



Research Article

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Gender based pharmacokinetics of omeprazole in healthy female subjects

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ABSTRACT

The objective of present study was to investigate the pharmacokinetics of omeprazole in healthy adult Pakistani female subjects on the basis of gender difference and ethnic diversity. Each of the twenty four volunteers was given 20 mg omeprazole capsules after the overnight fasting. Blood samples were obtained from them at regular intervals and analyzed by HPLC. Using the compartmental approach, plasma concentrations of omeprazole was used to compute the pharmacokinetic parameters. The value of maximum plasma conc. was $0.38 \pm 0.04 \mu\text{g/ml}$ at time 2.07 ± 0.22 hrs and area under the curve was $1.89 \pm 0.23 \mu\text{g.h/ml}$. Similarly absorption half life was 1.82 ± 0.42 hrs and elimination rate constant was $0.48 \pm 0.08 \text{ hr}^{-1}$. Volume of distribution was investigated as $0.39 \pm 0.07 \text{ l/kg}$ while total body clearance was measured as $0.19 \pm 0.02 \text{ l/hr/kg}$. On the other hand, mean residence time was 4.14 ± 0.32 hrs. The pharmacokinetic parameters of omeprazole in Pakistani females showed variations from previously determined in adults, so revealed that gender difference and ethnic diversity may exist for various physiological and molecular factors which disturb the pharmacokinetics of drug.

Keywords: Pharmacokinetics, Proton pump inhibitors, Omeprazole, Compartment open model, Gender difference

INTRODUCTION

Proton pump inhibitors (PPIs) are most extensively used therapeutic class for the treatment of peptic ulcer, helicobacter pylori infections, gastroesophageal reflux disease (GERD) and Zollinger – Ellison syndrome [1]. Omeprazole (5-methoxy-2-[[[4-methoxy-3, 5-dimethyl-2-pyridinyl] methyl] sulfonyl]-1H benzimidazole) is weak base and lipophilic with pKa 4 and 8.8 hence degraded in acid conditions [2]. Omeprazole binds with secretory sites of the gastric parietal cells of stomach and suppresses the H^+/K^+ ATPase enzyme (gastric acid pump) hence gastric acid secretions are inhibited [3]. Omeprazole shows the bioavailability of 20% to 30% after single dose and follows nonlinear pharmacokinetics [4]. Primarily it is metabolized by hepatic cytochrome P450 isoenzyme CYP2C19 to 5-Hydroxy-omeprazole [5; 6] but not metabolized significantly by CYP3A4 isoenzyme which is very important cytochrome isoenzyme responsible for metabolism of most drugs [7].

In the past, mostly women were excluded from the clinical pharmacokinetic studies due to the risk of childbearing potentials and the studies in which both women and men were included, results were grouped together and there was no analysis of gender difference [8]. Typically males have more body weight than females. The difference in body

weight can affect body water spaces, blood flow to the organs, organs functions and muscles mass thus can affect the pharmacokinetics of various drugs [9]. Similarly females have more adipose tissues than males which can also affect the apparent volume of distribution for various lipophilic drugs [10].

Gender difference is also related to steroid hormones level. The *in vivo* enzyme activity may also be related to gender difference because females have higher levels of progesterone than males [11]. Males have higher glomerular filtration rate (GFR) than females because GFR is in direct proportionality with body weight so renal clearance may also be affected by gender difference [9]. Similarly the level of plasma protein globulin may also be affected by gender difference so can make serious influence on the bindings of drugs [12]. It was reported that the emptying of solids from stomach is slow in females as compared to males [13]. There are large levels of CYP3A4 in gut [14] and the gender related difference in CYP3A4 levels could affect the bioavailability of drugs [11].

Pharmacokinetics of omeprazole has been determined by considering the ethnic diversity [15], genetic polymorphism [16] and population pharmacokinetics [17] but gender difference was not considered in these studies. To the best of our knowledge, there is no proper pharmacokinetics data of omeprazole in local females. Therefore, in Pakistani population there is need to evaluate the pharmacokinetics of omeprazole in healthy females. In view of the preceding lines the present study was designed for the investigation of pharmacokinetics of omeprazole in the local healthy adult female subjects.

EXPERIMENTAL SECTION

Subjects and study design

The study was single dosed, opened, single centered and parallel. Twenty four healthy adult female subjects were selected after the clearance of their previous medication history that they have not taken any medication from last two months, physically examined by a registered medical practitioner and all routine medical tests were conducted. Clinical tests results were normal in all female participants as shown in Table 1. All possible adverse effects and risk factors were informed to all subjects and other details related to the research. Each individual was furnished written consent before the start of the experiment. The experimental protocol was approved by the medical superintendent and chairman of the ethics committee of Aftab Cure Hospital and was conducted according to the declarations of Helsinki 1964 and guidelines of FDA for studying gender difference in clinical evaluation of drugs. The volunteers having obesity, intolerance to omeprazole and those donated blood prior to study initiation were not included in the study. The subjects were asked to abstain from smoking, caffeinated beverages, chocolates, grapes and cruciferous fruits 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 [18].

