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Pharmacokinetics and urinary excretion of eprosartan in Chinese healthy volunteers of different gender

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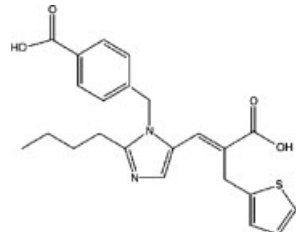
The study aims to evaluate the pharmacokinetics and urinary excretion of eprosartan in Chinese healthy volunteers and to study the effect of gender on pharmacokinetics of eprosartan. Twenty healthy volunteers (ten men and ten women) were recruited for an open trial and received a single dose of 600 mg eprosartan. Using a validated LC/MS/MS method, plasma and urinary concentrations of eprosartan were defermined. The following pharmacokinetic parameters were elucidated after administration: the area under the plasma concentration versus time curve from 0 to 32 h ($AUC_{0-32\,h}$) 14818.75 ± 7312.11 ng · h/mL, the area under the plasma concentration versus time curve from 0 to infinite ($AUC_{0-\infty}$) 15081.62 ± 7379.63 ng · h/mL, peak plasma concentration (C_{max}) 3664.25 ± 1653.94 ng · h/mL, time to C_{max} (T_{max}) 1.63 ± 0.46 h, elimination half-life ($t_{1/2}$) 8.03 ± 4.04 h, apparent clearance (CL/F) 47.84 ± 19.21 L/h, apparent volume of distribution of the central compartment (V/F) 537.21 ± 287.91 L, renal clearance (CL_r) 1.33 ± 0.41 L/h, amount of unchanged eprosartan excreted into urine 18.44 ± 6.43 mg and fraction of unchanged eprosartan excreted into urine 3.07 ± 1.07 %. Our results also indicated that no gender differences were observed in the pharmacokinetics of eprosartan in Chinese healthy volunteers.

1. Introduction

Eprosartan mesylate is a highly selective non-peptide, nobiphenyl angiotensis II receptor antagonist that has been developed for the treatment of hypertension (McClella and Bolfour 1999).



The absolute bioavailability of eprosartan is about 13% (Tenero et al. 1998a), due to poor oral absorption. Peak plasma concentrations of eprosartan were observed one to two hours after an oral dose in the fasted state (Tenero et al. 1998a). Plasma concentrations of eprosartan increased in a dose dependent manner for doses between 100 and 800 mg, in a slightly less than dose proportional manner for higher doses (Chapelsky et al. 1998). The terminal elimination half-life of eprosartan is typically 5 to 9 h following oral administration. Administration of eprosartan with food delayed absorption with minor changes (< 25%) observed in C_{max} and AUC which was unlikely to be of clinical consequence (Tenero et al. 1998a). Plasma protein binding of eprosartan is approximately 98% and constant over the concentration range achieved with therapeutic doses (Martin et al. 1998). After intravenous administration of eprosartan total plasma clearance is low (130 mL/min), and the volume of distribution of eprosartan was small (13 L) (Tenero et al. 1998a).

The aim of the study was to evaluate basic pharmacokinetics parametes of eprosartan 600 mg and study the effect of gender on pharmacokinetics of eprosartan in healthy Chinese subjects.

2. Investigations and results

2.1. Pharmacokinetic results and urinary excretion

Non-compartimental pharmacokinetic (PK) analysis was used to analyze plasma drug concentration-time data. The following pharmacokinetic parameters were elucidated: the area under the plasma concentration versus time curve from 0 to 32 h ($AUC_{0-32\,h}$) 14818.75 ± 7312.11 ng · h/mL, the area under the plasma concentration versus time curve from 0 to infinite ($AUC_{0-\infty}$) 15081.62 ± 7379.63 ng · h/mL, peak plasma concentration (C_{max}) 3664.25 ± 1653.94 ng · h/mL, time to C_{max} (T_{max}) 1.63 ± 0.46 h, elimination half-life ($t_{1/2}$) 8.03 ± 4.04 h, apparent clearance (CL/F) 47.84 ± 19.21 L/h, apparent volume of distribution of the central compartment (V/F) 537.21 ± 287.91 L, renal clearance (CLr) 1.33 ± 0.41 L/h, amount of unchanged epro-

