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Oral Pharmacokinetics of Rabeprazole in Local Healthy Male Volunteers of Pakistan

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Abstract

The objective of present study was to investigate the pharmacokinetics of single orally administered 20 mg rabeprazole in local healthy subjects of Pakistan. Blood samples were collected at 0 hour before medication and at 0.5 to 12 hours post medication. Rabeprazole plasma concentration levels were determined by high performance liquid chromatography system with ultraviolet detector (HPLC-UV). Plasma concentration versus time data was used to compute the pharmacokinetic parameters with help of computer pharmacokinetic software APO, MW/PHRAM version 3.02 as mean ± SD. The value of maximum plasma concentration (C_{max}) was 0.18 ± 0.03 µg/mL at time 3.30 ± 0.60 h (T_{max}). The elimination half-life ($t_{1/2\beta}$) was 2.29 ± 0.42 h with elimination rate constant (β) as 0.31 ± 0.07 h^{-1}. The volume of distribution (V_d) was 0.98 ± 0.18 L/kg. Total body clearance (CL_B) was measured as 0.30 ± 0.08 L/h/kg. The decrease in $C_{max,}$ CL_B and an increase in $t_{1/2}$ and AUC indicated that change in pharmacokinetics of rabeprazole in local population under local indigenous conditions might be due to ethnic diversity, environmental and genetic influences.

Keywords: Pharmacokinetics, Proton pump inhibitors, Plasma concentration

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1. Introduction

The prescriptions of proton pump inhibitors have been increased in children during the last three decades. Rabeprazole, a third proton pump inhibitor was introduced in 1986 as a potent gastric acid inhibitor (Barron *et al*. 2007). The FDA approved indications of rabeprazole are esophagitis, gastroesophageal reflux disease, hyperacidity and peptic ulcer associated with *Helicobacter pylori* infections in triple regimen therapy with amoxicillin and clarithromycin (Sachs *et al*. 2006). Rabeprazole covalently binds and inhibits H^+ - K^+ ATPase enzyme in the parietal cells of stomach, as a result acid secretions are suppressed (Alia and Frank 2009). Rabeprazole has the strongest and fastest onset of action among all proton pump inhibitors that is 5 minutes (Besancon *et al*. 1997). Rabeprazole has a highest pK_a value of 5 among all proton pump inhibitors (Kromer *et al*. 1998). Similarly, a hypothesis was proposed that this high pH of rabeprazole might be responsible for suppressing the acid secretions for 24 hours after its administration as compared to other proton pump inhibitors (Pantoflickova *et al*. 2003).

Rabeprazole is unstable in acidic environment that's why it is formulated in enteric coated dosage form. After oral administration, it is relatively quickly absorbed as maximal plasma concentration (C_{max}) is reached between 2.8 and 5.1 ug/mL after dose. The pharmacokinetics of the molecule has been shown to be linear in the range of 10–80 mg and the overall bioavailability is 52% after administering 20 mg rabeprazole. Maximum plasma concentration and area under the curve (AUC) of the plasma concentrations are dose dependent and are proportional to the dose ingested while time to reach maximum plasma concentration (t_{max})

and half-life $t_{1/2}$ are dose independent. These parameters show that rabeprazole does not undergo the first-pass metabolism and it can be absorbed even in high doses (Swan *et al*. 1999). Rabeprazole does not accumulate on repeated administration as the elimination half-life is about 1 h after single and 1.5- 2 hrs after multiple administrations (Thjodleifsson and Cockburn, 1999; Fuhr and Jetter, 2002). The renal clearance of rabeprazole was ranged from 4.37 to 8.40 mL/min/kg (Yasuda *et al*., 1994)..

All other proton pump inhibitors such as omeprazole, lansoprazole, esomeprazole and pantoprazole are metabolized mainly by a cytochrome P450 isoenzyme CYP2C19 in the liver but rabeprazole is metabolized mainly through a nonenzymatic pathway to its major metabolite rabeprazole thioether and to a much lesser extent, by the cytochrome P450 isoenzymes CYP2C19 into demethylated rabeprazole and by CYP3A4 into rabeprazole sulfone. Rabeprazole pharmacokinetic data has been reported in previous studies in different populations (Anastacio *et al*. 1999, James *et al*. 2007, Horai *et al*. 2002 and Pete *et al*. 2011). However, pharmacokinetic data of rabeprazole in local Pakistani population is not available in literature. The aim of current piece of work was to determine pharmacokinetic parameters of rabeprazole in local healthy population of Pakistan using compartmental analysis and to detect pharmacokinetics differences under local indigenous conditions.

