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Research Article

PHARMACOKINETIC DRUG INTERACTION BETWEEN CLOPIDOGREL AND ESOMEPRAZOLE IN ADULT HEALTHY MALE VOLUNTEERS

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ABSTRACT

Objective: Proton pump inhibitors (PPIs) are known to impair cytochrome P2C19 mediated activation of clopidogrel, the antiplatelet agent used for cardiovascular risk prevention. Esomeprazole is an optical isomer of omeprazole with better efficacy and tolerability than conventional PPIs. Esomeprazole is often co-administered with clopidogrel considering the risk of associated gastrointestinal bleeding. This study was designed to determine the effect of esomeprazole on the mean pharmacokinetic profile clopidogrel.

Methods: A total of 14 adult healthy male participants who volunteered participation were enrolled, randomized equally into two cross-over sequences, dosed with clopidogrel and clopidogrel + esomeprazole in respective periods. Blood samples were collected through antecubital or forearm vein indwelling catheter. Concentration of clopidogrel parent prodrug in isolated plasma was determined using validated sensitive liquid chromatography – mass spectrometry. Pharmacokinetic modeling 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 participants co-dosed with esomeprazole (p=0.0483, 0.0011, and 0.0015, respectively). All other primary and secondary pharmacokinetic parameters displayed minor alterations during either period (p>0.05).

Conclusion: The non-significant alteration of clopidogrel pharmacokinetics by esomeprazole can be potentiated by underlying predisposing factors such as the presence of *CYP2C19* allelic variants and 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 antiplatelet therapy with clopidogrel.

Keywords: Clopidogrel, CYP2C19, Esomeprazole, Enzyme inhibition, Pharmacokinetics.

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INTRODUCTION

Clopidogrel is a platelet adenosine diphosphate receptor antagonist indicated for the prophylaxis of atherosclerotic events including myocardial infarction, ischemic stroke and vascular death manifested either by recent stroke, or established peripheral vascular disease [1]. It is a prodrug that requires a two-step oxidative biotransformation process for conversion into an inactive and active metabolite of clopidogrel (AMC) involving human carboxylesterase 1 and *CYP450* enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5 [2,3]. Besides the implication of diverse CYP450 enzymes in clopidogrel activation, the role of *CYP2C19* is prominent and well established [4]. Altered genetic patterns of *CYP2C19* are associated with diminished platelet response to clopidogrel treatment and poor cardiovascular outcomes [5,6]. It has been reported that 4-30% of patients treated with clopidogrel do not display adequate therapeutic response, while about 10% of patients face unpleasant bleeding events [7]. Various drugs that are substrates or inhibitors of *CYP2C19* tend to significantly alter clopidogrel pharmacokinetics precipitating impaired therapeutic response [8,9]. Proton pump inhibitors (PPI) are a class of potential antiulcer agents used for providing rapid symptom relief and healing in patients with peptic ulcer and gastroesophageal reflux disease [10]. PPIs are often prescribed with clopidogrel and low dose aspirin to prevent gastrointestinal (GI) bleeding and ulcers. Concomitant use of PPIs substantially decreases the risk of upper GI bleeding in patients receiving low-dose aspirin (LDA) and clopidogrel [11]. However, being inhibitors of the microsomal enzyme system, conventional PPIs such as omeprazole alter the mean pharmacokinetic profile of clopidogrel [12,13]. Co-administration of PPI and other *CYP450* inhibitors with clopidogrel decreases AMC concentration with a parallel increase in the concentration of clopidogrel parent prodrug (CPP) magnifying the risk of cardiovascular events [14,15]. Esomeprazole is an optical isomer of omeprazole and is being broadly considered over other conventional PPIs owing to its high systemic bioavailability and prolonged duration of action [16]. In spite of retaining the *CYP450* enzyme inhibition property of its parent racemic omeprazole, the standard 40 mg dose of esomeprazole is being widely used due to a better pharmacodynamic response such as improved symptom resolution and mucosal healing [17,18]. This study was hence designed to study the effect of esomeprazole on the pharmacokinetic profile of clopidogrel. We considered CPP profiling over AMC owing to its chemical instability and low circulating levels which make quantification in plasma intricate [19].

METHODS

Study site and approval

This study was conducted for a period of 2 months in a tertiary care hospital. The protocol was reviewed and approved by the Institutional Ethics Committee before study commencement (Ref No.: IEC/RVSIMS/2017/04). Consent from the hospital authorities was obtained before using the clinical facilities and subject enrolment.

