Comparative pharmacokinetics of Omeprazole and its metabolites in poor and extensive metabolizer Pakistani healthy volunteers and a review of different studies

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Abstract: This study was designed to evaluate a comparative single dose (40mg) pharmacokinetics (PK) of Omeprazole (OMP) and its two metabolites, 5-hydroxy Omeprazole (5-OH-OMP) and Omeprazole sulphone (OMP-S) in poor (PM) and extensive (EM) metabolizer Pakistani healthy adult volunteers. The frequency of CYP2C19 and CYP3A4 varies widely in different populations. The present study was conducted to evaluate the PK of OMP and its two metabolites in Pakistani population and to review different studies conducted after administration of single dose of OMP. Twenty two subjects were enrolled in this study and divided into two groups. The CYP2C19 phenotyping was evaluated by the metabolic ratio of OMP to 5-OH-OMP. It was a single dose, open label study and the blood samples from subjects were collected at different time intervals until 24 hours. The PK parameters were calculated using the PK-summit software. The metabolic ratio of area under the plasma concentration-time curve $AUC_{OMP/5\text{-}OH\text{-}OMP}$ was 1.86 ± 0.572 and13.84 ± 2.504 for EM and PM, respectively; maximum plasma concentration (C_{max}) of OMP was increased by two folds for PM while the AUC_{∞} was increased by 3 folds; the C_{max} and AUC_{∞} of 5-OH-OMP decreased for PM by 2 folds while there was 3 fold increase observed in the C_{max} and AUC_{∞} of OMP-S. The PK of OMP and its metabolites in different populations were also discussed, and issues regarding CYP2C19 and CYP3A4 genotyping were also extensively reviewed. In EM of CYP2C19 the concentration of 5-OH-OMP is higher while that of OMP-S is lower. This study as well as reported studies reveals that in PM of CYP2C19 more drugs are available for CYP3A4 to be metabolized. A correlation between CYP2C19 EM and PM activity with CYP3A4 needs to be established.

Keywords: Omeprazole, pharmacokinetics, poor and extensive metabolizer.

INTRODUCTION

Proton pump inhibitors (PPIs) are the most prescribed drugs for GIT problem and the second most prescribed drug worldwide (Vanderhoff and Tahboub, 2002). These are preferred over the H_2-receptor agonist on the basis of their safety as well as efficacy (Gillen *et al*., 1999, Gisbert *et al*., 2003). Omeprazole (OMP) is the prototype of this class (Mears and Kaplan, 1996) that suppresses gastric acid secretion by inhibiting the H^+/K^+ ATPase at the secretory surface of the gastric parietal cell (Lindberg *et al*., 1986). It is mainly used in the treatment of duodenal and gastric ulcers, gastroesophageal reflux disease, esophagitis and Zollinger-Ellison syndrome (Lamers *et al*., 1984). It is also prescribed in combination with Amoxicillin and Clarithromycin for eradication of *Helicobacter pylori* infection (Lind *et al*., 1996). OMP is extensively metabolized in the liver mainly by CYP2C19 and partially by CYP3A4 (Ogilvie *et al*., 2011). High inter- and intra-population differences have been reported in the pharmacokinetic (PK) parameters of OMP. The main reason for this inter- and intra-population variation is the phenotypes of CYP2C19 (Baudhuin, 2012). On the basis of CYP2C19 phenotyping, population can be classified as poor metabolizer (PM) and extensive metabolizer (EM) of CYP2C19 (Panchabhai *et al*., 2006). The frequency of CYP2C19 PM phenotypes varies significantly among different populations and ultimately effecting the PK (especially metabolism) of substrates of CYP2C19 (Desta *et al*., 2002). If the parent drug is active then its AUC, C_{max} will be higher for PM than EM and will have a more pronounce effect on the disease. Similarly, the clearance for PM of CYP2C19 will be less than that of EM (Bertilsson *et al*., 1989, Qin *et al*., 1999, Herrlin *et al*., 2003). Due to this variation, populations of different ethnicity respond differently to OMP for the treatment of *H. pylori* (Bayerdörffer *et al*., 1995, Al-Assi *et al*., 1995). Similarly, OMP raises intragastric pH of PM of CYP2C19 to a greater extent than EM. OMP has proved to be more effective in treating rebleeding due to peptic ulcers in Chinese where the frequency of PM is high (Lau *et al*., 2000). Studies have also shown that OMP is a substrate and also an inhibitor of efflux P-glycoprotein (P-gp), and thus the MDR1 polymorphism may also alter the activity of OMP (Anglicheau *et al*., 2004, Pauli-Magnus *et al*., 2001). It is possible that along

