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Omeprazole and atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation in patients undergoing percutaneous coronary intervention in a tertiary health care system: A prospective drug–drug interaction study

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ABSTRACT

Background: Clopidogrel, a prodrug is found to be less effective in inhibiting the platelet aggregation when administered along with PPI's in patients undergoing cardiac stent, ST segment elevated Myocardial infarction (STEMI) followed by percutaneous coronary intervention (PCI). Clopidogrel binds to CYP2C19, a hepatic enzyme to get converted to its active metabolite in order to achieve desired pharmacological activity. The cytochrome P450 3A4 which is partially involved in the metabolism of clopidogrel also metabolizes statins, mainly atorvastatin to the greater extent.
Methodology: In the current study patients on PPI's with dual antiplatelet therapy and patients on PPI's and statins with dual antiplatelet therapy are considered to understand the potential drug–drug interactions (pDDI) among the South Asian population. Platelet aggregation was measured in 61 patients undergoing coronary artery stent implantation treated with clopidogrel and aspirin along with PPI's and statins.
Results: It was observed that omeprazole and atorvastatin, but not pantoprazole and rosuvastatin, inhibited the antiplatelet activity of clopidogrel. The percent platelet aggregation was 72 ± 6 ($p = 0.001$) and 43 ± 23 ($p = 0.027$) in the presence of clopidogrel with omeprazole and pantoprazole respectively. Aggregation was found to be 91 ± 4 ($p = 0.001$) and 12 ± 23 ($p = 0.031$) in the presence of clopidogrel with atorvastatin and rosuvastatin respectively.
Conclusion: A prominent drug–drug interaction was observed with patients on dual antiplatelet therapy along with omeprazole and atorvastatin.

1. Introduction

Clinical studies have indicated a potential drug–drug interaction (pDDI) between dual antiplatelets (clopidogrel and aspirin) and clinically prescribed PPI's like omeprazole, pantoprazole, esomeprazole [1] and statins such as atorvastatin and rosuvastatin. Health care in tertiary system consider drug–drug interactions as the major concern due to the alarming mortality rate associated with these interactions. The competitive binding of several classes of drugs to a single metabolic enzyme, cytochrome P450 which are most likely to be present in the liver and other hepatic tissues, leading to drug–drug interaction. These cytochrome P450 enzymes alter the pharmacology of one drug due to competitive binding of the other drug [2], thus leading to major pharmacokinetic interaction.

Drug–drug interactions have become an important issue in health care. It is now realized 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. In the future, it may help to identify individuals at greatest risk of drug interactions and adverse events [2].

Clopidogrel belongs to a thienopyridine class of drugs which inhibits platelet aggregation in the patients undergoing percutaneous coronary intervention and also reduces coronary stent thrombosis and myocardial infarction [3–5]. Clopidogrel converts to its active metabolite by

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forming a disulfide bridge with adenosine diphosphate (ADP) receptor and exhibits antiplatelet effect [6–9]. In animals, especially rats it's found that cytochrome P450 1A2 is responsible for the activation of clopidogrel [7], whereas in humans the activation of clopidogrel is mostly by the cytochrome P450 2C19 and partly by 3A4 [9].

Patients receiving antiplatelet therapy are most commonly prescribed with PPI's to reduce the gastrointestinal bleeding [10]. Cardiovascular events, stroke, myocardial infarction and mortality continue to occur in patients with vascular diseases because of competitive binding of the ADP receptor blocker clopidogrel and PPI's to the isoenzymes 2C19 [11,12]. Patients with acute coronary syndrome are most likely to have elevated levels of cholesterol which makes it necessary for statin therapy. Thus evaluation of each drug concentration in a poly prescription becomes atmost important.

The American College of Cardiology/American Heart Association 2007 Unstable Angina/Non-ST-Segment Elevation Myocardial Infarction guidelines recommend concomitant PPI therapy with aspirin and clopidogrel in patients with a history of gastrointestinal bleeding [13]. Consequently, the number of patients affected by a PPI–clopidogrel interaction could be substantial. In fact, a combined total of 100 million prescriptions are written for both PPIs and clopidogrel annually [14]. However, this does not include all omeprazole use since, at some strengths, it is available over-the-counter. It has been hypothesized that PPI use concurrently with clopidogrel will increase the risk of major adverse cardiac events [15].