Subject recruitment and confidentiality

Adult healthy male volunteers who were willing to participate were screened for factors that restrict their enrolment. All participants underwent a screening procedure comprising demographics, personal history, medical history, and clinical laboratory investigations before enrolment. The study protocol was explained to volunteer in his native language under the supervision of a registered medical practitioner. Participants were enrolled into the study only on 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

A total of 14 participants who met the inclusion criterion were enrolled into the study.

Study sequences and design

This randomized control study of 2 × 2 crossover design had two sequences on either period as shown in Table 1.

Inclusion criterion

- Healthy human male participants in the age sequence between 18 and 55 years and body mass index (BMI) within the range of 18.5-25 kg/m^2 with body weight not <50 kg
- Participants with no evidence of underlying disease during screening and medical history
- Participants whose screening laboratory values are within normal limits
- Participants should not have consumed any medication or furanocoumarin-containing fruit products 72 hrs before dosing and throughout the study periods.

Exclusion criterion

- Participants with history of smoking, alcohol dependence, and alcohol abuse within the past 1 year
- Participants with history of abuse with amphetamines, cocaine, tetra hydro cannabinoids, benzodiazepines, barbiturates, and opioids within 1 year
- Participants with allergy or significant history of hypersensitivity or idiosyncratic reactions to clopidogrel or esomeprazole
- Participants with systolic blood pressure (BP) <100 and >130 mmHg, diastolic pressure <60 and >80 mmHg and pulse rate <60 and >100 beats/min during screening
- Participants with history of dysphagia or difficulty in coming for follow-up
- Participants who had suffered any clinically significant illness within 1 month before study commencement
- Participants diagnosed with ulceration or history of gastric and/or duodenal ulcer during screening.

Sampling method

Blood samples were obtained from antecubital 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 heparinized saline was injected into the intravenous cannula to prevent clot formation. 5 ml of blood sample was collected 1 hr before dosing. 5 ml of post-dose blood samples were collected at the following time points (hours): 0.17, 0.33, 0.5, 0.67, 1.0, 1.5, 2.0, 3.0, 6.0, 8.0, and 12.0. Mean±standard deviation (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 ethylenediaminetetraacetic acid as an anticoagulant.

Table 1: Study sequences and 2×2 crossover design

Simple crossover design	Clopidogrel (number of participants)	Esomeprazole + Clopidogrel (number of participants)
Period 1	7[a]	7[b]
Period 2	7[b]	7[a]

[a]Participants dosed with clopidogrel in period I and both esomeprazole and clopidogrel in period II after a washout period of 15 days (Sequence I).
[b]Participants dosed with both esomeprazole and clopidogrel in period I and clopidogrel in period II after a washout period of 15 days (Sequence II)

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-labeled 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 bisulfate and ticlopidine 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 4.6 mm × 150 mm dimension and 5 µm diameter was employed. 80:20% v/v acetonitrile: 10 mM ammonium acetate, respectively, was used as mobile phase. The column flow rate was 1 ml/min and injection volume of 10.0 µL. Protein precipitation technique was employed for extraction of the drug before loading into LC-MS. Four replicates of three different level quality control samples (high, medium, and low) were analyzed 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 $t_{½}$, volume of distribution (V_d), clearance (Cl), area under the curve ($AUC_{(0-t)}$), $AUC_{(0-\infty)}$, area under mean curve (AUMC), and mean residence time (MRT) were calculated using PKSOLVER add-in for Microsoft Excel 2010. Pharmacokinetic parameters were based on the plasma concentration time using extravascular one-compartmental model.

Statistical analysis

Statistical analyses were performed using International Business Machines – Statistical Package for the Social Sciences (IBM – SPSS) 20.0. Statistical significance of difference in population means between and within participants 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 and maximum). Choice of descriptive and inferential statistical method was based on distribution normality as determined through normal probability plot.

RESULTS

Demographics and clinical parameters

A total of 19 healthy male volunteers who expressed willingness to participate underwent screening. Five volunteers who did not meet the inclusion criterion were restricted participation. Age wise distribution of 14 participants enrolled into the study is shown in Table 2. The subject dropout rate was 0% as all participants turned for period II after a washout period and no subject withdrew before completion of the study during either period.

