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Rapid and ultra-rapid metabolizers with *CYP2C19**17 polymorphism do not respond to standard therapy with proton pump inhibitors

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ABSTRACT

Introduction and objective: Polymorphisms in genes encoding drug metabolizing enzymes may lead to varied enzyme activity and inter-individual variability in drug efficacy and/or toxicity. Since *CYP2C19* and *CYP3A4* genes code for enzymes involved in metabolizing wide variety of drugs including proton pump inhibitors, we sought to identify polymorphisms in these genes in order to study their impact on drug metabolism in subjects.
Methods: DNA was isolated from healthy individuals including tribals and genotyped for 11 single nucleotide polymorphisms in *CYP2C19* and 6 polymorphisms in *CYP3A4*. Individuals were categorized into different phenotypes based on their drug metabolizing genotype. Volunteers from each group were administered proton pump inhibitors (Esomeprazole, Pantoprazole; 40 mg/day) for 5 days followed by pharmacokinetic studies and measurement of intra-gastric pH.
Results: Of the 17 polymorphisms studied, only *CYP2C19**2,*3,*17 and *CYP3A4**1B polymorphisms were observed. In comparison to urban individuals, a significantly ($p = 0.0003$) higher number of poor metabolizers were noted in the tribal individuals. Pantoprazole was found to be most effective in poor metabolizers in terms of area under the curve and Tmax. No significant difference was observed in the intra-gastric pH at baseline and day 6 in rapid and ultra-rapid metabolizers.
Conclusion: Our study has demonstrated that 19.7% of our subjects are carriers of the *CYP2C19**17 allele who did not respond to the standard dose of proton pump inhibitors. Genetic screening to identify subjects with variant alleles would thus be useful for personalization of therapy with proton pump inhibitors.

1. Introduction

Proton pump inhibitors (PPIs), which irreversibly inhibit gastric acid pump (H+/K+ ATPase) function are the most potent gastric acid-suppressing agents in clinical use. PPIs are widely used for prevention and treatment of various acid-related diseases including gastrointestinal reflux disease (GERD), duodenal ulcers, peptic ulcers, reflux esophagitis and other hyper acidic conditions. Of these, GERD is the frequently reported gastrointestinal disease worldwide causing significant societal and economic burden (Shaheen et al., 2006), auguring treatment with PPIs. However, up to 40% of GERD patients report partial or complete lack of relief of their symptoms in response to treatment with PPIs. Polymorphisms in drug metabolizing enzymes is listed as one of the factors responsible for the demonstrated PPI resistance (Cicala, 2013; Clarke and Pandolfino, 2012), apart from other factors (Zerbib et al., 2011). All of the PPIs are usually metabolized in the liver involving different isoenzymes of the cytochrome P 450 (CYP) family before their elimination (Hagymasi et al., 2011). Genes encoding *CYP2C19* and *CYP3A4* are extensively polymorphic with 34 variant alleles known for *CYP2C19* and >30 variant alleles for *CYP3A4* (http://www.cypalleles.ki.se/cyp2c19.html; http://www.cypalleles.ki.se/cyp3a4.html) including both synonymous and non-synonymous variants. Earlier studies have classified subjects as extensive and poor metabolizers based on their ability to metabolize PPIs (Goldstein, 2001; Desta et al., 2002). Extensive metabolizers were subjects with wild type allele for the enzyme whereas subjects who carry polymorphisms *CYP2C19**2 and *CYP2C19**3 were classified as poor metabolizers. These polymorphisms have been studied widely in different populations (Goldstein et al., 1997) with reported frequencies ranging from 6 to 39%. Subsequent studies led to identification of other loss of function polymorphisms (*CYP2C19**4 to *12) in the same gene, leading to production of a defective enzyme and conferring poor metabolizer phenotype to their carriers (Rosemary and Adithan, 2007) (Table 1). In 2006, a new

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Table 1
Allelic variants of the genes (CYP2C19 and CYP3A4).