2. Material and Methods

Subjects and study design

The study design was single dose, parallel, open labeled and single centered. Twelve healthy male subjects, 15-18 years old having body weight 35.125 ±3.68 kg (Mean ± SD) were selected to conduct the study at the Institute of Pharmacy, Physiology and Pharmacology, University of Agriculture, Faisalabad. Each subject was furnished with written consent before the start of the experiment. All the subjects were selected on the basis of their previous medical history and physical examination. It was made sure with the help of diagnostic clinical tests that all subjects were Hepatitis B and Hepatitis C negative.

The subjects were asked to abstain from smoking, caffeinated beverages, chocolate, 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. The study protocol was approved from the Director Graduate Studies (Institutional Ethical Committee), University of Agriculture, Faisalabad, Pakistan and was conducted in accordance with the 1964 declaration of Helsinki and its later amendments. Reference standard powder of rabeprazole was procured from local pharmaceutical company. Rabixin® capsules (Rabeprazole 20 mg capsules) of Genetics Pharmaceuticals, Karachi, Pakistan were procured from the local market.

Blood Sampling

After the overnight fasting, the selected volunteers were given 20 mg Rabixin® capsules orally. Blood samples were collected in heparinised plastic centrifuge tubes at 0 h before medication and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h post medication. The pH of each sample was measured with pH meter. The blood samples were then centrifuged at 4000 rpm for 30 minutes. Plasma was separated from the blood samples and preserved at -30 ºC until analysis (Mikiko *et al*. 2006).

Standard solution and standard curve

Working standards having rabeprazole concentrations 0.05 – 10 µg/mL were prepared from the stock solution of 1 mg/mL. These concentrations were prepared in methanol with 0.1% diethyl amine. Each of these concentration solutions was injected to the reversed phase, isocratic high performance liquid chromatography (HPLC) system at the flow rate of 0.8 mL/min. The injection volume was 20 µL. The mobile phase consisted of phosphate buffer (0.05 M, pH = 7.0) and acetonitrile (50:50 v/v). The HPLC system was equipped with Column C18 (Thermo, BDS Hypersil. 5 µm; 4.6 mm × 250 mm) and ultraviolet detector. The detection was carried out at 35°C temperature and at 288nm wavelength. Peak areas were recorded at the retention time of 5.9 minutes. Concentrations versus peak areas data were plotted on a graph to construct the calibration curve. The curve was linear over the range of 0.05 - 10 µg/mL (R^2 = 0.9992 = 1635.2x-21204y) as shown in Fig. 1**.**

Sample preparation and analysis

Plasma sample of 1 mL was first alkalinised with 1mL of phosphate buffer (0.05 M, pH = 10.40). Then plasma was extracted with 5 mL of diethyl ether-dichloromethane (90:10 v/v). The organic phase was separated and evaporated at 40 ºC to dryness in oven. Drug residues were dissolved into 100 µL of methanol having 0.1% diethyl amine and were injected to the HPLC system. Rabeprazole in samples was compared with rabeprazole working standard. The peaks obtained on the chromatograms of plasma samples were similar to the peak of rabeprazole (working standard) at the retention time of 5.9 minutes.

Pharmacokinetic analysis

Concentration verses time data was utilized for the calculation of pharmacokinetics parameters with the help of computer software program APO pharmacological analysis MW/PHRAM version 3.02 by F. Rombout, (Holland, copyright 1987-1991) through one compartment open model approach.

Statistical analyses

Mean ± SD as well as 95% confidence interval was calculated for each parameter with the help of computer software SPSS (Statistical Package for the Social Scientists) 13.0 as shown in Table-1.