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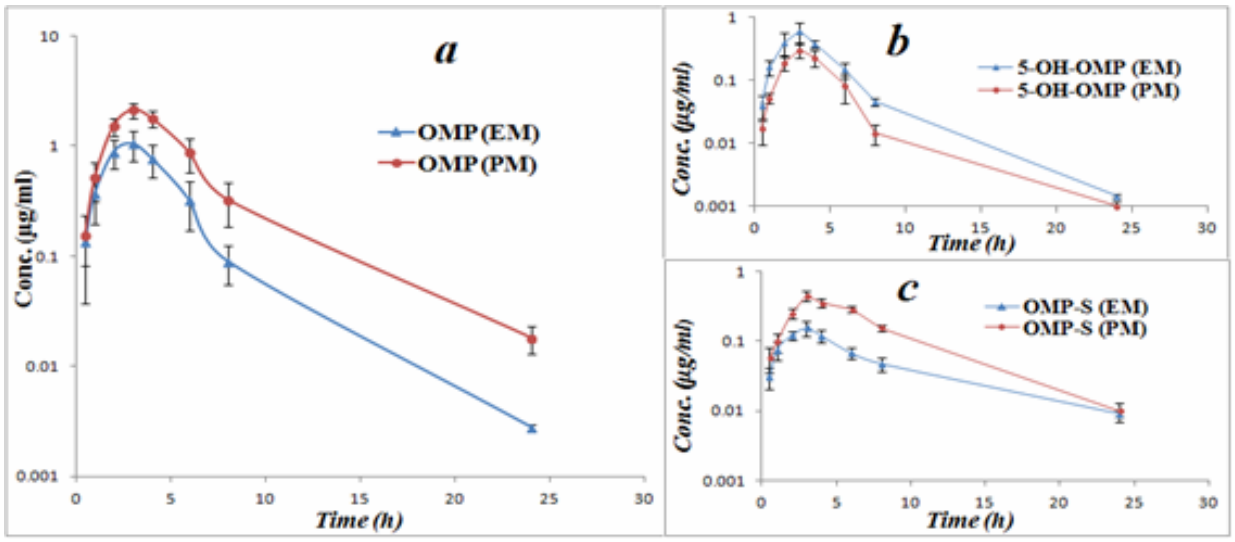

Fig. 1: Plasma concentration of OMP (a), 5-OH-OMP (b) and OMP-S (c) as a function of time for EM (▲) and PM (•) in healthy Pakistani human volunteers

with CYP2C19 polymorphism, the MDR1 polymorphism may also be responsible for the high inter-individual differences in the PK parameters. PK of OMP and its metabolites have been extensively studied in different populations. In the present study, comparative PK of OMP and its metabolites were evaluated in PM and EM healthy volunteers from Pakistan and studies conducted so far in different populations were critically reviewed.

MATERIAL AND METHODS

Study design

The study was conducted at biopharmaceutics laboratory in University of Peshawar, Pakistan. A prospective interventional case- control clinical study was designed. This study was conducted as per the principles of the "world medical association (WMA) declaration of Helsinki *Ethical principles for medical research involving human subjects*" and its amendments. Study protocol was approved by the Ethical Committee of the Department of Pharmacy, University of Peshawar, Pakistan.

Selection of healthy human volunteers

Healthy volunteers (n=22) were enrolled. Written informed consent form was obtained from all volunteers before starting of the study and various biochemical tests were performed to evaluate their health status, including hemoglobin (Hb), bilirubin, SGPT, hepatitis B and C, lipid profile (low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides), blood pressure, heart rate and ECG. The subjects were also tested for *H. pylori*. All the volunteers were non smokers and were prohibited to take any drug during the study.

Study protocol

All the volunteers were directed not to take any medication (including herbal medicines) two weeks prior to the study and during the clinical trial. After an overnight fast, all healthy volunteers received 40 mg of OMP (Omega 40mg, Ferozsons Laboratories (Pvt.) Ltd, Pakistan) with full glass of water. The medication was administered orally to the volunteers at 8 am. Two standard meals were provided to all volunteers (11 am and 4 pm).

Sample collection

Approximately 3mL of blood was collected from each volunteer at 0, 0.5, 1, 2, 3, 4, 6, 8 and 24 hours, in heparinized tubes. The samples were then centrifuged at 10000 rpm for 8 minutes. After centrifugation the plasma was transferred into properly labeled eppendorf tubes and stored at a temperature of -20°C until analysis. The samples were analyzed using Liquid Chromatography-Mass Spectrometry method. The mobile phase consisted of 0.1% formic acid in acetonitrile and 0.1% formic acid in water (40/60 v/v) using Hichom RP18 (150 × 3.0 mm, 3 µm UK) as a stationary phase interfaced with a LTQ Orbitrap mass spectrometer (Ahamd, 2014).

Pharmacokinetics studies

The plasma concentration of OMP, 5-OH-OMP and OMP-S as a function of time was plotted on semi logarithmic graphs as shown in fig. 1. Various PK parameters were calculated using the PK Summit® software.

The C_{max} and t_{max} were determined by inspection of individual plasma concentration-time profile of OMP, 5-OH-OMP and OMP-S. The AUC_{∞} was determined by trapezoidal rule. The elimination half life was determined by $t_{1/2}$ = 0.693/k. The apparent oral clearance was determined by dose/[AUC].

Table 1: Some of the important reported PK parameters of OMP in different populations, when single dose was administered orally where Hm is homozygous extensive metabolizer while Ht is heterozygous extensive metabolizer