Drugs and chemicals

Reference standard powder of omeprazole was procured from a pharmaceutical company while omeprazole 20 mg capsules of local pharmaceutical company were purchased from the market. Disodium hydrogen phosphate, monopotassium phosphate solution, diethyl ether, acetonitrile, dichloromethane (E. Merk, Darmstadt, Germany) and deionized water were of HPLC grade.

Treatment protocol and blood sampling

After the overnight fasting, the female volunteers were given 20 mg omeprazole capsules orally. Blood samples were collected at 0 hr before medication and then at 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 10 hrs after medication. The pH of each sample was measured with pH meter. The blood samples were then centrifuged at 4000 rpm for 30 mins. Plasma was separated from the blood samples and preserved at -20 °C until analyzed.

Table 1: Clinical tests results of female participants

Tests	Units	Values
Hb	gm/dl	11.44±0.23
Serum bilirubin	mg/dl	0.57±0.4
Serum creatinine	mg/dl	0.69±0.02
Serum cholestrol	mg/dl	129.8±8.5
Serum triglyceride	mg/dl	81.63±9.32
HDL cholesterol	mg/dl	30.25±4.3
LDL cholesterol	mg/dl	69.88±4.3

Hb = hemoglobin, HDL = high density lipoproteins, LDL = low density lipoproteins.

Extraction of drug

Plasma samples were thawed and 0.5 ml of plasma was mixed with 6 ml of 1:1 diethyl ether/dichloromethane (v/v) and 100 μ l disodium hydrogen phosphate (0.1 M) in the centrifuge tubes. Above reaction mixture was shaken on vortex mixer for 5 mins. Then this mixture was centrifuged at 2000 revolutions per min and organic phase was evaporated by passing nitrogen stream at 35 °C and remaining residues were used [19].

HPLC analysis

Standards of omeprazole were made in the drug free plasma having the concentrations from 0.05 to 2.5 μ g/ml. The residue of omeprazole was dissolved in 200 μ l of mobile phase and then 20 μ l of sample was injected into the chromatographic system at the flow rate of 0.8 ml/min. This assay was carried out at 35°C temperature and 302 nm wavelengths. The reversed phase, isocratic high performance liquid chromatography system equipped with liquid chromatographic pump Sykam S1122, sample injector Sykam S5111, C18 column (Thermo, BDS Hypersil. 5 μ m; 4.6 mm \times 250 mm) and UV visible detector Sykam S3210 was used to analyze the omeprazole plasma concentrations. Mobile phase was made by mixing of acetonitrile : monopotassium phosphate buffer solution 30 mM in ratio of 33 : 67 (V/V) of pH 6.5 in water. The separation was achieved at the retention time of 17 mins and compared with standard. The plasma concentration versus time data of omeprazole was semilogarithmically prepared.

Pharmacokinetic analysis

The pharmacokinetic parameters through two compartment open model were computed with the computer program MW/PHRAM version 3.02 by F. Rombout, a MEDI WARE product APO pharmacological analysis, copy right 1987-1991.

Statistical analysis

The omeprazole concentration of plasma samples was tabulated and parameters were further subjected to parametric comparison between groups in MS-Excel statistical tools. Then mean \pm S.D and 95 % confidence limit was analyzed from the data.

RESULTS AND DISCUSSION

The plasma concentration time profile of omeprazole following 20 mg of dose in female volunteers is shown in Figure 1. From omeprazole plasma concentrations, the different pharmacokinetic parameters were measured as shown in Table 2.

The values for plasma concentration of omeprazole at different time intervals were determined following the oral administration of 20 mg omeprazole. The mean \pm SD (mean \pm standard deviation) of omeprazole at 0.5 hr was calculated as 0.07 ± 0.02 μ g/ml. With the passage of time it reached at maximum concentration of 0.55 ± 0.06 μ g/ml at 2 hrs and then declined with the passage of time and at last became 0.06 ± 0.01 μ g/ml at eight hrs. The minimum effective concentration of omeprazole is 0.05 μ g/ml [20]. Thus the omeprazole minimum effective concentration was maintained at eight hrs.

The value of C_{max} in present study was similar to 0.35 ± 0.051 μ g/ml in Mexican males [21] but was lower than 0.6 ± 0.06 μ g/ml determined in Bangladeshi males [22] and 0.48 ± 0.28 μ g/ml determined in another study on Mexican males [23]. These variations may be due gender related differences in the gut levels of CYP3A4 which could affect the systemic availability of drug. Similarly gastric acid secretions, gastric emptying time, intestinal transit rate and gastrointestinal blood flow are other factors which may affect the drug absorption regarding gender difference. Moreover, ethnic difference and biopharmaceutical factors like difference in excipients, dissolution rate, manufacturing processes and analytical techniques may also influence the plasma concentration of drug.

