Disposition kinetics of omeprazole in healthy female volunteers in Pakistan

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Abstract*:* Omeprazole (OMP) a proton pump inhibitor is widely used to suppress gastric acid secretions of parietal cells of stomach and metabolized predominantly by CYP2C19. The objective of the present study was to investigate the pharmacokinetics and dosage regimen of OMP, after its single oral administration in eight healthy adult female subjects. Blood samples were collected at different time intervals after oral administration and their pH was measured. Plasma concentration of OMP was determined by high performance liquid chromatography (HPLC) system equipped with UV-visible Detector. The concentration versus time data was used to compute the pharmacokinetic parameters with the help of computer software programme MW/PHRAM APO version 3.02.Peak plasma concentration was (C_{max}) 0.38±0.04 µg/ml achieved at 2.07±0.22 hrs. The elimination half-life ($t_{1/2}\beta$) was1.82±0.42 hrs. Volume of distribution (Vd) in the present study was 0.40±0.07 l/kg with total body clearance (Cl_B) 0.19±0.02 l/hr/kg and area under the curve (AUC) 1.89 ±0.23 µg.hr/ml.The pharmacokinetic properties which are different from the literature after oral administration of 20 mg OMP in eight healthy female volunteers may be due to the variations of environment and genetic variation between Pakistan and drug manufacturing of foreign countries.

Keywords: Omeprazole, Pharmacokinetic parameters, peak plasma concentration, elimination half-life, volume of distribution.

INTRODUCTION

Omeprazole (OMP) is an effective and suitable proton pump inhibitor (PPI) which decreases acid production in the stomach. Primarily it is metabolized by hepatic cytochrome P450 isoenzyme CYP2C19 5-Hydroxy-Omeprazole (Ahmad *et al.,* 2011) but not metabolized significantly by CYP3A4 isoenzyme which is very important cytochrome isoenzyme responsible for metabolism of most drugs (Faruquee *et al.,* 2010). OMP is prescribed for various gastrointestinal diseases such as duodenal or gastric ulcer, gastroesophageal reflux disease, eradication of *Helicobacter pylori*, liver cirrhosis with peptic ulcer and Zollinger-Ellison syndrome (Kumar *et al.,* 2003; Hegar *et al.,* 2013)

Bioavailability of OMP is significantly impairs by food, therefore, patients are advised to take OMP with an empty stomach with a glass of water. Plasma protein binding of OMP is approximately 95% (Regardh *et al.,* 1985). Half-life ($T_{1/2}$) of OMP is less than one hr and it is cleared entirely from plasma within 3-4 hrs (Cederberg *et al.,* 1989).

In recent years the acid related problems have dramatically influenced by PPIs especially by OMP. In spite of this it is confirmed by various studies that PPIs have superior activity over H_2 -receptor antagonists (histamine). To treat the gastrointestinal problems related to more acid secretions it is necessary to maintain the intragastric pH more than 4 to heal the peptic lesions, which is well attained by PPIs. Polymorphism exhibited by P450A2C19, so wide variability is present in pharmacokinetics between inter-individuals. This enzyme is related to metabolism of PPIs. Hence, to explore variations in pharmacokinetics of PPIs in inter-individual is in interest (Rani & Padh, 2006).

Pakistan is importing finished and raw drugs for the veterinary as well as human health programs. Drug development protocols supported by preclinical as well as clinical analysis are under process in drug exporting countries where genome, body weight and animal and environmental conditions are different than the drug importing countries where these drugs are used ultimately. Several studies have indicated that pharmacokinetics behaviour, renal clearance, optimal dosage and urinary excretion of the analysed drugs are different under indigenous conditions when compared with drugs reported in the literature or in the products supplied by manufacturers. These variations describe the environmental influences on the genetics which are manifested by characteristics biochemical and physiological parameters which ultimately affect the bio disposition and fate of the drug in a population. Hence it is necessary that an optimal dosage regimen should be based on pharmacokinetic properties investigated in environment and species in which a drug is to be clinically employed (Javed *et al.,* 2003; Shahzadi *et al.,* 2011).

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In view of the preceding lines the present study will be designed for the investigation of pharmacokinetics of OMP in the local healthy female subjects.