Allele	rsID	Chromosome	Exon	Nucleotide change	Effect	Predicted enzyme activity
CYP2C19*1		10		None	Wild type	Normal enzyme activity
CYP2C19*2	rs4244285	10	5	c.681G > A	Splicing defect; I331V	Non functional
CYP2C19*3	rs4986893	10	4	c.636G > A	W212X, Stop codon	Non functional
CYP2C19*4	rs28399504	10	1	c.1A > G	Loss of initiation codon	Non functional
CYP2C19*5	rs56337013	10	9	c.1297C > T	R433W	Non functional
CYP2C19*6	rs72552267	10	3	c.395G > A	R132Q	Non functional
CYP2C19*7	rs72558186	10	5	IV S5 + 2T > A	Splicing defect I331V	Non functional
CYP2C19*8	rs41291556	10	3	c.358T > C	W120R	Non functional
CYP2C19*9	rs17884712	10	3	c.431G > A	R144H	Decreased function
CYP2C19*10	rs6413438	10	5	c.680C > T	P227L	Decreased function
CYP2C19*12	rs55640102	10	9	c.1473A > C	X491C 26 extra a.a	Unstable
CYP2C19*17	rs12248560	10	5′Regulatory	c.991A > G	Increased gene transcription	Increased function
CYP3A4*1B	rs2740574	7	5′Flanking	392A > G	392A > G	Normal enzyme activity
CYP3A4*3	rs4986910	7	12	c.1334T > C	M445T	Normal enzyme activity
CYP3A4*15	rs4986907	7	6	c.485G > A	R162Q	normal protein expression
CYP3A4*17	rs4987161	7	7	c.566T > C	F189S	Decreased enzyme activity
CYP3A4*18	rs28371759	7	10	c.878T > C	L293P	Decreased function
CYP3A4 *19	rs4986913	7	12	c.1399C > T	P467S	Normal

Table showing details of the 17 polymorphisms under study. Information shown in the table has been obtained from CYP allele nomenclature website (http://www.cypalleles.ki.se/cyp2c19.html; http://www.cypalleles.ki.se/cyp3a4.html).

polymorphism (*CYP2C19*17) was identified, which showed gain of function (increased enzyme activity) with a reported frequency of 18% both in Swedes and Ethiopians and 4% in Chinese population (Sim et al., 2006). *CYP3A4*1B, reported as a 290A > G substitution in the 5′-flanking region of *CYP3A4* may result in reduced activity of *CYP3A4* enzyme. The effect of *CYP3A4*1B polymorphism is still not clear. While few studies have reported a decrease in the activity of the enzyme (Min and Ellingrod, 2003), few others have shown an increase (Rebbeck et al., 1998) or no effect (Westlind et al., 1999). *CYP3A4* has other non-synonymous polymorphisms like *3, *15 and *18 resulting in increased metabolism of vitamin D2 (Gupta et al., 2005), testosterone (Dai et al., 2001) and midazolam (Kang et al., 2008) respectively. *CYP3A4*17 reportedly showed decreased metabolism of nifedipine (Lee, 2004) and *CYP3A4*19 shows activity similar to wild type protein (Westlind et al., 1999) (Table 1).

Pharmacokinetic analysis revealed that the systemic drug exposure (Area under curve; AUC) varies widely between groups; AUC for omeprazole, lansoprazole and rabeprazole were found to be 7.5, 4.5 and 4-fold higher in poor metabolizers than in extensive metabolizers (Klotz, 2006). Since the pharmacodynamic response to PPIs is related to their AUC, intra-gastric pH is usually more elevated in poor metabolizers (PMs) in comparison with other groups. Studies with subjects treated with omeprazole and pantoprazole demonstrated that a *17 polymorphism may lead to less acid-inhibition and decreased AUC when compared with wild type (Hunfeld et al., 2008). Though further studies indicated *CYP2C19*17 to be associated with increased enzymatic activity, it is still not clear as to whether carriers of this polymorphism are to be classified as Ultra-rapid (URM) metabolizers or rapid metabolizers (RM) (Li-Wan-Po et al., 2010).

