Proton Pump Inhibitor and Plavix Interaction: An Update

Background

Clopidogrel (Plavix) is a prodrug. It’s metabolized in the liver to the active form that inhibits platelet aggregation.\(^1\) Cytochrome P450 2C19 (CYP2C19) is one of the enzymes involved in the activation of clopidogrel.\(^2\) Proton pump inhibitors (PPIs) can inhibit CYP2C19 metabolism.\(^5\) Patients who have a myocardial infarction (MI) or undergo stent placement and take clopidogrel are sometimes prescribed a prophylactic PPI to reduce the risk of GI bleeding.\(^3\) Pharmacodynamic and retrospective studies first built a case that PPIs might reduce clopidogrel’s antiplatelet effect and increase the risk for cardiovascular events.\(^2\) This document reviews the data for an interaction between PPIs and clopidogrel.

Evidence for an Interaction

The impetus for the retrospective studies that first looked at cardiovascular outcomes in patients taking clopidogrel plus a PPI was a trial evaluating the potential effect of omeprazole on platelet reactivity in patients taking clopidogrel. This study was published in January 2008 by Gilard et al.\(^2\)

The randomized, double-blind, placebo-controlled study included 140 patients undergoing coronary artery stent placement. They all received aspirin and clopidogrel, and were assigned to receive either omeprazole 20 mg daily or placebo for seven days. The primary endpoint of the study was platelet reactivity, as indicated by the platelet reactivity index (PRI). The platelet reactivity index is inversely related to clopidogrel’s effectiveness at reducing platelet activation. Some experts consider a good response to clopidogrel as a platelet reactivity index <50%.\(^2\)

The mean platelet reactivity index was similar for both groups prior to treatment (83.2% in the placebo group and 83.9% in the treatment group). On day seven, the mean platelet reactivity index was 39.8% in the placebo group and 51.4% in the PPI treatment group (p<0.0001). More patients in the PPI treatment group had a platelet reactivity index >50% (indicating poor response to clopidogrel) compared to patients in the placebo group (60.9% vs 26.7%, respectively; p<0.0001).\(^2\)

As a result of this preliminary study, an insurance claims review of around 1000 patients taking clopidogrel and a PPI was conducted by Aetna. Patients were divided into two groups: exposure to a PPI for less than six months (low exposure), and exposure to a PPI for six months or more (high exposure). Almost 5000 patients on clopidogrel with no exposure to a PPI served as the control group.\(^6\)

One year MI rates were 1.38% in the control group, 3.08% in the low exposure group, and 5.03% in the high exposure group. The difference between the control group and the high exposure group was statistically significant (p<0.05). The difference between the control group and the high exposure group remained significant even with adjustment for differences in co-morbidities between the groups.\(^6\)

Another case-control study by Juurlink et al looked at 734 patients who were readmitted with MI or died within 90 days after discharge from hospitalization for acute MI. These cases were matched with 2057 controls. Controls were matched for age, receipt of PCI in the hospital, date of hospital discharge, and predicted probability of short-term mortality.\(^7\)

All patients included in the study filled a script for clopidogrel within three days after hospital discharge following treatment for acute MI.\(^7\)

Cases were noted to be sicker than controls. They were more likely to have heart failure, diabetes, or renal insufficiency.\(^7\)

Current PPI (lansoprazole, omeprazole, pantoprazole, or rabeprazole) use was associated with an almost 30% increased risk for readmission for MI (odds ratio [OR] 1.27, 95% confidence interval [CI] 1.03-1.57). No association was
found between use of an H2-blocker and readmission.\(^7\)

When data for individual proton pump inhibitors were examined, an association between pantoprazole and recurrent MI was not seen. Other PPIs combined (lansoprazole, omeprazole, and rabeprazole) with pantoprazole excluded, were associated with a 40% increase in the risk for recurrent MI within 90 days of hospital discharge (OR 1.40, CI 1.10-1.77). Based on these numbers, between 7% and 14% of readmissions due to reinfarction within 90 days from initial discharge could be associated with concomitant use of clopidogrel and a PPI.\(^7\)