MATERIALS AND METHODS

Study Design and volunteer selection

Complete information regarding experiment was provided to the volunteers both in verbal and in black and white. Each individual was furnished written consent before the start of the experiment. Eight healthy adult female subjects were selected to conduct the experiment at the Institute of Pharmacy, Physiology and Pharmacology, University of Agriculture, Faisalabad. The whole experiment was carried out in accordance with the guidelines of the directorate of graduate studies and institutional ethical committee. All the subjects, 24-28 years old (25.75 ± 0.314 years) having body weight 55-60 kg (55.125 ± 1.30 kg) were selected on the basis of their previous medical history. The subjects were asked to abstain from smoking, caffeinated beverages, chocolate and grape fruit prior and during the entire study as they interfere with cytochrome P450 enzymes which finally affect the drug metabolism. The subjects were given the same diet throughout the study period.

Drug administration

A commercial preparation of OMP, capsules Omega®, 20mg (Ferozsons Laboratories Limited, Rawalpindi, Pakistan) was used in the present study. After the overnight fasting, the selected female volunteers were given cap. Omega® 20mg orally.

Sample collection

Blood samples were collected in heparinized plastic centrifuge tubes. Prior to the drug administration, a control blood sample were also collected from every subject. Following administration of OMP, the blood samples were drawn at 0.5, 1, 1.5, 2, 3, 4, 6, 8 hrs. The pH of each sample was measured with pH meter. The blood samples were then centrifuged at 4000 rmp for 30 minutes. Plasma was separated from the blood samples and preserved at -20 ºC until analysis (Vlase *et al.,* 2010).

Extraction of drug from plasma

Plasma sample (0.5 ml) was mixed with 6 ml of 1:1 diethyl ether/dichloromethane (v/v) and 100 µL disodium hydrogen phosphate (0.1 M) in the centrifuge tubes. Above reaction mixture was shaken on vortex mixer for 5 minutes. Then this mixture was be centrifuged at 2000 revolutions per minute and organic phase was separated (Vlase *et al.,* 2010).

OMP analysis

HPLC technique equipped with Column C18 nova pack (75 mm x 4.6 mm, 3.5µm) and UV detector. The residue of OMP 50µl was dissolved in 200µl of mobile phase and a sample was injected into the chromatographic system at the flow rate of 1.5ml/min. This assay was carried out at 35°C. Mobile phase was consisting of acetonitrile: Monopotassium phosphate solution 30mM in ratio of 33:67 (V/V) of pH 6.5 (Vlase *et al.,* 2010).

Preparation of the standard solution

Stock solution of standard OMP was made in the drug free plasma samples collected before the drug administration as controlled samples having the concentrations of standard OMP 0.05-2.5 µg/ml shown in fig. 1.

Pharmacokinetic parameters

Pharmacokinetic calculations was computed with the computer programme MW/PHRAM APO version 3.02 by F. Rombout, in the cooperation with University Centre for Pharmacy, Department of Pharmacology and Therapeutics, University of Gronigen and Medi/Ware, copy right 1987-1991.

RESULTS

Pharmacokinetics

The pharmacokinetics is the mathematical description of the concentrations of the drug with the passage of time at different time intervals within the body. The concentration versus time data of 20 mg OMP in the 8 healthy female volunteers was plotted on semilogrithmic graph as shown in fig. 2. The two compartment open model was applied for present study data. The different pharmacokinetic parameters were determined through the computer programme MW/PHRAM APO version 3.02 by F. Rombout, a MEDI WARE product APO. The results with their mean values after the administration of 20 mg of OMP in eight healthy female volunteers of different pharmacokinetic parameters maximum plasma concentration (C_{max}), time to reach the maximum concentration (T_{max}), area under the curve (AUC), elimination half-life ($t_{1/2\beta}$), volume of distribution (Vd) and total body clearance (Cl_B) were 0.38±0.04 µg/ml, 2.07±0.22 hrs, 1.89±0.23µg.hr/ml, 1.82±0.42 hrs, 0.40± 0.07 l/kg and0.19±0.02 l/hr/kg respectively as shown in table 1.