Phenotype		Dose (mg)	Population	C_{max} (µg/mL)	t_{max} (h)	AUC_t (µg-h/mL)	AUC_∞ (µg-h/mL)	CL/F	$t_{1/2}$ (h)	Ref
EM	NC*	40	Pakistani	1.05 ±0.403	2.47± 0.535	-	4.036± 1.24	136.715 ±81.47 mL/h/kg	1.11± 0.46	Present Study
		20	Korean	0.381 ±0.054	1.7± 0.3	0.749 ±0.082	0.778± 0.078	*475 ± 64.2 mL/h/kg*	1.4± 0.2	(Sohn *et al*., 1992a)
		40	Japanese	0.555 ±0.085	-	1.299 ±0.407	-	-	-	(Kita *et al*., 2002)
		20	Japanese	0.475 ±0.354		0.716 ±0 .620	-	18.39± 17.55mL/min/kg	0.6± 0.2	(Yasuda *et al*., 1995)
		40	Chinese	0.68 ±0.048	1.5	-	3.211± 0.386	12.36±1.76 L/h	1.79± 0.18	(Chen *et al*., 2009)
		20	Swedish	0.242	1	0.38	-	-	0.7	(Andersson *et al*., 1998)
		20	Swedish	0.106 ±0.076	-	0.243 ±0.221	-	1.4±0.8 L/h/kg	-	(Tybring *et al*., 1997)
		40	German	0.997	1.05	-	2.539	16.1 L/h	0.84	(Rost and Roots, 1996)
		20	Iranian	0.283 ±0.113	1.75± 0.63	0.455 ±0.155	0.481± 0.175	-	2.04± 0.82	(Mostafavi and Tavakoli, 2004)
	Hm	40	HK Chinese	0.727 ±0.246	-	-	1.444± 0.705	0.56±0.28 L/h/kg	0.96± 0.59	(Yin *et al*., 2004)
		20	Japanese	0.251 ±0.046	-	0.618 ±0.141	-	-	1.1± 0.08	(Sakai *et al*., 2001)
			Japanese	-	-	0.523 ±0.12	-	-	-	(Shirai *et al*., 2001)
		20	Jordanian	0.152 ±0.01	1.95± 0.17	-	0.251± 0.016	1.243±0.12L/h/k g	0.9± 0.07	(Shilbayeh and Tutunji, 2006)
		40	Japanese	0.554	2.5	-	1.164	-	1.2	(Uno *et al*., 2007)
		20	Swedish	0.135±0. 061	-	0.247 ±0.087	-	1.24±0.44l/h.kg	0.71± 0.23	(Chang *et al*., 1995)
		20	Chinese	0.513 ±0.294	-	-	1.664± 0.745	13.5±8.5mL/h	1.99± 0.66	(Hu *et al*., 2007)
	Ht	40	HK Chinese	0.867 ±0.310			2.39± 0.677	0.29±0.08L/h/kg	1.2± 0.35	(Yin *et al*., 2004)
		20	Japanese	0.623 ±0.149	-	1.061 ±0.269	-	-	1.18± 0.2	(Sakai *et al*., 2001)
		20	Japanese	-	-	1.09±0.144	-	-	-	(Shirai *et al*., 2001)
			Jordanian	0.327 ±0.017	1.99± 0.15	-	0.669± 0.044	0.453± 0.03L/h/kg	1.37± 0.11	(Shilbayeh and Tutunji, 2006)
		40	Japanese	1.142	2.3		3.093	603	1.1	(Uno *et al*., 2007)
		20	Swedish	0.347 ±0.046	-	0.907 ±0.057	-	0.31±0.04mL/h	1.91± 0.24	(Chang *et al*., 1995)
		20	Chinese	0.56 ±0.294	-	-	1.759± 0.838	12±4mL/h	1.45± 0.24	(Hu *et al*., 2007)
PM		40	Pakistani	2.132 ±0.805	3.09± 0.23	-	14.25±3.631	36.53±9.23 mL/h/kg	1.951 ± 0.654	Present Study
		20	Korean	1.049 ±0.072	2.3± 0.2	4.482 ±0.264	5.33± 0.392	59.5± 3.6mL/h/kg	3.2	(Sohn *et al*., 1992a)
		40	Japanese	4.982 ±1.051	-	18.412 ±2.137	-	-	-	(Kita *et al*., 2002)
		20	Japanese	1.45 ±0.333	-	4.493 ±1.134	-	-	2.1± 0.6	(Yasuda *et al*., 1995)
		40	Chinese	1.838 ±0.42	1.75		6.534± 0.655	6.17± 0.67l/h	2.73± 0.24	(Chen *et al*., 2009)
		20	Swedish	0.90735	2	4.002	-	-	2.2	(Andersson *et al*., 1998)
			Swedish	0.511 ±0.076	-	1.835 ±0.447	-	0.13± 0.05L/h/kg	-	(Tybring *et al*., 1997)
		40	German	2.27	4.48	-	11.83	3.83 L/h	3.89	(Rost and Roots, 1996)

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Phenotype	Dose (mg)	Population	C_{max} (µg/mL)	t_{max} (h)	AUC_t (µg-h/mL)	AUC_∞ (µg-h/mL)	CL/F	$t_{1/2}$ (h)	Ref
	20	Iranian	0.676 &0.923	4 & 3	2.075	2.57 & 1.72	4.853 & 1.930	4 & 1.5	(Mostafavi and Tavakoli, 2004)
	40	HK Chinese	2.23 ±0.390	-	-	7.974± 2.074	0.09± 0.03 L/h/kg	2.12± 0.57	(Yin *et al*., 2004)
	20	Japanese	1.07 ±0.185	-	4.587±0.681	-	-	2.41± 0.15	(Sakai *et al*., 2001)
	20	Japanese	-	-	5.606±1.055	-	-	-	(Shirai *et al*., 2001)
		Jordanian	0.538 ±0.033	2.5± 0.26	-	2.34± 0.264	0.127± 0.01	2.42± 0.183	(Shilbayeh and Tutunji, 2006)
	40	Japanese	2.72	2.3	-	10.511	-	-	(Uno *et al*., 2007)
	20	Swedish	1.035 ±0.368	-	4.924±1.37	-	0.06± 0.01l/h/kg	2.68± 0.69	(Chang *et al*., 1995)
	20	Chinese	1.15 ±0.333	-	-	6.827± 2.454	3.8±2 mL/h	2.42 ±0.5	(Hu *et al*., 2007)
Genotype	40	CYP2C19*1/*1	0.727	2.1	-	1.432	48 L/h	1.2	(Baldwin *et al*., 2008)
	20	CYP2C19*1/*1	-	-	-	0.64	-	-	(Li-Wan-Po *et al*., 2010)
	20	CYP2C19*1/*17	-	-	-	0.49	-	-	(Li-Wan-Po *et al*., 2010)
	40	CYP2C19*17/*17	0.499	2.1	-	0.68	61L/h	0.9	(Baldwin *et al*., 2008)
	40	H1/H1	0.723 ±0.067	2.1± 0.2	-	1.385± 0.184	-	0.8 ±0.1	(Jin *et al*., 2009)
		H2/H2	2.022 ±0.583	4.0± 1.0	-	7.808± 1.211	-	2.3 ±0.2	
		H1/H2	1.003 ±0.163	2.4± 0.4	-	2.69 ± 0.565	-	1.1 ±0.2	
		H1/H3	1.008 ±0.185	2.2± 0.3	-	2.521± 0.542	-	0.9 ±0.1	
		H2/H3	2.177 ±0.142	3.0± 0.3	-	10.828 ±1.523	-	2.8 ±0.2	

