important issue concerning the clinical evidence of drug interaction is whether it is a class effect. Analyses of individual PPIs have associated omeprazole and rabeprazole with adverse outcomes, while pantoprazole was shown to be relatively benign when analyzed separately.^{5,20} Conversely, the Clopidogrel Medco Outcomes study noted a class effect but, due to lack of use, did not analyze rabeprazole.²² Preliminary evidence suggests that CYP2C19 inhibition is the driving factor of the interaction.²⁴ Therefore, the magnitude of a clopidogrel interaction could depend on the effect that each PPI has on the CYP2C19 isoenzyme.

Several studies have compared the degree of CYP2C19 inhibition by the currently used PPIs (e.g., omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole). Li et al. compared the potency of the previously mentioned PPIs with regards to the inhibition of CYP2C19.²⁵ The inhibition of CYP2C19 by the PPIs was measured in vitro using S-mephenytoin 4-hydroxylation as a marker reaction. Lansoprazole was shown to be the most potent inhibitor of CYP2C19, whereas pantoprazole and rabeprazole were the least inhibitory. In another in vitro study comparing rabeprazole and omeprazole, rabeprazole was shown to have approximately half the potential of omeprazole to inhibit CYP2C19.²⁶ Pharmacokinetic interaction profiles among

individual PPIs vary greatly. Omeprazole, having been on the market the longest, has undergone the most thorough investigation of its drug-drug interaction. It is metabolized through both the CYP3A4 and CYP2C19 isoenzyme, but has a 10-fold greater affinity to the latter.²⁷

The currently available PPIs include omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole. 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. The relative contribution of this latter pathway in general metabolism differs among drugs and has been reported to be omeprazole = esomeprazole > pantoprazole > lansoprazole > rabeprazole.²⁸ This scheme explains the importance of the CYP2C19 pathway in the biotransformation of the PPIs. Based on available data, the evidence for an interaction with clopidogrel is most compelling for omeprazole. Unfortunately, the results from the studies using lansoprazole, esomeprazole, and pantoprazole cannot be directly compared with those shown with omeprazole. It is too early to suggest that an interaction between the other PPIs and clopidogrel does not exist.

DEALING WITH THE PPI-CLOPIDOGREL INTERACTION

How to respond to the PPI-clopidogrel interaction remains a matter of debate. Some have suggested that PPIs should simply be avoided in patients taking clopidogrel. This is bad advice and reflects the gross oversimplification of an exceedingly complex topic. Others have argued that the PPI-clopidogrel interaction is of no consequence. Although it is probably true for most patients, the interactions do occur in considerable cases. For clinicians uncertain how to address this drug interaction in practice, Juurlink et al.,²⁹ have proposed three simple steps: 1. Evaluate the necessity of PPI therapy. Although PPIs are necessary for some patients, many others take the drugs for dubious indications. In these patients, treatment with a histamine H2 antagonist or antacid may suffice. 2. Consider using pantoprazole when a PPI is indicated. 3. When dual therapy is necessary, taking the PPI at least 4 hours after clopidogrel should minimize the risk of interaction.²⁹

CONCLUSION

In patients with coronary artery diseases, oral antiplatelet therapy decreases ischemic risks, but this therapy may possibly increase bleeding complications. Concomitant use of NSAIDs further raises the risk of GI bleeding. From the ACCF/ACG/AHA 2008 expert consensus recommendations, clinicians should pay attention to the gastroprotection strategies consist of the use of PPIs in patients with high risk of GI bleeding and eradication of *H. pylori* in patients with a history of ulcers. PPIs are the preferred agents for the therapy and prophylaxis of NSAID- and ASA-associated GI injury. Substitution of clopidogrel for ASA is not a recommended strategy to reduce the risk of recurrent ulcer bleeding in high-risk patients and is inferior to the combination of ASA plus PPI. Available studies suggest that among patients taking clopidogrel following acute myocardial infarction, the concomitant use of a PPI that inhibits cytochrome P450 CYP2C19 (omeprazole, lansoprazole or rabeprazole) is associated with an increased risk of recurrent myocardial infarction. This effect, which is not seen with pantoprazole therapy, presumably reflects varying degrees of inhibition in the metabolic bioactivation of clopidogrel. In situations when both clopidogrel and a PPI are indicated, pantoprazole should be used since it is the PPI least likely to interact with clopidogrel. Ranitidine or another H₂-receptor antagonist may be an appropriate alternative for patients who require acid-lowering therapy.

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