DISCUSSION

Maximum concentration (C_{max})

The values of plasma concentration of OMP calculated at different time intervals it was 0.07±0.02µg/ml at 0.5 hr and its concentration increases with the passage of time and becomes the maximum after two hrs and 0.06±0.01 µg/ml at 8 hrs. C_{max} was recorded 0.38±0.04 µg/ml after 20mg single oral dose in female healthy volunteers.C_{max} was evaluated in adult male and female subjects was 0.35 µg/ml following the oral administration of 20 mg single dose of OMP (Farinha *et al.,* 1999) while C_{max} was

recorded 0.55µg/ml in another study in healthy volunteers (Dettmar *et al.,* 2006). The $C_{max}$was investigated 0.48± 0.28µg/ml with 20 mg of OMP on 34 healthy Mexican adults both in males and females after oral dosing of 20 mg (Poo *et al.,* 2008), while another study on Mexican healthy adults only in male subjects the C_{max} was0.35± 0.051 µg/ml (Flores-Murrieta *et al.*,2009) which were closer to our study. In Bangladeshi population C_{max} was studied of two different oral formulations of OMP (20mg) in male healthy subjects was 0.6±0.06 and 0.5±0.08µg/ml (Hasan *et al.,* 2009) which was slight higher than present study.

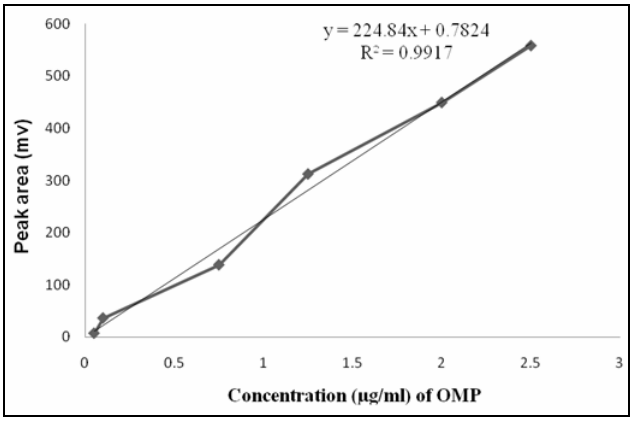

Fig. 1: Standard curve of OMP in plasma

Time for peak concentration (T_{max})

T_{max} of the present study and that of literature same in some studies and different from other studies. The difference might be due to genetic variations and indigenous conditions where it employed. The T_{max} of the present study was 2.07±0.22 hrs. T_{max} evaluated in healthy subjects was 2.33 hrs near to present study (Gunasekaran & Hassall, 2006). Another study was carried on two different formulations of OMP in healthy subjects with wash out period of 15 days and values evaluated were 0.91±0.4 and 2.0±0.9 hrs having non-significant results from present study (Poo *et al.,* 2008). Flores-Murrieta *et al., (*2009) and Mostafavi & Tavakoli (2004) worked on two different formulations of OMP withT_{max}2.63±0.24, 2.26±0.22 and 2.40±0.88 hrs, 1.75±0.63hrs respectively while in another study it was investigated as 2.37 hrs (Rani &Padh,2006) closer to present study.

Half-life ($T_{1/2\beta}$)

The half-life of single dose of OMP with mean was 1.82± 0.42 hrs. In one study $T_{1/2\,\beta}$ was calculated in two different formulations of OMP mean ± S.D was 1.82±0.68 h and 2.04±0.82 h in healthy subjects (Mostafavi & Tavakoli, 2004) which was similar to present study while in another study its value was determined as 2.76 hrs in poor metabolizers and 1.65 hrs for extensive metabolizers of OMP in healthy Indian subjects (Rani & Padh, 2006) which was slight different from present study. In one study its value was studied 0 .96 hrs in healthy subjects after oral administration (Vlase *et al.,* 2010) which was less than present study. The $T_{1/2\,\beta}$ was investigated 0.91± 0.4 hrs with 20 mg of OMP on 34 healthy Mexican adults both in males and females (Poo *et al.,* 2008) while in another study$T_{1/2\,\beta}$ of OMP evaluated in healthy female subjects was 2.3±0.8 hrs (Nazir *et al.,* 2013) with non-significant difference from present study. The half-life in Iranian healthy population was investigated 0.8 ± 0.3 hrs (Ala *et al.,* 2013) was less than present study. The half-life of the present study not significantly differs from some studies conducted on the healthy subjects of different countries and significantly differs from other studies. It might be due to genetic or geographical variations, which influence the biological and physiological factors which ultimately affects the half-life of the drug.

