Clinical Pharmacology: Advances and Applications

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REVIEW

The interaction between clopidogrel and proton pump inhibitors (PPI): is there any clinical relevance?

This article was published in the following Dove Press journal:
Clinical Pharmacology: Advances and Applications
3 September 2010
Number of times this article has been viewed

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Abstract: The potential interaction between clopidogrel and proton pump inhibitors (PPI) in patients with acute coronary syndrome (ACS) raises serious concerns for cardiologists. However, in patients on this combination of drugs, there is no conclusive evidence of an increase in adverse cardiovascular events. From pharmacologic and pharmacodynamic perspectives, there is a real interaction between clopidogrel and PPIs because of the competitive inhibition of CYP2C19 isoenzyme which is required for biotransformation of clopidogrel to its active metabolite. The consequent decrease in the availability of this active metabolite leads to attenuation of antiplatelet efficacy of clopidogrel. In several observational trials, it was shown that decreased antiplatelet effect of clopidogrel due to PPIs may translate into poor cardiovascular outcomes. However, an incomplete RCT (COGENT) and a *post hoc* analysis of two large trials (PRINCIPLE-TIMI 44 and TRITON-TIMI 38 trial) showed no significant adverse cardiovascular events with this combination. Caution is however needed in patients who are hypometabolizers of clopidogrel putting them at a higher risk of adverse coronary events. Since 3% of patients are likely to be hypometabolizers of clopidogrel, routine combination of clopidogrel and PPIs should be avoided. There is a heightened awareness of this interaction following multiple advisory warnings. At the same time, one should not withhold PPIs in patients who are at a high risk of developing gastrointestinal (GI) bleeding. In these patients, selected choices of PPI such as pantoprazole may be helpful and for low risk patients, serious consideration should be given to H_2 receptor antagonists or antacids. Therefore, while not compromising the cardioprotective effect of antiplatelet agents, the gastroprotective benefit of PPI should be strongly considered in patients who need both. Health care providers should remain alert to more outcome data. Future researchers will need to demonstrate the safety of coadministration of PPIs and clopidogrel and trials should be powered to detect major adverse cardiovascular events and facilitate risk stratification based on genetic polymorphism.

Keywords: clopidogrel, proton pump inhibitors (PPIs), acute coronary syndrome (ACS), cardiovascular events, anti-platelet agents

Background

Dual antiplatelet therapy (DAT) is a standard of care in the management of unstable angina, non-ST elevation myocardial infarction (NSTEMI) and acute coronary syndrome (ACS) undergoing PCI. Long term use of DAT is considered to be important for the patency of drug-eluting stents (DES). Furthermore, the antiplatelet action of clopidogrel is of critical importance for the reduction of abrupt thrombotic occlusion of stents. Hyporesponsiveness to clopidogrel has been found to be an independent predictor of cardiovascular events in patients with ACS undergoing percutaneous interventions especially in CYP2C19 genetic polymorphism.[1–3]

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There is a consensus for the use of prolonged DAT regimen after coronary stents especially DES to prevent late and very late stent thrombosis. However, there is a concern for the increased gastrointestinal (GI) bleed in the setting of long term use of DAT, which is the rationale for the use of proton pump inhibitors (PPIs). In this setting of long term DAT regimen, guidelines suggest the use of PPIs to prevent GI bleed. However, there is an ongoing debate about the increased major adverse cardiovascular events (MACE) when PPIs are used in conjunction with clopidogrel. Recently, the US Food and Drug Administration (FDA) has issued a warning that one of the PPIs (Omeprazole) reduces the antiplatelet activity of clopidogrel by 50%. The FDA warning caused a debate in the medical community which has often centered on the decreased efficacy of clopidogrel with concomitant use of PPIs.[4,5]

