

Issues in Hemostasis: Antiplatelet Agents and PPIs

Antiplatelet agents, and specifically the thienopyridines such as clopidogrel and ticlopidine, are commonly used to reduce cardiovascular events and often in combination with aspirin. The thienopyridines are antagonists to the platelet cell surface ADP receptor; when this receptor is blocked, subsequent ADP-mediated activation of the GP IIb/IIIa receptor is inhibited. Use of thienopyridines inhibits 40%-60% of ADP-induced platelet aggregation in 3-5 days, and the thienopyridines lead to some antiplatelet activity for 7-10 days. Patients treated with thienopyridines and aspirin are often given PPIs as well to reduce the risk of gastrointestinal bleeding.

Clopidogrel is a prodrug, which requires conversion by the liver to an active metabolite. This occurs mainly via the CYP3A4 and CYP2C19 pathways. All PPIs are potent inhibitors of CYP2C19 activity. Some patients (many east Asians and others) have a CYP2C19 loss of function polymorphism, which leads to a marked decrease in platelet response to clopidogrel in these patients. The half life of clopidogrel is very short (less than 2 hours), but the effect of the drug is much more long-lasting because of the irreversible binding of the active metabolite of clopidogrel to the platelet receptor. PPIs similarly have a short half life in the plasma, but a long duration of action because of their irreversible binding to the proton pump.

Recent studies have examined the effect of PPIs on the action of clopidogrel. In an ex-vivo study of patients who received aspirin and clopidogrel after placement of a coronary stent,

omeprazole was found to decrease the antiplatelet effect of clopidogrel (1). Another study found that other PPIs, specifically esomeprazole or pantoprazole, had no effect on the antiplatelet activity of clopidogrel (2). A retrospective cohort study of 14000 patients who had undergone cardiac stent placement and who were on clopidogrel found that patients taking both drugs had more major cardiovascular events but also had more cardiovascular risk factors (3). Several other observational studies published in 2009 showed that patients taking both clopidogrel and PPIs had a small but significantly increased risk of adverse cardiovascular events (hazard ratios 1.25-1.5). (4-5)

There is only one prospective randomized placebo controlled trial of omeprazole versus placebo in patients using clopidogrel and aspirin (COGENT). Unfortunately, this study was terminated prematurely due to bankruptcy of the sponsor, but preliminary analysis showed no difference in cardiovascular events between these two groups (hazard ratio 1.02, 0.7-1.51)

Based on the positive results of some (but not all) observational studies, and the fact that there is a plausible mechanism by which PPIs and clopidogrel might interact, some regulatory agencies such as the FDA have warned that “health care workers should re-evaluate the need for starting or continuing treatment with a PPI in patients taking clopidogrel (6). Clopidogrel labeling has recently been changed to say that “concomitant use of drugs that inhibit CYP2C19 (such as omeprazole) should be discouraged (7).

The bottom line for now is that it would appear that the data to support these conclusions are observational in nature, and indeed not all observational studies have shown the same effect. Moreover, the only randomized placebo controlled trial looking at this issue

was terminated early, but preliminary analysis showed no clinically relevant adverse cardiovascular interactions between clopidogrel and PPIs. Finally, if there were to be an interaction where PPIs diminish clopidogrel efficacy, it would be by competitively inhibiting clopidogrel metabolism. Since both drugs are designed to be taken once daily, and their half life in the blood is very short (although duration of action is long), separation of their dosing by more than 12 hours theoretically should prevent any competitive inhibition of CYP2C19 metabolism and therefore should prevent any significant clinical interaction between these two agents.

References

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