Though the mechanism of action of all PPIs is similar, the physicochemical properties of these drugs result in variations in the degree of acid suppression, as well as the speed of onset of acid inhibition (Robinson and Horn, 2003). Further polymorphisms in drug metabolizing genes result in different genotypes causing inter-individual variation in the rate of metabolism of PPIs. In addition, much less is known about polymorphisms of *CYP2C19* in Indian tribal populations with extensive consanguinity. Since such differences may impact the clinical performance of PPIs in different populations, we designed the present study to (1) estimate the frequencies of different polymorphisms in *CYP2C19* and *CYP3A4* in urban and tribal Indian populations and (2) study the effect of these polymorphisms on pharmacokinetic and pharmacodynamic properties of commonly administered PPIs such as Esomeprazole and Pantoprazole, (EPZ and PPZ).

2. Materials and methods

2.1. Study design

This is a study involving healthy Indian subjects from urban and tribal areas of Telangana state. Subjects were categorized into five different phenotypes (normal, intermediate, poor, rapid and ultra-rapid metabolizers) of PPIs based on their genotype. Subjects from each phenotype were also administered PPIs (Esomeprazole and Pantoprazole) under fasting conditions and the plasma PPI levels were measured subsequently. A mandatory washout period was included when subjects were administered more than one PPI. Intra-gastric pH was measured in subjects to measure response to administered PPI.

2.2. Study groups

Healthy urban and tribal subjects (Koya and Naik tribes) were recruited for genotyping and for pharmacokinetic and pharmacodynamic analysis. All participants were clinically evaluated and confirmed to be healthy. Written informed consent was obtained from all subjects and all protocols used in the study were approved by the Institutional Ethics Committee.

2.3. DNA isolation and genotyping

Peripheral blood (4 mL) was collected from all subjects in EDTA vaccutainers. DNA was isolated from leucocytes using QIAamp® DNA Blood Maxi kit (Qiagen, Netherlands), quantified and stored at −20 °C until further use. DNA samples were genotyped for all the polymorphisms of *CYP2C19* and *CYP3A4* mentioned in Table 1. Genotyping was performed using competitive allele specific PCR system (KASPar) kit obtained from KBiosciences (LCGC Genomics, London) using Step One Real time PCR (Life Technologies, USA). KlusterCaller™ software was used to determine genotypes based on clusters and an online excel based software (version 1.05) was used for haplotype analysis of *CYP2C19* alleles (Eliades and Eliades, 2009).

2.4. Pharmacokinetic and pharmacodynamic studies

Subjects were categorized into 5 groups based on their genotype (Normal, intermediate, poor, rapid & ultra-rapid metabolizers) for the pharmacokinetics/dynamics (http://www.cypalleles.ki.se/cyp2c19.html; Goldstein et al., 1997). Volunteers from each category were orally

Table 2
Demographic characteristics of study subjects.

	Urban population	Tribals	p value*
Number	460	100	–
Males/females (%)	343/117(74.5/25.5)	47/53(47/53)	0.04
Age (years)	31.53 ± 10.36	33.22 ± 11.5	0.14
BMI (kg/m^2)	23.78 ± 3.96	24.14 ± 4.88	0.43

Body mass index (BMI) was calculated as a ratio of weight in kilograms to height in meter square. *2 tailed p value calculated using student's *t*-test and chi square test; $p < 0.05$ was considered to be significant.

administered individual PPIs (Esomeprazole and Pantoprazole; 40 mg/day with 240 mL of water at 9.00 AM) for 5 days. Blood samples were collected periodically for the determination of plasma PPI concentration at 0, 1, 2, 4, 6 and 24 h after the dose on first and last day of administration. A mandatory wash out period of two weeks was maintained when more than one drug was administered. Plasma concentrations of the drugs were estimated as described by Noubarani et al. (Noubarani et al., 2010) using a Waters e2695 Alliance HPLC system (Medford, MA, USA). The maximum plasma concentration (Cmax) of each drug and the time to reach Cmax (Tmax) was determined directly from the individual concentration-time data. Area under the Curve (AUC) was calculated by non-compartmental methods. The area under the plasma concentration-time curve from time zero to the last sampling time (AUC 0-t) was calculated by the trapezoidal rule using PKsolver (Ver 2.0). (Zhang et al., 2010) Intra-gastric pH was recorded on day 1 (baseline prior to taking the PPI) and day 6 (24 h after taking PPI on the 5th day) of the study using the ComforTec Z pH monitoring unit (Sandhill Scientific, Colorado, USA) equipped with a single channel reference probe introduced per-nasally into the body of the stomach (about 40–45 cm beyond the oral cavity).