A third published retrospective study by Ho et al looked at a cohort of patients from VA hospitals. Patients who were discharged after treatment for acute MI or unstable angina were included. There were 8205 patients who filled prescriptions for clopidogrel at a VA outpatient pharmacy. The primary outcome for this study was the combined endpoint of all-cause mortality or rehospitalization for acute coronary syndrome (ACS). Secondary outcomes were death, revascularization, and rehospitalization for ACS. Patients were followed for a median of 521 days.\(^8\)

Of the cohort of 8205 patients who filled prescriptions for clopidogrel, 5244 (63.9%) were also prescribed a PPI (lansoprazole, omeprazole, pantoprazole, or rabeprazole). About two-thirds of patients were prescribed omeprazole, about 3% were prescribed rabeprazole, and less than 1% were prescribed lansoprazole or pantoprazole. Remaining patients were prescribed more than one PPI during follow-up. As in the Juurlink study, patients who got clopidogrel and a PPI were older and had more comorbid conditions.\(^8\)

Around 21% of patients on clopidogrel without a PPI were readmitted for ACS or died. This is compared to 30% who got both clopidogrel and a PPI and met the primary endpoint. In patients who were taking clopidogrel plus a PPI, the adjusted risk for rehospitalization was increased (OR 1.86, 95% CI 1.57-2.20) and the adjusted risk for revascularization was increased (OR 1.49, 95% CI 1.30-1.71). The risk for all-cause death was not significantly increased.\(^8\)

The association between use of clopidogrel plus a PPI and a higher risk for adverse outcomes remained when patients with a history of GI bleeding were excluded, and when patients with an H2-antagonist during follow-up were excluded.\(^3\)

For patients who weren’t taking clopidogrel after hospital discharge, a prescription for a PPI was not associated with an increased risk for adverse outcomes.\(^8\)

Another retrospective study, a Medco insurance claims review by Stanek et al, looked at more than 15,000 post-PCI patients taking clopidogrel. Subjects were classified as having no PPI therapy (n=9862) or as having filed a prescription claim for a PPI (n=6828). All PPIs were represented in this study.\(^26\)

The risk for major adverse cardiovascular events at one year was significantly greater in patients who filed an insurance claim for a PPI compared to those who did not (25.1% vs 17.9%, HR 1.51, 95% CI 1.39-1.64, p<0.0001).\(^26\)

All individual PPIs were examined, except for rabeprazole, because there were an insufficient number of patients to analyze. For each PPI, there was a significant increase in the one-year risk for major adverse cardiovascular events in comparison with no PPI use. Hazard ratios ranged from 1.39 with lansoprazole and omeprazole to 1.61 with pantoprazole. These data lent support to the idea that the interaction between clopidogrel and PPIs is a class effect.\(^26\)

While retrospective data continue to be presented and/or published, more data from randomized controlled trials have emerged as well. Post-hoc analyses from PRINCIPLE-TIMI 44 and TRITON-TIMI 38 have been published. Both of these studies compared the effects of clopidogrel and prasugrel, another thienopyridine. Results from the post-hoc analyses suggest that PPIs can reduce clopidogrel’s effect on platelet inhibition, but not worsen clinical outcomes.\(^33\)

In the Proton Pump Inhibitors and Clopidogrel Association (PACA) trial, post-stent patients who received pantoprazole plus clopidogrel 150 mg once daily had a better platelet response to clopidogrel compared to patients who received omeprazole plus clopidogrel 150 mg once daily. Almost half of patients taking omeprazole were non-responders to clopidogrel, compared to about 25% of patients taking pantoprazole.\(^26\)

Preliminary data from the Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) study were presented in September 2009. An analysis of the data was subsequently published in November 2010.\(^26\) COGENT
(n=3,761) looked at the risk for cardiovascular events (i.e., cardiovascular death, non-fatal MI, CABG, or PCI), and GI events (i.e., bleeding or ulcer) in subjects receiving a combination pill containing clopidogrel 75 mg plus omeprazole 20 mg compared with those who got clopidogrel 75 mg alone. All subjects were also taking aspirin.37

