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Hospitalist Update

New Guidance on Concomitant Use of PPIs and Clopidogrel

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Over the past year, confusion has ensued as to whether patients who take clopidogrel should also take PPIs. The potential benefits of antiplatelet therapy for patients with CV disease have been amply demonstrated, especially among patients at higher risk for CV events. However, antiplatelet drugs such as clopidogrel increase the risk for upper GI bleeding from pre-existing ulcers and other breaks in the GI tract. Because PPIs suppress gastric acid production, they are often used in concert with antiplatelet drugs in an effort to reduce the risk of GI bleeding. Research published over the last year has suggested an adverse interaction between these drugs that may lessen the antiplatelet effects of clopidogrel and thereby place patients at an increased risk of CV events. The recent publication of a randomized trial (COGENT) of 3761 patients with CV disease who were treated with clopidogrel demonstrated a 56% decrease in GI bleeding in those receiving a PPI compared to those who did not. There is now a published consensus document from three national medical associations supporting the concomitant use of clopidogrel and a PPI in patients with CV disease who are also at high risk of an upper GI bleed; the recommendations from the American College of Cardiology Foundation, the American College of Gastroenterology and the American Heart Association are:

A. Use of PPIs is recommended for patients with a history of upper GI bleeding or for those with multiple risk factors for GI bleeding

B. PPIs are not recommended to reduce upper GI bleeding in patients who have a low risk of upper GI bleeding and who have much less potential to benefit from such prophylactic therapy

C. Future studies are required to assess the impact of concomitant PPI and antiplatelet therapy among the small subset of high-risk CV patients with an impaired ability to metabolize antiplatelet drugs

D. Decisions regarding the combined use of PPIs and antiplatelet drugs (cont)

(cont) must be individualized and not made as a matter of routine.

DISCUSSION: Thienopyridine therapy (which includes clopidogrel) as been evaluated as an alternative to or an additive to aspirin therapy (dual antiplatelet therapy) for CV events. The absolute risk reduction from clopidogrel is greater in patients with a higher CV risk, particularly in those with acute coronary syndrome or in those who have had a coronary stent placed.

In patients with ACS without ST segment elevation, dual antiplatelet therapy with clopidogrel and aspirin reduced the risk of cardiac death, MI or stroke from 11.4% to 9.3% compared to aspirin treatment alone; this finding was irrespective of whether patients were revascularized or treated medically but the addition of clopidogrel increased major bleeding from 2.7% to 3.7%. In patients with ST segment elevation MI treated with fibrinolytics, the addition of clopidogrel to aspirin reduced major CV events over 30 days from 10.9% to 9.1% but increased major bleeding complications from 1.7% to 1.9%.

Dual antiplatelet therapy reduces stent thrombosis following percutaneous coronary intervention (PCI); those who receive bare metal stents should be on clopidogrel for at least 1 month while those who receive drug eluting stents are recommended to stay on dual antiplatelet therapy for at least 12 months. For patients with chronic atrial fibrillation who are unable to take vitamin K antagonists, adding clopidogrel to ASA therapy was found to reduce the rate of major vascular events from 7.6% to 6.8% and stroke from 3.3% to 2.4% but was associated with an increased risk of bleeding (2% per year).

Several risk factors for GI bleeding in the setting of antiplatelet therapy have been consistently reported. A history of bleeding or other complications from peptic ulcer disease is the strongest risk factor for upper GI bleeding; advanced age also significantly increases the absolute risk of upper GI bleeding. The use of anticoagulants, steroids or NSAIDs has been associated with GI bleeding, as has the presence of H. pylori infection. The relative risk of GI bleeding increases in concert with the number of adverse risk factors that are present in any given individual. There is limited data on the mortality attributable to GI bleeding in patients on clopidogrel alone or in combination with aspirin but the relative risk for death from a GI bleed has been estimated at 2.5 and GI bleeding appears to be a significant predictor of death, even after adjustment for CV morbidity, age, sex, diabetes, PCI status and concomitant therapy.

