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Interaction between clopidogrel and proton pump inhibitors: A clinical overview

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ABSTRACT

Most proton pump inhibitors inhibit the bioactivation of clopidogrel to its active metabolite. The clinical significance of this drug interaction is unknown. Over recent years there has been much debate about whether some or all proton pump inhibitors might reduce the effectiveness of clopidogrel because of a drug interaction at the cytochrome P450 2C19 enzyme. Clopidogrel is a prodrug that is metabolized to an active form, and this process occur primarily via cytochrome P450 2C19. Proton pump inhibitors inhibit cytochrome P450 enzyme to varying degrees, and the studies showed that the combined use of clopidogrel with omeprazole or lansoprazole leads to reduction in activity of clopidogrel as measured by platelet aggregation and associated biomarkers. This suggests that there is a potentially important pharmacokinetic interaction between these drugs when used at therapeutic doses. Evidence to date has been conflicting; some studies have observed an increased risk of vascular events in patients receiving clopidogrel and proton pump inhibitors, while others, including an underpowered randomized trial, found no increased risk.

Keywords: Clopidogrel, Proton Pump Inhibitors (PPIs), Acute Coronary Syndromes (ACS), Percutaneous Coronary Interventions (PCIs).

INTRODUCTION

Drug-drug interactions have become an important issue in health care. It is known that many drug-drug interactions can be explained by alterations in the metabolic enzymes that are present in the liver and other extra-hepatic tissues. Many of the major pharmacokinetic interactions between drugs are due to hepatic cytochrome P450 (P450 or CYP) enzymes being affected by previous administration of other drugs.

After coadministration, some drugs act as potent enzyme inducers, whereas others are inhibitors. However, reports of enzyme inhibition are very much more common. Understanding these mechanisms of enzyme inhibition or induction is extremely important in order to give appropriate multiple-drug therapies. Clopidogrel is a widely prescribed thienopyridine for the prevention of atherothrombotic complications following acute coronary syndromes (ACS) or percutaneous coronary interventions (PCIs). Clopidogrel is a prodrug that has no intrinsic antiplatelet activity without activation by hepatic metabolism through the cytochrome P450 (CYP) system. Multiple CYP enzymes have been implicated in this process, but recently the CYP2C19 enzyme has assumed predominance as it is involved in both sequential oxidative steps. The possibility of drug interactions limiting clopidogrel's efficacy was raised several years following in vitro statin and clopidogrel studies, but without

definitive clinical confirmation of increased adverse outcomes. Recently, mechanistic in vitro studies have suggested that proton pump inhibitors (PPIs) may diminish clopidogrel's clinical efficacy via CYP2C19 competitive inhibition. Consistent with these in vitro observations, several clinical studies have shown higher cardiovascular events in clopidogrel patients exposed to PPIs compared to those not exposed, leading the Food and Drug Administration (FDA) and the European Medicines Agency to issue public alerts recommending the avoidance of prescribing PPIs in patients who also take clopidogrel. However, as the studies have largely been nonexperimental, the possibility of a spurious association due to bias needs to be attentively considered.

This is a clinically important question as many cardiac patients are also at high risk of gastrointestinal (GI) bleeding (due to age, smoking and concomitantly prescribed drugs), and PPIs may substantially mitigate this risk. The MEDLINE and EMBASE electronic databases was reviewed without any language restriction, combining search terms for clopidogrel ("clopidogrel" OR "Plavix" OR "thienopyridine"), PPIs ("PPI" OR "omeprazole" OR "lansoprazole" OR "pantoprazole" OR "esomeprazole" OR "rabeprazole") with those for cardiovascular outcomes ("mortality" OR "cardiovascular disease" OR "heart disease" OR "CAD" OR "MI" OR "UA" OR "coronary angiography" OR "coronary restenosis" OR "PCI" OR "stroke") and drug interaction ("interaction" OR "inhibition" OR "CYP2C19"). References of relevant identified articles were hand-searched for additional studies. Abstracts from medical organization conferences (American Heart Association, American College of Cardiology, European Society of Cardiology and Transcatheter Cardiovascular Therapeutics) were manually searched from 2005.
Mechanistic in vitro studies measuring platelet aggregation were therefore excluded. Two investigators independently reviewed articles for inclusion and study quality. Both reviewers examined the methodology component independently of the study results, but given the publicity surrounding the individual studies it was impossible to ensure that the reviewers were totally blinded to the outcomes. It was planned to resolve disagreements by consensus, but there was perfect agreement between the investigators on their initial assessments. This systematic review was performed according to the PRISMA guidelines.