The phase III study was stopped early, at the end of 2008 and at about 75% enrollment, because the sponsor declared bankruptcy.22 Analysis of the data suggests that adding omeprazole to clopidogrel and aspirin does not increase the risk for cardiovascular events compared with clopidogrel and aspirin alone. Interestingly, COGENT did show that adding omeprazole to clopidogrel and aspirin reduces GI events significantly (1.1% with omeprazole vs 2.9% without omeprazole at 180 days; HR 0.34, 95% CI 0.03 to 0.56, p=0.001). Omeprazole also reduced the rate of overt upper GI bleeding (HR 0.13, 95% CI 0.03 to 0.56, p=0.001).37,46

Study Limitations

There are limitations to the available data concerning the interaction of clopidogrel with proton pump inhibitors. For example, in the study by Gilard et al, the number of “clopidogrel-resistant” subjects in each group wasn’t known.4 Recruitment of only known clopidogrel-responsive patients might have provided a clearer picture of the potential interaction between clopidogrel and omeprazole.3

Additionally, the mechanism for the interaction between clopidogrel and omeprazole wasn’t studied by Gilard et al. Since the mechanism is thought to involve inhibition of CYP2C19 by omeprazole, inclusion of patients with CYP2C19 polymorphism (genetically reduced CYP2C19 activity which occurs in about 30% of individuals) might have influenced the results.3

Another consideration is that more data are needed to show the correlation between platelet reactivity tests and the risk for thrombotic events.3 Without a more definitive relationship, the significance of the potential interaction between omeprazole (or any PPI) and clopidogrel is unclear.3 However, the results of the retrospective reviews did suggest that clinical outcomes are affected by the interaction between proton pump inhibitors and clopidogrel.6

There are also limitations to the retrospective studies. The results of the Aetna claims review were consistent when data from a subset of patients with specific comorbidities (i.e., diabetes, heart failure, hypertension, hyperlipidemia, ischemic heart disease) were examined. But, for all retrospective studies, there’s always a possibility that confounders remain unaccounted for.

Also, the specific PPIs used in the Aetna claims review were not reported. This information might have helped clarify which proton pump inhibitors are more or less likely to interact with clopidogrel. The Ho study may have helped to elucidate this, but the number of patients taking a PPI other than omeprazole was very small.7

Another limitation of the Ho, Juurlink, and Stanek studies is that the case patients were sicker than the controls. It has been suggested that a higher incidence of diabetes in the case group in the Juurlink study could be responsible for the difference in outcomes.9

Regarding the PRINCIPLE-TIMI 44 and TRITON-TIMI 38 post-hoc analyses, experts point out that subjects overall were younger and healthier than in some of the other studies where patients received clopidogrel and a PPI. As such, they say it’s still a good idea to use caution with PPIs and clopidogrel, especially in older patients with more comorbidities like diabetes and renal failure. They also stress the importance of patient compliance with antiplatelet therapy, which was likely better in these RCTs than in the real-life setting of observational studies, for ensuring optimal effectiveness.34

One of the potential problems with the COGENT data, besides the fact that the study did not reach full enrollment, is that the product used was a proprietary combination tablet. It had different release kinetics than commercially available clopidogrel and omeprazole products. The combination tablet was designed to release omeprazole later than clopidogrel. While there’s no proof that it makes a difference, some experts have suggested that giving the doses of clopidogrel and PPI at different times of day might be a good idea.37 However, there are data showing that the reduction in clopidogrel’s effect occurs regardless of whether the drugs are taken at the same time or up to 12 hours apart.39,40,45

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Mechanism for the Interaction

The potential interaction between PPIs and clopidogrel has been controversial. There are data from RCTs which did not show a negative effect of a PPI added to clopidogrel on cardiovascular outcomes.\(^{6,8,25,41,42}\) Data from platelet aggregation studies are mixed. Some studies show an effect of PPIs on clopidogrel platelet inhibition whereas others do not.\(^{2,13,14,36}\) And retrospective, observational data suggest that patients who get a PPI in addition to clopidogrel are at higher risk for cardiovascular events.\(^{6,8,25,41,42}\)

