Do proton pump inhibitors reduce the clinical efficacy of clopidogrel?

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Background

Clopidogrel is a thienopyridine antiplatelet drug used for preventing cardiovascular (CV) events. It is given prophylactically as an alternative to aspirin in patients with chronic occlusive peripheral disease or other atherosclerotic conditions which increase the risk of thromboembolic conditions, such as myocardial infarction (MI), peripheral arterial thromboembolism and stroke. Clopidogrel is also used with aspirin in acute coronary syndromes (ACS), including myocardial infarction (MI) and unstable angina, and in coronary stenting [1, 2]. Clopidogrel and aspirin are associated with an increased risk of gastrointestinal (GI) bleeding, particularly in patients' with a past history of GI bleeding and gastric ulcers [1, 2].

There are currently 5 proton pump inhibitors (PPIs) available in the United Kingdom (UK): omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole [1]. PPIs are used in the management of gastro-oesophageal reflux disease (GORD) and acute upper gastrointestinal bleeding [1, 3, 4].

In 2009 the European Medicines Agency (EMA) highlighted that clopidogrel may be less effective in patients receiving proton pump inhibitors and therefore increase the risk of adverse CV effects [5]. Subsequently the Food and Drug Administration (FDA) in the United States and the Medicines and Healthcare Regulatory Agency (MHRA) in the UK advised that use of omeprazole [6, 7] and esomeprazole [6, 8] should be discouraged in patients taking clopidogrel.

Answer

Clopidogrel is converted to its active metabolite by the liver cytochrome P450 isoenzymes, mainly CYP2C19 and CYP3A4 [8-10]. All PPIs are also metabolised by these isoenzymes [8]. All PPIs can inhibit CYP2C19 to varying degrees, so some PPIs may inhibit the metabolic activation of clopidogrel. Clopidogrel absorption may be increased by inhibition of the P-glycoprotein intestinal efflux transporter. PPIs inhibit P-glycoprotein, however there is a lack of correlation between *in vivo* reports and the predicted effect from *in vitro* studies [10].

The evidence for this interaction is based mainly on platelet reactivity studies. There is little data from placebo controlled, randomised studies and there are no trials which have been designed to directly compare and quantify the effects of different PPIs in patients also taking clopidogrel [8, 10].

A study by Gilard *et al* published in 2008, first highlighted the possibility of interaction between omeprazole and clopidogrel [11]. This was a double blind, placebo controlled trial in which 140 consecutive patients undergoing PCI and receiving 75mg/day aspirin plus clopidogrel (loading dose 300mg, followed by 75mg daily) were randomised to receive either omeprazole (20mg/day) or placebo for 7 days. The effectiveness of clopidogrel was assessed by changes in platelet reactivity index (PRI). Baseline values of PRI in the placebo and omeprazole groups were not statistically different (83.2% and 83.9% respectively). However, on day 7 there was a significant difference in the mean PRI between the 2 groups (39.8% ± 15.4% in the placebo group vs. 51.4% ± 16.4%; $p<0.0001$ in the omeprazole group). The study authors concluded that omeprazole significantly decreased the inhibitory effect of clopidogrel on platelet function.

Since 2008, several other similar studies have assessed the impact of dexlansoprazole, lansoprazole, omeprazole, esomeprazole and pantoprazole on the efficacy of clopidogrel by measuring differences in platelet reactivity before and during co-administration with the PPI in both healthy adult volunteers and patients. The results have been mixed and it is unclear if the differences on the surrogate markers observed in these studies, translate into differences in clinical outcomes [9, 10, 12-18].

Most of the available data regarding the effect of this interaction on clinical outcomes is from either retrospective studies or prospective observational studies [19-47]. The data from these trials is conflicting, showing either an increased risk of major adverse cardiovascular events (MACE) [19-29], or little or no increased risk of MACE or re-hospitalisation [30-47]. A small number of studies appear to show that use of PPIs alone is associated with an increased risk of MACE [29, 34, 35, 45, 46], although this was disputed by a recent meta-analysis [48].