2.5. Statistical analysis

Descriptive statistical measures were presented for continuous variables and frequency distribution for categorical variables. Statistically significant differences among pharmacokinetic parameters of different *CYP2C19* genotypes were determined using the Kruskal–Wallis (H) test. Student's *t*-test and chi square test were used for continuous and categorical variables based on the sample size. P values <0.05 were considered statistically significant with two sided tail. The analysis was carried out using the trial version of MedCalc for Windows, (MedCalc Software, Ostend, Belgium) and Graph pad Quickcalc (Graphpad.com, 2015).

3. Results and discussion

3.1. Study subjects

Healthy urban subjects (n = 400) and tribals (n = 100) from two different tribes (Koya n = 56 and Naik n = 44) were recruited for the genotyping study apart from the 60 subjects recruited for pharmacokinetic and pharmacodynamics studies. Out of the 60 subjects recruited for the latter studies, 23 subjects volunteered for the study with a single drug and 6 volunteered for both drugs. Out of these 29 subjects, intragastric pH could be measured in 8 individuals. Demographic details of the study subjects are given in Table 2.

3.2. Allelic frequency in study subjects

Out of the 17 SNPs studied in the 560 subjects, only 4 variants (*2, *3, *17 in *CYP2C19* gene and *1B in *CYP3A4* gene) were observed with all the other studied alleles belonging to the wild type. The minor allele frequencies of *CYP2C19* *2, *3, *17 and *CYP3A4**1B were 0.41, 0.01, 0.17 and 0.06 respectively and were found to be in Hardy Weinberg equilibrium. Based on the *CYP2C19* genotype, the 560 subjects were divided into five phenotype groups, namely Normal (*1/*1, *2/*17, *3/*17), Poor (*2/*2, *2/*3), Intermediate (*1/*2, *1/*3), Rapid (*1/*17) and Ultra-rapid metabolizers (*17/*17) (http://www.cypalleles.ki.se/cyp2c19.html; Goldstein et al., 1997; Furuta et al., 2005). *CYP3A4* *1B genotype was not considered for classification of the subjects since it would not influence enzyme expression (Westlind et al., 1999).

3.3. CYP2C19 genotype and drug metabolizing phenotype in urban and tribal subjects

*CYP2C19**2 was the most frequently identified variant allele both in urban and tribal subjects. However, the percentage of subjects in each phenotype group differed among urban and tribal subjects. The percentage of normal, intermediate, rapid and ultra-rapid metabolizers was less in tribal subjects when compared to the urban subjects (Table 3). Tribal subjects also had a significantly higher number ($p = 0.0003$) of poor metabolizers (31%) as compared to the urban population (15%).

3.4. Metabolism of PPIs in different phenotypes

Upon estimating plasma drug concentration at different time points, AUCt, Cmax and Tmax were calculated to obtain a measure of the pharmacokinetic profile for each drug. In comparison to other PPIs, pantoprazole was found to be most effective for poor metabolizers since the drug was found to be absorbed in much lesser time as evidenced by the observed AUCt and Tmax values. There was a significant difference among the groups in AUCt at day 1 pharmacokinetics of Esomeprazole ($p = 0.04$) and also for Tmax ($p = 0.035$) on day 5 of esomeprazole (Table 4). No significant difference was observed in any of the parameters for pantoprazole.

Since pantoprazole was found to be more effective as mentioned above, we compared its influence on intra-gastric pH with that of esomeprazole, a preferred frontline PPI in clinical practice. Table 5 depicts results obtained in this regard. Administration of pantoprazole for 5 days resulted in improved gastric acid suppression as compared

Table 3
Comparison of different phenotypes in urbans and tribal subjects.