Rationale for the use of PPIs with DAT

By virtue of their aggregation and homeostasis properties, platelets play a pivotal role in the repair of damaged vascular endothelium. A DAT regimen impairs the role of early homeostasis and the healing of gastric erosions when used along with other medications such as nonsteroidal anti-inflammatory drugs (NSAID) and acetylsalicylic acid (ASA).[6] This issue of increased bleeding has been noted in the initial trials of ACS such as CAPRIE[7] (Clopidogrel versus Aspirin in Patients at Risk of Ischemic events), CURE[8] (Clopidogrel in Unstable Angina to prevent Recurrent Events), CHARISMA[9] (The Clopidogrel for High atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance), and MATCH[10] (Management of Atherosclerosis with Clopidogrel in High risk patients). Recent evidence indicated that the dual anti-platelet regimen was the most significant risk factor associated with serious and fatal GI bleeding in high risk survivors of myocardial infarction.[11] As described in the guidelines,[6] PPIs are the preferred agents for both prophylaxis and treatment of GI side effect of DAT regimen. The consensus document therefore advocates the use of PPIs in ACS patients with a history of GI bleed.

Concerns regarding the use of clopidogrel with PPIs

Recently, there has been controversy and intense debate over the increased MACE with concurrent use of PPIs with clopidogrel in the treatment of CAD.[12–14] There is a growing body of evidence that PPIs may diminish the anti-platelet activity of clopidogrel. Furthermore, the concern regarding the concurrent use of PPIs and clopidogrel has grown due to the widespread use of PPIs and recent FDA advisory regarding the interaction of omeprazole and clopidogrel. The increased MACE may be due to decreased antiplatelet effect of clopidogrel with concomitant use of PPIs as noted in the FDA Advisory, which can be accessed at (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm204253.htm.)

While DAT regimen with clopidogrel and aspirin has been shown to significantly lower the cardiovascular events in patient undergoing PCI, a significant number of events still occur in this population[15] and these events may be due to suboptimal platelet inhibition in certain subset of patients taking the combination of clopidogrel and PPIs.[5] The consequent variable platelet response in these patients predisposes them to early or late stent thrombosis. The other factors for platelet hyporesponsiveness include noncompliance with medications and genetic predisposition. Therefore, Sharma et al[5] have suggested the use of a platelet function test in patients with high risk of stent thrombosis or where it is felt that concomitant use of PPIs may be causing a significant interaction.

Understanding PPI interaction with clopidogrel

To appreciate the PPI-clopidogrel interaction, one needs to understand the metabolic pathways and pharmacokinetics of these drugs. The genetic cause for variable pharmacokinetic responses can be measured by differences in plasma concentration of active metabolites, and variable pharmacodynamic response is measured as differences in the extent of maximal platelet aggregation based on exposure to active metabolites by platelet function testing. Clopidogrel is a potent anti-platelet agent whose action is mediated by irreversible inhibition of purinergic receptor P2Y12.[16,17] It is a prodrug and requires two-step oxidation by hepatic cytochrome P450 enzyme system to convert clopidogrel into an active metabolite. This active metabolite works on the ADP receptors of platelets for its efficacy. These two oxidation steps involve CYP3A, CYP2B6, CYP2C9, and CYP2C19 isoenzymes.[18,19] Biotransformation of clopidogrel has two competing metabolic pathways with the first major pathway leading to 85% of the drug being inactivated by plasma esterases and the remaining 15% undergoing two oxidative steps for conversion into the active metabolite. Both of these steps require CYP2C19 for the biotransformation of clopidogrel to its active metabolite. Juurlink et al[13] estimated that CYP2C19 inhibiting PPIs

collectively were associated with a 40% relative increase in recurrent myocardial infarction.[13] The exception is pantoprazole which has higher inhibition of CYP2C9 rather than CYP2C19,[20] which may be why pantoprazole is a preferable PPI agent by virtue of it being a less competitive inhibitor of CYP2C19 than other PPIs.

In vitro study researchers have also demonstrated an association of this polymorphism in individuals with certain hypofunctioning alleles (loss of Function allele) of CYP2C19 and a diminished pharmacodynamic response measured by platelet function testing.[21] This change in pharmacokinetic and pharmacodynamic response was most seen in CYP2C19 genetic polymorphism which is involved in both the sequential oxidative steps of clopidogrel prior to generation of its active metabolite.

