

SETON Network Notes

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Do Proton Pump Inhibitors (PPIs) Influence The Efficacy of Clopidogrel (Plavix®)?

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Background

The 2008 ACCF/ACG/AHA Guidelines recommend the use of a PPI with dual antiplatelet therapy (DAT = aspirin + clopidogrel).¹ The 2007 ACC/AHA Guidelines for Unstable Angina and NSTEMI recommend a PPI in patients with prior GI bleed if treating with aspirin, clopidogrel or both.² This therapy has become increasingly common, despite scant evidence to support the role of PPIs in reducing GI bleeding in these populations. Recent reports suggest an interaction between clopidogrel and PPIs that could lead to increased thrombotic events.

What is the proposed mechanism of this drug interaction?

The efficacy of clopidogrel, a prodrug, relies on CYP2C19 (and to a lesser extent CYP3A4) for metabolism to an active metabolite.³ Proton pump inhibitors competitively inhibit CYP2C19 and, theoretically, could inhibit the conversion of clopidogrel to its active metabolite.

Are there other potential explanations for increased thrombotic events?

About 30 percent of the population are “poor responders” to standard doses of clopidogrel. Greater than 90 percent of poor responders have been identified as having at least one copy of the 2C19*2 allele, which is associated with decreased platelet response to clopidogrel.⁴ The allele is present in about 20 percent of Caucasians, 18 percent of Mexican-Americans, 30 percent of African-Americans, and 50 percent of Asians.^{5,6} This has been proposed to account for 12 percent of diminished clopidogrel response and poorer cardiovascular outcomes.⁷

Is this interaction well-documented in the literature?

Many of the published clinical trials that reported this interaction were observational and small, and used surrogate endpoints for thrombosis (e.g., platelet reactivity index, VASP, aggregometry, etc...)^{8,9} In these reports, patients receiving clopidogrel in combination with a PPI were less responsive to clopidogrel.

Several publications have resulted from review of large pharmacy databases.^{10,11,12} These reviews have allowed for comparison of clinical outcomes among large groups of patients who received a PPI and those who did not. Cardiac events were increased in the PPI groups. Events were not increased in patients who received H2 antagonists.¹² Due to the retrospective nature of these analyses, factors that might have contributed to increased cardiovascular risk were not controlled (i.e., ethnicity, baseline drug therapy, compliance with PPI or clopidogrel therapy, etc...).

Several recent trials have not demonstrated an increased risk with clopidogrel + PPI therapy.^{13,14}

Have all PPIs been proven to interact with clopidogrel?

PPIs vary in the degree to which they inhibit CYP2C19. Early reports indicated that this interaction occurred most often (even exclusively) with omeprazole, which is likely the most potent inhibitor of CYP2C19. This may be because omeprazole has been on the market the longest. Additional trials have documented increased cardiac events with all PPIs studied (omeprazole, esomeprazole, lansoprazole and pantoprazole).^{11,15} Limitations associated with the retrospective, observational design of these trials make it difficult to link this interaction with any particular PPI. Most studies have not specified which PPIs were used and failed to account for OTC PPI use.

Has the FDA made a statement regarding this interaction?

Yes. On Nov. 17, 2009, the FDA released a statement.¹⁶ Based on unpublished clinical trial data, the FDA has asked the manufacturer of clopidogrel to update their package labeling to reflect an interaction between clopidogrel and omeprazole (Prilosec®/Prilosec OTC®). Key points from the FDA statement include:

1. “Concomitant use of omeprazole (Prilosec®) and clopidogrel (Plavix®) should be avoided because of the effect on clopidogrel’s active metabolite levels and anti-clotting activity”.
2. Separating the dose of clopidogrel and omeprazole will not reduce the drug interaction.
3. Other drugs that should be avoided in combination with clopidogrel because of the potential for a similar interaction include esomeprazole (Nexium®), cimetidine, fluconazole, ketoconazole, etravirine, fluoxetine and others.
4. “At this time, the FDA does not have sufficient information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to make specific recommendations about their co-administration”.
5. There is no evidence of a similar drug interaction between clopidogrel and most H2 antagonists, including ranitidine (Zantac®), famotidine (Pepcid®) and nizatidine (Axid®).

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How should I assess patients receiving the combination of clopidogrel and a PPI?

