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Clopidogrel and PPI interaction?

New evidence suggests PPI's, other than pantoprazole, may interfere with activation of clopidogrel, leaving patients at risk of recurrent MIs when using the combination. Past research has found an association with PPIs as a class and recurrent CV events in combination with clopidogrel. While we still need further evidence from randomized controlled trials, **the information we have to date indicates pantoprazole is the safest PPI in combination with clopidogrel. It is logical to choose pantoprazole in PPI-naïve patients who are also treated with clopidogrel, assuming a PPI is in fact indicated. As for patients already on clopidogrel with any other PPI, there's not much evidence to guide recommendations, though switching from omeprazole or esomeprazole to another PPI may be a safe approach. This would be a good time to assess the appropriateness of the PPI.**

Why are we talking about this?

A retrospective nested case-control study was released early by CMAJ on January 28, 2009.[1] The premise of the study was to determine if an association exists between the use of PPIs in combination with clopidogrel and increased risk of a recurrent MI. The researchers used records from Ontario hospital databases. Patients who had been admitted to hospital with an MI and had clopidogrel filled within three days of hospital discharge were included in the study. The patients were followed for 90 days, or until a recurrent MI, whichever was first. Patients who experienced a recurrent MI within the 90 days (cases) were matched to control patients (on average three controls for each case) who were not readmitted for MI. The researchers then checked records for exposure to PPIs. The results reported were that cases who had been on pantoprazole had a similar risk of recurrent MI as the controls. Cases who had been on any other PPI (omeprazole, lansoprazole or rabeprazole) experienced a greater rate of recurrent MI compared to controls. The adjusted odds ratio was 1.27. While 1.27 may seem like a significant increased risk, we must keep in mind potential bias and confounding are associated with case-control studies and , therefore, interpretation of these results is limited..

What are the study limitations?

Considering the design of this study, cause and effect cannot be established and important confounding factors could not be controlled (lifestyle, blood pressure, dyslipidemias). There were several statistically significant differences between the groups at baseline: the cases had higher rates of acute renal insufficiency, CHF, DM, and cancer. Furthermore, the use of ACE inhibitors, beta-blockers and statins was lower in the cases. The authors adjusted for these factors, but just how much the adjustment was able to reduce error is hard to say. The break down of the 'other' PPI's was not reported so it is not possible to determine if one PPI was used more commonly or if there was even distribution among the PPI's . It should be noted esomeprazole was not one of the included PPIs. Genetic polymorphisms of CYP 2C19 ,[2] which could cause reduced activation of clopidogrel have been documented.[3] Polymorphisms were not accounted for in the study.

Can this be explained?

The theory, which is not new, is that because CYP 2C19 is involved in the activation of clopidogrel to its active metabolite, PPIs that inhibit CYP 2C19 may reduce the effectiveness of clopidogrel. The question becomes do we choose PPIs to be used in combination with clopidogrel based on their inhibition of 2C19? There is no indication pantoprazole inhibits 2C19 and this was the only PPI that did not increase the risk of recurrent MI. Unfortunately, there is not 100% agreement on the inhibition properties of the PPIs. (See below)

For sake of argument, perhaps the mechanism is not solely reliant on 2C19 inhibition. The platelet reactivity index (PRI) has been used as a measure of clopidogrel activity. PRIs >50% indicate poor response to clopidogrel. In an ex vivo study, PRIs measured when clopidogrel was combined with omeprazole and placebo were reported as 51.4% and 39.8%, respectively.[4] This result had been expected because omeprazole is a known strong 2C19 inhibitor.[5] In a similarly designed study,[6] esomeprazole, also a 2C19 inhibitor[7] resulted in PRIs no different than those of pantoprazole and placebo, which would not be expected based on the 2C19 inhibition theory. The PRIs in the esomeprazole study were all around 50%, much higher than placebo results of the omeprazole study and so the results are difficult to interpret. While PRI is related to platelet activation, there has also been no direct correlation made between PRIs and thrombotic events.

If we accept the 2C19 inhibition theory, omeprazole and esomeprazole would be expected to confer the largest risk of clopidogrel inactivation and subsequent CV events. Lansoprazole and rabeprazole would be expected to interfere to a lesser degree, and pantoprazole minimally, if at all. A few epidemiological studies have found PPIs to be associated with an increased risk of MI;[8,9] in these studies, all PPIs have been considered as a class. The latest CMAJ study is the first to identify a difference among the PPIs, a difference which can be explained theoretically.

Who should be on a PPI?

Recent American guidelines[10] recommend prophylaxis therapy with PPI in the following patients requiring clopidogrel therapy:

- History of ulcer
- GI bleeding
- Dual antiplatelet therapy
- Concomitant anticoagulant therapy
- At least two risk factors:
    - Age > 60 yo
    - Corticosteroid use
    - Dyspepsia or GERD symptoms

2C19 inhibition by PPI's

Omeprazole – good evidence omeprazole inhibits 2C19 in vitro[5] and in vivo[7]

Lansoprazole – has been implicated as an inhibitor by some references; has in vitro inhibition[7] but this hasn't translated to in vivo inhibition.[11]

Pantoprazole – does not appear to inhibit in vitro[12] or in vivo.[13]

Esomeprazole – slightly weaker inhibitory potency than omeprazole, though seems to have similar significance to omeprazole in vivo.[7]

Rabeprazole – most suggest rabeprazole lacks major CYP inhibition; however in vitro study has shown its thioether metabolite inhibits 2C19;[7] effect in vivo not known.

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