Shahran Ala (BCPS) [1]
Fatemeh Zanad (Pharm D) [2]
Mohammad Reza Shiran (PhD) [*3]

1- Faculty of Pharmacy, Clinical Pharmacy, Mazandaran University of Medical Sciences, Sari, Mazandaran, Iran.
2- Research Center for Psychiatry and Behavioral Sciences, Faculty of Medicine, Mazandaran University of Medical Sciences and Health Services, Sari, Iran.
3- Department of Pharmacology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.

* Correspondence:
Mohammad Reza Shiran, Department of Pharmacology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.

E-mail: mr.shiran@gmail.com
Tel: 0098 151 3543081-3
Fax: 0098 151 3543081

Population pharmacokinetics of omeprazole in a random Iranian population

Abstract

Background: Omeprazole is metabolized predominantly by CYP2C19, a polymorphically expressed enzymes that show marked interindividual and interethnic variation. These variations cause a substantial differences that have been reported in the pharmacokinetics of omeprazole. The aim of the present study was to evaluate the pharmacokinetic parameters of omeprazole in a random Iranian population.

Methods: From the 20 subjects, only 17 healthy unrelated individuals of either sex (9 females age range 22-24 years) participated in the study. After an overnight fasting, a sample of blood was collected. The subjects received a single oral dose of 40 mg capsule of omeprazole (losec) and blood samples were taken up to 8 hours. Omeprazole was analyzed by the HPLC method and population pharmacokinetic analysis was performed using population pharmacokinetic modelling software P-Pharm.

Results: The mean value for apparent plasma clearance (CL/F) was 20.8 ± 6.9 (L.h^{-1}). The corresponding value for apparent volume of distribution (V/F), and $t_{1/2}$ beta were 21.6 ± 7.5 (L) and 0.8 ± 0.3 (h), respectively. A comparison of the weight normalized V/F and CL/F of omeprazole between males and females revealed that both parameters were significantly higher in females than males ($p \leq 0.03$).

Conclusion: These results show a substantial interindividual variability in omeprazole pharmacokinetics and this might affect the therapeutic effects of omeprazole as reported previously.

Keywords: Population pharmacokinetics, Omeprazole, Iranian

Proton pump inhibitors (PPIs) have influenced the management of acid-peptic disorders dramatically over the last years. Omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole are the most available PPIs on the market. Omeprazole selectively and irreversibly inhibit the gastric hydrogen/potassium adenosine triphosphatase (H$^+$/K$^+$-exchanging ATPase), part of the `proton pump' that performs the final step in the acid secretory process (1). The elimination of omeprazole is mostly due to hepatic metabolic clearance, followed by renal and fecal excretion of metabolites and hepatic impairment can result seven to nine fold increase in the area under the plasma concentration - time curve for all proton pump inhibitors (2-7). Omeprazole is metabolized predominantly by CYP 2C19 (responsible for 80% of clearance) with dose-dependent enzyme saturation, and has a lower affinity for CYP 3A4 (2, 8, 9). CYP2C19 is polymorphically expressed, and the individuals who are deficient in the major enzyme are poor metabolizers of omeprazole. This occurs in about 2-4% of Caucasians, 20% of Asians (e.g. Chinese, Japanese, and Koreans) and about 0.68-3% of Iranian (10-13). Furuta et al. have reported that the differences in CYP2C19 genotype has been recognized commonly as a major factor influencing the pharmacokinetics of omeprazole and therefore therapeutic outcomes various ethnic populations (14-16).

The aim of the present study was to characterize the pharmacokinetics of omeprazole after a single oral dose in healthy volunteers and to increase the understanding of the contribution of factors such as demographics to variability in the pharmacokinetics of omeprazole in a random Iranian population.