CONCLUSION

In summary, it was found that, among patients taking clopidogrel following acute myocardial infarction, the concomitant use of a proton pump inhibitor that inhibits cytochrome P450 2C19 (omeprazole, lansoprazole or Rabeprazole) was associated with an increased risk of recurrent myocardial infarction. This effect, which was not seen with pantoprazole therapy, presumably reflects inhibition of the metabolic bioactivation of clopidogrel. Our findings highlight a widely unappreciated, common and completely avoidable drug interaction in a population at high risk of recurrent coronary events. Pending further data regarding the clinical significance of drug interactions with clopidogrel, we believe that concomitant treatment with clopidogrel and proton pump inhibitors other than pantoprazole should be minimized when possible. Ranitidine or another H2-receptor antagonist may be an appropriate alternative for patients who require acid-lowering therapy. If a proton pump inhibitor is required, pantoprazole should be used[2].

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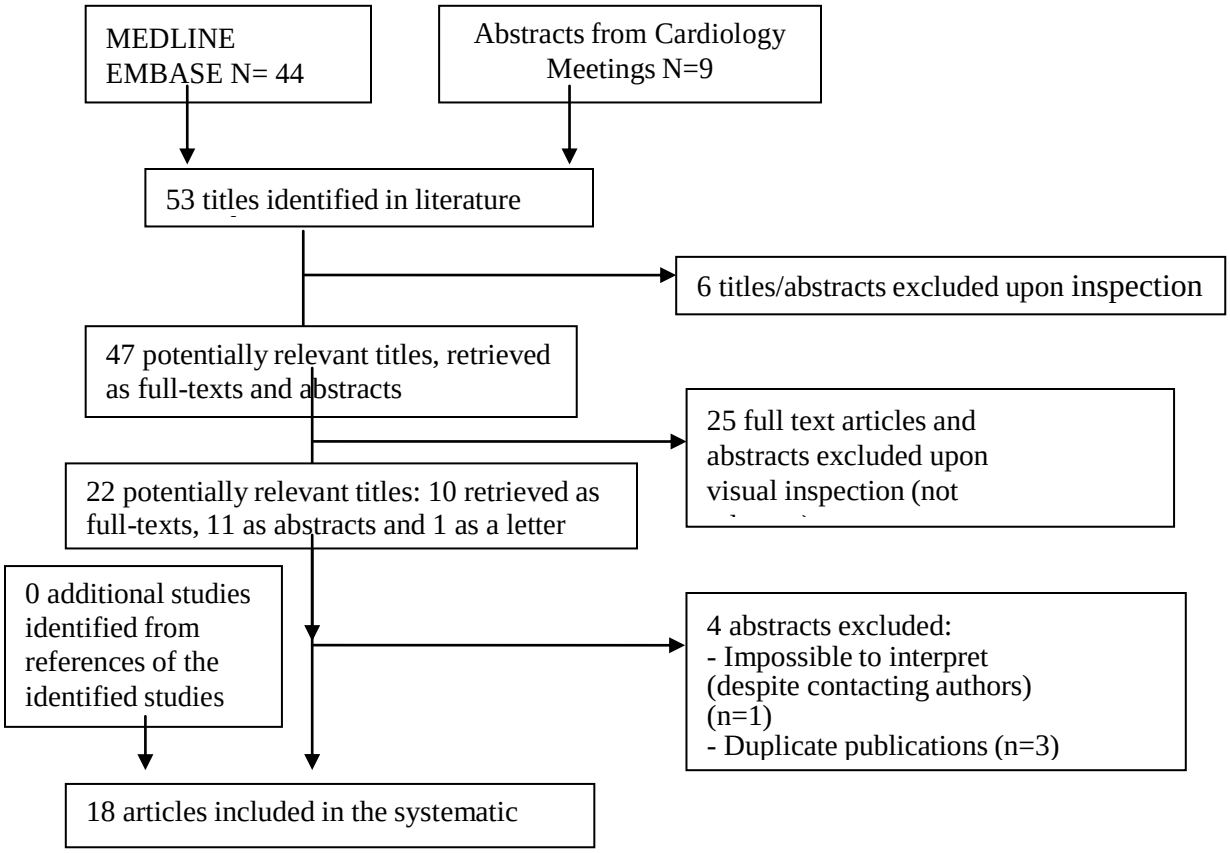

Figure 1: Flow diagram of selection process of studies included in the review.

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