The mechanism favored is inhibition of CYP2C19 metabolism of clopidogrel to its active form. But this mechanism was questioned in the past by some experts. In the Ho study, rabeprazole, which has the least inhibitory effect on CYP2C19, was associated with worse outcomes than omeprazole.\(^{8}\)

It has been suggested that an increase in gastric pH might reduce the absorption of clopidogrel. However, there are data showing that this mechanism is unlikely because increases in gastric pH by H2-blockers did not affect the pharmacokinetics of clopidogrel.\(^{15}\) Other factors that are known to adversely influence the antiplatelet action of clopidogrel include genetics (CYP2C19 polymorphism), poor compliance, and diabetes.

An individual’s genotype for CYP2C19 affects the antiplatelet activity of clopidogrel. About 30% of blacks and whites, and more than 50% of Asians have a polymorphism that causes reduced activation of clopidogrel.\(^{12,30,31}\) There are data showing that exposure to the active form of clopidogrel is reduced by around one-third in these patients. Plus, when these patients are treated with clopidogrel for ACS, their risk for adverse cardiovascular outcomes might be more than 50% greater than patients who don’t have this polymorphism.\(^{12,30,31}\) In fact, the most recent data on CYP2C19 genotype and its effects on clopidogrel showed that people with the common loss-of-function variant CYP2C19*2 have a diminished response to clopidogrel. Additionally, these individuals, when treated with clopidogrel, have double the risk for a cardiovascular ischemic event or death during one year after PCI compared to individuals without the polymorphism who are being treated with clopidogrel.\(^{35}\)

Is the Interaction a Class Effect?

Esomeprazole (Nexium), omeprazole (Prilosec). There are more data suggesting omeprazole has an association with a reduction in the efficacy of clopidogrel than for any other PPI.\(^{52}\) In fact, product labeling for clopidogrel now warns to avoid concomitant use with omeprazole.\(^{45}\)

Esomeprazole was shown in a randomized clinical trial to significantly reduce platelet inhibition with clopidogrel.\(^{52}\) Avoiding use of esomeprazole with clopidogrel was recommended in the 2009 FDA release warning about reduced efficacy of clopidogrel with PPIs.\(^{38}\)

 Dexlansoprazole (Dexilant), lansoprazole (Prevacid), and pantoprazole (Protonix [U.S.], Pantoloc [Canada]). Lansoprazole and pantoprazole do not appear to inhibit drug metabolism of CYP2C19 substrates, although they do inhibit CYP2C19 in vitro. This may be because lansoprazole and pantoprazole are reversible inhibitors of CYP2C19, in comparison with esomeprazole and omeprazole, which are irreversible inhibitors.\(^{48}\) Product labeling for dexlansoprazole indicates that it isn’t likely to inhibit CYP2C19 in vitro or in vivo.\(^{47,53}\)

There are a number of studies looking at the potential interaction between pantoprazole and clopidogrel. At least three studies looking at the effect of PPIs on platelet aggregation with clopidogrel showed no significant effect of pantoprazole.\(^{13,18,48}\) Data from PACA strengthen the case for choosing pantoprazole for patients taking clopidogrel.\(^{36}\) Pantoprazole was shown in the Juurlink study to not have an effect on clinical outcomes in patients taking a PPI and clopidogrel.\(^{7}\) The validity of these data has been questioned because of the small number of patients in the sample.\(^{16,17}\) In contrast, the Stanek study did show an association between pantoprazole and an increased risk for major adverse cardiovascular events.\(^{26}\) Another retrospective study also showed an increase in the risk of mortality when patients were taking pantoprazole plus clopidogrel compared to those not taking a PPI.\(^{42}\)