Methods

After the approval of the study by the Research Ethics Committee of Mazandaran University of Medical Sciences, from the 20 subjects, only 17 healthy unrelated individuals of either sex (9 females, age range 22-24 year) participated in the study after giving their written informed consent. The subjects with known HIV positive serology and who were taking known CYPs inhibitors or inducers were excluded from the study.

Chemicals and drugs: Omeprazole capsules (40 mg) were obtained from commercial Iranian suppliers. Omeprazole powder was a gift from the Temad drug company (Temad, Iran). The other chemicals were of HPLC or analytical grade and were purchased by commercial suppliers. Ultra-pure water was obtained using a Milli-Q water purification system.

Blood Sampling: Following a three-week abstinence from any medication, each subject underwent a short physical examination including vital signs and measurement of weight (kg) and biochemical tests to assess renal and hepatic functions. After an overnight fasting, a sample of blood (analyzed to confirm abstinence) was collected. The subjects received a single oral dose of 40 mg capsule of omeprazole (losec) with 250 ml water. They fasted over 2 h post-dose and peripheral venous blood samples (10 ml) were taken up to 8 hours. After centrifugation for 5-min (1000 g), the plasma samples were stored at -18°C pending assay.

Assay of Omeprazole: Plasma was treated according to the method of Lagerstrom et al. with some modifications (17). One ml of thawed sample was mixed with chloramphenicol as internal standard (IS) (50 µl of 200 µg/ml), 4 ml of methyl-tert butyle ether. The mixture was vortex-mixed for 15 min using a Multi-Tube Vortexer (Parsazma Laboratories, Iran). After centrifugation for 10 min at 3000 rpm the upper organic layer was transferred to a 10 ml conical glass tube and evaporated to dryness under a stream of nitrogen at room tempreature. The residue was dissolved in 150 µl of methanol and vortex-mixed for 30 sec and a 100 µl aliquot, injected onto the HPLC. The chromatographic separation of omeprazole was performed on a Luna C18 analytical column (3µM particle size, 4.60 mm×150 mm I.D.) (ODS), using an isocratic mobile phase of methanol-water (50:50, v/v), which was degassed by Knauer degaser, and delivered at a flow-rate of 1ml /min. The between-day coefficients of variation for assay of drug at a concentration range of 10- 2500 ng/mL were 8% or less**.**

Pharmacokinetics analysis: Pharmacokinetic analysis was carried out using population pharmacokinetic modelling software P-Pharm (P-Pharm., version 1.5. Inna Phase, Ceretil, France). Various population pharmacokinetic models were fitted to the data. The selection of the best model was based on the lowest value of the Akaike Information Criteria (AIC), visual inspection of residuals for systematic error and the predicted versus actual concentration plots. Initial estimates of the pharmacokinetic parameters were derived from values reported in the literature or using a simplex algorithm method. Statistical analysis was performed using SPSS for Windows (ver.12, SPSS Inc., Chicago, USA). For comparing non-paired clinical data, an independent sample t-test was used. In all cases, $p < 0.05$ was taken as statistically significant.

Results

Twenty healthy subjects were recruited and seventeen of them completed the study. A summary of their demographic characteristics is shown in table 1. There were no significant differences in the characteristic of age between males and females (p=0.73). The weight was significantly higher in males than in females (p=0.034).

Table 1. Characteristics of 17 subjects who completed the study

Variables	Sex	Mean (range)	SD	95% CI on the mean	
				Lower	Upper
Age (year)	F (9)	22.89 (21-25)	1.17	22.13	23.65
	M (8)	22.63 (19-25)	1.77	21.40	23.85
	All (17)	22.76 (19-25)	1.44	22.08	23.45
Weight (kg)	F (9)	55.75 (49-62)	5.85	50.01	61.49
	M (8)	74.13 (62-113)	16.38	62.77	85.48
	All (17)	68 (49-113)	16.19	58.84	77.16