Simon et al[17] investigated clinical events including death from any cause, AMI, and nonfatal stroke at one year in a group of 2,207 patients with genetic polymorphism of CYP2C19. In individuals with hypofunctioning CYP2C19 alleles, clinical events were significantly higher; 21.5% versus 13.3% when compared to noncarriers. Furthermore, in subgroups that underwent PCI, cardiovascular events were 3.58 times more likely in carriers of hypofunctioning alleles than noncarriers. Mega et al[1] investigated the association of CYP2C19 and plasma concentration of clopidogrel metabolite with its resultant effect on platelet function in healthy volunteers and then evaluated the association of genetic role of CYP2C19 polymorphism and cardiovascular outcomes in a subgroup of 1,477 patients in TRITON-TIMI-38 (trial to assess improvement in therapeutic outcome by optimizing platelet inhibition with prasugrel TIMI-38).[22] Carriers with one hypofunctioning allele of CYP2C19 had decreased level of clopidogrel metabolite with reduction in anti-platelet activity by platelet function testing. Consequently, there was an increased risk of cardiovascular death, AMI, or stroke in carriers of hypofunctioning CYP2C19 alleles and those with the CYP2C19*2 allele had a threefold increase of stent thrombosis. These differences were seen soon after administration of clopidogrel. These study results clearly demonstrate the impact of CYP2C19 isoenzymes on the anti-platelet activity of clopidogrel.

Drugs which interfere with function of CYP2C19 may alter the active metabolite of clopidogrel and thereby adversely impacting its antiplatelet activity. PPIs are thought to diminish the activity of clopidogrel via competitive inhibition of CYP2C19 isoenzymes. Other drugs which compete for the same isoenzymes for their biotransformation can also impact the generation of active clopidogrel metabolite. In this instance, clopidogrel and PPIs have to compete for same isoenzyme (CYP2C19) which is involved in both of the oxidative steps for biotransformation of clopidogrel into its active metabolite. This may lead to a variable response in platelet aggregation. *In vitro*, varying degrees of CYP2C19 inhibition have been demonstrated by different PPIs.[20] PPIs are competitive inhibitors of CYP2C19 to a varying degree, maximally with esomeprazole, followed by omeprazole, pantoprazole, and rabeprazole.[20] These findings provide a possible explanation for the hypothesis that different PPIs diminish antiplatelet activity of clopidogrel to a varying degree and this interaction leads to decreased inhibition of platelet activation as reflected in platelet function testing.

The role of the concurrent use of PPIs with clopidogrel and their effect on platelet function were assessed in the analysis of PRINCIPLE-TIMI-44 data (Prasugrel In Comparison to Clopidogrel for Inhibition of Platelet activation and Aggregation)[23] and TRITON-TIMI-38[22] and it was found that PPIs lowered inhibition of platelet aggregation (IPA) significantly in patents taking a PPI and clopidogrel simultaneously.[24] Therefore, drug interactions and genetic variation in CYP3A4, CYP3A5, and CYP2C19 are implicated in the decrease of active clopidogrel metabolite production. This has lead to CYP2C19 genotyping recommendations in patients with concurrent use of clopidogrel and CYP2C19 inhibitors.[25] Similarly, drugs which are potent inhibitors of CYP2C19 isoenzyme could be expected to have a similar effect on the generation of active clopidogrel metabolites. Several other drugs may interfere with production of clopidogrel metabolites and decrease platelet function inhibition. These include cimetidine, etravirine, fluoxetine, fluconazole, ketoconazole, variconazole, felbamate, fluvoxamime, and ticlopidine.

As initially demonstrated by Gilard et al this potential interaction was most notable with PPIs.[26] These authors evaluated the efficacy of an anti-platelet regimen by monitoring the platelet function testing by VASP – one of several commercially available tests to check platelet function. This was an observational study including 105 consecutive patients receiving aspirin and clopidogrel after coronary artery stenting. All patients had IPA tests by VASP to study possible interactions between clopidogrel and use of concomitant drugs such as statins, B-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and PPIs. Only in PPI users was higher platelet reactivity by VASP testing found as compared to nonusers (61.4 ± 23.3 versus 49.5 ± 16.3).[26]