Data from 5 randomised trials has subsequently been analysed in an attempt to quantify the effect of PPIs on the efficacy of clopidogrel [18, 49 - 52]. In all of these studies, clopidogrel was being used in the management of ACS as part of dual anti-platelet therapy.

The COGENT study was an international, double blind, placebo-controlled, parallel group, double dummy randomised controlled trial (RCT), investigating the efficacy and safety of a fixed dose combination known as CGT-2168, which contained clopidogrel 75mg and omeprazole 20mg. 3,873 patients with either ACS or undergoing PCI randomly received CGT-2168 or clopidogrel plus placebo. The primary endpoints were a composite of upper GI bleeding or bleeding presumed of GI origin and a composite of CV death, non-fatal MI, coronary revascularisation or ischemic stroke. This study was halted early due to funding issues, but had originally planned to recruit 5000 patients. From the 3,761 patients who were analysed, there were 109 CV events; 54 in the placebo group and 55 in the omeprazole group, with no significant difference in the rate of the primary CV end point between the two groups (p = 0.98). The event rate at 180 days after randomisation was 5.7% in the placebo group and 4.9 % in the omeprazole group; hazard ratio (HR) with omeprazole was 0.99, 95% CI 0.68-1.44; p = 0.96. The study authors concluded that there was no apparent CV interaction between clopidogrel and omeprazole, but that the results could not rule out a clinically meaningful difference in CV events due to the use of a PPI. In addition, the prophylactic use of a PPI reduced the rate of upper GI bleeding among patients receiving aspirin and clopidogrel [49].

The TRITON-TIMI 38 trial was a multicentre, double-blind, phase-3 RCT involving 13,608 patients with ACS who were undergoing elective PCI and were randomly assigned to either prasugrel, 60mg loading dose followed by 10mg once daily; (n=6813) or clopidogrel, 300mg loading dose followed by 75mg once daily; (n = 6795). The primary endpoint was the composite of CV death, non-fatal MI or non-fatal stroke. This study was designed to directly compare the effect of prasugrel and clopidogrel on clinical outcomes. The use of a PPI was at the discretion of the physician in charge of the patient. 33% of patients were on a PPI at randomisation. No association existed between PPI use and the risk of the primary endpoint for patients treated with clopidogrel (adjusted HR = 0.94; 95% CI 0.80-1.1, p = 0.460). The study authors concluded that overall PPI use was not associated with an increased risk of CV events in patients treated with either clopidogrel or prasugrel and that their findings do not support the need to avoid concomitant use of PPIs for gastric protection in patients receiving thienopyridine therapy who are at increased risk of gastrointestinal bleeding [18].

The PLATO trial was a multi-centre, double blind, phase 3 RCT. 18,624 ACS patients, undergoing PCI, were randomly assigned to either clopidogrel (300mg loading dose followed by 75mg once daily) or ticagrelor (180mg loading dose, followed by 75 mg twice daily). The use of a PPI or other gastric acid suppressive therapy was at the discretion of the patient's physician. The primary endpoint was the 12 month composite of CV death, MI or stroke. 6,539 (35.2%) patients were recorded to be taking

a PPI, including 3,200 (48.9%) on omeprazole, 1967 (30.1%) on pantoprazole, 764 (11.7%) on esomeprazole, 510 (7.8%) on lansoprazole and 97 (1.5%) on rabeprazole. The number of patients who experienced CV death, MI or stroke in the PPI treatment group was 398 (13.0%) versus 611 (10.9%) in the non PPI group (unadjusted HR = 1.22, 95% CI: 1.08-1.39). The primary endpoint rates did not differ in patients taking specific PPIs and from those patients taking non-PPI gastrointestinal treatments such as histamine-2 receptor antagonists (H2RA). Omeprazole treated patients had a significantly higher rate of the primary endpoint when compared with patients receiving no GI treatments (unadjusted HR = 1.41, 95% CI: 1.19-1.68). The study authors concluded that the use of a PPI was independently associated with a higher rate of CV events in patients with ACS receiving clopidogrel and that the findings do not support the need to avoid concomitant PPI use with clopidogrel [50].

