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Research Article

INTERACTION STUDY OF ESOMEPRAZOLE AND CLOPIDOGREL IN CARDIOVASCULAR PATIENTS

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ABSTRACT

Methods: Twenty one coronary artery disease patients of both genders who expressed willingness to participate underwent screening, randomized equally into two cross-over sequences, dosed with clopidogrel and clopidogrel + esomeprazole in respective periods. Blood samples were collected through ante-cubital or forearm vein indwelling catheter. Concentration of clopidogrel parent prodrug in isolated plasma was determined using validated sensitive liquid chromatography – mass spectrometry. Pharmacokinetic modelling was carried out using PKSOLVER add in for Microsoft Excel.

Results: The pharmacokinetic profile of clopidogrel was non-significantly altered by esomeprazole. Statistically significant difference in peak plasma concentration, apparent volume of distribution and clearance of clopidogrel was observed only during period II in subjects co-dosed with esomeprazole (P Value = 0.0483, 0.0011 and 0.0015 respectively). All other primary and secondary pharmacokinetic parameters displayed minor alterations during either periods (P value<0.05).

Conclusion: The non-significant alteration of clopidogrel pharmacokinetics by esomeprazole can be potentiated by underlying predisposing factors such as presence of *CYP2C19* allelic variants, increasing the risk of cardiovascular events. Hence co-administration of clopidogrel and esomeprazole should be under clinical monitoring and is not recommended in poor responders of anti-platelet therapy with clopidogrel.

INTRODUCTION

United State Food and Drug Administration (USFDA) authorised Clopidogrel as a prophylactic agent for cardiovascular diseases, in the year 1998. Being an adenosine diphosphate receptor antagonist, Clopidogrel is used to avert stroke and heart attack in individuals with high risk. Clopidogrel is highly recommended for prevention of atherosclerotic plague in population with pervious conditions of myocardial infraction, acute coronary syndrome, peripheral artery disease, peripheral vascular disease [1,2] and vascular death either followed by stroke or peripheral vascular disease.

The American heart association and American college of Cardiology suggest Clopidogrel treatment in people with:

- Myocardial infraction with ST elevation [3]:
- As a loading dose for acute percutaneous coronary intervention PCI, and as full year adjuvant therapy for those receiving vascular stent.
- As a loading dose for fibrinolytic therapy for followed for minimum of 14 days.
- Non-ST elevation of myocardial infraction [4] or unstable angina
- In PCI patient intolerable to aspirin therapy are given a

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loading dose and maintenance therapy

- In medium to high risk patient, a maintenance therapy up to 12 months is given in case of invasive treatment strategy [5].
- Stable ischemic heart disease [6] as a viable monotherapy in patients with who cannot withstand aspirin in combination Clopidogrel in some patients at high risk.

Other treatment recommendations Clopidogrel as an alternative antiplatelet agent for people having aspirin intolerance. As a preventive medication for thrombosis in people undergoing coronary stent placement [7]. Clopidogrel therapy though considered to be safer, has some rare serious adverse reactions like hemorrhage and thrombotic thrombocytopenic purpura [8] (in 4 per 1,000,000 patients). Hemorrhagic conditions seem to worsen when Clopidogrel is given in combination Aspirin [9].

Clopidogrel inhibits the ADP receptors present on the cell membranes of the platelets and prevent platelet aggregation. The inhibitory activity of the Clopidogrel is observed after two hours of the loading dose. It is dosed generally at 600mg or 300mg. The rapid action of drug is to the shorter half-life [0.5 - 1.0 h] of its active metabolite [10-12]. Clopidogrel undergoes two-step oxidative biotransformation process with help of human carboxyl esterase 1(CES1) and CYP450 enzymes like CYP1A2, CYP2C19, CYP2B6, CYP2C9 and CYP3A4/5 [13,14]. These enzymes help in conversion of inactive metabolites into active ones [15-17]. CYP2C19 plays a major role in metabolism of various drugs like antidepressants, barbiturates, antimalarial, antitumor and proton pump inhibitors. It is also a major metabolizing enzyme for Clopidogrel [18]. A black box warning was issued by USFDA against Plavix in March 2010 that there is a high risk of treatment failure in CYP2C19 poor metabolizer. These patients constitute about 14% of all the patients [19,21]. This awareness was brought within the patients and healthcare communities. CYP2C19 poor metabolizers have lesser amount of active metabolite and hence lower inhibition of the platelets. This lower metabolism puts these patients at 3.58 times higher risk towards developing adverse cardiovascular like stroke, heart attack or even death [22,23]. It was also observed that patients with high functioning allele of CYP2C19 are 1.5 to 3.5 times less likely to face any major cardiovascular event than those with variant allele [24-27]. Clopidogrel tends to shows irregular response towards platelet aggregation due to multiple genetic patterns of CYP2C19 which in turn leads treatment failure. Reports suggest that about 4 - 30 percent of Clopidogrel patients did not show adequate therapeutic response and 10 percent had indicated adverse bleeding events [28,29]. Though Clopidogrel has less drug drug interactions, other agents that are also metabolized by the CYP2C19 greatly affect the pharmacokinetics resulting in poor therapeutic response. Aspirin and other thrombolytic agents were not affected by Clopidogrel when given in combination [30]. An increase in prevalence gastrointestinal bleeding was seen with Naproxen and is also expected with other Non-Steroidal anti-inflammatory drugs [31]. Proton pump inhibitors are generally given along with Clopidogrel to prevent such adverse events [32,33].