Clopidogrel and PPI interaction trials

After the initial observation of potential interaction of clopidogrel and PPIs, Gilard et al tested the hypothesis of potential PPI interaction with clopidogrel in a randomized trial; Omeprazole Clopidogrel Aspirin study (OCLA).[27] In this trial 124 patients undergoing PCI with a loading dose of 300 mg of clopidogrel with ASA and maintenance therapy were randomized to omeprazole 20 mg or placebo. Platelet Reactivity Index (PRI) by VASP has been shown to be predictive of MACE after percutaneous coronary interventions (PCI).[28] In this study, PRI was measured at 7 days and there was a significantly higher proportion of clopidogrel nonresponders defined as PRI $>$ 50% in the omeprazole group (60.9% versus 39.8%) by platelet function testing with VASP ($P < 0.0001$) although in a similar study, Siller-Matula et al also evaluated interaction of clopidogrel with two other PPIs: esomeprazole and pantoprazole and did not find any significant difference in PRI.[29]

Another retrospective study involved a database of Aetna Insurance patients where the insurance company reviewed its large medical and pharmacy database of patients with AMI who were taking clopidogrel with PPIs.[30] The database was divided into three groups; the first group with AMI took clopidogrel without PPI, used as control; the second group had low exposure to PPI (less than 182 days), and a third group had a higher exposure to PPI (more than 182 days). Event rates of MI were calculated at 1 year in these three groups; MI in Group 1 was 1.38%, in group 2 was 3.08%, and in Group 3 was 5.03%. When adjusted for comorbidities such as ischemic heart disease, hypertension, congestive heart failure (CHF), dyslipidemia, and diabetes mellitus, the differences remained significant among control and higher exposure groups ($P < 0.05$). However, this study had the inherent limitation of database studies.

The Clopidogrel Medco Outcome Study was a retrospective study of medical and pharmacy claims using National Medco Integrated Database file.[31] This was a large database with 14,383 patients who had PCI and stent deployment during the 1-year period of 2005–2006 and followed for another year for cardiovascular events. There was a significantly higher MACE in patients taking PPIs in conjunction with clopidogrel. This was evident in the group with a history of prior MI (39.8% versus 26.2%) or the group without prior MI (32.5% versus 21.2%).

Another population based and case controlled Ontario study carried out in Canada[13] was also used to investigate the relationship between the clopidogrel–PPI combination and cardiovascular outcomes. Patients aged 66 years or more with acute MI who were discharged on clopidogrel formed the sample. Investigators reviewed the rate of repeat hospitalization among patients who filled prescription of clopidogrel after MI without PPI and these patients were matched with patients who filled prescription of clopidogrel with PPI. After extensive multivariate analysis (MANOVA), a significant correlation between readmission for MI and clopidogrel–PPI use was noted as compared to the group without use of PPI. This was a population-based study with its inherent flaws and without adjustment for ethnicity, possible polymorphism, or noncompliance. Subanalysis of this data, based on the usage of different PPIs showed that pantoprazole, in conjunction with clopidogrel, did not lead to increased incidence of MI.

The significance of interaction between clopidogrel and PPIs was also investigated in a Veterans Health Administration study and the results were published in March 2009.[14] This was also a retrospective cohort study of 8,205 patients presenting with ACS from several veterans hospitals across the country during a period of 2003–2006. The data were analyzed for all cause mortality or rehospitalization for ACS among two groups; patients taking clopidogrel with PPI and those taking clopidogrel without PPI. In this study, 59.7% of patients were taking omeprazole. All cause mortality or rehospitalization for ACS was higher in the PPI group (29.8% versus 20.8%) and also in this group recurrent hospitalization was higher than that of non-PPI group (14.6% versus 6.9%, $P < 0.001$). Additionally, repeat revascularization was higher in the PPI group (15.5% versus 11.9%).