Table: Pharmacokinetic/statistical results (mean ± SD) of eprosartan in healthy subjects following a single dose of eprosartan 600 mg; all subjects (n = 20)

Parameters	Overall (arithmetic means ± SD)	Male (arithmetic means ± SD, n = 10)	Female (arithmetic means ± SD, n = 10)	Male versus female(P)
AUC_{0-t} (ng · h/ml)	14818.75 ± 7312.11	12620.44 ± 8004.25	17017.06 ± 6169.88	0.093[b]
$AUC_{0-\infty}$ (ng · h/ml)	15081.62 ± 7379.63	12778.21 ± 7969.59	17385.03 ± 6297.95	0.088[b]
C_{max} (ng/ml)	3664.25 ± 1653.94	3193.5 ± 1740.16	4135.00 ± 1501.46	0.129[b]
T_{max} (h)	1.63 ± 0.46	1.75 ± 0.49	1.50 ± 0.41	0.216[c]
$T_{1/2}$ (h)	8.03 ± 4.04	6.86 ± 3.95	9.20 ± 3.97	0.204[a]
K_e (1/h)	0.11 ± 0.05	0.12 ± 0.05	0.09 ± 0.03	0.057[a]
V/F (L)	537.21 ± 287.91	564.27 ± 343.76	510.14 ± 234.95	0.686[a]
Cl/F (mL/min)	797.37 ± 320.16	917.00 ± 253.69	677.74 ± 346.75	0.095[a]
Clr/F (mL/min)	22.14 ± 6.0	22.94 ± 8.56	21.34 ± 4.79	0.609[a]
Ae (mg)	18.44 ± 6.43	15.74 ± 5.62	21.14 ± 6.28	0.058[a]
fe (%)	3.07 ± 1.07	2.62 ± 0.94	3.52 ± 1.07	0.058[a]

a: ANOVA
b: Using log-transformation of the data before ANOVA
c: Nonparametric Test

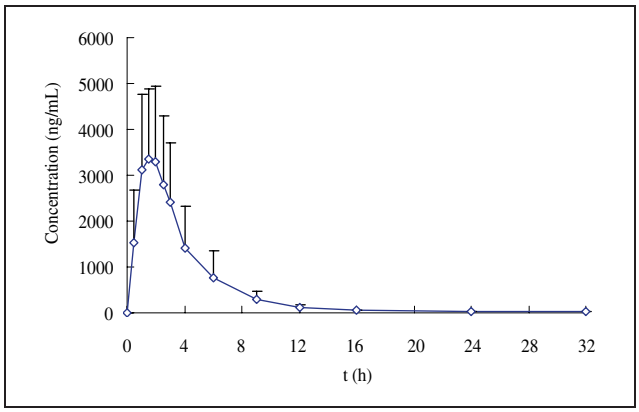


Fig. 1: Mean plasma concentration-time curve of eprosartan for 20 volunteers after a single oral administration of 600 mg eprosartan

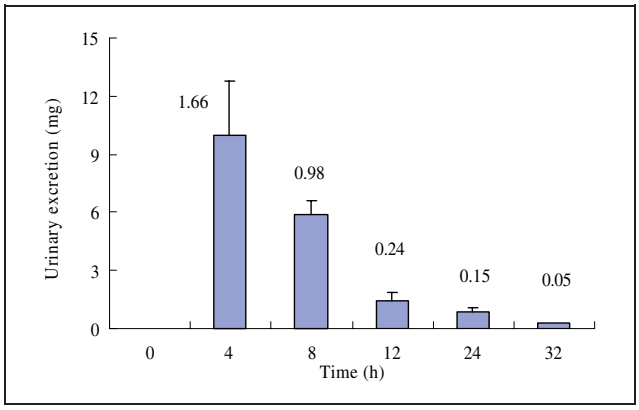


Fig. 2: Mean urinary excretion profile of eprosartan following of 600 mg eprosartan. Results are expressed as mean ± SD. Values indicated at the top of the bars represent the eliminated fraction as a percentage of intake

sartan excreted into urine 18.44 ± 6.43 mg and fraction of unchanged eprosartan excreted into urine 3.07 ± 1.07 %. No statistically significant differences in pharmacokinetic parameters between male and female subjects were found. All pharmacokinetic parameters for eprosartan and statistical results are summarized in the Table. Mean plasma concentration-time curve and mean urinary excretion profile for eprosartan were shown in Fig. 1 and Fig. 2.