Phenotype	Genotype	Urban population(n = 460)	Tribals (n = 100)	p value*
Normal metabolizer	CYP2C19*1/CYP2C19*1	69 (15%)	13 (13%)	0.43
	CYP2C19*2/CYP2C19*17	62 (13.4%)	10 (10%)	
	CYP2C19*3/CYP2C19*17	0	01 (1%)	
Intermediate metabolizer	CYP2C19*1/CYP2C19*2	167 (36.3%)	33 (33%)	0.71
	CYP2C19*1/CYP2C19*3	01 (0.2%)	01 (1%)	
Poor metabolizer	CYP2C19*2/CYP2C19*2	67 (14.5%)	28 (28%)	0.0003
	CYP2C19*2/CYP2C19*3	03 (0.65%)	03 (3%)	
Rapid metabolizer	CYP2C19*1/CYP2C19*17	76 (16.5%)	10 (10%)	0.13
Ultra-rapid metabolizer	CYP2C19*17/CYP2C19*17	15 (3.2%)	01 (1%)	0.36

Table showing categorization of study subjects into different groups based on their genotype (http://www.cypalleles.ki.se/cyp2c19.html; Goldstein et al., 1997; Furuta et al., 2005).
* p value was obtained using chi square test; $p < 0.05$ was considered to be significant with two tailed test.

Table 4
Pharmacokinetic profiles of proton pump inhibitors for different phenotypes.

	Day I				Day V		
	Group(n)[a]	Tmax(Hr)*	Cmax(μg/ml)*	AUC(μg/ml/Hr)*	Tmax(Hr)*	Cmax(μg/ml)*	AUC(μg/ml/Hr)*
PPZ	PM(3)	4.67 ± 1.15	5.94 ± 2.45	21.00 ± 10.13	1.67 ± 0.57	11.97 ± 1.80	43.48 ± 5.50
	NM(2)	2.00 ± 0.00	4.57 ± 2.87	14.73 ± 5.83	2.75 ± 1.76	3.19 ± 3.86	10.59 ± 13.36
	IM(2)	4.00 ± 2.83	3.94 ± 0.44	17.65 ± 7.44	4.00 ± 0.00	9.57 ± 0.42	24.24 ± 14.14
	RM(1)	2.00	9.32	21.49	1.50	5.46	9.12
	UM(1)	2.00	4.31	12.39	4.00	4.14	7.18
	p value*	0.27	0.45	0.72	0.29	0.13	0.17
EPZ	PM(5)	3.60 ± 0.89	9.31 ± 4.86	27.49 ± 11.30	2.60 ± 1.34	3.61 ± 2.45	11.27 ± 7.30
	IM(8)	7.25 ± 6.92	4.03 ± 2.41	12.36 ± 8.07	1.44 ± 1.21	6.58 ± 5.29	15.13 ± 11.68
	NM(7)	6.00 ± 8.00	6.23 ± 2.84	19.74 ± 12.73	1.86 ± 1.07	6.27 ± 1.94	15.92 ± 4.90
	RM(4)	2.25 ± 2.06	3.34 ± 3.11	8.21 ± 6.88	1.13 ± 0.85	2.80 ± 2.23	8.29 ± 7.75
	UM(3)	4.50 ± 0.87	7.75 ± 3.01	24.58 ± 11.96	0.17 ± 0.29	4.09 ± 7.09	8.19 ± 14.19
	p value*	0.09	0.09	0.048	0.035	0.46	0.63

Table showing area under the curve (AUC), maximum concentration of drug recorded (Cmax) and the corresponding time (Tmax) for Pantoprazole (PPZ) and Esomeprazole (EPZ).
[a] All pharmacokinetic parameters have been given as mean ± SD wherever applicable.
* p values were calculated using Kruskal Wallis test.

to esomeprazole in poor and intermediate metabolizers. In normal metabolizers, the change in intra-gastric pH was similar in case of pantoprazole and esomeprazole. Interestingly, noteworthy differences could not be observed in the intra-gastric pH at baseline and on day 6 in response to administration of esomeprazole or pantoprazole in rapid and ultra-rapid metabolizers who are carriers of gain of function polymorphism *CYP2C19**17 (Table 5).

