Proton Pump Inhibitors and Clopidogrel – What is the current status?

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- It is increasingly recognized that anti-platelet agents such as clopidogrel are associated with increased rates of GI bleeding, similar to that seen with cardioprotective doses of ASA.
- When administered in combination with ASA, clopidogrel is particularly potent in increasing the risk for upper GI bleeding[i].
- Consequently, proton pump inhibitors (PPIs) are frequently prescribed to reduce bleeding risk.
- Clopidogrel is a pro-drug, which requires cytochrome P-450 metabolism (specifically via the iso-enzyme CYP2C19) to an active form.
- CYP2C19 can be inhibited by PPI's thereby reducing the formation of the active clopidogrel metabolite. Reduced clopidogrel platelet inhibition is associated with an increased risk for cardiovascular events. There appear to be differences between PPIs in their ability to inhibit the CYP2C19 enzyme when assessed *in vitro*[ii].
- An example of this drug-drug interaction is seen in the OCLA study where omeprazole significantly decreased the clopidogrel inhibitory effect on platelet function[iii].
- Because of this and other reports, the FDA has requested additional studies to further characterize this potential interaction.
- One factor that may influence future conclusions is the issue of reduced-function CYP2C19 alleles. It has now been shown that carriers of the reduced-function allele have significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major adverse cardiovascular events than do non-carriers[iv]. To date, there are no published reports of the interaction between these alleles and PPI's. The distribution of these reduced function alleles in the general population and in various disease states is unknown.
- Several recent observational studies using administrative data have examined the PPI-clopidogrel interaction:
    - A recent Canadian investigation examined provincial hospital discharge data of 2,791 subjects after treatment for myocardial infarction. The investigators found that readmission rates for cardiovascular events within 90 days were statistically higher in those patients taking PPI's in addition to clopidogrel (adjusted odds ratio 1.27, 95% CI 1.03 – 1.57)[v].

- A similar American study using Veteran's Affairs data from 8,205 subjects identified an increased risk for cardiovascular events of (adjusted odds ratio 1.25; 95% CI, 1.11-1.41) for patients taking PPI and clopidogrel together[vi]. The investigators did not examine differences among various PPIs

- Another observational study nested within a randomized controlled trial of 13,608 acute coronary syndrome patients taking clopidogrel found no impact of PPI on cardiovascular death, MI or stroke (Hazard ratio = 0.94; 95% CI = 0.80 to 1.11)[vii]

- A recent randomized controlled trial has shed some new light on this question. In the COGENT-1 trial, 3627 patients with cardiovascular disease were randomized to either clopidogrel + omeprazole or clopidogrel alone[viii]. After a mean follow up interval of 133 days, there was no difference in cardiovascular events between groups. However, there was a significant decrease in gastrointestinal bleeding in the omperazole treated group.

- A systematic review of the evidence relating to PPI interaction with clopidogrel identified 23 studies evaluating 93,278 patients. There was a large degree of heterogeneity between studies with propensity matched studies showing no increase in cardiovascular risk in those taking PPIs whereas there was an increased risk in other types of observational studies. There was no increase in overall mortality (RR = 1.09; 95% CI = 0.94 to 1.26) in the 13 studies that reported this outcome[ix].

Summary:

- There is biologic plausibility for an interaction between PPIs and clopidogrel based on inhibition of the CYP2C19 enzyme.
- While *in vitro* and some observational data suggest a possible drug interaction, evidence from a recent randomized clinical trial and propensity matched observational studies suggest no increased cardiovascular risk associated with combined PPI-clopidogrel use.
- PPI's are effective in reducing GI bleeding associated with anti-platelet therapy.

Recommendations:

- Patients at high risk of GI bleeding (e.g. previous peptic ulcer disease, multiple medical co-morbidities) in the setting of clopidogrel use require PPI prophylaxis as they are at increased risk of mortality from GI bleeding.
- H_2 receptor antagonists are ineffective in this setting and should not be used[x].
- PPI use should be restricted to clopidogrel using subjects who are at significantly increased risk of adverse GI events or who have absolute indications for PPI, and in patients who cannot achieve satisfactory symptom control on alternate acid-reducing strategies.

References

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