2.2. Safety results

Eprosartan was safe and well tolerated by all subjects. During the course of the study, no adverse event was reported. No drop-out or death occurred. There were no marked changes in hematological, biochemistry and urinalysis parameters. Mean systolic and diastolic blood pressure values were slightly lowered during treatment period. At different times (0.5, 1, 2, 4, 6 12 h) after medication intake, the mean systolic blood pressure reduction ranged from 2.8 to 7.3 mmHg for all subjects, and mean diastolic blood pressure was also decreased from 1.6 to 3.9 mmHg. At the study point, i.e. 32 h after dosing, systolic as well as diastolic blood pressure values returned to the levels before the intake of study medication approximately. 0.5 h, 1 h, 2 h, 4 h, 12 h after dosing, pulse rate values were lightly lowered in healthy subjects, ranging 1.6 to 6 beats per minute. 12-lead ECGs were recorded at screening and post study assessment, and no clinically relevant morphological ECG changes were reported.

3. Discussion

Chapelsky et al. (1998) reported that exposure to eprosartan increased with dose but in a less than proportional manner after single oral doses of 100-800 mg of eprosartan. For each two fold dose increase, area under the concentration-time (AUC) increased on average 1.6–1.8 times and maximum plasma drug concentration (C_{max}) increased on average 1.5 to 1.8 times. Tenero et al. (1998b) reported that in the USA $AUC_{0-\infty}$ and C_{max} were 2171 ng · h/mL and 498 ng/mL in young males and $AUC_{0-\infty}$ and C_{max} were 2322 ng · h/m and 599 ng/mL in young females after a single dose of 200 mg eprosartan. The results about effect of gender on pharmacokinetics in Chinese healthy volunteers are consistent with those of the study performed by Tenero et al. (1998b). The results on t_{max} and $t_{1/2}$ are consistent with the study performed by Bottorff and Tenero (1999) in the USA. But there were two fold higher AUC and C_{max} values for eprosartan observed in Chinese healthy subjects as compared with the volunteers in the study performed by Tenero (1998b) in the USA. A pooled population pharmacokinetic analysis of 442 Caucasian and 29 non-Caucasian hypertensive patients showed that oral clearance and steady-state volume of distribution were not influenced by race. The reasons that our results were unconsistent with those studies may be as follows: first, different time, subject variance and different methods of eprosartan determination might lead to different results; second, oral clearance and steady-state volume of distribution might be influenced by race. The latter still needs to be confirmed.

4. Experimental

4.1. Teveten® tablets

Eprosartan (Teveten®) was supplied in tablets containing 600 mg active substance each. The medication was prepared by Solvay Pharmaceuticals.

4.2. Study subjects and design

Ten healthy male volunteers, aged 20-26 years with a body mass index between 20 and 25 $kg \cdot m^{-2}$, and ten healthy female volunteers, aged 21–22 years with a body mass index between 18–21 $kg \cdot m^{-2}$, gave informed consent to enter the study. Prior to the study, all subjects underwent physical examination, safety laboratory including blood chemistry, hematology and urine routine, ECG and vital signs. Serology (HCV, HBsAg, HIV1 and HIV2) of all subjects were checked as well. Females had a repeated serum pregnancy test both at screening visit and the day before the start of the study. Neither prior (within two weeks before the start of the study with the exception of paracetamol up to 48 h before the start of the study) nor concomitant medication was allowed with the exception of the use of contraceptive medication in females. During the course of the study, no other medications were allowed, except for treatment of adverse events. The study was performed at Clinical Pharmacology Center (Zhong Shan Hospital, Shanghai, China) and was approved by the local Medical Ethics Committee.

This was an open label, single-dose pharmacokinetics study planned with a total of 20 eligible subjects in total, 10 healthy volunteers per gender. On the morning of Day 1 (treatment period), each eligible subject was randomized to take a single oral dose of eprosartan 600 mg tablet after having fasted for at least 8 h at the study center. Eprosartan tablet was to be taken with 200 mL of water. The subjects fasted (except for water) for another 4 h after dosing. A standardized lunch was served not earlier than 4 h after dosing, a dinner not earlier than 10 h after dosing.