The T_{max} of the present study was nearly in agreement with previously determined 2.33 hrs in healthy subjects [24], 2.26 ± 0.22 hrs in healthy volunteers [21] and 2.0 ± 0.9 hrs determined in healthy subjects [23]. The variations in T_{max} are mostly due to slow dissolution rate of formulation or a decrease in absorption rate.

The value of $t_{1/2\beta}$ in present study was similar to $t_{1/2\beta}$ of 1.82 ± 0.68 hrs in healthy subjects [25] and to 2.3 ± 0.8 hrs in healthy females [26]. On the other hand, $t_{1/2\beta}$ in present study was much higher than 0.91 ± 0.4 hr in Mexican adult males and 0.7 ± 0.4 hr in Iranian healthy males [27]. This variation may be due to longer stay of drug in the

body or may be due to slow elimination of drug from the body in local females as compared to males in previous studies. Other factors which may influence pharmacokinetics parameters are ethnic diversity, physico – chemical properties of drug and formulations.

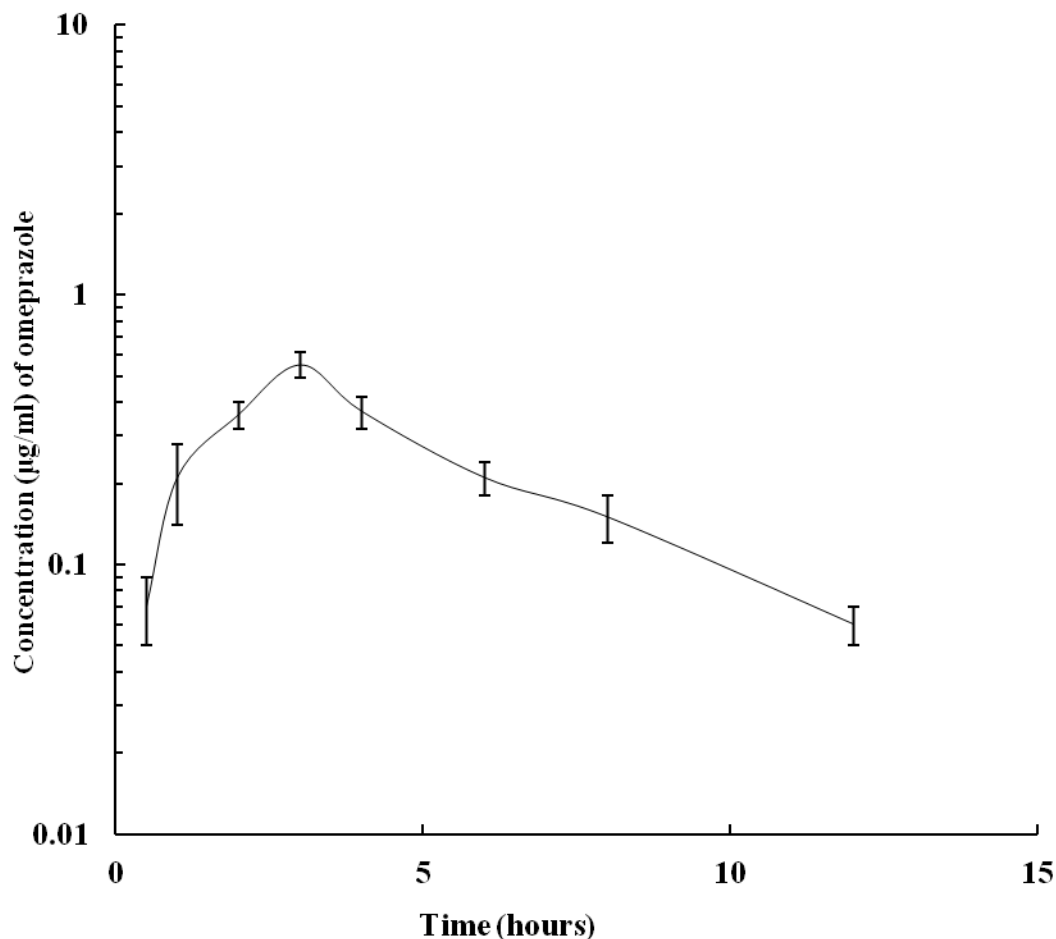


Figure 1.Mean \pm SD values of concentration ($\mu\text{g/ml}$) versus time after oral administration of 20 mg omeprazole in twenty four healthy female volunteers on semilogarithmic scale

In present study, V_d was in agreement with 0.32 ± 0.09 l/kg determined in healthy females [26] but less than 0.76 ± 0.26 l/kg determined in adults [28]. There was no proper determination of V_d in male volunteers alone in previous studies that's why proper description of the gender related differences in V_d was not possible. However these slight variations in currently studied V_d from previous studies reported in literature may be due to various factors which affect the drug distribution like plasma protein binding of drug, blood flow to various tissues, partition coefficient, lipid solubility of drug, pH and obesity [10].