Proton pump inhibitors (PPIs) are class of drugs that reduce the production of gastric acid. PPIs inhibit the potassium adenosine triphosphate in gastric parietal cells, which results in profound and long lasting antisecretory effects [36]. They acts by inhibiting the proton pump, the final pathway of acid secretion; which directly secretes Hydrogen ions into the gastric lumen thus are very effective against acid secretion [37]. These agents are widely used for peptic ulcer disease (PUD), NSAIDS induced ulceration and recurrence, and Helicobacter pylori associated ulcers and Zollinger Ellison syndrome. They are also used for symptomatic relief from Dyspepsia, Gastroesophageal Reflux Disease (GERD) and laryngopharyngeal reflux disease. They are administered on an empty stomach as food decreases their bioavailability [38-40]. Proton pump inhibitors are co-administered in patients receiving Clopidogrel, low dose of aspirin LDA and other NSAIDS [41]. They significantly decrease the risk of bleeding in the upper GI tract. Safety cautious measures were released by FDA against the use of Clopidogrel in combination with proton pump inhibitors like omeprazole and esomeprazole but pantoprazole was deemed safe [42,43]. Traditional PPIs like omeprazole inhibit the microsomal enzyme system and which further the mean pharmacokinetic profile of Clopidogrel [42] hence, their co administration will decrease the AMC concentration but would simultaneously increase the concentration of Clopidogrel thus resulting in high incidence of cardiovascular events [17,39]. On the other hand, Esomeprazole having high systemic bioavailability and long duration of duration of action [43].

METHODOLOGY

Study site and approval: This study was carried out for a period of two months in a tertiary care hospital. The protocol was reviewed and approved by the institutional ethics committee prior to study commencement (Ref no: IEC/RVSIMS/2017/01).Consent from the hospital authorities was obtained before using the clinical facilities and subject enrolment.

Subject recruitment and confidentiality: Coronary artery disease patients of both genders who were willing to participate were screened for factors that restrict their enrolment. All subjects underwent a screening procedure comprising of demographics, personal history, medical history and clinical laboratory investigations prior to enrolment. The study protocol was explained to volunteer in his/her native language under the supervision of a registered medical practitioner. Subjects were enrolled into the study only upon provision of written informed consent. All data were documented in specially designed case report forms and access was restricted to the investigator to ensure non-violation of subject rights and confidentiality.

Sample size: 17 subjects who met the inclusion criterion were enrolled into the study.

Study sequences and design: This randomized control study of 2x2 cross overdesign had two sequences on either period as shown in Table 1.

1. Subjects dosed with clopidogrel in period I and both esomeprazole and clopidogrel in period II after a washout period of 15 days (Sequence I).
2. Subjects dosed with both esomeprazole and clopidogrel in

period I and clopidogrel in period II after a washout period of 15 days (Sequence II).

Table 1 Study Sequences and 2x2 Cross over Design

Simple Cross –Over Design	Clopidogrel (No. of subjects)	Esomeprazole + Clopidogrel (No. of subjects)
Period 1	8[a]	9[b]
Period 2	9[b]	8[a]

Inclusion criterion

1. Adult patients of both genders with coronary artery disease with or without co-morbid conditions which restrict their participation.
2. Subjects whose screening laboratory values are within normal limits apart from the parameters underlying the exceptional co morbid conditions.