Strategies to prevent clopidogrel related upper GI bleeding have included histamine (H2) receptor antagonists and PPIs. In a randomized trial of 404 patients with peptic ulcer disease or esophagitis who were taking aspirin, fewer GI ulcers developed over 12 weeks in those assigned to Pepcid therapy compared to placebo; however, in other studies, H2 blockers did not significantly protect those on clopidogrel therapy. In a cohort of 987 patients who were prescribed clopidogrel and aspirin, PPI use was associated with a greater reduction in GI bleeding than use of H2 blockers.

Clopidogrel is a pro-drug, converted in-vivo to an active metabolite that irreversibly binds to the platelet adenosine diphosphate P2Y12 receptor, thereby inhibiting platelet aggregation. Clopidogrel requires hepatic cytochrome P450 metabolic activation to produce the active metabolite. Atorvastatin, omeprazole and several other drugs have been shown to competitively inhibit CYP activation of clopidogrel; to date, however, there is no consistent evidence that these drug interactions impact adverse cardiovascular events and they should not be withheld in patients for whom they have a strong indication. The concomitant use of PPIs may competitively inhibit activation of clopidogrel by CYP2C19, thereby attenuating its antiplatelet effect; coadministration of other CYP2C19 inhibitors may further reduce the efficacy of clopidogrel. Head to head comparison of the various PPIs has not demonstrated any significant difference in their effect on clopidogrel activity and the addition of a PPI to clopidogrel therapy has not been shown to have a consistent impact on the risk for CV events. Since the plasma half-lives of clopidogrel and all available PPIs are less than 2 hours, interactions between these drugs might be minimized by separating the time of their administration, even among poor CYP2C19 metabolizers.

All prescription medications have favorable and unfavorable effects and treatment decisions must be based on whether the potential benefit outweighs the potential for harm. The CV benefits of antiplatelet drugs are over-whelmingly documented, especially for those with ACS or those who undergo PCI. Since their use is also clearly associated with an increased risk of GI bleeding, the challenge for healthcare providers is to determine which patients are more likely to benefit from the addition of PPI therapy despite its potential effect on the activity of clopidogel. Hence the updated, consensus recommendations outlined above.

REFERENCES:

Abraham et al., ACCF/ACG/AHA 2010 Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines: A Focused Update of Expert Consensus on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use, J Am College of Cardiology 2010; 56, No 24, 2051-2066

Bates et al., Clopidogrel-Drug Interactions, State of the Art Paper, J Am College of Cardiology 2011; Vol 57, No 11, March 15, 2011

CASE REPORT

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UNUSUAL CAUSE OF RECURRENT PNEUMONIA

A 24 year old male presented with a 2 week history of cough, high fever and right– sided pleuritic chest pain; the pain radiated to the right clavicle and right arm. He noted associated wheezing and streaky hemoptysis. Treatment of his symptoms had been initiated with oral Levaquin with limited improvement.

The patient reported a history of recurrent pneumonia in his right lung over a period of 3 years. Other PMH was unremarkable with no history of DM, hypertension or TB. His only medication was the prn use of albuterol. The patient smoked cigarettes for 3 years but quit 1 year ago; he denied alcohol or illicit drug use. There was no family history of lung disease or lung cancer.

Exam on presentation was remarkable for T 36C, BP 114/77, P 67. He was alert and in no distress. HEENT was entirely normal with no cervical adenopathy. Chest exam was normal except for diminished breath sounds in the right lower lung. Cardiovascular, abdominal and neuromuscular examinations were entirely normal.

His CBC, CMP and EKG were normal; spirometry did not reveal any obstructive or restrictive defects.

A CXR demonstrated collapse of the right middle lobe and a CT of the chest confirmed the RML collapse and revealed the presence of an obstructing lesion in the right bronchus intermedius (**images on next page**).

A bronchoscopy was performed and an endobronchial biopsy was obtained; this revealed features typical of carcinoid. Staging with a PET/CT and octreotide scan was negative for metastases. Cardiothoracic Surgery was thus consulted; they performed a right middle lobectomy with a sleeve resection and reconstruction of the right bronchus intermedius.