CLINICAL VIEWPOINT

Clopidogrel and proton-pump inhibitor interaction: viewpoint and practical clinical approach

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The role of clopidogrel after percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS) is well supported by strong clinical evidence, which has led to a dramatic increase in its use.

The use of a combination of proton-pump inhibitors (PPIs) and clopidogrel has recently been questioned due to pharmacological interaction, with possible implications and effects on clinical outcome in patients using this combination. This has brought uncertainty and confusion into clinical practice.

There is a definite interaction between the two drugs, at a pharmacodynamic level; however, the clinical relevance remains uncertain.

In this article I will review the subject and suggest a management strategy, which I hope will be of help to clinicians dealing with these patients on a daily basis.

Introduction

Clopidogrel use has risen dramatically as its role after percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS) is now well established by large clinical trials, meta-analyses, and practice guidelines.[1-5]

Recently, the interaction between proton-pump inhibitors (PPIs) and clopidogrel has become headline news, and has been the subject of debate and uncertainty in clinical practice. Recent publications have raised concerns about the reduction in clopidogrel efficacy when taken with PPIs due to the inhibition of the CYP2C19 isoenzyme in the liver. There is no doubt that an interaction, at a pharmacodynamic level, exists; however, the clinical relevance and the impact on patients remains uncertain. Conflicting evidence exists for and against the clinical effect making it difficult to reach a definite and concrete conclusion regarding the concomitant use of clopidogrel and PPIs.

This possible interaction, of course, brings a sense of *déjà vu* with the similar concerns raised about the interaction between atorvastatin and clopidogrel, first described in 2003, but now largely dismissed.[6,7]

Everyday in practice brings many questions and queries from general practitioners and physicians in other specialties regarding this combination and whether it should be continued or stopped.

In this article, I will review the evidence published on the subject and will present the pharmacological basis of the interaction, and also suggest a management strategy for these patients, which I hope will help clinicians dealing with this issue in their daily practice.

Background

The interaction between PPIs and clopidogrel was first found between omeprazole and clopidogrel, and following that several other PPIs (esomeprazole, lansoprazole and pantoprazole) were found to have a small, *in vitro*, effect of attenuating clopidogrel's antiplatelet effect.[8-10] This was followed by several retrospective database evaluations that found higher rates of cardiac events (myocardial infarction, stent thrombosis and death) in patients taking clopidogrel with any PPI in comparison to those taking clopidogrel alone.[11-13] Following on from this, the US Food and Drug Administration (FDA) issued a recommendation: "healthcare providers should re-evaluate the need for starting or continuing treatment with a PPI, including over the counter, in patients taking clopidogrel. Patients taking clopidogrel should consult with their healthcare provider if they are currently taking or considering taking a PPI". The European Medicines Agency (EMA) followed suit and issued a statement that, due to concerns that PPIs may reduce the effectiveness of clopidogrel, the concomitant use of PPIs and clopidogrel is not advisable, unless absolutely necessary. Following that, the clopidogrel product information was amended to reflect this advice.

The pharmacological interaction

Clopidogrel is a prodrug that requires transformation to active metabolite for its antiplatelet effects. This transformation is catalysed by cytochrome (CYP) enzymes, producing a thiolactone intermediate first, and then an active metabolite that binds irreversibly to adenosine diphosphate (ADP) receptors on the platelet surface. The most important CYP in this process is CYP2C19, which can be influenced by other drugs.[14,15] In theory, any CYP2C19 inhibitors can attenuate clopidogrel bioactivation and in turn its antiplatelet effects. The most common CYP2C19 competitive inhibitors are PPIs. Other commonly used drugs include the antidepressants fluoxetine and fluvoxamine.

Common alleles of the polymorphic genes encoding the CYP enzymes usually confer reduced function. Patients who have a slow biotransformer phenotype do not have the same capability (as normal or even rapid biotransformers) of prodrug activation and will metabolise and excrete some of the clopidogrel without sufficient bioactivation. It is thought that up to one-third of patients are slow biotransformers, a genetic phenotype that is correlated with adverse cardiac events.[16] Interestingly, in the study addressing this issue, the authors adjusted for PPI use and no significant additional adverse effects related to PPI use were found regardless of the genetic CYP2C19 phenotype.[16]

Platelet aggregation studies

Two small studies suggested an interaction between PPIs and clopidogrel with increased platelet reactivity (≈25%), which was higher in patients treated with PPIs compared with those who are not, and this was confirmed in a clinical setting of coronary stenting.[17,18]

Several more studies provided additional evidence of a pharmacodynamic interaction between clopidogrel and PPIs, despite variability and uncertainty with regards to PPI dose. These studies showed consistent findings with omeprazole but not with esomeprazole or pantoprazole.[8,10,19]

