Medicines Q&As

Q&A 391.1

Do proton pump inhibitors reduce the clinical efficacy of clopidogrel?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

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Background

Clopidogrel is a thienopyridine antiplatelet drug used in thromboembolic disorders. 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 thrombo embolic 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 [1-3].

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 [4, 5].

The European Medicines Agency (EMA) have highlighted that clopidogrel may be less effective in patients receiving proton pump inhibitors [6]. The Food and Drug Administration (FDA) in the United States and the Medicines and Healthcare Regulatory Agency (MHRA) in the UK have advised that omeprazole and esomeprazole should be avoided in patients taking clopidogrel [7-8].

Answer

Clopidogrel is converted into its active metabolite by the liver cytochrome P450 isoenzymes, mainly CYP2C19 and CYP3A4 [3, 9]. All PPIs are also metabolised by these isoenzymes. Pharmacokinetic and pharmacodynamic studies have suggested that all PPIs inhibit CYP2C19 and CYP3A4 to different degrees, with the magnitude of inhibition varying between each PPI and laboratory assay used. [9-11]. In addition, clopidogrel absorption may also be reduced by inhibition of the P-glycoprotein intestinal efflux transporter. Most PPIs appear to affect this transport system although the effect is considered mild [9, 11, 12].

Evidence for this interaction is inconsistent. 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 [3, 9, 11].

A study by Gilard et al published in 2008, first highlighted the possibility of interaction between omeprazole and clopidogrel [13]. 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 7days. 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 and esomeprazole or 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, 11, 14-21].

Most of the available data regarding the effect of this interaction on clinical outcomes is from either retrospective studies or prospective observational studies [22-46]. The data from these trials is conflicting, showing either an increased risk of major adverse cardiovascular events (MACE) [22-29], or little or no increased risk of MACE or re-hospitalisation [30-46]. A small number of studies appear to show that use of PPIs alone is associated with an increased risk of MACE [34, 35, 45, 46].

Several meta-analyses have reviewed these retrospective studies [47-50]. An analysis by Siller-Matula et al, included 159,138 patients. Concomitant use of a PPI was associated with a 29% relative risk increase of MACE compared with no PPI treatment (Risk Ratio (RR) =1.29; 95% confidence interval (CI) 1.15-1.44, p< 0.001). The RR with pantoprazole was 1.23 (95% CI 0.95-1.59; p=0.11) and 1.05 (95% CI 0.79-1.40; P=0.72%) with omeprazole when compared with no PPI use. In 2 further subgroup analyses, concomitant PPI use corresponded to a 31% RR increase of myocardial infarction compared with non-PPI use (RR=1.31, 95% CI 1.12-1.53; p<0.001); but was not associated with an increase risk of death (RR=1.04, 95% CI 0.93-1.16; p=0.53) [47].

Data from 3 randomised controlled trials has subsequently been analysed in an attempt to quantify the effect of PPIs on the efficacy of clopidogrel [21, 51-52].

The COGENT study was an international, double blind, randomised, placebo-controlled, parallel group, double dummy study, 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 cardiovascular (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 cardiovascular events; 54 in the placebo group and 55 in the omeprazole group, with no significant difference in the rate of the primary cardiovascular 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 cardiovascular interaction between clopidogrel and omeprazole, but that the results could not rule out a clinically meaningful difference in cardiovascular 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 [51].

The TRITON-TIMI 38 trial was a multicentre, randomised, double-blind, phase-3 trial 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 cardiovascular 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 cardiovascular 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 [21].

The PLATO (the Platelet Inhibition and Patient Outcomes) trial was a multi-centre, randomised, double blind, phase 3 trial. 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
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.
- Pharmacokinetic and pharmacodynamic studies have suggested that all PPIs inhibit these isoenzymes to different degrees and therefore could affect the clinical efficacy of clopidogrel.
- There have been no randomised trials to date which have been specifically designed to 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.
- 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 PPI may outweigh the risk of reduced clopidogrel efficacy.
- Separate guidance produced by the AAC/ACG/AHA and ESC suggests that there is not enough evidence for a clinically meaningful interaction and that PPIs should not be withheld in patients on clopidogrel if they are clinically needed.
• The FDA, MHRA and EMA currently advise avoiding omeprazole and esomeprazole in patients taking clopidogrel.
• There is insufficient evidence available regarding which PPI is least likely to interact, however based on data from pharmacokinetic and pharmacodynamic studies and the small amount of data available from the COGENT study, the FDA suggest that pantoprazole is the least likely to interact.
• Stockley’s Drug interactions suggests that pantoprazole is the least likely to interact with clopidogrel and also suggest lansoprazole and rabeprazole as suitable alternatives.
• The effect or lack of effect of lansoprazole or rabeprazole on clopidogrel pharmacokinetics and its antiplatelet effect is not established and more prospective trials are needed to investigate this.

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

References
32. Combined clopidogrel and proton pump inhibitor therapy is associated with higher cardiovascular event rates after percutaneous coronary intervention: a report from the BASKET trial. Journal of Internal Medicine 2012; 271: 257-263.


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Quality Assurance

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Search strategy

- EMBASE "proton pump inhibitors",ti,ab + clopidogrel.ti,ab; CLOPIDOGREL+ PROTON PUMP INHIBITOR. [Limit to: Humans and Publication Year 2007-Current and (Languages English)]
- MEDLINE: clopidogrel.ti,ab + proton pump inhibitors",ti,ab, CLOPIDOGREL +; PROTON PUMP INHIBITOR. Limit to: Human and (Languages English) and Publication Year 2007-Current]
- IdisWeb: clopidogrel or "CLOPIDOGREL 20120645") (omeprazole or "ESOMEPRAZOLE 56260605") or "OMEPRAZOLE 56260602") and Drug(s): ("clopidogrel 20120645") antiulcer-proton pump inhib 56260600 and clopidogrel 20120645
- Drugdex: Search terms, clopidogrel, omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole.
- MHRA, FDA and EMEA websites. Search terms clopidogrel.
- BNF online, Martindale, AHFS DI online, Stockley’s Drug Interactions, Meyler’s side effects of drugs 15th ed. Search terms clopidogrel.
- National electronic Library for Medicine, NHS Evidence. Search term clopidogrel.
- NICE, Prodigy, European Society of Cardiology, Royal College of General Practitioners, British Medical Association, British Society of Gastroenterologists and American College of cardiology/American Heart Association websites. Search term clopidogrel.