Pharmacokinetic analysis: A one-compartment pharmacokinetic model with first-order input, first-order distributional rate constants and first-order elimination provided a significantly better fit to the concentration-time profiles compared than other models. A heteroscedastic error model ($1/y^2$) was more appropriate for all the analytes. A lognormal distribution best described the inter-subject variability in all population pharmacokinetic parameters. The population–derived Bayesian predicted vs observed total plasma concentrations and population mean and individual bayesian model fit to omeprazole concentrations are shown in figures 1 and 2, respectively.
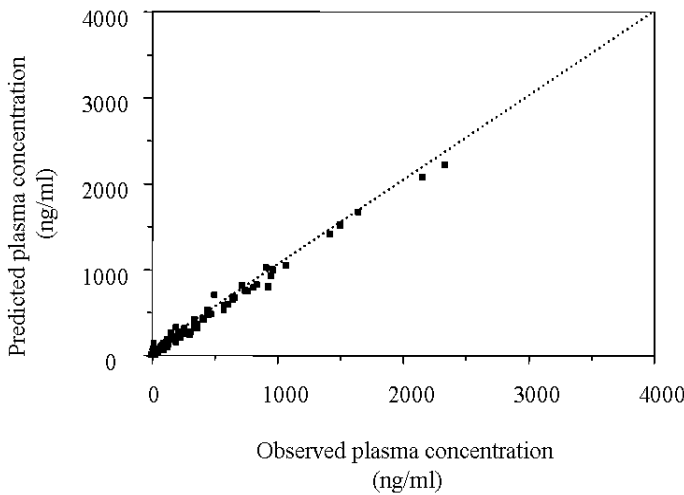

Figure 1. Population–derived Bayesian predicted vs observed total plasma concentrations after fitting of plasma concentration of omeprazole calculated from the best fitted model
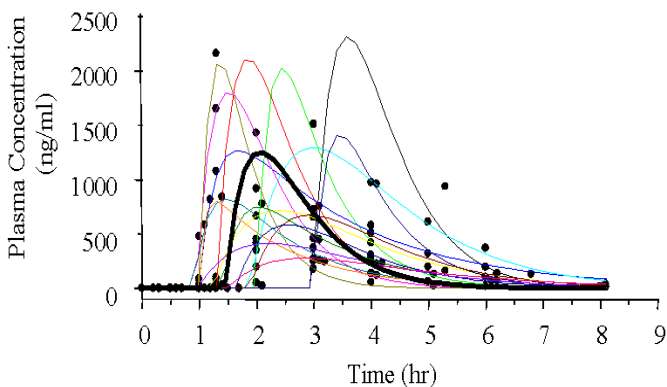

Figure 2. Population (bold line) and individual bayesian model fit to omeprazole concentrations

Pharmacokinetic parameter values for omeprazole: The mean disposition and absorption pharmacokinetic parameter values for omeprazole obtained from the best PK model are listed in tables 2 and 3, respectively.

Table 2. Mean disposition pharmacokinetic parameter values for omeprazole in 17 healthy subjects estimated from the best model.

PK parameters	Sex (N)	Mean	SD	95% CI on the mean	
				Lower	Upper
CL/F (L.h^{-1})	F (9)	21.7	4.8	18.0	25.4
	M (8)	19.7	9.0	12.2	27.3
	All (17)	20.8	6.9	17.2	24.3
V/F (L)	F (9)	25.7	6.2	21.0	30.5
	M (8)	17.0	6.3	11.7	22.3
	All (17)	21.6	7.5	17.7	25.5
$t_{1/2}$ beta (h)	F (9)	0.8	0.1	0.7	0.9
	M (8)	0.7	0.4	0.3	1.1
	All (17)	0.8	0.3	0.6	0.9

Table 3. Mean absorption pharmacokinetic parameter values for omeprazole in 17 healthy subjects estimated from the best model