Results and Discussion

Standard curve showing the good linearity over a range of rabeprazole concentrations is present in Fig. 1. The mean ± SD plasma concentration time profile of rabeprazole following 20 mg of dose is shown in Fig. 2. All the pharmacokinetic parameters were determined using one compartment open model approach. The results and mean ± S.D of various parameters are given in the Table-1. There was no abnormality in any subject during the study period as shown by the physical examination. No change was observed in heart rate and blood pressure.

Pharmacokinetic parameters

Maximum plasma drug concentration (C_{max})

In present study, C_{max} was 0.18 ± 0.03 µg/mL (Mean ± SD) for local population. This value of C_{max} was less from previously reported values as 0.401 µg/mL (Mean ± SD) (Anastacio *et al*. 1999), 557 ± 109 ng/mL (Mean ± SE) (James *et al*. 2007) but was close to the values as 204 ± 106 ng/mL (Mean ± SD) (Pete *et al*. 2011). This variation in values may be due to ethnic differences in drug absorption factors like active transport, efflux by P-glycoprotein, gut metabolism by CYP3A4 (Xie *et al*. 2001) and polymorphic CYP2C19 genotypes (Poolsup *et al*. 2000). That's why; it was reported that the pharmacokinetics of rabeprazole is dependent on polymorphic CYP2C19 genotype (Horai *et al*. 2002). Other possible factors of variation in the values of C_{max} are differences in excipients, manufacture process of the formulations and analytical techniques because it was reported that LCMS/MS is more sensitive than HPLC for drugs analysis (Lohitnavy *et al*. 2004).

Table 1: Pharmacokinetic parameters of rabeprazole following one compartment model

Parameters	C_{max} (µg/mL)	t_{max} (h)	$t_{½\beta}$ (h)	β (h^{-1})	V_d (L/Kg)	Cl_B (L/h/Kg)	AUC (µg.h/mL)	MRT (h)
Mean± SD	0.18 ± 0.03	3.30 ± 0.60	2.29 ± 0.42	0.31 ± 0.07	0.98 ± 0.18	0.30 ± 0.08	1.67 ± 0.45	6.60 ± 1.21
95%CI	0.15-0.21	2.7-3.9	1.87-2.71	0.24 - 0.38	0.8-1.16	0.22-0.38	1.22-2.12	5.39-7.81

SD = Standard deviation, **CI** = Confidence interval, **C_{max}** = maximum plasma concentration, **t_{max}** = time at which C_{max} achieved, **$t_{1/2\beta}$** = elimination half-life, **V_d** = volume of distribution, **$AUC_{0\ to\ \infty}$** = area under the curve, **MRT** = mean residence time, **Cl_B** = total body clearance

Time of peak plasma concentration (t_{max})

The value for t_{max} in present study was 3.30 ± 0.60 h (Mean ± SD). This value of t_{max} is in close agreement with previously reported values as 3.7 ± 1.0 h (Mean ± SD) (Anastacio *et al*. 1999), 3.9 ± 0.20 h (Mean ± SE) (James *et al*. 2007) but slightly differs from value in other study as 2.43 ± 1.43 h (Mean ± SD) (Pete *et al*. 2011).

Elimination half-life ($t_{1/2\beta}$)

In this study, the value of $t_{1/2\beta}$ was 2.29 ± 0.42 h (Mean ± SD). This value of $t_{1/2\beta}$ is different from previously reported studies as 1.7 ±1.7 h (Mean ± SD) (Anastacio *et al*. 1999), 1.04 ± 0.27 h (Mean ± SE) (James *et al*. 2007) and 1.9 ± 1.0 h (Mean ± SD) (Pete *et al*. 2011). This might be due to longer stay of drug in the body or due to slow elimination from the body. Possibility for this variation is due to genetic difference in polymorphic CYP2C19 genotypes in local population and previously studied Caucasians as reported for omeprazole (Caraco *et al*. 1996). Other factors may be physicochemical properties of drug and formulation (Mahmood *et al*. 2011). The value of elimination rate constant (β) was 0.31 ± 0.07 h^{-1}(Mean ± SD) in current study. The β was not calculated in previous studies for rabeprazole.

