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Review on Concomitant Use of Proton Pump Inhibitors [PPI] with Antiplatelet Agents

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ABSTRACT

Clopidogrel and proton pump inhibitors (PPI) are the two drugs which are commonly used in clinical settings. clopidogrel is an anti-platelet drug used for cardiovascular and cerebrovascular disease. The main drawback of long-term use of antiplatelet therapy is gastrointestinal bleeding so that the patients with antiplatelet drug is prescribed with proton pump inhibitors as a prophylactic measure.
Many studies suggest that proton pump inhibitors can reduce the antiplatelet effect of clopidogrel by inhibiting the enzyme CYP450.clopidogrel is a prodrug which is converted to active drug mainly by CYP2C19 in the liver. The same enzyme is responsible for the metabolism of proton pump inhibitors. Hence there is a possibility of interaction between clopidogrel and proton pump inhibitors. As a result, there is a chance of increasing cardiovascular events in patient taking proton pump inhibitors along with clopidogrel.

Keywords: [proton pump inhibitors, clopidogrel, gastrointestinal bleeding, prodrug, CYP450 enzyme, interaction]

INTRODUCTION

Antiplatelet drugs interfere with platelet function and are useful in prophylaxis of thromboembolic disorders [1]. According to data from various studies, clopidogrel is now the second-most widely prescribed medication in the world [2-10]. The main complication with the long-term use of antiplatelet therapy is gastrointestinal hemorrhage [11].

A randomized clinical trial support the use of PPI to reduce the rate of recurrent gastrointestinal bleeding in high-risk patient receiving aspirin. PPIs are commonly prescribed for patient receiving antiplatelet drug as a preventive measure. PPIs are typically administered to individual taking aspirin and clopidogrel in order to stop internal bleeding [12] . patients with serious coronary heart disease taking clopidogrel prophylactic use of proton pump inhibitor can reduce the rate of gastroduodenal bleeding [13].

At the same time some studies shows that PPI may prevent clopidogrel from have its antiplatelet effect. Patient taking clopidogrel and PPIs simultaneously after an acute coronary syndrome are at an increased risk of serious cardiovascular events as a result [14,15,16].

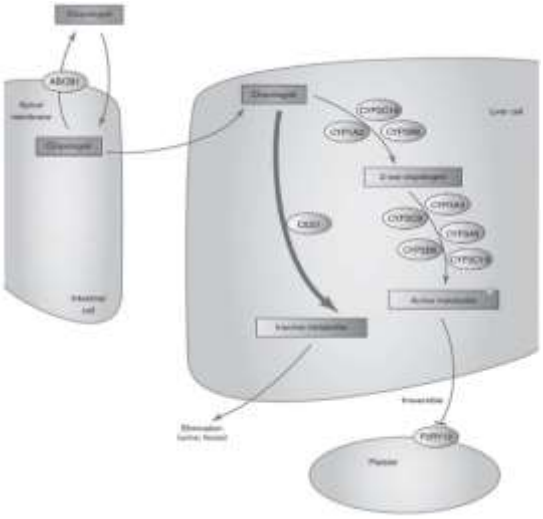
However, observational studies pointed out the possibility of a possible interaction between clopidogrel and PPIs that, if true, might have severe clinical complications[17,18].These investigations have been supported by the findings of ex vivo research, many of which have demonstrated that PPIs, most frequently omeprazole, inhibit the antiplatelet action of clopidogrel[19-21].The response of clopidogrel may also be impacted by genetic variations, which theoretically might also enhance the likelihood of medication interactions mediated by cytochrome P-

450[22-26]. These conflicts in concomitant use of clopidogrel and PPI lead to growing concerns of their risk.

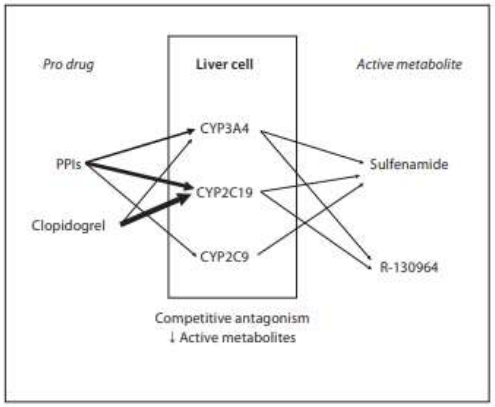
DISCUSSION

Clopidogrel, PPIs, and cytochrome P4502C19.

Clopidogrel is a thienopyridine derivative that specifically and permanently binds to the platelet purinergic receptor P2Y12 to prevent adenosine diphosphate-mediated platelet activation and aggregation [27,28]. The liver activates the prodrug clopidogrel [29], which is absorbed in the gut [30,31]. Two consecutive oxidative steps are necessary for the conversion. 2-Oxo-Clopidogrel is created in the first step, then it is transformed into the active metabolite. CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5 are considered as a cytochrome P450 enzymes involved in the metabolism of clopidogrel [32]. Figure 1



PPIs and clopidogrel interact in a way that makes them competitors for the same CYP2C19 enzyme. This enzyme not only breaks down PPIs but also transforms clopidogrel through its principal pathway into its active metabolite, which is linked to the platelet. P2Y12 ADP receptor via a disulfide bond that deactivates it. The existence of distinct metabolic pathways in each PPI is of paramount therapeutic importance. Omeprazole, lansoprazole, and pantoprazole are all metabolized primarily by the CYP2C19, CYP3A4, and CYP2C9 pathways, respectively. Both CYP2C19 and CYP3A4 are equally involved in the metabolism of rabeprazole[33]. Figure 2



The vasodilator-stimulated phosphoprotein test used in the randomized, double-blind OCLA (Omeprazole Clopidogrel Aspirin) research revealed that omeprazole considerably reduced the inhibitory effect of clopidogrel on platelet P2Y12 (VASP) [34].