The value of Cl_T in present study was nearly in agreement with 0.11 ± 0.02 l/hr/kg determined in healthy females [26] but was lower than 0.62 ± 0.27 l/hr/kg determined in adults [28]. Like V_d , Cl_T was also not determined properly in males alone previously so unable to justify variations on the basis of gender differences. Generally these variations may be due changes in blood flow to eliminating organs or inappropriate efficiency of drug eliminating organs.

The value of $AUC_{0 \text{ to } \infty}$ in present study was in accord with $2.05 \mu\text{g.hr/ml}$ determined in healthy volunteers [29] but was higher than $1.45 \mu\text{g.hr/ml}$ in male healthy subject [24], $1.09 \pm 0.85 \mu\text{g/hr/ml}$ in healthy Mexican adults [23] and $1.75 \pm 0.28 \mu\text{g.hr/ml}$ in healthy males [22]. This elevated $AUC_{0 \text{ to } \infty}$ may be due to slow elimination of drug from the body in females.

In present study, MRT was much higher than 2.2 hrs determined in healthy subjects at the dose of 20mg omeprazole in multiple unit pellet system formulation [30]. This higher value of MRT may be due to slow elimination of drug from eliminating organs which results in longer stay of drug in the body.

The value of K_{el} in present study was slightly lower than previously determined 0.753 hr^{-1} in healthy male subjects after the dose of 20mg omeprazole [19]. This variation may be due to ethnic diversity, renal functioning and low hepatic ratio.

Table 2: Pharmacokinetic parameters for a single oral dose of 20 mg omeprazole in healthy female volunteers

Parameter	Units	Mean \pm S.D.	95 % confidence limit
C_{max}	$\mu\text{g/ml}$	0.38 ± 0.04	0.35-0.42
T_{max}	hr	2.07 ± 0.22	1.89-2.25
K_{abs}	hr^{-1}	0.70 ± 0.16	0.56-0.83
$T_{1/2abs}$	hr	1.04 ± 0.24	0.83-1.23
A	$\mu\text{g/ml}$	0.40 ± 0.24	0.19-0.60
α	hr^{-1}	0.71 ± 0.29	0.46-0.96
$T_{1/2\alpha}$	hr	1.11 ± 0.46	0.73-1.50
B	$\mu\text{g/ml}$	0.51 ± 0.22	0.32-0.69
β	hr^{-1}	0.39 ± 0.09	0.31-0.47
$T_{1/2\beta}$	hr	1.82 ± 0.42	1.46-2.17
V_d	l/kg	0.39 ± 0.07	0.33-0.45
K_{el}	hr^{-1}	0.48 ± 0.08	0.41-0.55
K_{12}	hr^{-1}	0.77 ± 1.18	-0.21-1.77
K_{21}	hr^{-1}	0.57 ± 0.30	0.32-0.82
AUC	$\mu\text{g.hr/ml}$	1.89 ± 0.23	1.70-2.09
MRT	hr	4.14 ± 0.32	3.87-4.40
Cl_T	l/hr/kg	0.19 ± 0.02	0.17-0.21

C_{max} = maximum plasma concentration, T_{max} = time at which C_{max} achieved, K_{abs} = absorption rate constant, $T_{1/2abs}$ = absorption half life, A = the extrapolated zero time drug concentration of distribution phase, α = distribution rate constant, $T_{1/2\alpha}$ = distribution half life, B = extrapolated zero time drug concentration of elimination phase, β = overall elimination rate constant, $T_{1/2\beta}$ = elimination half life, V_d = volume of distribution, K_{el} = elimination rate constant, K_{12} = first order transfer rate constant for the transfer of drug from peripheral to central compartment, K_{21} = first order transfer rate constant for the transfer of drug from peripheral to central compartment, $AUC_{0 \text{ to } \infty}$ = area under the curve, MRT = mean residence time, Cl_T = total body clearance.

CONCLUSION

The results of present study have shown variations in pharmacokinetic parameters of omeprazole in females from previous studies in same and opposite genders. It was revealed that gender specific and ethnic differences have been identified for several physiological and molecular factors disturbing the pharmacokinetics of omeprazole in females. It is suggested that bioavailability and multiple dose pharmacokinetics of omeprazole should be determined in females versus male genders because single dose pharmacokinetics might not necessarily results in clinically significant gender effects in drug response.

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