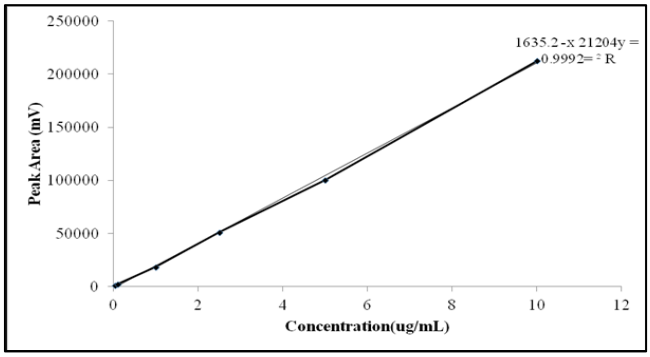

Figure 1: ***Standard Curve of Rabeprazole***

Volume of distribution (V_d)

In current study, V_d for local volunteers was 0.98 ± 0.18 L/kg (Mean ± SD). It was not reported in previous studies but preclinical report of V_d for rabeprazole was found as 0.37 L/kg. This higher value of V_d may be due to difference in concentration of albumin and α_1 – acid glycoprotein (Kiman *et al*. 2004), flow of the blood to the tissues, disease condition, age and genetic variability (Ritschel and Kearns, 2004). It seems that in the local population of Pakistan, a relatively major portion of administered dose is distributed into extracellular space and tissues and caution is therefore required in the selection of dose to overcome any side effects due to accumulation of drug in the body on long term use of the drug.

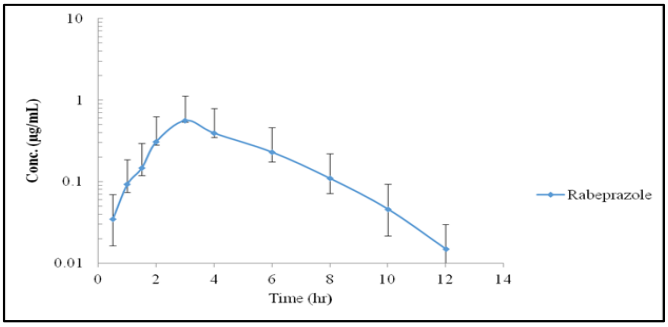

Figure 2: Concentration (µg/mL) versus time after oral administration of 20 mg rabeprazole in healthy male subjects on semilogarithimic scale

Renal clearance (CL_B)

In present study, the value of CL_B for local population was 0.30 ± 0.08 L/h/Kg (Mean ± SD). This observed value is lower than previously reported value as 550 ± 260 mL/min (Mean ± SD) (Anastacio *et al*. 1999). The difference may be due to ethnic diversity in polymorphic CYP2C19 genotypes as reported that CL_B of omeprazole was about 43% higher in American Caucasians CYP2C19 EMs genotypes than the Chinese CYP2C19 EMs genotypes (Caraco *et al*., 1996). Other physiological factors may include such as a decrease in the flow of blood to the eliminating organ or inefficiency of organ (Welling *et al*. 2006).

Area under the curve ($AUC_{0\ to\ \infty}$)

In current study, value of $AUC_{0\ to\ \infty}$ was 1.67 ± 0.45 µg.h/mL (Mean ± SD). This value is higher from previously reported values as 809 ± 544 ng.h/mL (Mean ± SD) (Anastacio *et al*. 1999), 557.8 ± 109.8 ng.h/mL (Mean ± SE) (James *et al*. 2007) and 785 ± 526 ng.h/mL (Mean ± SD) (Pete *et al*. 2011). This difference may be due to interethnic variations in metabolism by CYP3A4 and CYP2C19 isoenzymes as was observed between Koreans and Caucasians for Nifedipine (Yu *et al*. 2001).

Mean residence time (MRT)

MRT of orally administered rabeprazole in present study was 6.60 ± 1.21 h. MRT was not calculated for rabeprazole in previous studies.

Conclusion:

Present study demonstrates that administration of a single oral dose of 20 mg rabeprazole in Pakistani healthy subjects showed a decrease in C_{max}, CL_B and an increase in $t_{1/2}$ and $AUC_{0-\infty}$. MRT and β were also calculated for rabeprazole that were not available in previous literature. It can be concluded from present study that rabeprazole kinetics exhibited variations in Pakistani population as compared to those reported in literature due to different genetic morphology, local environmental conditions and dietary habits...

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