Further analysis of National Medco Integrated Database by Stanek and Flockhart[32] was presented at the SCAI scientific session of 2009. This study included 16,690 patients who received clopidogrel and PPIs within one month of stent deployment (BMS or DES) and were followed for 12 months. In this study, the use of PPIs together with clopidogrel increased MACE (25.1% versus 17.9%, respectively). There were enough patients to assess risk stratification for individual PPIs and the increased risk was seen among all PPIs including pantoprazole as compared to the earlier Canadian study. The subanalysis of CREDO data was performed to assess the effect of PPI–clopidogrel interaction at 28 days and in one year after PCI and this data was presented as an abstract at the 2008 AHA.[33] Clopidogrel reduced the MACE (death, MI, stroke) at 1 year regardless the use of PPI; however PPI use was independently associated with an increased 28 day MI/death and TVR.

While there are many clopidogrel–PPI studies which raise concern, others provide reassurance for use of PPI in

such patients. Simon et al[17] demonstrated that use of PPIs had no effect on overall clopidogrel efficacy in a study which was designed to determine the clinical effect of genetic polymorphism in patients taking clopidogrel after MI. The association between PPI use, IPA, and clinical outcome was assessed by an analysis of the PRINCIPLE-TIMI-44 and TRITON-TIMI-38 trials by O'Donoghue et al.[24] In these studies, no association was found between the use of PPIs and clinical outcomes for patients treated with clopidogrel and prasugrel. In this study, 33% of patients were taking PPIs at base line with a majority being on pantoprazole and omeprazole. These studies did not support avoidance of concomitant use of PPIs with clopidogrel and prasugrel.

The only prospective randomized control trial in which the clinical impact of the interaction between clopidogrel and omeprazole was assessed was recently presented at TCT 2009.[34] This trial, named Clopidogrel and optimization of Gastrointestinal events (COGENT), was a Phase III randomized double control trial which was designed to compare combination of clopidogrel and omeprazole (single pill CGT-2168 with clopidogrel 75 mg and omeprazole 20 mg) with clopidogrel. This study was prematurely terminated due to lack of funding after only 3,627 of a planned 5,000 patients had participated and the data were analyzed and presented after a mean follow up of 133 days. This analysis included 136 adjudicated cardiovascular events and 105 adjudicated GI events. It was reassuring that there was no clinically significant difference in MACE (cardiovascular death, nonfatal MI, CABG/PCI, or ischemic stroke) between the groups. However, there was a significant reduction in gastrointestinal events in patients who were on the combination treatment of clopidogrel and omeprazole. Although this is reassuring, this study is not powered enough to detect any differences in MACE due to early termination. Moreover, the combination of clopidogrel and omeprazole (CGT 2168) was a special formulation and may not have the same pharmacokinetic and pharmacogenomic effects as clopidogrel and omeprazole taken separately. Furthermore, the investigators pointed out the limitations of decision making based solely on observational studies. COGENT investigators indicated that combination of PPI with clopidogrel was harmless and decreased the incidence of GI bleed. The GI bleed-reducing benefit of PPIs in patients using a DAT regimen was also highlighted in a recent retrospective cohort study by Ray et al.[35] These researchers showed that concomitant use of PPI with clopidogrel in CAD is associated with fewer hospitalizations for gastrointestinal bleeds. Another recent retrospective review of PCI between 2001–2007[36] included a total of 2,646 patients on a DAT regimen after PCI and 28% of these patients were discharged on PPIs. In groups with or without PPI use, no differences in cardiovascular outcomes were noted. Interestingly, MACE was actually lower in the omeprazole and esomeprazole groups. The PPI–clopidogrel interaction was addressed in a recent meta-analysis of 93,278 patients[37] where investigators aimed to grade all the studies from relatively low quality to higher-quality evidence. Notably, as the quality of evidence improved, the risk of PPI–clopidogrel interaction was not as apparent. The randomized trial participants showed no significant differences in adverse cardiovascular risks. There is a clear need for more studies to address this issue and to investigate effects of individual PPIs on clopidogrel efficacy. Such studies should also involve investigations of the genetic components of hypofunctioning CYP2C19 alleles.