Table 2: PK parameters of 5-OH-OMP in different populations, where Hm is the extensive homozygous and Ht is extensive heterozygous metabolizers

Phenotype		Dose (mg)	Population	C_{max} (µg/mL)	t_{max} (h)	AUC_t (µg-h/mL)	AUC_∞ (µg-h/mL)	$t_{1/2}$ (h)	Ref
EM	NC*	40	Pakistani	0.61± 0.372	2.842± 0.375	-	2.721± 1.076	1.025± 0.485	Present study
		20	Korean	0.209± 0.018	1.7± 03	0.491± 0.029	0.508± 0.028	1.5± 0.2	(Sohn *et al*., 1992a)
		40	Japanese	0.236± 0.021	-	0.67± 0.021	-	-	(Kita *et al*., 2002)
		20	Japanese	0.306± 0.137	-	0.585± 0.242	-	1 ± 0.3	(Yasuda *et al*., 1995)
		40	Chinese	0.235± 0.075	1.75	-	1.108± 0.249	2.86± 0.57	(Chen *et al*., 2009)
		20	Swedish	0.244± 0.064	-	0.523± 0.153	-	-	(Tybring *et al*., 1997)
		40	German	0.336	1.2	-	0.9025	1.65	(Rost and Roots, 1996)
	Hm	40	HK Chinese	0.384± 0.181	-	-	0.712± 0.329	1.86± 1.11	(Yin *et al*., 2004)
		20	Japanese	0.095± 0.014	-	0.295± 0.0391	-	1.41± 0.20	(Sakai *et al*., 2001)
		20	Japanese	-	-	0.835± 0.106	-	-	(Shirai *et al*., 2001)
		40	Japanese	0.254	-	-	0.656	-	(Uno *et al*., 2007)
		20	Swedish	0.223± 0.074	-	0.529± 0.119	-	-	(Chang *et al*., 1995)
	Ht	40	HK Chinese	0.309± 0.127	-	-	0.833± 0.268	1.78± 0.95	(Yin *et al*., 2004)

Phenotype	Dose (mg)	Population	C_{max} (µg/mL)	t_{max} (h)	AUC_t (µg-h/mL)	AUC_∞ (µg-h/mL)	$t_{1/2}$ (h)	Ref
	20	Japanese	0.134± 0.032		0.409± 0.092	-	1.42± 0.36	(Sakai *et al*., 2001)
	20	-	-	-	0.83± 0.089	-	-	(Shirai *et al*., 2001)
	40	Japanese	0.234	-	-	0.706	-	(Uno *et al*., 2007)
	20	Swedish	0.209± 0.05	-	0.647± 0.15	-	-	(Chang *et al*., 1995)
PM	40	Pakistani	0.291± 0.072	3.23± 0.243		1.133± 0.195	2.909± 0.512	
	20	Korean	0.046± 0.005	2.3± 0.2	0.231	0.292	3.4± 0.4	(Sohn *et al*., 1992a)
	40	Japanese	0.156± 0.039	-	0.722± 0.072	-	-	(Kita *et al*., 2002)
	20	Japanese	0.064± 0.019	-	0.267± 0.089		2.5±0.7	(Yasuda *et al*., 1995)
	40	Chinese	0.101± 0.018	1.75		0.566± 0.09	1.57± 0.25	(Chen *et al*., 2009)
	20	Swedish	0.0357± 0.008	-	0.138± 0.034	-	-	(Tybring *et al*., 1997)
	40	German	0.155	1.9	-	0.884	1.79	(Rost and Roots, 1996)
	40	HK Chinese	0.069± 0.044	-	-	0.305± 0.143	2.78± 1.45	(Yin *et al*., 2004)
	20	Japanese	0.04± 0.008	-	0.346± 0.148	-	1.81± 0.41	(Sakai *et al*., 2001)
		Japanese	-	-	0.584± 0.251	-	-	(Shirai *et al*., 2001)
	40	Japanese	0.076	-	-	0.364	-	(Uno *et al*., 2007)
	20	Swedish	0.048± 0.019	-	0.278± 0.144	-	-	(Chang *et al*., 1995)
Genotype	40	CYP2C19*1/*1	0.553	2.4	-	1.21	1.3	(Baldwin *et al*., 2008)
	40	CYP2C19*17/*17	0.551	2.1	-	1.08	1.1	(Baldwin *et al*., 2008)
		H1/H1	0.454± 0.037	2.1± 0.2	-	1.017± 0.055	0.9±0.1	(Jin *et al*., 2009)
		H2/H2	0.212± 0.115	4.3± 0.9	-	0.798± 0.266	2.1±0.5	
		H1/H2	0.398± 0.051	2.4± 0.2	-	1.142± 0.196	1.2±0.1	
		H1/H3	0.411± 0.068	2.2± 0.3	-	1.122± 0.147	1.2±0.1	
		H2/H3	0.283± 0.135	3.2± 0.3	-	0.892± 0.171	3.2±0.5	