Prospective clinical trial data

Data are available from analysis of two recent randomised trials (PRINCIPLE-TIMI 44, TRITON-TIMI 38)[20] and a further prospective randomised trial, Clopidogrel and the Optimisation of Gastrointestinal Events (COGENT).[21] The analysis (which was not randomised) of the PRINCIPLE-TIMI 44 (201 patients) and TRITON-TIMI 38 (13,608 patients) trials showed that 26.4% and 33.3% of patients, respectively, were taking PPIs at the time of randomisation. No evidence of association between adverse cardiac events and PPI use was found and the authors concluded that there is no need to avoid concomitant use of PPIs, when clinically indicated, in patients taking clopidogrel.[20]

The third prospective trial (COGENT) was presented at the Transcatheter Cardiovascular Therapeutics (TCT), California, in September 2009.[21] A total of 3,627 patients received clopidogrel alone or a combination pill with clopidogrel and omeprazole. Both cardiovascular (CV) events and gastrointestinal (GI) events were evaluated and adjudicated. The CV end point was the composite of CV-related death, non-fatal myocardial infarction (MI), coronary artery bypass graft (CABG) or PCI, or ischaemic stroke. The GI end points were upper GI bleeding, a presumed occult GI bleed with a decrease in haemoglobin of ≥2 g/dL or a decrease in hematocrit of ≥10%, symptomatic gastroduodenal ulcer confirmed by endoscopy or radiology, pain of presumed GI origin with underlying multiple erosive disease confirmed by endoscopy, obstruction, or perforation.

No differences in the adjudicated CV events were found between the two groups. A favourable difference in GI outcomes was evident with the addition of a PPI to clopidogrel; this was associated with a 45% relative risk reduction for GI bleeding events compared with clopidogrel alone. The mean follow-up was 133 days with a maximum of 362 days and most significant adverse GI and CV events occurred early after the onset of ACS and PCI. These data from the COGENT trial provide reassurance that there is no clinically relevant adverse CV interaction between clopidogrel and PPIs.

It is important to note that the combination pill contained 75 mg clopidogrel around a core of delayed-release omeprazole. This is quite important in clinical practice as this combination separated the absorption of clopidogrel from that of the PPI and may have significantly reduced the competitive inhibition of CYP2C19 by omeprazole.

Observational trial data

Three observational studies have evaluated the clinical effect of clopidogrel and PPI interaction.[11,22,23] The conclusion in these studies was similar; the use of PPIs in combination with clopidogrel is associated with an increase in adverse events risk of around 25%. These events include MI, death, or re-hospitalisation for ACS. No association was seen between PPI use and adverse events in patients not receiving clopidogrel in two of these studies.[11,22] Two further observational studies, presented as abstracts, suggested an increased risk of adverse events with the combination.[13,24]

Observational studies have major limitations and lack the ability to fully account and adjust for confounding factors, making any firm conclusion quite difficult. For instance, patients who are treated with PPIs in the context of an admission with ACS may have more complex comorbidities and more significant coronary disease, and may be at an increased risk regardless of the use of PPIs. This, however, was not found in some of these observational studies.[11,22]

Clinical relevance

In assessing the interaction between PPIs and clopidogrel, many aspects have to be taken into account: the clinical effect of clopidogrel, the mechanistic effect of PPIs, and the pharmacodynamics and pharmacokinetics of both clopidogrel and PPIs. This would help to reach a conclusion about the true possible magnitude of PPIs' effect on clopidogrel benefits and will guide clinical decision making.

The benefit of clopidogrel is rather modest in general terms, although important clinically, depending on the indication. For instance, the number needed to treat in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study was 47 to avert one composite event (CV-related death, non-fatal MI or stroke).[3] This indicates a very modest benefit in general, and that attenuation by PPIs may not be noticeable clinically in patients, who may not gain significant effect from clopidogrel in the first place. However, the optimal use of clopidogrel in the immediate post-PCI and stenting phase remains of paramount importance. Similarly, clopidogrel use is also important in the medium to long term in patients who have received a drug-eluting stent

(DES) or who have undergone a high-risk PCI (e.g. left main stenting, last remaining vessel stenting, or previous stent thrombosis).