The PRODIGY trial was an unblinded, multicenter, 4-by-2 randomised trial comparing the efficacy of dual antiplatelet for 6 months and 24 months after the insertion of a drug-eluting stent. 1,970 patients were randomised to continue on antiplatelet therapy for 6 months (n = 983) or 24 months (n = 987). At 24-month follow-up, estimated rates of the primary efficacy endpoint, a composite of all-cause death, MI, or stroke, were similar for the 6 month and 24 month therapy arms (10% v 10.1%; p = 0.91). Amongst the 1,970 participants in the trial, 738 received a PPI with 671 (90.1%) on lansoprazole, 56 (7.6%) on pantoprazole and 11 (1.5%) on omeprazole, esomeprazole or rabeprazole. The difference in the primary end efficacy points (composite of all-cause death, MI, or stroke) was not statistically significant in patients using clopidogrel and a PPI compared to clopidogrel alone (9.2% vs 11.5%. Adjusted HR = 1.051, 95% CI: 0.79 – 1.40, p = 0.736). Bleeding rates (adjusted HR = 0.996, p = 0.98) and incidence of clinical adverse events (12.9% vs 14.9%. Adjusted HR = 0.99, p = 0.93) were also similar in both groups. The study concluded that the concomitant use of PPIs when clinically indicated in patients receiving clopidogrel is not associated with adverse clinical outcomes [51].

The TRILOGY ACS trial was a randomised, double-blind, double-dummy, active-control trial investigating whether aspirin plus prasugrel is superior to aspirin plus clopidogrel for long-term therapy in patients with unstable angina or non-ST elevated myocardial infarction who are treated medically without revascularisation. 7,243 patients under the age of 75 years were enrolled and received aspirin with either prasugrel (10 mg daily) or clopidogrel (75 mg daily). At a median follow-up of 17 months, the primary end point (composite of death from cardiovascular causes, MI, or stroke) among patients under the age of 75 years occurred in 13.9% of the prasugrel group and 16.0% of the clopidogrel group (HR = 0.91; 95% CI: 0.79 - 1.05, p = 0.21). In the clopidogrel group 836 (23.1%) were receiving a PPI, and in the prasugrel group 830 (22.9%) were receiving a PPI. The most common PPIs used were pantoprazole (n = 731) and omeprazole (n = 563). The analysis found that the use of PPIs did not result in a differential antiplatelet response between prasugrel and clopidogrel but was associated with a lower incidence of MI with prasugrel (Adjusted HR = 0.61, 95% CI: 0.42-0.88, p = 0.012). These findings were similar between omeprazole and pantoprazole [52].

Multiple meta-analyses and systematic reviews have reviewed the retrospective, prospective observational and randomised controlled studies [53-61]. Most state that PPIs increase the risk of MACE but not long-term mortality. However, one meta-analysis focussing on genetic factors in CYP2C19 function states that risk of MACE and mortality is increased with PPIs (although this is influenced by underlying risk) [54]. Another systematic review states that there is no increased risk of MACE with concomitant PPI and clopidogrel use [61].

One meta-analysis published in 2013 investigated the effects of individual PPIs and concomitant use with clopidogrel. This included 23 studies with 222,311 patients and found that pooled estimates of CV risk were significantly elevated for individual PPIs such as omeprazole, esomeprazole, lansoprazole, and pantoprazole when used with clopidogrel. However, meta-analysis of adverse CV risk in seven observational studies reporting on PPI therapy alone (without concomitant clopidogrel)

also found an elevated odds ratio of 1.28 (95% CI 1.14-1.44) compared with no clopidogrel/no PPI exposure. Meta-analysis of two randomized controlled trials did not show significant adverse CV effect from omeprazole or esomeprazole. The authors conclude that the absence of consistent evidence on differential CV risk amongst PPIs (particularly regarding safety of pantoprazole) is in direct opposition to the platelet function and pharmacokinetic data. The findings of increased CV risk with PPIs in the absence of clopidogrel suggest that confounding and bias are strong possibilities. The clinical validity or relevance of the hypothesized PPI-clopidogrel interaction remains questionable. For clinical practice, there is no particular reason to choose or avoid one particular PPI over another in clopidogrel treated patients who are high risk of GI events [60].