Product labeling for clopidogrel now suggests the use of pantoprazole since it has less of an effect on the pharmacological activity of clopidogrel.\(^{43,45}\) Plus, U.S. labeling for dexlansoprazole and lansoprazole state that these drugs reduce exposure to the active metabolite of
clopidogrel by only about 9% and 14%, respectively, and that clopidogrel-induced platelet inhibition is reduced in relation.\textsuperscript{47,49} These labeling changes are based on an unpublished study looking at the effects of dexlansoprazole and lansoprazole compared with esomeprazole and omeprazole on blood levels of clopidogrel’s active metabolite, as well as platelet aggregation. Reductions in clopidogrel’s active metabolite with omeprazole and esomeprazole were significant, and with dexlansoprazole or lansoprazole nonsignificant.\textsuperscript{50}

Rabeprazole (Aciphex [U.S.], Pariet [Canada]). Rabeprazole is an inhibitor of CYP2C19 \textit{in vitro}.	extsuperscript{52} The use of rabeprazole was associated with an increased risk for the primary endpoint of all-cause mortality, rehospitalization, and ACS in the Ho study.\textsuperscript{8} A limitation to this information is that rabeprazole was used in a very small number of patients. Rabeprazole has also been shown to reduce clopidogrel’s effect on platelet aggregation to a similar extent as omeprazole.\textsuperscript{51}

\textbf{Labeling Changes for Clopidogrel}

Product labeling for clopidogrel with regard to the interaction with PPIs has been changed more than once. In May 2009, U.S. clopidogrel labeling was updated. The new information included an explanation of CYP450 polymorphisms and the effect of CYP2C19 polymorphisms on the antiplatelet effect of clopidogrel. The labeling also discouraged the concomitant use of drugs that inhibit CYP2C19.\textsuperscript{19}

The FDA updated the clopidogrel product labeling once again in November 2009, with a stronger warning against using clopidogrel and omeprazole together. This was based on data from the manufacturer of clopidogrel that suggested omeprazole reduces the ability of clopidogrel to prevent platelet aggregation by around 50%. This effect was seen regardless of whether clopidogrel and omeprazole were taken at the same time, or 12 hours apart. This update also included a warning against using clopidogrel with other CYP2C19 inhibitors, including cimetidine, esomeprazole, etravirine (Intelen), felbamate (Felbatol), fluconazole, fluoxetine, fluvoxamine, ketoconazole, ticlopidine, and voriconazole.\textsuperscript{39}

The latest update to the U.S. clopidogrel product labeling with regard to PPI use transpired in August 2010. This change involved the removal of the recommendation against using specific CYP2C19 inhibitors as listed above. The wording was replaced with a warning to avoid the use of clopidogrel in combination with omeprazole or other strong or moderate CYP2C19 inhibitors.\textsuperscript{45}

Canadian \textit{Plavix} product labeling was updated in September 2009 concerning this interaction. The use of clopidogrel with CYP2C19 inhibitors (e.g., omeprazole, lansoprazole, cimetidine, ticlopidine, fluvoxamine, fluoxetine, moclobemide, felbamate, chloramphenicol, ketoconazole, etc) is discouraged.\textsuperscript{38,43}

\textbf{Who Should Get a PPI?}

The matter of which patients should receive a PPI, in light of the potential interaction, is controversial. Many practitioners have been reconsidering across-the-board PPI use in patients on dual antiplatelet therapy (clopidogrel plus aspirin).

The retrospective studies found that many patients who were prescribed aspirin and clopidogrel were also prescribed a PPI. This was in line with the consensus on using a PPI as the drug of choice to reduce the risk for bleeding in patients taking dual antiplatelet therapy.\textsuperscript{19} Other factors that increase the risk for bleeding include a history of ulcers, history of GI bleeding, age 60 years or more, concomitant corticosteroid or NSAID use, and GERD symptoms.\textsuperscript{19}

