

Wyoming Drug Utilization Review



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Proton Pump Inhibitor Drug-Drug Interactions

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Potentially significant drug-drug interactions for the class of proton pump inhibitors (PPIs) are given in Table 1.

Agents in the class include omeprazole, esomeprazole, rabeprazole, pantoprazole, and lansoprazole. Table 2 on

page 3 shows the potentially significant drug-drug interactions for omeprazole, which is primarily metabolized by cytochrome P450 isoenzymes CYP2C9 and CYP3A4. Results in Table 2 are adapted from Reference 3.

Interacting Agent	PPI Involved	Mechanism(s) of Interaction	Importance and Management	Therapeutic Recommendations
Ketoconazole / Itraconazole ¹	Whole class	Reduced stomach acidity reduces the bioavailability of ketoconazole	Established and of clinical importance	Switch to fluconazole
Methotrexate ¹	Omeprazole & possibly lansoprazole	Omeprazole inhibits the activity of a hydrogen-ion dependent mechanism in the kidney necessary for MTX excretion	Reports are contradictory; MTX toxicity may result; lansoprazole may result in a similar interaction	Consider discontinuing omeprazole 4-5 days prior to MTX; Pantoprazole may be a suitable alternative (requires confirmation); Ranitidine may be suitable
Theophylline ¹	Omeprazole & lansoprazole	Interaction possibly mediated through the induction of CYP1A2	Slight increases in half-life and clearance of theophylline have been noted; interaction is unlikely to be significant	No special precautions are likely necessary on concurrent use
Dipyridamole ¹	Whole class	Elevated stomach pH reduces the dissolution and absorption of dipyridamole	Not completely established; hypothesized	Antacids and H ₂ -blockers likely have a similar interaction
Enteric coated preparations ¹	Whole class	Elevated stomach pH causes premature dissolution of EC preparations	Not completely established	No evidence to support avoiding agents concurrently
Clarithromycin ¹	Lansoprazole / esomeprazole	Clarithromycin inhibits the CYP3A4-mediated metabolism of lansoprazole / esomeprazole	Serum concentrations of the PPIs is increased	Dose adjustment of the PPI is not necessarily required
Tacrolimus ^{1,2}	Lansoprazole	Tacrolimus is extensively metabolized by CYP3A4	One case report in which a patient experienced elevated serum concentrations	Not determined
Diazepam ⁴	Esomeprazole	Interference with CYP2C19	Decreased diazepam clearance	Unlikely to be clinically relevant

Table 1: Drug-drug interactions for PPIs

Plavix®

Melissa Stahlecker, PharmD

Clopidogrel (Plavix®) is a thienopyridine antiplatelet agent structurally related to ticlopidine (Ticlid®). It is approved for the reduction of atherosclerotic events (myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral arterial disease. Clopidogrel inhibits platelet aggregation by preventing adenosine diphosphate (ADP) from binding to its platelet receptor, resulting in inhibition of fibrinogen binding to the GP IIb/IIIa complex. Platelet inhibition induced by clopidogrel is dose dependent as well as irreversible. Because several days are required to achieve steady state with clopidogrel therapy, loading doses have been used to achieve a more rapid platelet anti-aggregatory effect: 300mg load, then 75mg daily is recommended.

Fast Facts about Clopidogrel (Plavix®)

- Absorption unaffected by food or antacids
- No dosage adjustments for elderly, renal impairment or mild-moderate hepatic impairment^{1,2,3}
- Unlike ticlopidine, clopidogrel is associated with a low risk of hematological toxicities (e.g., neutropenia, thrombocytopenia) and thus does not require routine monitoring of the complete blood count⁴
- No significant adverse effects have resulted from overdoses with clopidogrel⁴

Studies

The CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events) trial, a randomized, double-blind, parallel-group study, evaluated the efficacy of 75 mg/day

of clopidogrel (n = 9,599) compared with that of 325 mg/day of aspirin (n = 9,586). Clopidogrel was associated with a significant relative-risk reduction of 8.7%⁴: it can be estimated that, for every 1,000 patients treated for 1 year, clopidogrel would prevent 24 clinical events, compared to 9 events using aspirin. The only adverse effects more frequently associated with clopidogrel than aspirin were rash and diarrhea.