Exclusion criterion

- Subjects with history of smoking, alcohol dependence, and alcohol abuse within the past one year.
- Subjects with history of abuse with amphetamines, cocaine, tetra hydro cannabinoids, benzodiazepines, barbiturates and opioids within one year.
- Subjects with allergy or significant history of hypersensitivity or idiosyncratic reactions to clopidogrel or esomeprazole.
- Subjects with history of dysphagia or difficulty in coming for follow up.
- Subjects diagnosed with ulceration or history of gastric and/ or duodenal ulcer during screening.
- Subjects on medication with well established enzyme induction or inhibition property.

Sampling method

Blood samples were obtained from ante-cubital vein or forearm vein using an indwelling catheter. Heparin lock technique was used to prevent clotting of the indwelling catheter. After every blood sample collection, 0.5 ml of heparinised saline was injected into the intra venous cannula to prevent clot formation. 5ml of blood sample was collected one hour before dosing. 5ml of post dose blood samples were collected at the following time points (hours): 0.5, 1.0, 2.0, 4.0, 6.0, and 8.0. Mean ± SD loss of blood from each volunteer during the entire study was 130±5 ml. Blood samples were collected in pre-labeled serum separator vacutainers, containing tri-potassium ethylenediaminetetraaceticacid (K_3EDTA) as anti-coagulant.

Serum isolation and storage Blood samples were centrifuged at 4000 rpm for 10 minutes at a mean ± SD temperature of 4 ± 2°C within 45 minutes of blood collection. The resulting plasma sample was separated into two aliquots and stored in pre-labelled Eppendorf tubes at -70°C until analysis.

Estimation of plasma clopidogrel concentrations

CPP in human plasma was determined using sensitive liquid chromatography-mass spectrometry (LC-MS) technique. Clopidogrel bisulphate and ticlodipine obtained as gift samples were used as working and internal standard respectively. Thermo TSQ Quantum Ultra LC-MS system was used for determination. ZORBAX Eclipse Plus C18 column of 4.6mm x 150mm dimension and 5µm diameter was employed. 80:20% v/v acetonitrile: 10mM ammonium acetate respectively was used as mobile phase. The column flow rate was 1ml/min and injection volume of 10.0µL. Protein precipitation technique was employed for extraction of drug before loading into LC-MS. Four replicates of three different level quality control samples (High, Medium and Low) were analysed with each batch of subject samples.

Pharmacokinetic modeling

Peak plasma concentration (C_{max}) and time taken to attain C_{max}(t_{max}) were determined by visual inspection. Other pharmacokinetic parameters including $AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}\infty)}$, were calculated using PKSOLVER add-in for Microsoft Excel 2010. Pharmacokinetic parameters were based on the plasma – concentration time using extravascular non compartmental model.

Statistical analysis

Statistical analyses were carried out using International Business Machines-Statistical Package for the Social Sciences (IBM-SPSS) 20.0. Statistical significance of difference in population means between and within subjects was assessed by independent two sample and paired samples t-test respectively. Descriptive summary statistics are presented either as mean ± SD or as median (minimum, maximum). Choice of descriptive and inferential statistical method was based on distribution normality as determined through normal probability plot (Normal P-P).

RESULTS

Demographics and Clinical Parameters

Twenty one coronary artery disease patients of both genders who expressed willingness to participate underwent screening. Four volunteers who did not meet the inclusion criterion were restricted participation. Age wise distribution of 19 subjects enrolled into the study is shown in **Table 2** along with other demographic data summary and co morbid condition data in **Table 3.** The attrition rate was 10.5% as two subjects were withdrawn before completion of the study during either period.

Table 2 Summary of Demographics

S. No	Parameter	Frequency (N=17)		Mean ± SD
		Range	Number (%)	
1	Age (years)	18-38	0(0)	0.0 ± 0.0
		39-59	17 (100)	47.9 ± 5.5
2	Height (cm)	150-170	15 (88.3)	160.5 ± 0.05
		171-190	2 (11.7)	172.1± 0.00
3	Mass (kg)	50-65	6 (35.3)	73.29 ± 4.91
		66-80	11 (64.7)	59.84 ± 3.25
4	BMI (kg/m^2)	18-24.9	9 (53.0)	23.32 ± 0.98
		25.0-32.0	8(47.0)	29.54 ±2.62