The mean±SD age of the participants was 33±5.53 years with an age range of 24-44 years. All participants displayed normal BMI with a mean±SD value of 22.4±1.1 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 daily BP (p=0.471) and capillary blood glucose (p=0.092). However, statistically significant mean reduction was observed with red blood cells (RBC), hemoglobin, hematocrit and white blood cells (WBC), and platelets. In addition, statistically significant increase in serum creatinine was observed as shown in Table 3.

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. 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 Fig. 1.

$y = 0.0002523x + 0.1292$, correlation coefficient (r^2) =0.9946

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 on esomeprazole administration in either sequence. However, the difference was statistically significant only in Sequence I as shown in Figs. 2 and 3. Similar period effects of V/F and CL/F observed in Sequence I was not observed in Sequence II. Mean intra-subject and inter-subject variability data for clopidogrel expressed as the mean %CV are also given in Tables 4 and 5.

Intra-subject variability for $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, and C_{max} is 35.3%, 32.8%, and 29.4%, respectively. Intra-subject variability for secondary parameters including t_{max}, K_{el}, $t_{½}k_a$, V/F, CL/F, AUMC, and MRT is 14.9%, 18.9%, 14.9%, 30%, 32.8%, 35.9%, and 15.1%, respectively.

Inter-subject variability

Difference in pharmacokinetics of CPP was not observed between participants as shown in Figs. 4 and 5. Significant sequence effects of V/F and CL/F were observed during period II (p=0.0087 and 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. Inter-subject variability for secondary pharmacokinetic parameters including t_{max}, K_{el}, $t_{½}k_a$, V/F, CL/F, AUMC, and MRT is 16.4%, 23.6%, 25.0%, 26.8%, 29.0%, 31.7%, and 15.8%, respectively.

Table 2: Summary of demographics

S.No.	Parameter	Frequency (N=14)		Mean±SD
		Range	N (%)	
1.	Age (years)	18-35	8 (57.1)	29.2±3.3
		36-50	6 (42.9)	29.2±3.3
2.	Height (cm)	150-170	11 (78.6)	167.6±6.25
		171-190	3 (21.4)	167.6±6.25
3.	Mass (kg)	50-65	8 (57.1)	64.35±6.03
		66-80	6 (42.9)	64.35±6.03
4.	BMI (kg/m^2)	18-25	14 (100)	22.4±1.1

BMI: Body mass index

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 cannot be replaced with histamine receptor antagonists

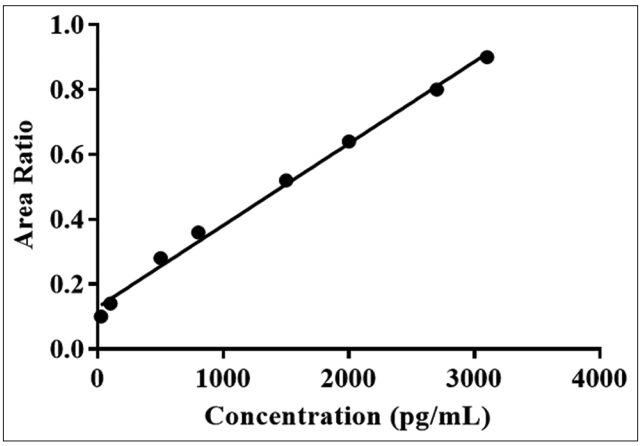

Fig. 1: Calibration curve for clopidogrel

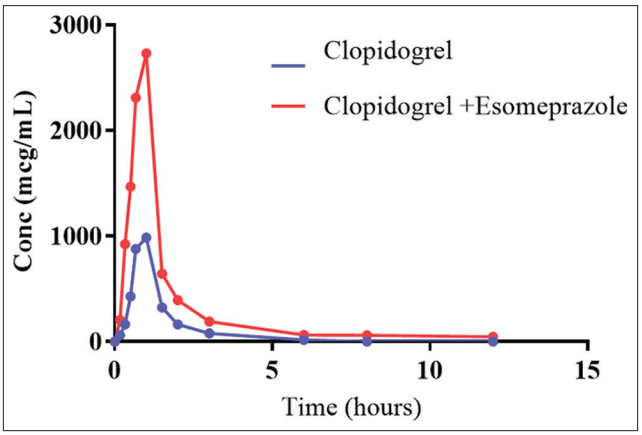

Fig. 2: Intra-subject variability observed in Sequence I

Table 3: Comparison of predosing 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.	Hemoglobin (g/dL)	13.65±1.06	13.14±1.0	0.0042*
3.	Hematocrit (%)	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