A study suggests that CYP2C19 enzyme which is responsible for metabolism of clopidogrel and PPIs may affect the genotype status. PPIs other than omeprazole should be used, especially by patients receiving clopidogrel and aspirin as part of a dual antiplatelet regimen [35].

A study conducted reported that there is an association between diminished biological action of clopidogrel and PPI treatment. A competitive effect of PPIs on CYP 2C19 might thus underlie clopidogrel's reduced effectiveness in patient receiving PPIs [36].

S Kenngott etal performed the study on clopidogrel and proton pump interaction and concluded that the clopidogrel -proton pump inhibitors interaction does not seem to be a PPI class effect. Rabeprazole did not affect in a subject with a clear omeprazole - clopidogrel interaction. The separate intake of PPI and clopidogrel may not be sufficient to prevent their interaction [37].

Gastrointestinal outcomes

A prominent potential side effect of antithrombotic therapy is gastrointestinal bleeding. Randomized studies have shown

that prophylactic use of PPIs and H2-receptor antagonists reduces the risk of endoscopically ascertained ulcers in patients receiving aspirin
[38,39].
A study reported that there is significant reduction in clinically manifested gastrointestinal bleeding in population taking PPIs compared with population taking placebo [40].
A study concluded that ulcer complication associated with long term use of low dose aspirin can be reduced by using lansoprazole [41].
Both the American Heart Association (AHA) and the American College of Cardiology (ACC) recommend anti platelet therapy following coronary stenting [42] . The combination of clopidogrel and PPI diminishes the risk of gastrointestinal bleeding [43].

Cardiovascular and Other Outcomes.
In patients with symptomatic atherosclerosis, non-ST elevation acute coronary syndrome (ACS), and ST segment elevation, clopidogrel is primarily suggested for the prevention of vascular ischemic events. Heart attack (MI) [15] .
As a preventative strategy to stop GI tract bleeding, proton pump inhibitors (PPIs) are administered to patients taking aspirin and clopidogrel. According studies, PPIs may prevent clopidogrel from acting as an antiplatelet drug. Patients taking clopidogrel and PPIs concurrently after an ACS 1-3 are at an increased risk for serious cardiovascular events due to inhibition of CYP2C19, the enzyme responsible for bioactivation clopidogrel, by PPIs [15-17].
A study conducted by K Shrestha on "The prevalence of co-administration of clopidogrel and proton pump inhibitors" reported that the residents taking combination of clopidogrel and PPI with or without aspirin for a significantly long duration which could increase the risk of adverse cardiovascular events [44].
A study reported that combined use of PPI and clopidogrel increase the risk of major cardiovascular events in patients with coronary artery disease [45].
A study reported that concomitant use of PPI and clopidogrel after acute myocardial infarction was associated with increased risk of recurrent myocardial infarction. But this effect was not seen with pantoprazole therapy [16].

Adverse Events
A study reported that the rate of serious adverse events did not differ significantly between the two groups that is patient receiving PPI and placebo. Diarrhoea was reported in 3.0% of patients receiving omeprazole, as compared with 1.8% of those receiving placebo. No patient had diarrhoea caused by infection with Clostridium difficile. There were no newly diagnosed cases of osteoporosis which is commonly seen in patients with long term use of PPI. One case of peripheral neuropathy was reported in the placebo group. There were no significant differences between the two groups in the rates of pneumonia, headache, nausea, anaemia, or fracture [40]
A study concluded that concomitant use of clopidogrel with PPI was associated with an increased risk of adverse outcomes than use of clopidogrel without PPI in ACS patient after hospital discharge. PPI reduce the benefits of clopidogrel [46].

FDA guidelines
FDA recommends some guidelines for the safe use of PPIs along with antiplatelet agents until further information is available [47]:

- Healthcare providers should continue to prescribe and patients should continue to take clopidogrel as directed, because clopidogrel has demonstrated benefits in preventing blood clots that could lead to a heart attack or stroke.
- Healthcare providers should re-evaluate the need for starting or continuing treatment with a PPI, including Prilosec OTC, in patients taking clopidogrel.

- Patients taking clopidogrel should consult with their healthcare provider if they are currently taking or considering taking a PPI, including Prilosec OTC.

Recommendations

- Prophylactic PPI should be used in patients taking dual antiplatelet therapy or previous history of gastrointestinal bleeding.
- The PPI of choice should be pantoprazole [33]

CONCLUSION

Prophylactic use of proton pump inhibitors with clopidogrel add benefit of reducing gastro intestinal problems but interaction between clopidogrel and proton pump inhibitors reduce the effect of clopidogrel and may also leads to severe cardiovascular problems. The prophylactic use of proton pump inhibitors for long term also precipitates adverse events such as clostridium difficile infections, hypomagnesaemia, osteoporosis etc. so that the prophylactic use of PPI should limit to those patients having severe gastric problems such as geriatric patient taking dual antiplatelet therapy for long term, previous history of gastro intestinal bleeding. The interaction between PPI-clopidogrel vary with different PPI. Pantoprazole is considered to be safer.

Declaration by Authors

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