BMI: Body mass index

Table 3 Co morbid conditions associated with the subjects

S. No	Co morbid condition	No. Of Patients
1.	Diabetes mellitus	05
2.	Hypertension	06
3.	Cerebrovascular disease	02
4.	Chronic Obstructive Pulmonary Disease	01

The mean ± SD age of the subjects was 47.9 ± 5.5 years with an age range of 39-59 years. 8 subjects (47.0%) were observed with either overweight or obese with a mean± SD BMI of

29.54±2.62 kg/m^2. Subject safety was monitored through clinical laboratory evaluations during screening and post-intervention, vital sign measurements during pre-intervention and at pre-determined time points post-intervention**.** Significant difference was not observed between day to day blood pressure (BP) (P=0.471) and capillary blood glucose (CBG) (P=0.092). However, statistically significant mean reduction was observed with red blood cells (RBC), haemoglobin, haematocrit and white blood cells (WBC) and platelets. In addition, statistically significant increase in serum creatinine was observed as shown in **Table 4**.

Table 4 Comparison of Pre-Dosing and Endpoint Biochemical Parameters

S. No.	Biochemical Parameter	Pre-Intervention	Post-Intervention	P values
1.	RBC (million/mm^3)	5.04±0.42	4.41±0.37	<0.0001*
2.	Haemoglobin (g/dL)	13.65±1.06	13.14±1.0	0.0042*
3.	Haematocrit (%)	43.35±2.14	38.21±2.08	<0.0001*
4.	Total WBC count (cells/mm^3)	8385.7±2469.4	6871.4±1572.7	0.0146**
5.	Polymorphs (%)	58.07±5.22	57.92±7.95	0.9431
6.	Lymphocytes (%)	32.07±6.04	35.71±7.76	0.0526
7.	Eosinophils (%)	4.85±2.89	4.14±1.12	0.3889
8.	Platelet (lakh cells/mm^3)	259.5±56.5	2.57±0.57	<0.0001*
9.	Random Blood Sugar (mg/dL)	89.14±12.97	95.57±10.21	0.2579
10.	Blood Urea Nitrogen (mg/dL)	10±3.29	7.57±2.45	0.0702
11.	Serum Creatinine (mg/dL)	0.77±0.11	0.96±0.09	0.0001*
12.	Bilirubin-total (mg/dL)	1.14±0.73	0.9±0.50	0.0447**
13.	Bilirubin – Direct (mg/dL)	0.3±0.18	0.26±0.08	0.3356
14.	Bilirubin – Indirect (mg/dL)	0.83±0.57	0.63±0.43	0.0538
15.	SGOT (U/L)	39.21±55.20	23±10.53	0.3024
16.	SGPT (U/L)	37.35±43.04	27.07±17.69	0.3722

SGOT: Serum glutamic-oxaloacetictransaminase, SGPT: Serum glutamic-pyruvic transaminase, *P Value <0.01, **P Value <0.05, P value obtained through paired student-t test.

Bioanalytical Parameters

The mean (SD) retention times of Clopidogrel and Ticlopidine were approximately 1.59 (0.5) and 1.77 (0.5) minutes respectively. The overall chromatography run time was 2.5 minutes.

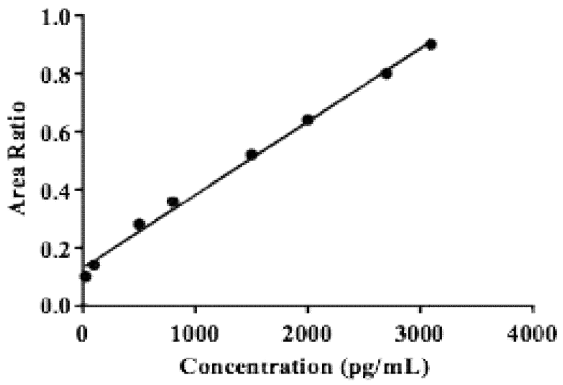

Fig 1 Calibration Curve for Clopidogrel y = 0.0002523x + 0.1292, Correlation Coefficient (r^2) =0.9946

The total accuracy for the quality control samples of Clopidogrel ranged from 97.13% to 101.59% with percentage coefficient of variation (%CV) ranging from 10.34% to 14.10%. The calibration curve for clopidogrel is shown in Figure 1.