*p<0.01, **p<0.05, p value obtained through paired Student's t-test. SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic-pyruvic transaminase, RBC: Red blood cell, WBC: White blood cell

Table 4: Effect of esomeprazole on CPP pharmacokinetics in Sequence I participants

S.No.	PK parameter	(Mean±SD)		%CV	p value
		Period 1[C]	Period 2[EC]		
1.	$t_{1/2}k_{a*}$	0.51±0.03	0.434±0.15	15.0	0.6034
2.	V/F	0.05±0.00	0.0196±0.00	42.0	**0.0011**
3.	CL/F	0.06±0.01	0.029±0.01	35.2	**0.0015**
4.	t_{max**}	0.78 (0.83, 0.65)	0.64 (1.18, 0.41)	15.2	0.5358
5.	C_{max}	632.27±92.1	1831.36±1186.4	41.5	**0.0483**
6.	K_{el}	1.24±0.01	1.52±0.01	15.4	0.2278
7.	$AUC_{(0-t)}$	1188.29±249.5	3461.74±2721.8	39.6	0.0897
8.	$AUC_{(0-\infty)}$	1329.141±200.0	3520.644±2705.7	35.2	0.1006
9.	AUMC	2067.691±377.1	5310.446±4612.2	28.7	0.149
10.	MRT	1.55±0.11	1.417368±0.45	15.2	0.5324

*Expressed as harmonic mean with pseudo-standard deviation, **Expressed as median (minimum, maximum), p values in bold text represent statistically significant difference (obtained by paired samples t-test). C: Clopidogrel, EC: Esomeprazole+clopidogrel. V/F, CL/F: Volume of distribution and clearance are expressed as a function of bioavailability, AUC: Area under the curve, AUMC: Area under mean curve, MRT: Mean residence time

Table 5: Effect of esomeprazole on CPP pharmacokinetics in Sequence II participants

S.No.	PK parameter	Mean±SD		%CV	p value
		Period 1[EC]	Period 2[C]		
1.	$t_{1/2}k_{a*}$	0.36±0.19	0.54±0.03	14.8	0.3048
2.	V/F	0.04±0.01	0.04±0.01	18.1	0.644
3.	CL/F	0.03±0.01	0.05±0.01	30.5	0.1424
4.	t_{max}	0.79 (1.40, 0.50)	0.78 (0.90, 0.76)	14.7	0.854
5.	C_{max}	982.66±209.3	702.43±154.9	17.2	0.0736
6.	K_{el}	0.94±0.01	1.18±0.01	22.3	0.2773
7.	$AUC_{(0-t)}$	2234.32±718.2	1415.5±371.4	31.0	0.0868
8.	$AUC_{(0-\infty)}$	2438.34±715.6	1568.37±378.5	30.5	0.888
9.	AUMC	5051.41±2730.0	2586.6±703.9	43.0	0.1127
10.	MRT	1.93±0.65	1.63±0.10	15.0	0.3536

*Expressed as harmonic mean with pseudo-standard deviation, **expressed as median (minimum, maximum), p value in this table represent no statistically significant difference (p>0.05) represent statistically significant difference (obtained by paired samples t-test). C: Clopidogrel, EC: Esomeprazole+clopidogrel, AUC: Area under the curve, AUMC: Area under mean curve, MRT: Mean residence time, V/F, CL/F: Volume of distribution and clearance are expressed as a function of bioavailability

(H_2RA) as they are associated with risk of mucosal erosion in patients receiving antiplatelet therapy [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 antiplatelet 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]. To avoid variability arising due to gender and considering the risk of comparatively higher predisposition to adverse drug reactions, women volunteers were not enrolled into the study [25,26]. Although *CYP2C19* activity is equal in both men and women, other factors such as higher gastric pH, gastric-bowel transit times, and altered V_d in women can cause variability in pharmacokinetics [27]. Bioavailability of clopidogrel active metabolite has been reported to be less in patients with higher body weight contributing to suboptimal treatment response [28]. Hence, to dodge the bias arising due to body weight, only participants with normal BMI (18.5-24.9 kg/m^2) were enrolled into the study. 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 hematological parameters including RBC, hemoglobin, WBC platelets was observed at the study end point. Although they did not manifest as adverse hematological reactions, the changes in parameters were statistically significant. However, diverse hematological adverse effects such as anemia, agranulocytosis, leukopenia, and thrombocytopenia have been reported in patients receiving clopidogrel or LDA [29]. AMC is extensively protein bound (94%) and hence minor change in plasma concentration would exert considerable effects on inhibition