The results from COGENT, which is the only randomized controlled trial to prove the efficacy of adding a PPI to clopidogrel and aspirin in reducing GI events, adds a new twist. Prior to this, some experts said that a PPI should NOT be automatically prescribed for every patient taking aspirin with clopidogrel, and that the presence of other risk factors for GI bleeding should be taken into consideration. At that time, the only data looking at PPIs for patients taking clopidogrel were retrospective. PPIs, but not H2-blockers, reduced the risk for upper GI bleeding in patients taking either clopidogrel or ticlopidine. Both PPIs and H2-blockers reduced the risk for bleeding from peptic ulcers in patients taking aspirin.\textsuperscript{21}

There were no studies looking specifically at the use of PPIs in patients with CAD on clopidogrel plus aspirin.\textsuperscript{16,19,20}

The most current consensus published in November 2010 on the concurrent use of PPIs and clopidogrel recommends using a PPI for...
clopidogrel patients at a high risk of bleeding. This includes those with a history of GI bleeding, which is the strongest and most consistent risk factor, and those with multiple risk factors for bleeding (i.e., older age; concomitant use of NSAIDs [including aspirin], steroids, or warfarin; and H. pylori infection). The consensus does not provide guidance on the choice of PPI. This is based on a lack of data comparing outcomes when different PPIs are used with clopidogrel. However, weaker inhibitors such as pantoprazole may be the best choices if a patient is also taking clopidogrel.

H2-blockers (e.g., famotidine, ranitidine, etc) are a potential alternative to PPIs. In fact, because of the concern about this interaction, some experts started recommending H2-blockers or antacids instead of PPIs for patients taking clopidogrel. However, H2-blockers appear to be less effective than PPIs. Some data suggest that H2-blockers at DOUBLE the usual dose can reduce the risk for peptic ulcers in patients taking NSAIDs. If clinical judgment leads to use of an H2-blocker in a patient taking clopidogrel, avoid cimetidine, since cimetidine inhibits CYP2C19. There is no evidence that the other H2-blockers or antacids interfere with the antiplatelet activity of clopidogrel.

A logical question is whether or not there are therapeutic alternatives to clopidogrel. Prasugrel (Effient) is now available. It doesn’t require activation solely via CYP2C19 to the active form, but it is activated by cytochrome P450 enzymes. Prasugrel is associated with a higher incidence of bleeding than clopidogrel in some patients, especially those over 75 years old, less than 60 kg, or who have a history of stroke. Prasugrel’s efficacy isn’t significantly affected by PPIs.

Ticagrelor (Brilinta) is another oral antiplatelet drug. Ticagrelor is not a thienopyridine, and unlike clopidogrel or prasugrel, its action is reversible. Ticagrelor is not metabolized by CYP2C19. Keep in mind that clopidogrel’s FDA- and Health Canada-approved indications differ from Brilinta and Effient.

Ticlopidine is another potential alternative since it isn’t affected by CYP2C19. However, its use has fallen out of favor because of an association with fatal thrombocytopenic purpura and neutropenia.

Conclusion

There’s evidence to suggest that omeprazole reduces clopidogrel’s antiplatelet effect [Evidence level B; lower quality RCT]. There are retrospective data to suggest an interaction between clopidogrel and PPIs, with more than a 30% increase in the risk for poor cardiovascular outcomes [Evidence level B; case-control studies].

Prospective data suggest the opposite, that adding a PPI to clopidogrel may not increase the risk for cardiac events. These data also strengthens the evidence that adding a PPI to clopidogrel plus aspirin reduces GI events.

The information about CYP2C19 inhibition and clopidogrel continues to unfold. In patients taking clopidogrel who require a PPI, lean toward dexlansoprazole, lansoprazole, or pantoprazole. Or consider using ticagrelor or prasugrel (Effient) to avoid the issue altogether.

Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the LEVEL OF EVIDENCE for the statements we publish.

<table>
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<th>Level</th>
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| A     | High-quality randomized controlled trial (RCT)  
       High-quality meta-analysis (quantitative systematic review) |
| B     | Nonrandomized clinical trial  
       Nonquantitative systematic review  
       Lower quality RCT  
       Clinical cohort study  
       Case-control study  
       Historical control  
       Epidemiologic study |
| C     | Consensus  
       Expert opinion |
| D     | Anecdotal evidence  
       In vitro or animal study |

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