4.3. Sample collection and analytical methods

Pharmacokinetic samples were collected pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 16, 24 and 32 h after dosing. 5 mL blood samples were collected by venous puncture or indwelling venous catheters into vacutainers containing lithium-heparin. Blood samples were cooled to 4 °C and then centrifuged at 1500 g for 10 min at 4 °C within 10 min after blood sampling. The plasma was separated and transferred into screw cap polypropylene tubes. Plasma samples were stored at the study center at -20 ° until shipment to the laboratory where eprosartan plasma concentrations were determined. Urine was collected pre-dose and 0–4, 4–8, 8–12, 12–24, 24–32 h post-dose. During the sampling periods, the urine was placed in a refrigerator. The volume and pH of each sample was measured after homogenization and documented. Two aliquots of 10 mL each were saved and stored like blood samples as outline above. The LC-MS/MS method for determination of eprosartan in human plasma and urine was validated in terms of linearity, extraction recovery, intra-batch and inter-batch precision and accuracy, specificity, stability and frozen-unfrozen test. In the study, the lower limit of quantification of eprosartan in plasma and in urine both were set at 5 ng/mL.

4.4. Determination of the plasma and urinary eprosartan pharmacokinetics

Non-compartimental pharmacokinetic (PK) analysis was used to analyze plasma drug concentration-time data. The parameters C_{max} (maximum observed concentration) and T_{max} (time to reach peak concentration) were obtained directly from the experimental observations without interpolation. The terminal slope (K_e) of the concentration-time curve was determined by log-linear regression of at least the last three points. Elimination half-life ($T_{1/2}$) of the terminal log-linear phase was calculated following the equation $0.693/K_e$. Area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0\to\infty}$) was determined by adding up the areas from time (0) to the time of last quantifiable concentration by trapezoidal methods ($AUC_{0\to t}$) and the extrapolated area. The extrapolated area was determined by dividing the last detectable concentration by the slope of terminal log-linear phase. The volume of distribution (Vd/F) was determined by dividing the administered dose (D) by the area under the plasma concentration-time curve extrapolated to infinity, and the terminal slope (K_e) of the concentration-time curve: $D/AUC_{0\to\infty} \times K_e$. The total body drug clearance (Cl/F) was determined by dividing the administered dose by the amount of unchanged eprosartan excreted into urine (A_e) determined by adding up the eprosartan in urine in sampling periods. The fraction of unchanged eprosartan excreted into urine (f_e) was determined by dividing the amount of unchanged eprosartan excreted into urine by the administered dose: $A_e/D \times 100\%$. Renal clearance of eprosartan (Clr/F) was determined by the amount of unchanged eprosartan excreted into urine by the area under the plasma concentration-time curve extrapolated to infinity: $A_e/AUC_{0\to\infty}$.

4.5. Statistical analysis

Pharmacokinetic parameters were summarized over the set of evaluable subjects by means and SD. For the testing of differences between males and females in respect of pharmacokinetic parameters, analysis of variance (ANOVA) and nonparametric test were used.

References

Bottorff MB, Tenero DM (1999) Pharmacokinetics of eprosartan in healthy subjects, patients with hypertension, and special populations. Pharmacotherapy 19: 73S–78S.

Chapelsky MC, Martin DE, Tenero DM (1998) A dose proportionality study of eprosartan in healthy male volunteers. J Clin Pharmacol 38: 34–39.

Martin DE, Chapelsky MC, Ilson B (1998) Pharmacokinetics and protein binding of eprosartan in healthy volunteers and in patients with varying degrees of renal impairment. J Clin Pharmacol 38: 129–137.

McClellan KJ, Balfour JA (1999) Eprosartan. Drugs 55: 713–718.

Tenero DM, Martin D, Iison B (1998a) Pharmacokinetics of intravenously and orally administered eprosartan in healthy males: absolute bioavailability and effect of food. Biopharm Drug Dispos 19: 351–356

Tenero DM, Martin DE, Miller AK (1998b) Effect of age and gender on the pharmacokinetics of eprosartan. Brit J Clin Pharmacol 46: 267–270.