Table 3: PK parameter of OMP-S in different population from the literature. Hm is the homozygus EM and ht is heterozygous EM

Genotype		Dose (mg)	Population	Cmax (µg/mL)	tmax (h)	AUC_t (µg-h/mL)	AUC_∞ (µg-h/mL)	$t_{1/2}$ (h)	Ref
EM	NC*	40	Pakistani	0.156±.031	2.91±0.749		0.565±0.187	2.082± 0.905	Present study
		20	Korean	0.102±13	2.0±0.4	0.541±.091	0.685±0.176	2.5 ± 0.4	(Sohn *et al*., 1992a)
		40	Japanese	0.137 ±0.02		0.576± 0.163			(Kita *et al*., 2002)

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Genotype		Dose (mg)	Population	Cmax (µg/mL)	tmax (h)	AUC_t (µg-h/mL)	AUC_∞ (µg-h/mL)	$t_{1/2}$ (h)	Ref
		20	Japanese	0.098± .042		0.423± 0.342		2.2±1.1	(Yasuda *et al*., 1995)
		40	Chinese	0.144 ±.014	1.75		0.696± 0.122	3.07± 0.44	(Chen *et al*., 2009)
		20	Swedish	0.057 ±.017		0.197± 0.08			(Tybring *et al*., 1997)
		40	German	0.324	2.3		2.37	3.07	(Rost and Roots, 1996)
	hm	40	HK Chinese	0.195 ±.056	-		1.117± 0.56	2.8 ± 1.3	(Yin *et al*., 2004)
		20	Japanese	0.072 ±.011	-	0.357± .075	-	2.38± 0.3	(Sakai *et al*., 2001)
		20			-	0.248± .065	-	-	(Shirai *et al*., 2001)
		40	Japanese	0.137	-		-	-	(Uno *et al*., 2007)
		20	Swedish	0.057±.019	-	0.186±0.051	-	-	(Chang *et al*., 1995)
	ht	40	HK Chinese	0.28± 0.059	-	0.875±0.305	2.313± 0.582	4.13± 2.12	(Yin *et al*., 2004)
		20	Japanese	0.11± 0.011	-	0.720±0.143	-	2.55± 0.42	(Sakai *et al*., 2001)
		20		-	-	0.875±0.305	-	-	(Shirai *et al*., 2001)
		40	Japanese	0.303	-	-	-	-	(Uno *et al*., 2007)
		20	Swedish	0.103 ±.036	-	0.561± 0202	-	-	(Chang *et al*., 1995)
PM		40	Pakistani	0.451 ±.072	3.15± 0.346	-	1.912± 0.74	3.782± 0.947	Present study
		20	Korean	0.28± 0.012	6.3± 0.7	2.507± 0.139	5.699± 0.353	10.6± 0.9	(Sohn *et al*., 1992a)
		40	Japanese	0.594 ±.129		5.087±1.026	-	-	(Kita *et al*., 2002)
		20	Japanese	0.3± 0.044		4.206±0.859	-	6.7±2.0	(Yasuda *et al*., 1995)
		40	Chinese	0.314 ±.069	3.0		2.057± 0397	4.16± 0.34	(Chen *et al*., 2009)
		20	Swedish	0.297 ±.045		1.667±0.045	-	-	(Tybring *et al*., 1997)
		40	German	0.714	4.5	-	9.53	8.33	(Rost and Roots, 1996)
		40	HK Chinese	0.602± .139	-	-	8.488± 1.976	7.79± 3.06	(Yin *et al*., 2004)
		20	Japanese	0.258 ±.032	-	2.794±0.414	-	4.52± 0.65	(Sakai *et al*., 2001)
		20	Japanese		4.816± 0.433	-	-	-	(Shirai *et al*., 2001)
		40	Japanese	1.36	-	-	-	-	(Uno *et al*., 2007)
		20	Swedish	0.331± .141		2.257± 1.13	-	-	(Chang *et al*., 1995)
Genotype		40	CYP2C19* 1/*1	0.203	2.6	-	1.20	3.3	(Baldwin *et al*., 2008)
		40	CYP2C19* 17*17	0.121	2.2	-	0.39	1.9	(Baldwin *et al*., 2008)
		40	H1/H1	0.187± 0.018	2.8± 0.3	-	0.898± 0.163	2.4 ± 0.4	(Jin *et al*., 2009)
			H2/H2	0.681± 0.26	5.3 ±1.3	-	9.475± 1.553	10.9± 1.3	
			H1/H2	0.219± 0.032	2.7± 0.2	-	1.763± 0.492	4.5 ± 0.7	
			H1/H3	0.292± 0.072	3.4± 0.4	-	2.003± 0.598	3.8 ± 0.5	
			H2/H3	0.535 ±.057	5.3± 1.3	-	14.444± 2.86	19.3± 3.5	

Table 4: Comparison of different genotypic groups within populations, showing increase in folds of [AUC] of the genotypic group written with the digits