Studies have shown newer antiplatelet agents, some in combination with aspirin, to be more effective in secondary prevention of coronary events. Typical doses of aspirin for the secondary prevention of stroke (325 mg per day) were evaluated against low-dose aspirin (50 mg per day) in combination with dipyridamole (400 mg per day and clopidogrel 75 mg per day). The investigators interpreted a computer-generated analysis taking into account mortality rates and adverse events from major clinical trials. The study found that the combination of aspirin and dipyridamole was more beneficial at a lower cost when analyzed for quality of adjusted life years (QALY) versus aspirin alone.^{6,7} Clopidogrel was shown to be more effective, but also more costly than long-term aspirin therapy; however it was still found to be marginally cost-effective when compared to aspirin 325mg. Overall, compared with aspirin, both the dipyridamole/aspirin combination and clopidogrel were determined to be cost-effective therapies for the secondary prevention of stroke.

Aspirin has long been the cornerstone of therapy for patients undergoing coronary intervention. Addition of an adenosine diphosphate receptor antagonist (ticlopidine or clopidogrel) to aspirin therapy leads to even greater protec-

Recommendations for Clopidogrel from the 6th ACCP Guidelines for Various Coronary Events

ischemic stroke	Aspirin 50 to 325mg QD; the combination of aspirin 25mg and extended-release dipyridamole 200mg BID; or clopidogrel 75mg QD as all acceptable options for initial therapy (grade 1A). ⁹
myocardial infarction	Aspirin 75 to 162.5mg and to continue therapy indefinitely (grade 1A). For patients intolerant to aspirin, clopidogrel 75mg QD should be used (grade 1A). ¹⁰
revascularization	Aspirin 325mg QD starting 6 hours after the operations and continuing for one year (grade 1A). For patients intolerant to aspirin, clopidogrel 300mg loading dose 6 hours post operatively, then 75mg QD for one year (grade 2C). ¹¹
chronic extremity arterial insufficiency	Life-long therapy with aspirin 81 to 325mg QD in the absence of contraindications (grade 1C+). Clopidogrel may be superior to aspirin in patients with intermittent claudication and peripheral vascular disease, and should be strongly considered (grade 2A). ¹²
percutaneous coronary intervention	Long-term aspirin therapy 80 to 325mg QD (grade 1A) as well as adjunctive therapy with clopidogrel 300mg load and 75mg QD for at least 30 days (grade 2A). ¹³

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Interacting Agent	Major CYP450 Isoenzyme Involved	Effect on Interacting Agent
Caffeine	CYP1A2	Increased metabolism
Carbamazepine	CYP2C8(?)	Decreased clearance
Diazepam/triazolam	CYP2C19	Decreased clearance
Nifedipine	CYP3A4	(Decreased clearance)
Phenytoin	CYP2C9	Decreased clearance
Warfarin	CYP2C9	(Decreased clearance)
Bismuth	Absorption	Increased absorption
Digoxin	Absorption	(Increased absorption)
Cyclosporine ²	--	Not understood; adjust cyclosporine dosage if needed
Fluvoxamine	CYP2C19	Omeprazole clearance is reduced

Table 2: Drug-drug interactions for omeprazole
(Results in parentheses are of questionable significance.)

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continued from page 2 (Plavix®)

tion The PCI-Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) has provided excellent data regarding the benefit of continuing clopidogrel with aspirin beyond four weeks.⁸ The CREDO trial also found that combined treatment for one year leads to significant reduction in irreversible atherothrombotic events compared to 4 weeks of treatment.⁸ The WRIST trial found clopidogrel to be cost-effective in percutaneous coronary intervention and in-stent restenosis when used in combination with aspirin and treated for one year: patients who received 6 months of therapy experienced a 36% rate of major cardiac events and 35% rate of revascularization, while the 12 month group experienced rates of 21% (P<0.01) and 20% (P=0.009) respectively.⁸

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Wyoming PharmAssist is a new program created by the Wyoming Department of Health, in collaboration with the University of Wyoming School of Pharmacy and with the support of AARP of Wyoming. The goal of Wyoming PharmAssist is to provide Wyoming citizens with the opportunity to meet face-to-face with a registered pharmacist who will review their medications and health history. The pharmacist will analyze their personal information for possible drug interactions and therapeutic duplications, and at the same time, provide them with possible ways to reduce their monthly medication costs. The consultation costs the client \$5 and the Department of Health reimburses the pharmacy consultant \$70.

The toll-free number to call to sign up for the program or request further information is 1-877-246-4114. Wyoming PharmAssist is not a consumer drug information hotline. Specific questions about medications should be referred to a local pharmacist.

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