3.5. Discussion

Several studies have clearly demonstrated an association between polymorphisms in *CYP2C19* and *CYP3A4* genes and the drug metabolizing enzyme activity (Collet et al., 2009; Geisler et al., 2008; Taubert et al., 2009). In this study we evaluated the frequencies of these polymorphisms in Indian population, studied their effect on PPI metabolism and gastric acid suppression apart from obtaining insights into related aspects in tribal populations. We found that 16.5% (76/460) of the urban subjects are rapid metabolizers, 3.2% (15/460) are ultra-rapid metabolizers (Table 3), who did not respond to standard dose of PPIs (Table 5). To our knowledge, this is the first study from India which has comprehensively genotyped the well characterized, non-synonymous variants in the *CYP2C19* and *CYP3A4* genes. Further, most of the earlier studies have focused more on *CYP2C19**2 and *CYP2C19**3 alleles only but not on other loss of function polymorphisms that have been included in the present study. Efforts have also been made to correlate results obtained upon genotyping with PPI metabolism.

In view of the importance of cytochrome P450 enzymes in drug metabolism, several studies have earlier been conducted to establish frequency of related gene polymorphisms in different populations. In our study focusing on PPI metabolism, *CYP2C19**2 was found to be the most common allele occurring at a higher frequency of 41%, as compared to other Asian populations (28–30.3%) (He et al., 2002; Sugimoto et al., 2008) and African Americans (25%) (Kudzi et al., 2009). *CYP2C19**3 variant allele was also detected at a lesser frequency of 0.8% in our study as opposed to other Asian populations (3.4–10%.) (He et al., 2002; Sugimoto et al., 2008). We found *CYP2C19**17 genotype (associated with increased enzyme function) to occur at a higher allelic frequency (17%) in comparison 2–4% reported in other Asians (Pedersen et al., 2010). The allelic frequency of *CYP3A4* *1B, which was not detected earlier in Asians like Korean, Chinese and Japanese populations (Lee et al., 2013) was found to be 6% in the present study.

In order to correlate the results of genotyping with PPI metabolism, we have investigated the pharmacokinetics of various proton pump inhibitors in different subjects. Studies with pantoprazole showed that poor metabolizers had the highest AUC and ultra-rapid metabolizers had the lowest AUC on both day I and day V. Poor metabolizers had significantly higher values of AUC and Cmax ($p = 0.03$ and 0.02 respectively; unpaired *t*-test, 2 tailed p value) when compared to normal metabolizers. This data is in consonance with observations made with Caucasians (Hunfeld et al., 2010). Subjects with *CYP2C19**17 polymorphism had lower AUC values on both day I and day V when compared to those without detectable polymorphism, akin to findings made with Caucasians (Hunfeld et al., 2008). Another study conducted on Caucasian volunteers after single oral dose of pantoprazole also reported similar results, concluding that the *CYP2C19**2 and *17 polymorphisms have significant impact on pantoprazole pharmacokinetics (Gawronska-Szklarz et al., 2012). After ascertaining the impact of these polymorphisms on pharmacokinetics of pantoprazole, we studied its effect on intra-gastric pH and observed that pantoprazole showed genotype dependent acid inhibition with less acid inhibition in subjects

Table 5
Intra-gastric pH of subjects for different phenotypes.