Population	Dose	OMP AUC			5-OH-OMP AUC			OMP-S AUC			Reference
		Hm vs. Ht	Hm vs. PM	Ht vs. PM	Hm vs. Ht	Hm vs. PM	Ht vs. PM	Hm vs. Ht	Hm vs. PM	Ht vs. PM	
HK Chinese	40mg	1.7 Ht	7.6 PM	4.3 PM	1.2 Ht	2.3 Hm	2.7Ht	2.07 Ht	7.7 PM	3.8 PM	(Yin *et al*., 2004)
Japanese	20mg	1.71 Ht	7.42 PM	4.3 PM	1.38 Ht	1.2 PM	1.2 Ht	2.0 Ht	7.8 PM	3.8 PM	(Sakai *et al*., 2001)
Japanese		2.8 Ht	5.5 PM	3.3 PM	1.0 Hm	1.4 Hm	1.4 Ht	3.5 Ht	19.4 PM	5.5 PM	(Shirai *et al*., 2001)

Continue…

Continued…

Population	Dose	OMP AUC			5-OH-OMP AUC			OMP-S AUC			Reference
		Hm vs. Ht	Hm vs. PM	Ht vs. PM	Hm vs. Ht	Hm vs. PM	Ht vs. PM	Hm vs. Ht	Hm vs. PM	Ht vs. PM	
HK Chinese	40mg	1.7 Ht	7.6 PM	4.3 PM	1.2 Ht	2.3 Hm	2.7Ht	2.07 Ht	7.7 PM	3.8 PM	(Yin *et al*., 2004)
Japanese	20mg	1.71 Ht	7.42 PM	4.3 PM	1.38 Ht	1.2 PM	1.2 Ht	2.0 Ht	7.8 PM	3.8 PM	(Sakai *et al*., 2001)
Jordanian	20mg	2.8 Ht	9.3 PM	3.3 PM	-	-	-	-	-	-	(Shilbayeh and Tutunji, 2006)
Japanese	40mg	2.6 Ht	9.0 PM	3.4 PM	1.1 Ht	1.8 Hm	1.9 Ht	-	-	-	(Uno *et al*., 2007)
Swedish	20mg	3.6 Ht	19.8 PM	5.4 PM	1.2 Ht	1.9 Hm	2.3 Ht	3.0 Ht	12.1 PM	5.5 PM	(Chang *et al*., 1995)
Chinese	20mg	1.06 Ht	4.1 PM	3.9 PM	-	-	-	-	-	-	(Hu *et al*., 2007)

Population Classified only as EM and PM of CYP2C19					
		OMP AUC EM vs. PM	5-OH-OMP AUC EM vs. PM	OMP-S AUC EM vs. PM	
Pakistani	40mg	2.7 PM	2.4 EM	3.8 PM	Present study
Korean	20mg	6.9 PM	1.7 EM	8.3 PM	(Sohn *et al*., 1992a)
Japanese	40mg	14.3 PM	1.15 PM	8.8 PM	(Kita *et al*., 2002)
Japanese	20mg	6.3 PM	2.2 EM	9.9 PM	(Yasuda *et al*., 1995)
Chinese	40mg	2.0 PM	2.0 EM	3.0 PM	(Chen *et al*., 2009)
Swedish	20mg	10.5 PM	-	-	(Andersson *et al*., 1998)
Swedish	20mg	7.6 PM	3.7 EM	8.5 PM	(Tybring *et al*., 1997)
German	40mg	4.7 PM	1.02 EM	3.6 PM	(Rost and Roots, 1996)
Iranian	20mg	2.9 PM	-	-	(Mostafavi and Tavakoli, 2004)

* EM not classified as Hm or Ht

Phenotyping of volunteers

The subjects were divided into EM and PM of CYP2C19. The classification was on the basis of drug metabolite ratio of AUC_{∞} (OMP/5-OH-OMP).

RESULTS

Demographic profile of volunteers

The height (mean ± SD) of the volunteers recruited for the study was 66±1.8 inches (ranged between 61-69 inches). The weight (mean ± SD) was 144±9 lbs that ranged between 132-160 lbs (60-73kg).The age (mean ± SD) of the volunteers was 25±2 years. All the volunteers in this study were having normal BMI (mean ± SD), i.e., 23±1. In the present study the results and discussions are based on non-compartmental model because it requires fewer assumptions for the data generating process but the data needs to be collected in a structured way (Jaki and Wolfsegger, 2012).

Among the 22 volunteers, 18 volunteers were grouped in EM while 4 were PM of CYP2C19. In previous reported studies, the subjects were genotyped as homozygous (Hm), heterozygous (Ht) extensive metabolizer and poor metabolizer. The division in present study was made on the basis of OMP to 5-OH-OMP ratio of AUC. Such classification, on the basis of phenotyping is also reported in literature (Panchabhai *et al*., 2006). $AUC_{OMP/5\text{-}OH\text{-}OMP}$ for EM was 1.86±0.572 while for PM it was 13.84± 2.504. $AUC_{OMP/OMP\text{-}S}$ for EM and PM was 9.74±4.98 and 10.38±4.08, respectively. Results showed that the C_{max} of OMP was double and the AUC_{∞} was triple in PM as compared to EM. On the other hand, C_{max} and AUC_{∞} of 5-OH-OMP were double in EM as compared to PM, and the C_{max} and AUC_{∞} of OMP-S in PM was triple as compared to EM. The PK parameters of OMP, 5-OH-OMP and OMP are presented in table 1, 2 and 3, respectively.

