



Indian Health Service
IHS National Pharmacy and Therapeutics Committee
Update:
Clopidogrel/Proton Pump Inhibitor Drug Interaction
March 2011



The NPTC reviewed the data associated with the clopidogrel and proton pump inhibitor (PPI) interaction at the March 2011 meeting. The purpose of this document is to provide an update from the NPTC regarding recent recommendations from the FDA concerning clopidogrel and PPI's from a historical standpoint and provide an update related to recently published literature on this subject.

Background:

On January 26, 2009, the FDA issued an “Early Communication” regarding clopidogrel bisulfate (Plavix) and its use when combined with PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole). In that document, the FDA warned that some reports suggest a potential for certain PPIs to reduce the efficacy of clopidogrel while other reports do not. At that time, the FDA recommended “Healthcare providers should re-evaluate the need for starting or continuing treatment with a PPI, including Prilosec OTC, in patients taking clopidogrel.

On November 17, 2009, the FDA provided an update to the labeling of clopidogrel regarding the drug interaction with omeprazole. Omeprazole is an inhibitor of CYP2C19, the enzyme responsible for converting clopidogrel to its active form. Of note, providers should consider other CYP2C19 inhibitors when prescribing clopidogrel, which include: cimetidine, fluconazole, ketoconazole and fluoxetine (among others). Some studies have identified a lack of CYP2C19 activity with the PPI pantoprazole, however its clinical application has been questioned by lack of correlation with clinical outcomes.¹⁻² Of note, this update also included esomeprazole.

On October 27, 2010, the FDA issued an additional update related to this subject. It was not a Drug Safety Communication, but a reminder of their recommendation. With this update, the FDA did modify its previous recommendation to only omeprazole use. As such, the FDA recommends “against the concomitant use of Plavix (clopidogrel) and omeprazole because the co-administration can result in significant reductions in clopidogrel’s active metabolite levels and antiplatelet activity.”

The NPTC reviewed these recommendations and presented a thorough review of the available literature associated with this interaction. Based upon this research, the NPTC concluded that these data should be viewed with some caution as much of the evidence and recommendations are based upon studies that are non-randomized and utilize pharmacokinetic and pharmacodynamic data (antiplatelet activity and platelet reactivity assays) versus clinical outcomes. Data from the Clopidogrel and Optimization of Gastrointestinal Events (COGENT) study compared clopidogrel/omeprazole versus clopidogrel/placebo and showed a reduction in GI bleeding with no difference in cardiovascular events.³ It should be noted; this was a trial with a GI focus and was stopped early because of the difference in GI events. Additional conclusions were that the available clinical data do not support a negative clinical outcome associated with concomitant use of PPI/clopidogrel, including omeprazole. A similar view was noted in a systematic review by Lima, et al., in 2010. They found the association between clopidogrel and PPIs in studies of low quality and with increased risk for bias and found an overall lack of high quality evidence supporting a clinically significant interaction.⁴ Additionally, the ACCF/ACG/AHA 2010 Expert Consensus Document published similar findings and recommend employing a risk to benefit ratio to selection of appropriate agents with consideration of both cardiovascular and GI complications.⁵ This group

also felt that PPIs are appropriate options for patients with multiple GI bleeding risk factors and who require antiplatelet therapy.

One may consider the use of other means to reduce stomach acid such as H2 blockers (except cimetidine) or antacids. It should be noted that H2 blockers are not as effective as PPIs at preventing GI ulcer in patients taking thienopyridines, but are a reasonable alternative for those at low risk for GI bleeding.⁵ Other PPIs vary as to the level of inhibition and no specific recommendations were made concerning other PPI's due to lack of available data. If a patient is on clopidogrel and a PPI is specifically indicated, such as a hypersecretory conditions, it would be reasonable to discuss the benefit to risk of this combination and the use of other PPIs.

The NPTC continues to watch these discussions and the clinical evidence and will review and modify the National Core Formulary as clinically necessary. If you should have additional questions, please feel free to submit an email to nptc1@ihs.gov.

References:

1. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ*. Mar 31 2009;180(7):713-718.
2. Khaliq SC, Cheng-Lai A. Drug interaction between clopidogrel and proton pump inhibitors. *Cardiol Rev*. Jul-Aug 2009;17(4):198-200.
3. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med*. Nov 11 2010;363(20):1909-1917.
4. Lima JP, Brophy JM. The potential interaction between clopidogrel and proton pump inhibitors: a systematic review. *BMC Med*. 2010;8:81.
5. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation*. Dec 14 2010;122(24):2619-2633.

Supplementary Information:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm190836.htm>

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm079520.htm>

<http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm190825.htm>

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm190784.htm>

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm079520.htm>

†American College of Cardiology Foundation/American College of Gastroenterology/American Heart Association

*For additional references associated with this topic, please email nptc1@ihs.gov