Phenotype	Drug(n)	Baseline pH	pH on Day 6
Poor metabolizer	Esomeprazole(2)	2.45 ± 1.76	3.00 ± 2.82
	Pantoprazole(2)	1.40 ± 0.70	5.25 ± 0.35
Normal metabolizer	Esomeprazole(1)	0.40	3.40
	Pantoprazole(1)	1.50	4.10
Intermediate metabolizer	Esomeprazole(1)	2.00	4.10
	Pantoprazole(2)	1.70 ± 0.14	6.15 ± 0.07
Rapid metabolizer	Esomeprazole(1)	1.25	1.20
Ultra-rapid metabolizer	Esomeprazole(1)	2.00	2.40
	Pantoprazole(1)	1.30	1.20

Table showing intra gastric pH values in subjects categorized into various groups. pH was recorded using a nasal probe before and after administering PPI for 5 days. Values have been given as mean ± SD wherever applicable.

with *1/*1 genotype and stronger acid inhibition in subjects with *1/*2 and *2/*2 genotype. Our results are similar to the pharmacodynamics data of Caucasians (Hunfeld et al., 2010), where they found similar genotype dependent acid inhibition with pantoprazole. There were, however, no differences observed in the intra-gastric pH at baseline and on day 6 in subjects with *17/*17 genotype.

Similar studies with esomeprazole showed that normal metabolizers had highest value of AUC whereas ultra-rapid metabolizers showed lower value of AUC on day V. These results are in contrast to those made with Caucasians (Hunfeld et al., 2012) where AUC was observed to be maximum in poor metabolizers, indicating differences in the metabolism of esomeprazole. Pharmacokinetic parameters were found to be similar between the two genotypes in normal metabolizers, (subjects carrying *1/*1 and *2/*17). This was further confirmed by unpaired *t*-test that revealed no significant difference between the two genotypes ($p > 0.5$, unpaired *t*-test). The effect of *CYP2C19**17 polymorphism was observed only in homozygous condition (*17/*17).

We studied the frequency of these polymorphisms in subjects belonging to two tribal groups from our state which are endogamous populations, ethnically and culturally distinct from the urban population. This difference was replicated in the results obtained, the frequency of *CYP2C19**2 polymorphism in tribal subjects (0.49) was more than the urban subjects, whereas the frequency of *CYP2C19**17 (0.12) was lesser. The number of poor metabolizers in the tribal subjects was significantly ($p = 0.0003$) higher than the urban subjects. Based on pharmacokinetics data we observed that the effect of *CYP2C19**2 polymorphism seems to be more dominant in the studied population, especially in the compound heterozygous condition (*2/*3 and *2/*17). Pharmacokinetic profiles of *2/*3, were similar to those of *1/*2. *CYP2C19**17 polymorphism was found to be more effective in homozygous mutant condition than heterozygous state. No significant difference (Two tailed p value > 0.07 for AUCt, Cmax and Tmax; unpaired *t*-test) was observed in the pharmacokinetics of RM (*1/*17) and NM (*1/*1). Carriers of *CYP2C19**17 allele did not show much change in intra-gastric pH from baseline to day 6 post ingestion.

4. Conclusion

We demonstrate that it is important to identify and optimize appropriate dosage regimen for rapid and ultra-rapid metabolizers, as the standard dosage does not seem to efficiently inhibiting acid secretion. Although the sample size for pharmacokinetic and pharmacodynamic studies is a limitation, our study indicates the impact of these polymorphisms not only on PPI metabolism but also on other drugs that are metabolized by *CYP2C19*. Despite limitations, our study has established the impact of various alleles of *CYP2C19* on metabolism of PPIs in our population. Out of the 36.3% variants, 20% are carriers of the *CYP2C19**17 allele who did not respond to the standard dose. Therefore, we conclude that screening and identification of subjects carrying variant alleles is necessary for personalization of dosage.

Author contributions

Neha Deshpande and Sharanya Vuddagiri collected samples, performed research, data analysis, data interpretation and drafted the paper. Dr. V.V. Ravikanth contributed to data analysis, data interpretation and drafting the paper. Dr. H.V.V. Murthy performed statistical analysis and revised the paper. Dr. Sasikala Mitnala contributed to the design of the study and revised the paper. Dr. Rupa Banerjee and Dr. Manu Tandan contributed to the design of the study and revised the paper. Dr. D. Nageshwar Reddy contributed to the design of the study, data analysis and approval of the final version of the paper.

All authors have given their approval for the final version of the paper and the authorship list.

Conflict of interests

None declared.

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