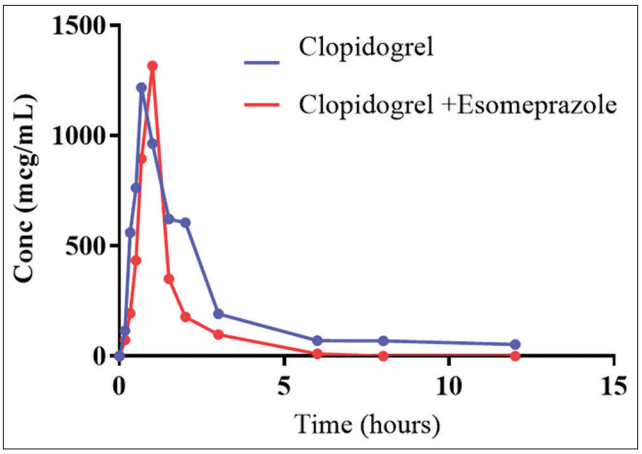

Fig. 3: Intra-subject variability in Sequence II

of platelet aggregation [30,31]. The pharmacologically active form of clopidogrel is clopidogrel thiol or AMC. Clopidogrel thiol is chemically unstable and has low circulating levels which make its determination in any biological matrix problematic [15]. Hence, we quantified CPP since a 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 insignificant alteration of CPP pharmacokinetics by esomeprazole. Although insignificant,

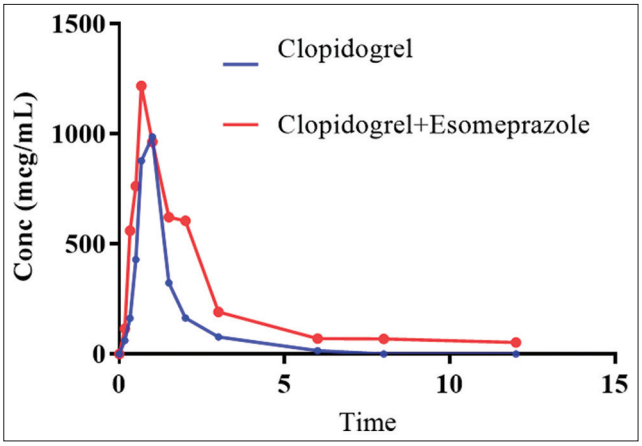

Fig. 4: Inter-subject variability in period I

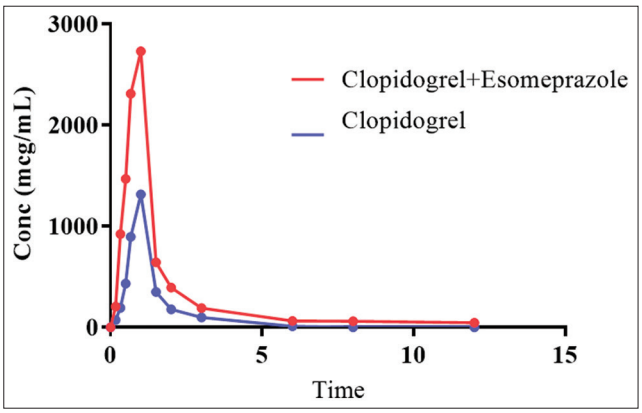

Fig. 5: Inter-subject variability in period II

variations in both primary and secondary parameters were observed during intra- and inter-subject variability analysis. C_{max} of CPP was found to be increased by esomeprazole in both the sequences with a statistically significant increase in period II (ΔC_{max}=1199.09 pg/ml, p=0.0483). A transient increase in exposure to CPP with insignificant change in mean pharmacokinetic profile was observed on esomeprazole co-administration. Thus, systemic availability of AMC decreases and hence the exposure enhancing cardiovascular risks [32,33]. Significant alterations in clopidogrel V/F and CL/F observed in period II were not considered for further interpretation as such a difference was very negligible in period I. Hence change in clopidogrel V/F and CL/F could not be solely attributed to esomeprazole.

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 and enzyme inhibitors [34-37]. Although observed to be minor, severity of the interaction may be enhanced in patients with these underlying factors which decrease exposure to AMC. Hence, despite insignificant 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 insignificantly altered by co-administration of esomeprazole. Minor changes in pharmacokinetic parameters observed could, however, be potentiated in the 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 antiplatelet therapy with clopidogrel. 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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