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CLOPIDOGREL & POSSIBLE INTERACTION BETWEEN PROTON PUMP INHIBITORS

This bulletin supersedes PostScript Extra No 17, April 2010

- It is still not clear whether there is definitely a clinically relevant interaction between PPIs and clopidogrel as available data are conflicting.
- Although there is extrapolation from in vitro studies that some PPIs may be less likely to interact with clopidogrel there does not appear to be any evidence from clinical practice that any one PPI is better than another in this respect.
- Prescribers should consider the risk of GI side effects versus the risk of adverse cardiac events when considering co-prescription of a PPI and clopidogrel.

Background

Previous PostScript articles have discussed the possible interaction between clopidogrel and proton pump inhibitors (PPIs).^{1,2} The latest advice from PostScript was that if a patient is taking clopidogrel and requires a PPI the formulary choice would be lansoprazole.² This was based on a recommendation from the EMA that the interaction was not a class effect and only concomitant use of clopidogrel and omeprazole or esomeprazole should be discouraged.³

This issue of PostScript Extra supersedes Postscript Extra 17, April 2010 and reflects any new evidence published since then.

What is the latest evidence regarding the possible interaction between PPIs and clopidogrel?

The initial information which indicated there may be a problem with concomitant administration of clopidogrel and PPIs was from observational studies. Since then, COGENT, a randomised controlled trial (RCT) has been published which investigated the effect of co-administering omeprazole and clopidogrel on GI and cardiac side effects. This is, to date, the only RCT which has examined the interaction between PPIs and clopidogrel.⁴

COGENT was designed to compare rates of upper GI clinical events between patients treated with clopidogrel and patients treated with a fixed combination product of 75mg clopidogrel and 20mg omeprazole in a delayed release formulation. The original trial design stated GI and CV events as the primary and secondary outcome measures, respectively.⁵ The gastrointestinal event rate was 1.1% with omeprazole-clopidogrel combination and 2.9% with clopidogrel alone (hazard ratio with omeprazole 0.34; 95% CI 0.18 to 0.63; $p < 0.001$). The rate of cardiovascular adverse events was 4.9% with omeprazole-clopidogrel combination and 5.7% with clopidogrel alone (hazard ratio with omeprazole 0.99; 95% CI 0.68 to 1.44; $p = 0.96$). Therefore use of omeprazole was found to significantly reduce the risk of GI bleeding without increasing the risk of cardiovascular adverse events. However, the study was terminated early which reduces its statistical power and the confidence interval for cardiovascular side effects is wide so there can be limited certainty around the findings.⁴

Neither the MHRA nor the EMA have issued any further advice after the publication of this study. However shortly after the publication of COGENT, the FDA issued a

statement re-iterating their alert sent to healthcare professionals in November 2009 advising against concurrent use of clopidogrel and omeprazole.^{6,7}

The interaction between clopidogrel and PPIs has been examined recently in systematic reviews and meta-analyses.⁸⁻¹¹ In general, the studies included in these reviews, investigate the effects of PPIs as a class on the incidence on major adverse cardiac events in patients who are treated with clopidogrel and include patients taking any PPI. In a meta-analysis of 25 studies (including COGENT, two post-hoc analyses of randomised trials, 20 retrospective data analyses of cohort studies and two case-control studies) concomitant use of clopidogrel and PPIs was associated with a 29% relative risk of increase in major adverse cardiac events and a 31% relative risk of increase in MI but was not associated with an increased risk of death.⁸

Another meta-analysis of 13 studies (nine cohort studies, three post-hoc analyses of RCTs and a nested case control study) reported that PPIs increased the risk of major adverse cardiac events (OR 1.41; 95% CI 1.34 to 1.48; $p < 0.001$) and mortality (OR 1.18; 95% CI 1.07 to 1.30; $p < 0.001$) in clopidogrel-treated patients. However, the impact of PPI use was significantly influenced by baseline cardiovascular risk and was significant only in high risk patients.⁹

A third meta-analysis of 23 studies (a majority were retrospective studies based on registries of patients undergoing percutaneous coronary intervention (PCI), or part of a health insurance database, including unpublished studies) found that concomitant PPI and clopidogrel use may be associated with an increase in cardiovascular adverse events. There was substantial heterogeneity among the studies and the evidence for the interaction was, therefore, potentially biased or confounded. No increase in mortality was found to be associated with concurrent use of clopidogrel and PPIs.¹⁰

A further systematic review of 18 studies (13 judged to be of low scientific quality and 5 of moderate/high quality) found that 10 of the 13 low quality studies reported an association between concomitant clopidogrel-PPI use and a harmful interaction whereas none of the five moderate/high quality studies found an association. The outcomes examined varied between the studies but mortality, MI, stroke, angina, CABG, revascularisation and stent thrombosis were among the endpoints investigated.¹¹

Choice of PPI

- Most of the studies included in the systematic reviews have investigated the interaction between clopidogrel and PPIs as a class. There was no indication from these reviews that any one PPI was safer than another
- No prospective studies compare the effects of individual PPIs when they are given to clopidogrel treated patients.¹²
- Current advice from the EMA is to avoid the use of omeprazole or esomeprazole in patients receiving clopidogrel.³
- A study is currently underway which specifically aims to determine the effects of various PPIs on platelet aggregation in patients undergoing PCI treated with dual antiplatelet therapy.¹³ It is hoped that the results of this study should help to answer the question of which PPI is preferable.¹⁴

Prescribing Notes

For patients currently on clopidogrel and a PPI or if you plan to prescribe clopidogrel with a PPI the following points should be considered:

- For patients who are prescribed clopidogrel antiplatelet monotherapy after a stroke, reassess the need for a PPI. Consider stopping the PPI if appropriate or changing to ranitidine. If a PPI is considered essential lansoprazole would be the NHSGGC formulary choice.¹⁵
- For patients prescribed clopidogrel antiplatelet monotherapy for the prevention of CHD reassess the need for clopidogrel versus aspirin. Consider changing to aspirin unless aspirin contra-indicated or aspirin and a PPI previously not tolerated.
- Consider whether gastroprotection is indicated. Patients should only be prescribed gastroprotection if there is a clear clinical need or if the patients are at high risk of a GI bleed.
- Some of the high risk factors for a GI bleed include a history of GI bleeding, history of peptic ulcer disease, concomitant therapy with aspirin, NSAIDs, oral corticosteroids, anti-coagulants or selective serotonin re-uptake inhibitors (SSRIs), alcohol intake and advancing age.
- If gastroprotection is indicated and the patient remains on clopidogrel, lansoprazole would be the NHSGGC formulary choice of PPI.¹⁵ Alternatively ranitidine could be considered.
- The need for continued gastroprotection should be reviewed when a treatment course of dual antiplatelet therapy is completed.

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