Clopidogrel and Omeprazole Drug Interaction
National Clinical Recommendations
February 2024

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT.

Issue:

On November 17, 2009 the Food and Drug Administration (FDA) notified healthcare professionals of new safety information concerning a drug interaction between clopidogrel and omeprazole.[1] FDA updated this guidance periodically through 10/27/2010. All safety alerts on this topic are now archived.[2] Current prescribing information for clopidogrel states "Avoid concomitant use of Plavix with omeprazole or esomeprazole."[3] This review aims to review recent clinical practice guidelines (published in the past 5 years) to determine the clinical relevance and practice recommendations regarding the clopidogrel-omeprazole drug interaction.

Background:

Clopidogrel is a prodrug and requires biotransformation to the active metabolite. This occurs via the hepatic cytochrome P450 (CYP) 2C19 enzyme, which is the same metabolic pathway used by proton pump inhibitors (PPIs). Theoretically, this may result in competitive inhibition when both clopidogrel and a PPI, like omeprazole, are given concurrently. In turn, a decreased concentration of the active clopidogrel moiety could be possible which would result in a decreased effect on platelet aggregation factors.

While recent meta-analyses that combine observational cohort and randomized controlled trials (RCTs) of PPI and clopidogrel use demonstrate concomitant use is correlated with an increased CV event risk; it is important to note the significance of this correlation is lost when evaluation is limited to RCTs and propensity score matching (PSM) of observational cohorts.[4-8]

Society Guideline Recommendations

Society guidelines in both cardiology and gastroenterology have since made recommendations regarding the use of concurrent clopidogrel and omeprazole:

2022 ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease[9]

- "For patients with GERD on clopidogrel who have LA grade C or D esophagitis or whose GERD symptoms are not adequately controlled with alternative medical therapies, the highest quality data available suggest that the established benefits of PPI treatment outweigh their proposed but highly questionable cardiovascular risks."

2023 AHA Guidelines for Chronic Coronary Artery Disease[10]

- "Increased bleeding including gastrointestinal bleeding is a common side effect of DAPT; the mitigation of this risk has been an area of clinical investigation. SAPT (aspirin or clopidogrel) compared with DAPT leads to lower gastric or small intestinal mucosal injury. Aspirin increases gastroduodenal ulcer formation. When combined with aspirin therapy, P2Y12 inhibitors can promote gastric ulcer bleeding. Clopidogrel is a prodrug that requires cytochrome CYP P450 2C19 for metabolism to its active form. PPIs are also metabolized by the P450 system, thereby leading to concern for inadequate clopidogrel therapy in those on both PPIs and DAPT. The FDA has added a boxed warning to avoid use of omeprazole with clopidogrel as well as other potent CYP 2C19 inhibitors, including esomeprazole. Several studies assessed the safety and efficacy of PPI in the context of DAPT. A meta-analysis of 6 RCTs (6,930 patients) showed that the use of PPIs is associated with a reduced risk of gastrointestinal bleeding in patients treated with DAPT after PCI. No significant differences were observed in the incidence of MACE, MI, and all-cause death in patients with CAD on DAPT and PPIs."

2023 ESC Guidelines for the Management of Acute Coronary Syndromes[11]

- Section 13.3.7. "Proton pump inhibitors (PPIs) reduce the risk of upper gastroduodenal bleeding in patients treated with antiplatelet agents. Therapy with a PPI is indicated for patients receiving any antithrombotic regimen who are at high risk of gastrointestinal bleeding (for details see Section 8.2.2.3, Bleeding risk assessment, in the Supplementary data online). PPIs that inhibit CYP2C19, particularly omeprazole and esomeprazole, may reduce the pharmacodynamic response to clopidogrel, though there is no strong evidence that this results in an increased risk of ischaemic events or stent thrombosis in clinical trials and propensity score-matched studies. Importantly, no interaction between the concomitant use of PPIs and aspirin, prasugrel or ticagrelor has been observed."

Recommendations:

- We recommend deprescribing PPIs according to the 2022 ACG Clinical Practice Update on De-Prescribing of Proton Pump Inhibitors[12] as much as possible.
- Given the lack of adverse cardiovascular effects of concurrent omeprazole and clopidogrel use as outlined in the above 2023 AHA, 2023 ESC, and 2022 ACG guidelines, we do not recommend limiting omeprazole use in patients on clopidogrel.

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