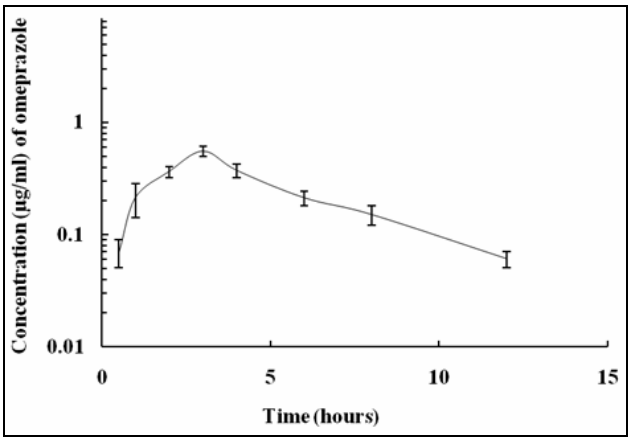

Fig. 2: Mean ± SD values of concentration (µg/ml) versus time after oral administration of 20 mg OMP in eight healthy female volunteers on semilogarithimic scale

Apparent volume of distribution (Vd)

The apparent Vd of the present study was investigated as 0.40±0.07 l/kg. The value of the Vd showed that OMP not widely distributed in the body organ of humans. The value of the Vd was studied 0.76±0.26 l/kg and 0.66± 0.25 l/kg in adults and children patients suffering from gastroesophageal reflux disease (GERD) respectively following (Marier *et al.,* 2004) was less than present study. The Vd was recorded 0.32±0.09 l/kg in healthy female subjects after the single dose of OMP 40 mg administration (Nazir *et al.,* 2013) was similar with higher dose. Ala *et al.,* (2013) investigated Vd in Iranian healthy population was 0.39±0.13 l/h/kg.

Total body clearance (Cl_B)

The Cl_B of the present study reported as 0.19±0.02 l/hr/kg. Marier *et al.,* (2004) evaluated was 0.62±0.27 l/hr/kgin healthy adults and 0.51±0.34 l/hr/kg in children suffered from GERD was higher from normal healthy female in present study. The value of the Cl_B was studied 0.11±0.02 l/h/kg in healthy female subjects (Nazir *et al.,* 2013) similar to our study. Variation in the total body

Table 1: Mean ± SD values of disposition pharmacokinetic parameters of OMP following oral administration of a single 20 mg dose in eight healthy female volunteers

Volunteer No.	C_{max} (µg/ml)	T_{max} (hr)	$T_{1/2\beta}$ (hr)	Vd (l/kg)	Cl_B (1/hr/kg)	AUC (µg.hr/ml)
1	0.32	2.36	1.43	0.47	0.21	1.72
2	0.35	2.32	1.30	0.37	0.20	1.82
3	0.35	2.18	1.29	0.40	0.21	1.75
4	0.42	1.84	1.74	0.33	0.17	1.86
5	0.40	2.12	2.24	0.54	0.17	2.20
6	0.37	1.77	2.16	0.39	0.23	1.58
7	0.41	1.89	2.21	0.35	0.18	2.01
8	0.44	2.11	2.16	0.34	0.17	2.23
Mean ± S.D	0.38 ± 0.04	2.07 ± 0.22	1.82 ± 0.42	0.40 ± 0.07	0.19 ± 0.02	1.89±0.23

clearance may be due to genetic variation or most probably attributes the different formulations used in the different studies.

Area under the curve (AUC)

Mean value of AUC was 1.89 ± 0.23 µg.hr/ml. AUC was investigated 2.05 µg.hr/ml in healthy volunteers for three days doses of 20 mg OMP (Dettmar *et al.,* 2006) was slight higher than present study. A study was conducted on the AUC investigation was 1.45µg.hr/ml on male healthy subjects with single dose of 20 mg of OMP (Gunasekaran & Hassall, 2006) was less than present study. A study was carried by Poo *et al.,* (2008) to determine the AUC on 34 healthy Mexican adult subjects was having less value than present study as 1.09±0.85 µg/ml/h. Hasan *et al.,* (2009) worked on AUC in healthy male subjects the value was 1.75±0.28 µg.hr/ml having non-significant difference from present study. The AUC was studied in 24 healthy subjects under fasting and fed state on two different products of 20 mg OMP, the values were 1.93±1.6 and 1.76±1.3µg.hr/l respectively (Vaz-da-Silva *et al.,* 2005). There is not significant differences are observed of area under the curve of the present study and that of different studies conducted in the healthy subjects.

CONCLUSIONS

The pharmacokinetic properties of OMP were not significantly differ from the literature but slight variation from the literature after oral administration of 20 mg OMP in eight healthy female volunteers may be due to the genetic and environmental variations. It is concluded from the study that dosage adjustment is required according to the kinetic behaviour of the drug under indigenous conditions.

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