PK parameters	Sex (N)	Mean	SD	95% CI on the mean	
				Lower	Upper
Ka (h^{-1})	F (9)	1.5	1.0	0.8	2.3
	M (8)	1.6	1.4	0.4	2.8
	All (17)	1.6	1.2	1.0	2.2
Lag time (h)	F (9)	1.3	0.4	1.1	1.6
	M (8)	1.5	0.7	0.9	2.1
	All (17)	1.4	0.5	1.1	1.7

With the exception of the CL/F and V/F, there was no significant difference in pharmacokinetic parameters between males and females. A comparison of the weight normalized V/F and CL/F of omeprazole between males and females is shown in figure 3. The CL/F and V/F of omeprazole were significantly higher in females than males ($p \leq 0.03$; figure 3).
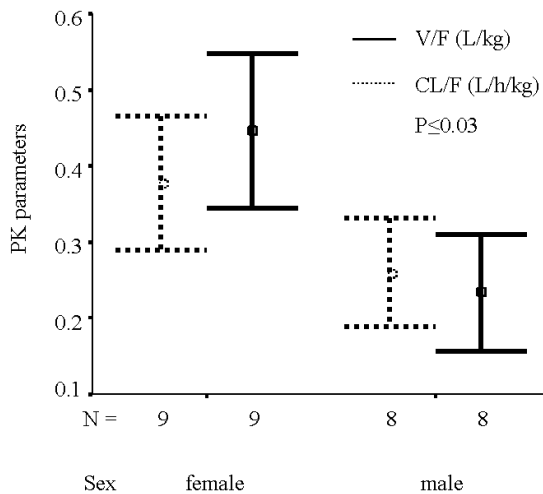
Figure 3. A comparison of the weight normalized V/F (solid lines) and CL/F (dashed lines) of omeprazole between males and females subjects. The CL/F and V/F of omeprazole were significantly higher in females than males (p≤0.03). The rectangles represent the mean values and the bar lines indicate 95 % CI on the mean.

Discussion

Omeprazole and other proton pump inhibitors are metabolized in the liver by P450 cytochromes and this subject has been reviewed previously (9, 18-20). Omeprazole is metabolized mainly by CYP 2C19 (responsible for 80% of clearance) with dose-dependent enzyme saturation, and has a lower afinity for CYP 3A4, which may function as a high capacity enzyme that prevents very high omeprazole concentrations (2, 8, 9). The CYP2C19 is polymorphically expressed, and the individuals who are deficient in the major enzyme are poor metabolisers of omeprazole. This occurs in about 2-4% of Caucasians, 20% of Asians (e.g. Chinese, Japanese, and Koreans) (10) and about 0.68-3% of Iranian. (11-13).

Therefore, the rate of apparent clearance of omeprazole has been reported to be relatively variable with values ranging from 3-67 (L. h^{-1}) (21). The observed mean values of apparent clearance of omeprazole in the present study was comparable with the previous reports (9, 21-24). However, the results of the present study showed a substantial interindividual variability in omeprazole pharmacokinetics that might affect the therapeutic effects of omeprazole as reported previously (14, 16).

The observed mean values of CL/F of omeprazole in the present study was comparable with those reported in the litrature (9, 21-24), however, our results showed that females had significantly greater weight normalized apparent clearance values than men.

This might be due to the differences in CYP3A4 expression between the two sexes. Recently, Wolbold et al. (25) have shown that CYP3A4 is differentially expressed between the two sexes, with women expressing about twice the amount of the enzyme on the basis of microsomal protein content. Thus, women might need higher doses of omeprazole compared to men to achieve the same therapeutic outcome.

The results of the present study also showed that women had significantly greater weight normalized apparent volume of distribution values than men. A possible explanation for these findings is that, although men had greater mean body weight (resulting in a higher volume of distribution), fat represents a greater proportion of body weight in female subjects, which would result in a greater mean volume of distribution per kg body weight. It also might be due to the differences in plasma protein binding observed between males and females.

Acknowledgments

Conflic of Interest: There is no conflict of interest.

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