Intra Subject Variability - Effect of Esomeprazole on the Pharmacokinetics of CPP

The mean pharmacokinetic profile of CPP was not found to be altered significantly by esomeprazole co-administration. C_{max} of CPP was increased upon esomeprazole administration in either sequence. However, difference was statistically significant only in sequence I as shown in Figure 2 and 3. Similar period effects of V/F and CL/F observed in sequence I was not observed in sequence 2. Mean intra-subject and inter-subject variability data for clopidogrel expressed as the mean %CV (% coefficient of variation) are also in given in Table 5 and 6.

Table 5 Effect of Esomeprazole on CPP Pharmacokinetics in Sequence I Subjects

S. No	PK Parameter	Period 1^C (Mean±SD)	Period 2^{EC} (Mean±SD)	%CV	P-Value
1.	C_{max}	2047.42±1956.1	1354.38±635.2	40.60	**0.0311**
2.	$AUC_{(0-t)}$	1573.23±2422.6	1130.78±1499.1	46.92	**0.0288**
3.	$AUC_{(0-\infty)}$	1666.78±645.0	1273.212±1827.0	106.80	0.0842

C: Clopidogrel, EC: Esomeprazole + Clopidogrel

P Values in bold text represent statistically significant difference (obtained by paired samples t-test).

Table 6 Effect of Esomeprazole on CPP Pharmacokinetics in Sequence II Subjects

S. No.	PK Parameter	Period 1^{EC} (Mean±SD)	Period 2^C (Mean±SD)	%CV	P value
1.	C_{max}	1196.84± 472.01	1216.02± 621.38	37.60	0.0711
2.	$AUC_{(0-t)}$	1845.18± 932.27	1681.34± 881.31	53.82	0.0207
3.	$AUC_{(0-\infty)}$	2126.89± 1219.70	1850.81±1028.11	56.34	0.0107

C: Clopidogrel, EC: Esomeprazole + Clopidogrel

P Values in bold text represent statistically significant difference (obtained by paired samples t-test).

Intra-subject variability for $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and C_{max} are 50.3%, 81.5% and 39.1% respectively.

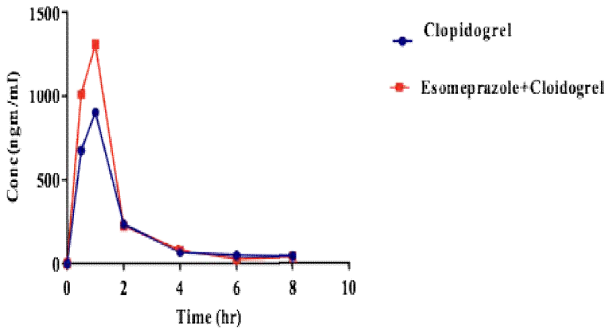

Fig 2 Intra-subject Variability observed in sequence I

Inter-Subject Variability

Difference in pharmacokinetics of CPP was not observed between subjects as shown in **Figure 4 and 5.** Significant sequence effects of V/F and CL/F were observed during period II (P value = 0.0087 & 0.0097 respectively). The %CV of inter-subject variability for primary pharmacokinetic parameters including $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and C_{max} are 31.6%, 29.0% and 20.6% respectively.