1. Determine the indication for the PPI.
 - If the PPI has been initiated for stress-ulcer prophylaxis, determine whether the patient meets established criteria for stress ulcer prophylaxis.
 - If the patient was receiving a PPI at home for GERD with minimal or no symptoms, consider recommending a switch to an H2 antagonist or a trial of no drug therapy.
2. Patients should generally receive a PPI with clopidogrel in the following situations:
 - Dual antiplatelet therapy (aspirin + clopidogrel) in older patients and those with a history of GI bleed or ulcer.
 - Concomitant NSAID use – especially patients at high risk of GI bleed.

Recommendations:

- Though all PPIs may interact with clopidogrel, avoid omeprazole and esomeprazole.
- Reserve PPIs for patients at increased risk of GI bleed or with a clearly documented need for PPI therapy (severe GERD that is unresponsive to other drug classes).
- The drug interaction potential is the same with IV PPI therapy.
- Utilize H2 antagonists when possible, but recognize that H2 antagonists will not be appropriate alternatives in patients at increased risk of GI bleed.

Seton Family of Hospitals' Antimicrobial Stewardship

Many hospitals throughout the country have implemented antimicrobial stewardship programs. The major rationale for stewardship is that antimicrobial resistance continues to climb, yet only a limited amount of novel antimicrobials are currently in research and development to treat these resistant organisms. This leads to the increased use of older, more toxic antimicrobials such as colistin. Antimicrobial stewardship is a collaborative effort among health care practitioners to improve patient care and health care outcomes. The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America published national guidelines for development of inpatient antimicrobial stewardship programs. This is accomplished through limiting the inappropriate use of antibiotics as well as optimizing antibiotic selection, dosing, route and duration of therapy to maximize clinical cure or prevent infection while decreasing the emergence of resistance and adverse drug effects. The Anti-Infectives Monitoring Subcommittee (AIMS) is a Seton Family of Hospitals (SFH) committee consisting of infectious diseases physicians, infectious diseases pharmacists, infection control practitioners and the microbiology director. This committee oversees and develops policies, treatment pathways and guidelines to promote and implement antimicrobial stewardship within SFH. One goal of the SFH program is to limit the use of agents that have been associated with collateral damage, or the selection of drug resistant organisms. The main culprits of collateral damage include third-generation cephalosporins (ceftriaxone, cefotaxime), fluoroquinolones (ciprofloxacin, moxifloxacin, levofloxacin) and clindamycin. These agents have been associated with the increased prevalence of MRSA (methicillin-resistant *Staphylococcus aureus*), VRE (vancomycin-resistant enterococcus), ESBLs (extended-spectrum β -lactamase producing organisms) or *Clostridium difficile*. Local susceptibilities should be considered when selecting empiric agents and streamlining to the most appropriate narrow spectrum antibiotic should be performed once culture results become available. Infectious diseases resources can be found on the SFH Antimicrobial Management Web site: http://intranet/clinicalres/antimicrobial_management/

P&T News

- Due to the number of infusion-related reactions reported with the intravenous administration of **moxifloxacin**, the Network P&T committee approved AIMS' recommendation to increase the standard infusion time to two hours.
- **Donnatal** and **GI Cocktail** (Maalox, lidocaine and donnatal elixir) have been removed from the SFH formulary. The reason for the formulary removal is two fold: 1) most manufacturers have discontinued donnatal production causing a national shortage and 2) belladonna alkaloids with phenobarbital are not FDA-approved products. Because there is no equivalent for GI Cocktail, an automatic substitution cannot be recommended at this time. If an antispasmodic is warranted, dicyclomine (Bentyl®) or hyoscyamine (Levsin®) is available.
- **Lacosamide (Vimpat®)**, a new antiepileptic drug approved for use as adjunctive therapy for the treatment of partial-onset seizures in adult patients with epilepsy, was added to the SFH formulary. Since the bioavailability of the oral lacosamide tablet is 100 percent, lacosamide was also added to the Network IV to PO conversion policy.
- **Buprenorphine/naloxone (Suboxone®)** was added to the SFH formulary. Suboxone® is indicated for maintenance treatment of opioid dependence, but is often prescribed for chronic pain management therapy (non-FDA approved indication). It is important to continue Suboxone® therapy upon admission to prevent acute withdrawal.