Advisory warnings

An intense controversy has arisen regarding concurrent use of PPIs and clopidogrel. In spite of strong evidence for minimal or no interaction from prospective trials, government authorities such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMEA) have issued statements regarding the potential interaction of concomitant use of clopidogrel and PPIs.[38,39] The initial FDA announcement on January 2009 cautioned health care professionals about prescribing omeprazole and clopidogrel and health care workers were urged to reevaluate the need for continuing treatment with PPI including PRILOSEC OTC. Subsequently, presentation of the Clopidogrel Medco Outcome study[32] at the SCAI 2009 led to an advisory by SCAI. While acknowledging the need for further studies, SCAI urged cardiologists to consider using H2 receptor antagonists or antacids instead of PPI in patients with DAT therapy after PCI. Furthermore, the FDA issued an advisory statement on March 12th 2010 after a crossover study in 40 healthy participants, 10 each in the four CYP2C19 metabolizer groups, required by FDA and carried out by a manufacturer. In this study pharmacokinetics and antiplatelet effects of clopidogrel were investigated in 40 healthy volunteers with four metabolizer groups; ultra-rapid metabolizer, extensive metabolizer, intermediate metabolizer, and poor metabolizer. Each group of 10 volunteers were randomly assigned to two types of treatments: 300 mg loading followed by maintenance dose of 75 mg, or loading of 600 mg and maintenance dose of 150 mg.[25] Based on this crossover study, the FDA required

a boxed warning for clopidogrel to caution that poor metabolizers of clopidogrel may not receive full protection from MI, stroke, and cardiovascular death. The boxed warning further states that tests are available to determine genetic profile of CYP2C19 isoenzymes to predict if patients will ineffectively convert clopidogrel to active metabolite. The FDA advised health care workers to consider an alternative anti-platelet regimen or alternative dosing strategies of clopidogrel in such poor metabolizers.

Fact or fiction

The current studies suggesting a possible interaction between clopidogrel and PPIs raise a serious concern without any definite conclusion. From a pharmacologic perspective, this interaction is a reality with uncertain clinical implications. In certain subgroups, coadministration of PPIs and clopidogrel may be harmful. There are a strong pharmacodynamic data suggesting that the interaction between clopidogrel and PPI exists, especially with omeprazole. This may lead to attenuation of the anti-platelet effect of clopidogrel as measured by IPA testing. While the importance of routine platelet functions testing may be uncertain, it may be useful in high risk patients to assure the adequacy of platelet inhibition.[5] Accumulating data support the hypothesis that suboptimal platelet inhibition may translate into adverse cardiovascular events. Future studies will be needed to investigate effect of individual PPI interaction with clopidogrel. Researchers will also need to address the role of genetics in this interaction.

However, the reality of clinical practice is that while we wait for such studies, we still need to make daily decisions on our patients. It is prudent that PPIs not be the routine practice in patients on DAT therapy until further data are available and an alternative approach for GI prophylaxis should be considered such as ranitidine or famotidine (Pepcid).[6] Pepcid has been shown to be effective in the prevention of gastric and duodenal ulcers and esophagitis in patients taking ASA.[40] Alternatively, if a PPI is required, newer thienopyridine agents such as prasugrel may be considered.

Observational studies could be used to establish an association and generate hypotheses which need to be tested in randomized controlled trials. Therefore, in view of discordant results among many observational studies and the only incomplete randomized controlled study, there is a great need for further randomized controlled studies.