Furthermore, PPIs do not abolish clopidogrel's effect completely, but, rather, attenuate this effect, as demonstrated in studies of platelet aggregation.[18] This indicates that some clopidogrel effect is still evident despite PPI use. This was shown when the platelet reactivity index decreased to 51.4% with PPI treatment from a baseline of 83.9%.[18]

PPIs are metabolised and eliminated from the body rapidly, with a half-life ranging from 0.5 to two hours. Consequently, the competitive inhibition of CYP2C19 is short lived and happens only early on after taking PPIs when their level is high enough to interfere with CYP2C19. This means that the inhibitory effect of PPIs taken once a day will be very minimal after the first few hours and will have a small impact on attenuating clopidogrel effect. This may explain the results of the COGENT trial.[21]

Viewpoint on clinical management

How clinicians should manage the issue of concomitant PPIs and clopidogrel remains debatable. There are two groups of practitioners, the first advocate the complete avoidance of PPIs in patients taking clopidogrel, which is an overestimation of the retrospective evidence, and probably bad practice. On the other hand, the second group believe that the interaction is of no consequence and should not be avoided. This again may be hazardous as undoubtedly there will be an interaction and an adverse effect in some patients, given the large number of patients using these drugs and the abovementioned pharmacodynamic interactions.

I believe a middle-ground and common-sense approach to these patients would help with the uncertainty in clinical practice and reduce the chances of adverse effects. I propose the following approach, which I have been using in my practice when advising my colleagues in general practice and other specialties.

Patients who are in definite need of the use of PPIs, such as history of recent GI bleed, confirmed gastric or duodenal ulcers, Barrett's oesophagus:

- A PPI can be given but should be taken at least four to six hours before clopidogrel. This will allow sufficient time for its inhibitory effect to wear off and will minimise the chances of interaction with clopidogrel. Based on that, I advise that PPIs are taken in the morning and clopidogrel taken at midday. This will also allow for a twice-daily dosing of PPIs, when required. If, however, there is any concern, given the increased non-compliance with multiple dosing, then taking clopidogrel in the morning and the PPI at night may ensure better compliance and be safer.
- Furthermore, in those patients who require PPIs, I advise the use of pantoprazole in place of omeprazole or lansoprazole. This is due to the fact that pantoprazole does not appear to have as significant an inhibitory effect on CYP2C19 as other PPIs and showed no association with adverse CV events in observational studies.[22,25] The Committee on Human Medicinal Products (CHMP) has recommended replacing the class warning for all PPIs with a warning stating that only the concomitant use of clopidogrel and omeprazole or esomeprazole should be discouraged.[26]

On the other hand, the many patients who have less than firm, and perhaps a dubious indication for PPIs, such as unconfirmed GI pathology, can be given histamine H_2 inhibitors (cimetidine is best avoided as it has its own drug interactions) or simple antacids in place of PPIs, which should be sufficient and would eliminate possible PPI and clopidogrel interaction.

Healthcare professionals should:

- Be aware that some patients may be poor metabolisers of clopidogrel. They do not effectively convert clopidogrel to its active form because of low CYP2C19 activity. The effectiveness of clopidogrel as a preventive therapy is reduced in these patients.
- Be aware that tests are available to determine patients' CYP2C19 status.
- Consider use of other antiplatelet medications (such as prasugrel) or alternative dosing strategies for clopidogrel (i.e. 150 mg/day) in patients who have been identified as poor metabolisers.
- Be aware that although a higher-dose regimen (600 mg loading dose followed by 150 mg once daily) in poor metabolisers increases antiplatelet response, an appropriate dose regimen for poor metabolisers has not been established in a clinical outcome trial.

Conclusion

An interaction between PPIs and clopidogrel does exist, at a pharmacodynamic level, with possible clinical effects and implications. However, the results of *ex vivo* platelet assays and the clinical outcome are questionable. In a small group of patients, with a genetic disposition, this interaction may have a real impact on their clinical course and may lead to adverse CV events. However, for the majority of patients, it perhaps carries no significant threat and has no serious impact on their clinical outcome.

Observational data and platelet assays are not a substitute for randomised-controlled trials and, while they are indeed factual, their application in a clinical care setting may be questionable. Large and randomised-controlled trials to this effect will help address this issue and eliminate the uncertainty among clinicians caring for the large number of patients who are using clopidogrel.

In the meantime, clinicians should not stop prescribing PPIs in patients who are using clopidogrel and are at high risk of GI bleed, and should apply the common-sense approach proposed in liaison with their interventional cardiologist colleagues to safely ensure the best possible outcome for these patients

Conflict of interest

None declared.

Key messages

- The use of dual antiplatelet therapy with aspirin and clopidogrel is paramount after percutaneous coronary intervention (PCI), particularly after the use of drug-eluting stents or in high-risk cases
- PPIs reduce the effect of clopidogrel by interfering with its metabolism through CYP2C19 with a definite pharmacologic interaction, the clinical significance of which remains uncertain
- Avoidance of concomitant use of PPIs in patients who require clopidogrel is desirable, however, when PPIs are indicated, pantoprazole is preferable and should be given more than six hours apart from clopidogrel

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