Guidance produced by the National Institute for Health and Clinical Excellence (NICE) in the UK currently recommends co-prescribing PPIs with aspirin in patients who are at high risk of acute GI bleeds but makes no recommendation regarding PPI prophylaxis in high risk patients on clopidogrel [3, 4].

The American College of Cardiology Foundation and the American Heart Association state that although proton-pump inhibitors (e.g., omeprazole) can affect clopidogrel metabolism and result in diminished antiplatelet activity in vitro, these pharmacokinetic effects do not appear to be associated with worse clinical outcomes [62].

The EMA and the MHRA advise that PPIs, other than omeprazole and esomeprazole, or alternative drugs such as ranitidine should be considered if the patient is taking clopidogrel [5, 6, 9]. An expert position paper on the use of PPIs in patients with CV disease and antithrombotic therapy from the European Society of Cardiology states that there is no conclusive evidence to discourage PPIs with clopidogrel, but there is evidence of benefit in terms of bleeding reduction. PPIs should be carefully prescribed if indicated. A PPI with less CYP2C19 inhibitory capacity (e.g. pantoprazole) may represent a more optimal treatment option than a PPI with high CYP2C19 inhibitory capacity (e.g. omeprazole) [63]. Lansoprazole and rabeprazole are also possible alternatives to omeprazole [9].

Summary

- Clopidogrel is converted into its active metabolite by the liver cytochrome P450 isoenzymes, mainly CYP2C19 and CYP3A4. All PPIs are also metabolised via the cytochrome P450 system, particularly CYP2C19 and CYP3A4.
- All PPIs inhibit these isoenzymes to different degrees and therefore could affect the clinical efficacy of clopidogrel.
- There have been no RCTs to date to specifically assess the effect of PPIs on clinical outcomes in patients taking clopidogrel.
- Secondary analyses of the COGENT, TRITON-TIMI 38 and PLATO trials have not shown an increased risk of major adverse cardiovascular events in patients taking PPIs and clopidogrel together.
- Most of the meta-analyses and systematic reviews published suggest an increased risk of MACE when PPIs are administered with clopidogrel but no increase in long-term mortality
- Treatment decisions regarding concomitant use of clopidogrel and PPIs must balance the overall risks and benefits and consider the risk of cardiovascular and gastrointestinal complications in individual patients. In some patients the benefits of a PPI may outweigh the risk of reduced clopidogrel efficacy.
- The FDA, MHRA and EMA discourage use of omeprazole and esomeprazole in patients taking clopidogrel.
- There is insufficient evidence regarding which PPI is least likely to interact. Based on data from pharmacokinetic and pharmacodynamic studies and the COGENT study, pantoprazole is the least likely to interact and lansoprazole and rabeprazole are also suitable alternatives.

Limitations

This document does not consider potential interactions between other antiplatelet agents and PPIs or between clopidogrel and other CYP2C19 inhibitors.

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Search strategy
- EMBASE: exp CLOPIDOGREL/it [it=Drug Interaction] + exp PROTON PUMP INHIBITOR/it [it=Drug Interaction] [Limit to: Human and English Language and Publication Year 2016-2019]

- MEDLINE: [[clopidogrel.ti,ab,af + exp PROTON PUMP INHIBITORS] + exp DRUG INTERACTIONS/] [Limit to: English Language and Humans and Publication Year 2016-2019]
- Drugdex: Search terms, clopidogrel, omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole.
- MHRA, FDA, EMEA, BNF online, Martindale, AHFS online, Stockley's Drug Interactions, NICE, CKS, NICE Evidence, Cochrane library. Search term clopidogrel.