CYP2C19 Phenotype and genotype dilemma

In early days of OMP, there was no classification of EM or PM and all the subjects were used to be in a single group (Cederberg *et al*., 1993). In mid 1990s the subjects were used to be divided into EM or PM by analyzing the CYP2C19 gene from isolated DNA though polymerase chain reaction (PCR) or by determining the of AUC or C_{max} ratio of OMP to 5-OH-OMP. The phenotypic status is associated with CYP2C19 gene. The phenotypic classification on the basis of genotype is complex. So far about 19 variant alleles has been discovered(Yang and Lin, 2010). In the most common classification, the CYP2C19*1/*1 are classified as Hm EMs, CYP2C19*1/ *2 or *1/*3, are Ht EMs and CYP2C19*2/*2 or *2/*3 are PM(Uno *et al*., 2007, Hu *et al*., 2007). A study conducted in Indian Tamilian has predicted the phenotype according to the genotype as; EM (CYP2C19*1/*1 & CYP2C19*2/*17), Ht EM or intermediate metabolizer

(CYP2C19*1/*2), PM (CYP2C19*2/*2), Ht Ultra metabolizer (CY2C19*1/*17) and Ultra metabolizer (CYP2C19*17/*17) (Anichavezhi *et al.*, 2012). Another study conducted earlier by A. Li-Wan-Po *et al* states that CYP2C19*17 can be classified as Hm EM rather than as ultra rapid metabolizer and it has no utility in drugs with wide therapeutic window such as OMP(Li-Wan-Po *et al*., 2010). Similarly, a study conducted by R. M. Baldwin *et al* on HmCYP2C19*17 carriers suggests that this type of genotype had a higher metabolism of OMP than wild-type carriers (CYP2C19*1/*1) with higher average CL/F of OMP in homozygous *17 carriers. However, none of them had a more extensive omeprazole metabolism than the most extensive of the wild-type carriers(Baldwin *et al*., 2008). CYP2C19*1/*1 and CYP2C19*17/*17 carriers are all EM of OMP, the *17 carriers are relatively more EM, on the other hand the wild type carriers have a larger inter-individual variation (Rosenborg *et al*., 2008). In a Korean study, the subjects were divided into five groups on the basis of Haplotype analysis i.e., H1/H1, H2/H2, H1/H2, HI/H3 and H2/H3 where H3/H3 was absent in the subjects under study (Jin *et al.*, 2009). In another study in which Korean healthy volunteers were divided into different CYP2C19 genotype i.e. *1/*1, *1/*2, *1/*3,*1/*17,*2/*2,*2/*3,*3/*3,*2/*17 and *3/*17 using a multiplex PCR and pyrosequencing method (Kim *et al*., 2010). This is a broader classification of CYP2C19 genotyping and PK of OMP and its metabolites has not been evaluated in these genotypic groups. Despite of advances in genotyping, still other tools such as probit plots are used to assign different phenotype to individuals (Shilbayeh and Tutunji, 2006, Gonzalez *et al*., 2003).

DISCUSSION

The present study showed lower concentrations of 5-OH metabolites in PM while increased OMP concentration compared with the higher concentrations of 5-OH-OMP and lower concentrations of the parent drug in EM. Different studies have also classified the volunteers into PM and EM, the data of reported studies are depicted in table 1, 2&3 for OMP, 5-OH-OMP and OMP-S. It has been reported that 13-23% of the Asian subjects are PM of CYP2C19(Ferguson *et al*., 1998). In Asian population the two mutant alleles, CYP2C19*2 and CYP2C19*3 are responsible for the poor metabolism of OMP (Kaneko *et al*., 1999). In present study, the higher inter-individual variation in 5-OH-OMP concentrations is due to genotypic variation among individual.

The C_{max} values of OMP in present study are in accordance with other studies. The wide range for the C_{max} reflects great inter-individual differences in Pakistani population and the EM dominate compared with the PM. In the reported studies as shown in table 1, 2 and 3, when the C_{max} of 5-OH-OMP increases, the corresponding value of OMP-S decreases. This type of paradigm is followed in EM where the activity of the CYP2C19 is high. Whereas it is vice-versa in case of PM and shows increased level of OMP-S and decreased level of 5-OH-OMP. In present study the plasma level of 5-OH-OMP were higher than OMP-S indicating that most of the volunteers in present study are the EM of OMP.

The t_{max} of OMP in present study was 2.789±0.535h. In literature different values of t_{max} has been reported as shown in table 1. The present study reveals that the t_{max} was slightly higher than the reported values. It was in the range of 2-3h. The t_{max} for 5-OH-OMP varied from 1.75 to 3hs in the reported studies (table 2). Similarly the t_{max} for OMP-S also varied in the range of 2 to 3 table 3. The t_{max} for OMP-S also varies from individual to individual. Some studies also suggested wide variation between the t_{max} of these two metabolites. The present data of metabolites showed similar pattern as observed in a Chinese population table 2 & 3, but it does not necessarily mean that there is any genotypic co-relation between the two populations.

The AUC_{∞} of OMP in present study was slightly higher than the reported AUC_{∞}. The reason for this may be that the t_{max} was relatively longer for OMP, though the C_{max} values were not high enough however; it showed direct correlation with the plasma OMP concentration. The AUC of OMP different populations with different doses are shown in table 1.