Management strategies

Multiple warnings have heightened the awareness of PPI-clopidogrel interaction. On March 12th 2010, the FDA approved a third label change for clopidogrel with a "boxed warning" regarding diminished clopidogrel efficacy in patients with decreased CYP2C19 function due to genetic polymorphism. Recently, the American College of Cardiology Task Force published a clinical expert consensus document to make recommendations for practicing physicians relating to this issue.[41,42] Therefore, one should avoid combining clopidogrel and PPIs unless there is a compelling indication. One should also keep in mind that there is a 3% prevalence of poor metabolizers.[25] At the same time, it is prudent not to withhold PPIs in patients at high risk for GI bleeding. In these patients, pantoprazole may be the PPI of choice. For low risk patients, serious consideration should be given to H2 receptor antagonists or antacids. Patients should also be advised to avoid self-medicating with omeprazole while they are on clopidogrel. They should also be educated about the possible interaction between PPIs and clopidogrel and the risk of ACS in such settings. It is now accepted that genetic polymorphism of CYPC219 decreases the active metabolite of clopidogrel, leading to a decrease in antiplatelet activity. In such situations, an alternate anti-platelet agent such as prasugrel may be needed. Prasugrel is also a prodrug which was shown to reduce ischemic events and stent thrombosis in the TRITON-TIMI-38 trial.[22] This drug has not been shown to have a significant interaction from CYP2C19 enzyme polymorphism.[43] Use of prasugrel may be a good alternative in patients known to be poor metabolizers or poor to intermediate metabolizers requiring PPIs for GI bleed prophylaxis. Irrespective of advisories, the benefits of PPIs in the GI bleed prophylaxis should not be overlooked.[35] Therefore, in ACS patients at risk for GI bleed, the cardioprotective benefit of clopidogrel and the gastroprotective effects of PPIs should be kept in mind. By COGENT, *post hoc* analysis of PRINCIPLE-TIMI-44 and TRITON-TIMI-38 trials showed no pharmacodynamic interaction of clopidogrel with PPIs nor any adverse cardiovascular outcomes. However, health care providers should remain on high alert as further data unfolds. The statement and guidelines for physicians published by ACCF/AHA task force on clopidogrel clinical alert are of great interest.[41,42] The expert panel feels that a majority of ACS/coronary stent patients on clopidogrel do well without a need for genetic or platelet function testing. However, a minority of patients especially the high risk group may be prone to adverse clinical events such as cardiovascular

and/or cerebrovascular ischemic and/or hemorrhagic events due to a significant variability in individual responses to clopidogrel. This variability in platelet function response to clopidogrel is due to genetic polymorphism of CYP2C19 and occasionally genetic polymorphism of ABCB1 may also play a role. Loss of function may be due to CYP2C19*2 or *3 (poor metabolizers) and conversely gain of function may be due to CYP2C19*17 variant (hyper-rapid or ultra-rapid metabolizers). However, some experts argue that the predictive value of genetic variant testing is as low as 12% to 20%. Obviously, multiple nongenetic factors including noncompliance with clopidogrel and a concomitant use of PPIs may play a significant role. Therefore, there is no expert consensus on routine genetic or platelet function testing. However, certain guidelines have been proposed in high risk patients who have the following clinical conditions: diabetes mellitus, chronic renal failure, diffuse three vessels, left main disease, and diffuse cerebrovascular atherosclerotic disease. In these patients, the expert panel recommends that genetic or platelet function testing should be considered to identify and adequately treat clopidogrel hyporesponders. Alternatively, clinicians may empirically double the dose of clopidogrel and other steps include usage of other agents such as prasugrel and ticagrelor (when approved), as these are not influenced by CYP2C19 genetic variants. However, there is potential bleeding issue with some of these agents and, in fact, prasugrel is contraindicated in patients who have experienced strokes. Finally, consideration should be given to cilostazol addition to clopidogrel and ASA regimen.[44] In rare instances, cilostazol may be used alone,[45,46] however, the concern for inadequate platelet inhibition remains. Therefore, platelet function testing may prove to be an ideal way of ensuring the therapeutic range of platelet function inhibition in various clinical situations.

Conclusion

In several observation studies, it has been suggested that a true pharmacologic interaction exists between clopidogrel and PPIs. Pharmacodynamic data suggest that competitive inhibition of CYP2C19 by PPIs decreases the availability of the active metabolite of clopidogrel and therefore diminishes its anti-platelet efficacy. This attenuation of anti-platelet effect of clopidogrel in conjunction with PPI has been supported in many platelet function studies and recent data has further shown that the decreased anti-platelet effect of clopidogrel translates into adverse cardiovascular outcomes. Therefore, routine use of PPIs should be avoided. Even though the results of the MEDCO study[32] suggested interaction of all PPIs with clopidogrel, the Ontario study[13] did not show an increase in MACE with pantoprazole because of its minimal effect on CYP2C19. Therefore, there is growing support for pantoprazole as the PPI of choice with clopidogrel therapy.

Disclosure

The authors report no conflicts of interest in this work.

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