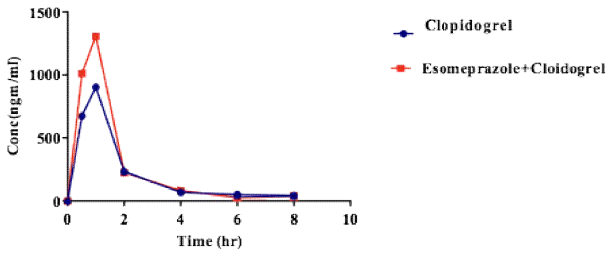

Fig 3 Intra-subject Variability in Sequence II

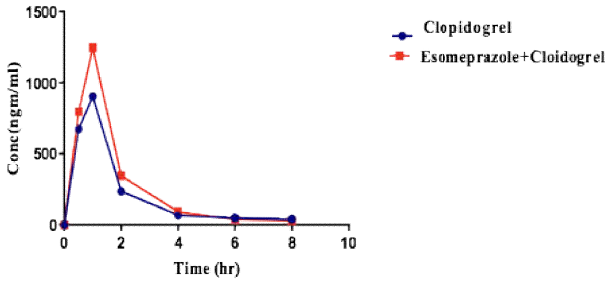

Fig 4 Inter individual variability in Period- I Patients

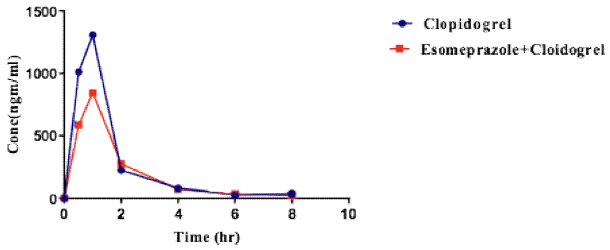

Fig 5 Inter individual variability in Period- II patients

DISCUSSION

Clopidogrel and LDA are often combined with PPIs considering the associated risk of GI ulceration and bleeding. Despite the well-established potential to interact with clopidogrel through major *CYP2C19* inhibition, PPI's can be replaced with histamine receptor antagonists (H_2RA) [20]. Therefore, it is crucial to identify PPIs with optimal enzyme inhibition property and high potency to prevent GI events in patients receiving clopidogrel, as non-adherence to anti-platelet agents develops after experiencing GI bleeding potentiating the risk of ischemic events [21]. In addition, the risk of cardiovascular events is precipitated by factors that impair production of AMC from CPP. Concentrations of CPP and AMC are known to be altered by several patient specific variables including demographics, personal and medical history, organ function and concomitant medication [22-24]. Volunteers with any other demographic factor, personal and medical history that may impair the results of the study were limited participation. Clinical laboratory investigations were carried out pre- and post-intervention to ensure subject safety. A gross decrease in haematological parameters including RBC, haemoglobin, WBC platelets was observed at the study end point. Though they did not manifest as adverse haematological reactions, the changes in parameters were statistically significant. However, diverse haematological adverse effects such as anaemia, agranulocytosis, leukopenia and thrombocytopenia have been reported in patients receiving clopidogrel or low dose aspirin [29]. AMC is extensively protein bound (94%) and hence minor change in plasma concentration would exert considerable effects on inhibition of platelet aggregation [30, 31]. The pharmacologically active form of clopidogrel is clopidogrelthiol or AMC. Clopidogrelthiol is chemically unstable and has low circulating levels which make its determination in any biological matrix problematic [15]. Hence, we quantified CPP since decrease in AMC is often accompanied by a parallel increase in CPP. Thus, considering the possible inverse relationship between CPP and AMC, CPP profiling was used as an indirect measure of AMC pharmacokinetics.

PPIs are well known to alter the pharmacokinetics of clopidogrel by impairing prodrug activation. We herein report significant alteration of CPP pharmacokinetics by esomeprazole. Significant, variations in both primary and secondary parameters were observed during intra and inter-subject variability analysis. A transient increase in exposure to CPP with significant change in mean pharmacokinetic profile was observed upon esomeprazole co-administration. Thus, systemic availability of AMC decreases and hence the exposure enhancing cardiovascular risks [32, 33].

The magnitude of the studied interaction tends to be minor from our observations. Pharmacodynamic response to clopidogrel is largely affected by factors that decrease its bioavailability such as food, antacids and those that impair AMC production such as*CYP450* allelic variations, enzyme inhibitors [34-37]. Apart from the inhibitory property of esomeprazole over clopidogrel, severity of the interaction may be enhanced in patients with the underlying factors like co morbid conditions, food, over the counter (OTC) medicines etc. which decrease exposure to AMC. Hence, because of significant changes in pharmacokinetic profile, use of esomeprazole is not recommended in patients who are poor responders to clopidogrel so as to ensure adequate inhibition of platelet receptor activity.

CONCLUSION

The pharmacokinetic profile of CPP was found to be significantly altered by co-administration of esomeprazole in patients with coronary artery disease. However, changes in pharmacokinetic parameters observed could however be potentiated in presence of underlying risk factors. Hence concomitant administration of clopidogrel and esomeprazole should be under keen clinical supervision and is not recommended in poor responders to anti-platelet therapy with clopidogrel. We recommend choosing H_2 receptor antagonists (H_2RA) in place of PPIs to manage GI bleeding in the patients on antiplatelet therapy. The principal limitation of this study is that CPP concentrations were used as an indirect measure of AMC pharmacokinetics due to practical difficulties in AMC quantification. In spite of being previously reported, the reliability of such an assumption is often questionable as AMC concentrations may not merely have inverse relationships with that of CPP. Hence, further studies are necessary to study this interaction with direct AMC profiling with pharmacodynamic response monitoring.

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