Different isoforms of cytochrome P450 (CYP) metabolized different types of substrates (or drugs molecule) and make them soluble during biotransformation. Therefore, fate of any drug molecule depends on how they are treated or metabolized by CYP isoform. There is a need to develop models for predicting substrate specificity of major isoforms of P450, in order to understand whether a given drug will be metabolized or not. *In-silico* method for predicting the metabolizing capability of major isoforms (e.g. CYP 3A4, 2D6, 1A2, 2C9 and 2C19) has been explained [16].

2. Material and methodology

In the current study, patients with acute coronary syndrome and other cardiovascular diseases followed by stent implantation and percutaneous coronary intervention, where prospectively evaluated for platelet aggregation studies. Patients with prescription of clopidogrel and aspirin along with PPI's and statins were under consideration.

The institutional review board approved the protocol, and a written informed consent was signed by the patient/patient care taker, before commencing the study.

i. **Study site:** This study was conducted in JSS College of Pharmacy and Department of Cardiology, JSS Medical College and Hospital, Mysore.
ii. **Study design:** This was a prospective bioanalytical study.
iii. **Study period:** The study was conducted over a period of 19 months, from the month of June 2014 to December 2015.
iv. **Study subjects:** The study subjects were enrolled into the study based on the study criteria
v. **Study criteria**

a. **Inclusion criteria**

1. Male or female between the ages of 40 to 60 years, inclusive who are admitted in the hospital (in-patients)
2. Females must have negative results for pregnancy tests performed: at Screening on a urine specimen obtained within 2 weeks prior to initial study drug administration.
3. Body Mass Index (BMI) is 19 to 26, inclusive. BMI is calculated as weight in kg divided by the square of height measured in meters.
4. A condition of MI, stroke, heart attack etc. with percutaneous coronary intervention admitted in the cardiology/other department in the hospital.
5. Patients receiving the above said medications
6. Must voluntarily sign and date each informed consent, prior to the initiation of any screening or study-specific procedures.

b. **Exclusion criteria**

1. History of significant sensitivity to any drug.
2. Requirement for any over-the-counter and/or prescription medication other than above mentioned, vitamins and/or herbal supplements, on a regular basis.
3. Use of any medications (other than OTC/prescription), vitamins and/or herbal supplements, within the 1-week period prior to study drug administration.
4. Recent (6-month) history of drug or alcohol abuse.
5. Use of known inhibitors (e.g., ketoconazole) or inducers (e.g., carbamazepine) of cytochrome P450 3A (CYP3A) within 1 month prior to study drug administration.

vi. **Investigation and study protocols**

The institutional review board approved the study protocols and written informed consent was obtained from each subject before enrollment. In the study, 61 patients undergoing successful elective coronary artery stent implantation received an oral loading dose of 300 mg of clopidogrel (PLAVIX™) followed by 75 mg/day for 28 days.

Subjects enrolled for the study had undergone primary percutaneous coronary intervention followed by stent implantation, a standard diagnostic treatment. All patients were enrolled and studied prospectively. All the subjects received 300 mg of aspirin (NUSPRIN™) on admission and 200 mg/day thereafter throughout the study period.

Platelet aggregation activity was tested in blood samples withdrawn in the pathology laboratory 60 ± 5 min after administration of chewable aspirin (baseline).

Eight patients were on PPI's alone, among them five were prescribed with 40 mg of omeprazole (PRIOSEC™) twice daily and three were on pantoprazole (PANTODAC™) 40 mg twice daily. Seventeen patients were on dual antiplatelet therapy along with PPI's.

Out of eleven patients on statin therapy, six were taking 40 mg of atorvastatin (AVAS™) a day, and five were taking either 40 mg (n 5) of rosuvastatin (CRESTOR™) once daily. Platelet aggregation was measured before clopidogrel administration and 24 h later. Platelet aggregation measurements were repeated in ten patients on clopidogrel and aspirin alone and fifteen patients on clopidogrel plus PPI's and statins 24 days after successful stent implantation.

Subjects were divided into 5 quartiles depending on the patients who were on prescribed medications. Platelet aggregation induced by the ADP was measured at 24 h compared with the baseline at 0 h after the administration of clopidogrel loading dose was measured. Percentage aggregation was presented were presented categorically in the 5 quartiles. Mantel–Haenszel [2] analysis was used to test the linear trend. Patients of first quartile were compared with second till fifth quartiles using a 2-tailed Fisher's test. Variables were presented as mean ± SD.

Baseline demography and clinical characteristics of patients on dual antiplatelet therapy, PPI's and statins individually and in combinations are mentioned in Table 1.