Evaluating the Effect of Six Proton Pump Inhibitors on the Antiplatelet Effects of Clopidogrel

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Background and Goal: Cytochrome P450 (CYP) enzymes are responsible for the conversion of clopidogrel into its active metabolite and the metabolism of proton pump inhibitors (PPIs), which may also inhibit CYP enzymes. A current Food and Drug Administration advisory suggests avoiding esomeprazole and omeprazole while taking clopidogrel because of concerns that PPIs may compromise clopidogrel's antiplatelet effects. The objective of the present study was to examine the robustness of this interaction using a well-controlled study design in a population of participants free of confounders. *Materials and Methods:* Twenty-eight healthy male participants, with a mean age 24.2 ± 3.2, were randomized to an incomplete crossover design schedule. Participants underwent platelet aggregation testing after clopidogrel alone, while on clopidogrel in combination with 1 of 3 PPIs (40 mg of pantoprazole, 20 mg of omeprazole, 20 mg of rabeprazole, 40 mg of esomeprazole, 30 mg of lansoprazole, or 30 mg of dexlansoprazole), and during 1 week of clopidogrel-only washout periods. *Findings:* The median platelet aggregation to adenosine diphosphate during a drug-free baseline was 10Ω (2.5 interquartile range) of impedance and decreased to 0Ω on clopidogrel alone. Aggregation did not significantly change with concomitant use of PPIs and clopidogrel. *Conclusion:* These data do not demonstrate a significant interaction between common individual PPIs and clopidogrel in healthy volunteers who respond to clopidogrel alone. This adds data to a growing body of evidence indicating that the addition of a PPI may have a weak effect on clopidogrel's antiplatelet properties, and may only be relevant in specific clinical circumstances. **Key Words:** Proton pump inhibitors—clopidogrel—interaction—healthy volunteers—antiplatelet.

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Introduction

Clopidogrel is commonly prescribed for the indication of acute coronary syndrome and arterial thromboembolism prophylaxis or to reduce the risk of other vascular death.[1,2] Clopidogrel is a prodrug that requires the cytochrome P450 (CYP) metabolizing enzyme families to form an active metabolite, primarily relying on CYP2C19 but also utilizing metabolic pathways involving CYP3A4, CYP2C9, CYP1A2, and CYP2B6.[3] The active thiol metabolite irreversibly blocks adenosine diphosphate (ADP) from binding to the $P2Y_{12}$ receptor on the platelet, ultimately preventing aggregation. The inhibition of platelet aggregation can be seen as early as

2 hours, and the maximum inhibition of platelet aggregation occurs in approximately 7 days without a loading dose.[4] Since the active metabolite irreversibly binds to the ADP receptor, the drug will block ADP from binding for the lifetime of the platelet, which is approximately 5-7 days in healthy volunteers.[5-7] Proton pump inhibitors (PPIs) have been documented to be inhibitors of the CYP2C19 enzyme and cosubstrates for CYP3A4, the major enzymes needed to activate clopidogrel; therefore, concomitant use with clopidogrel poses a potential clinical concern.[8]

PPIs have become first-line treatment for gastroesophogeal reflux disease and may be useful in patients undergoing antiplatelet therapy who are at higher risk of gastrointestinal bleeding or ulcerations. In 2009, initial studies suggested there was an increased risk of adverse cardiovascular events in patients taking both PPIs and clopidogrel. The Food and Drug Administration responded in November of 2009 by updating the label of clopidogrel to include a drug interaction warning of omeprazole and esomeprazole due to interference in metabolism via CYP2C19.[9] The warnings also mention other PPIs, which could inhibit the enzyme to varying degrees. Afterward, further specifications were made in the form of the suggestion to use a different agent (dexlansoprazole, lansoprazole, or pantoprazole) with minimal enzyme-specific inhibitory effects on clopidogrel metabolism.[10] These warnings had a profound impact on prescribing patterns, and a 2014 report by Kashour et al found that more than half of patients who were previously on concomitant omeprazole and clopidogrel therapy were switched to a different PPI.[11] In reference to these warnings, Gerhard commented, "the magnitude of potential harm of concomitant use (of clopidogrel with PPIs) is fundamentally limited by the risk and benefits of each individual drug."[12]

There is some laboratory evidence to suggest that a clinically significant interaction occurs between clopidogrel and omeprazole or esomeprazole; however, various studies evaluating platelet response with concomitant use of PPIs and clopidogrel have failed to consistently demonstrate the same interactions across the class of drugs. A VASP analysis of platelet reactivity revealed that fewer patients exhibited resistance to clopidogrel when taking concomitant pantoprazole compared with those taking concomitant omeprazole.[13] On the other hand, Angiolillo et al published results indicating an interaction between clopidogrel and omeprazole, but not between clopidogrel and pantoprazole.[14] In a separate study, both pantoprazole and esomeprazole were found not to impair clopidogrel, as opposed to the inhibitory effects of omeprazole.[15] Reports have also shown lansoprazole's interaction with clopidogrel to be prominent in a patient population that has a higher initial inhibition of platelet aggregation.[16] A study of healthy volunteers disclosed that not only does 80 mg of concomitant omeprazole decrease the net exposure to clopidogrel's active metabolite by 31%, but it also statistically significantly decreases the antiplatelet effects of clopidogrel.[17] The same study demonstrated therapeutic doses of dexlansoprazole and lansoprazole had less significant interactions with clopidogrel than esomeprazole and omeprazole. Conversely, lansoprazole was reported to decrease the inhibition of platelet aggregation antiplatelet effects of clopidogrel in participants showing a robust response to clopidogrel alone.[16] Arbel et al demonstrated that platelet reactivity was increased in patients undergoing dual antiplatelet therapy with aspirin and clopidogrel with concomitant use of omeprazole compared with the use of pantoprazole, the histamine antagonist famotidine, or baseline.[18]

There is an abundance of conflicting data coming from studies reporting the effect of PPIs on clopidogrel's antiplatelet effects. An examination of these studies reveals potential confounders in exploring the fundamental questions of whether PPIs interact with clopidogrel and the potential strength of this interaction. These confounders include concomitant use of aspirin, assumptions regarding the relationship between changes in clopidogrel active metabolite concentrations and the magnitude of antiplatelet effect, and other medications used concomitantly.

The interaction between clopidogrel and PPIs has also been evaluated in clinical outcome studies. In 2010, the COGENT trial, published in the *New England Journal of Medicine*, failed to demonstrate an increased risk of cardiovascular events in patients who were undergoing dual antiplatelet therapy; however, a clinically meaningful interaction could not be ruled out due to a wide confidence interval surrounding the hazard ratio.[19] While this was a randomized, controlled trial with a large study population, its results are confounded by the concomitant use of aspirin, which may blunt the effects of any interaction. A 2012 study by Bhurke et al found a significant increase in risk for adverse cardiovascular events in acute coronary syndrome patients who were concomitant users of a PPI and clopidogrel as compared with clopidogrel users alone. However, the matched 1:1 design of PPI users to nonusers failed to take into account that users of a PPI generally have significantly more comorbidities and concomitant medications.[20] Leonard et al recently studied the risk of acute ischemic stroke when a PPI is added to a clopidogrel regimen.[21] This study examined the effects of 4 different PPIs and found no significant increase in risk associated with concomitant use in any group.

The present crossover study seeks to determine whether each PPI causes an individual significant change in platelet aggregation when compared with clopidogrel alone in healthy volunteers, eliminating intersubject variability in CYP isoenzyme activity as a result. To our knowledge, this is the first study to examine the effects of all 6 PPIs on the antiplatelet function of clopidogrel in a head-to-head comparison.