The AUC_{∞} for OMP in present study was a slightly higher than the reported values (table 1), for 5-OH-OMP it was close to the reported values (table 2) and the extent of OMP-S formation was very small in comparison with the reported values (table 3). The higher values of OMP in the present study may be due to the decreased formation of OMP-S. Furthermore, in the 18EM volunteers the AUC_{∞} for the hydroxy metabolite was high while for OMP-S it was low. In case of PM, the OMP AUC_{∞} values were high, the AUC_{∞} decreased for 5-OH-OMP and increased for OMP-S.CL/F of OMP has been expressed in different units in literature as depicted in table1.The CL/F of OMP in the present study showed the same tendency as in the reported studies. The CL/F was high for EM as compared to PM. The mean half-life of OMP for EM was 1.1± 0.456h, which is in accordance to reported values as shown in table 3. In the reported studies, it can be observed that in some cases the elimination half-life was higher for ht EM while in some instances, it was higher for Hm EM (table 1). So, Ht or Hm EM is not a definitive factor responsible for an increase or decrease in elimination half-life. High elimination half-life have been reported for PM (Sohn *et al*., 1992b). In present study, the half-life of OMP for PM was higher as compared to EM and in accordance to the reported studies. The mean ± SD elimination half-life for 5-OH-OMP was 1.025±0 .585h, while the reported values for EM were in the range of 1.5-

2.86 h (table 2).The PM half-life decreased as compared to the reported studies, as result the C_{max} and [AUC] of 5-OH-OMP were relatively high as compared to reported studies. The elimination half life of OMP-S was slightly lower for EM as compared to the reported studies while it was higher for PM as compared to EM in the present study. The elimination half life of OMP-S in PM was less than that of reported studies table 3.

A comparison was made for the AUC of OMP, 5-OH-OMP and OMP-S among the different genotypic groups within different populations depicted in table 4. In all the studies, the AUC of OMP increased for Ht EM as compared to Hm EM. Similarly the AUC of PM for OMP increased as compared to the Hm or Ht EM. The AUC of 5-OH-OMP was reported to be greater for EM than PM with the exception of thee different studies in Japanese. The AUC of OMP-S increased for all the PM as compared to EM within all the studies as shown in the second part of table 4.

In the present study single dose OMP studies were considered only. It is evident from literature that multiple dose of OMP in PM does not alter the AUC significantly while in EM significant increase was observed (Andersson *et al*., 1998). Even after repeated doses the AUC of OMP was still significantly higher for PM than EM. Similarly the AUC of OMP-S was significantly different both after single and repeated doses while the 5-OH-OMP was not altered significantly(Yasuda *et al*., 1995).It is also evident from the repeated doses that rise in intragastric pH is dependent on OMP concentration i.e., pH is more effectively controlled in PM as compared to Ht EM and Hm EM, respectively (Sagar *et al*., 2000).The phenotyping is still a concern, in the present study as well as some reported studies non-genotypic approach has been adopted. This type of phenotyping has certain limitations for example, in one study, a subject showed high AUC of OMP as compared to the rest of 29 volunteers (Noubarani *et al*., 2012). In another study, one subject phenotyped as Ultra-rapid metabolizer was having high levels of 5-OH-OMP (4.552µg/mL)(Gonzalez *et al*., 2003). These statistical outliers can be given their identity by properly genotyping these subjects.

OMP is also metabolized by CYP3A4 to a lesser extent to OMP-S. In all the studies so far conducted the emphasis has been on OMP, 5-OH-OMP and the different genotypes of CYP2C19. Pharmacokinetic parameters of OMP-S have been reported in literature as shown in table 3 but little attention has been paid to CYP3A4 phenotyping or genotyping. There are evidences in literature where CYP3A4 inhibition or induction altered the PK of OMP and its metabolites. For instance, clarithromycin is metabolized in liver by CYP3A4 (Rodrigues *et al*., 1997). When clarithromycin co-administered with OMP, it significantly increased the plasma concentration of OMP while OMP-S was significantly decreased in hm EM, ht EM and PM. The plasma concentration of 5-OH-OMP increased for hm EM and ht EM significantly while decreased for the PM but not significantly (Furuta *et al*., 1999). In another study, CYP3A4 inducer carbamazepine decreased AUC of OMP and 5-OH-OMP not significantly while the increase in OMP-S was also not significant (Bertilsson *et al*., 1997). Diazepam like OMP is metabolized by CYP2C19 and CYP3A4. When Diazepam is administered with CYP3A4 inhibitor diltiazem, it alters the PK of diazepam irrespective of the CYP2C19 genotypes (Kosuge *et al*., 2001). CYP3A4 is the most abundant CYP450 in humans, shows high inter-individual variation in its activity due to polymorphism (Matsumura *et al*., 2004, Elens *et al*., 2011, Hsieh *et al*., 2001). No doubt, CYP2C19 is mainly responsible for metabolism of OMP but CYP3A4 genotyping should also be considered for OMP and other drugs which are metabolized by both CYP2C19 and CYP3A4.

CONCLUSION

In conclusion, the PK parameters such as C_{max}, AUC, and CL/F of OMP, 5-OH-OMP and OMP-S are in accordance to the previously reported studies. The concentration of 5-OH-OMP decreased in PM of CYP2C19 while OMP-S increased. In case of EM of CYP2C19 the concentration of 5-OH-OMP is higher while that of OMP-S is lower. It was concluded from this study as well as from the previous studies that in PM of CYP2C19 more drug is available for CYP3A4 to be metabolized. However, a correlation between CYP2C19 EM and PM activity with CYP3A4 needs to be established further. Furthermore, it is difficult to classify individuals into ultra rapid, intermediate, extensive or poor only from the genotype information though in literature this classification is available. OMP is a safe drug and well tolerated, the genotyping of CYP2C19 or CYP3A4 does not matter that much in its sole use. But OMP co-administration with other substrates of CYP2C19 for suspected drug-drug interaction requires genotyping but at this stage genotyping for dose selection is very difficult. Though extensive literature is available on the phenotyping and genotyping of CYP2C19 but to classify individuals into ultra-rapid metabolizer, EM or intermediate PM or PM on the basis of genotype is very difficult.

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