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Pharmacokinetic and safety profile of olmesartan medoxomil in healthy Chinese subjects after single and multiple administrations

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The primary aim of this study was to investigate the pharmacokinetics and safety of daily oral doses of olmesartan medoxomil administered to healthy Chinese subjects for 7 days. All 14 subjects (8 males/6 females) received a single dose of 20 mg olmesartan medoxomil and followed by multiple oral doses of 20 mg olmesartan medoxomil once daily for 7 days. Blood and urine samples were obtained for a 48-h pharmacokinetic evaluation on two PK days (Day 1 and Day 9). The systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate were determined at the scheduled time for safety evaluation. The concentration of RNH-6270 (olmesartan, the unique available metabolite of olmesartan medoxomil *in vivo*) in plasma and urine were determined with HPLC-MS/MS method after solid-phase extraction. Pharmacokinetic parameters t_{max}, C_{max}, $t_{1/2}$, AUC (0, 24 h), $AUC_{0-\infty}$, and CLr of RNH-6270 were derived from the concentration-time profiles for single- and multiple-dose administration. The pharmacokinetic parameters were summarized by gender and treatment factors which were tested by ANOVA. The results showed that there was no significant difference between male and female. Safety results showed that the decrease of blood pressure was consistent with increase of concentration of RNH-6270 and heart rate was consistent. Based above analysis, it was concluded that olmesartan medoxomil 20 mg was safe and there were no any accumulation in healthy Chinese subjects after multiple-dose.

1. Introduction

Olmesartan medoxomil is a new non-peptide angiotensin type 1 (AT1) receptor antagonist (Koga et al. 2002) and has been approved for the treatment of hypertension in the United States, Europe and some Asian countries. In three head-to-head clinical trials, it was found that olmesartan was more effective than other angiotensin II receptor antagonists (AIIRAs, ARBs) tested at their recommended doses in patients with essential hypertension (Oparil et al. 2001; Stumpe 2004; Brunner and Laeis 2003).

Olmesartan medoxomil is cleaved rapidly by an endogenous esterase to release active metabolite (olmesartan, RNH-6270) after oral administration (Schwocho and Masonson 2001). After administration of [^{14}C] olmesartan medoxomil, olmesartan was the only measurable radiolabelled component observed in the extracts of plasma and feces, indicating complete metabolism of the pro-drug to olmesartan without further metabolism. Approximate 9.9–16.3% olmesartan is excreted unchanged in the urine and 64.6–89.6% olmesartan is excreted unchanged in the feces (Laeis et al. 2001).

The present study was performed for the first time to investigate the safety and pharmacokinetics of olmesartan medoxomil by giving single and multiple oral administrations to healthy Chinese subjects.

2. Investigations and results

2.1. Pharmacokinetic parameters

All subjects completed the study and were included in the PK analysis. Figure 1 shows the pharmacokinetic profile of olmesartan for all subjects on Day 1 and Day 9. Olmesartan was rapidly absorbed under fasting conditions, reaching mean C_{max} of about $600\ ng \cdot ml^{-1}$ at approximately 1.5 h. The pharmacokinetic parameters are shown in Table 1. Trough concentration on Day 6 and Day 9 were 14.90 ± 5.01 and $14.91 \pm 6.48\ ng \cdot ml^{-1}$. About 1.7 mg and 2.0 mg olmesartan were excreted in urine in the first 12 and 48 h, respectively. If olmesartan medoxomil was totally metabolized to olmesartan in subjects (Laeis et al. 2001), the excretion rate from urine was about 10.6% in the first 12 h and 1.9% in the second 12 h.

The estimates of pharmacokinetic parameters on Day 1 and Day 9 were essentially identical without statistically significant differences (Table 1). The steady state was reached after 3 continuous repeated doses. No significant accumulation ($R = 0.90 \pm 0.14$) was observed by comparing AUC (0, 24 h) on Day 1 and Day 9. Also, statistical comparison of PK parameters between genders using ANOVA revealed no statistically significant difference with one exception for C_{max} ($p = 0.031$). Slightly lower AUCs (approximately 10%) and C_{max} values (approximately

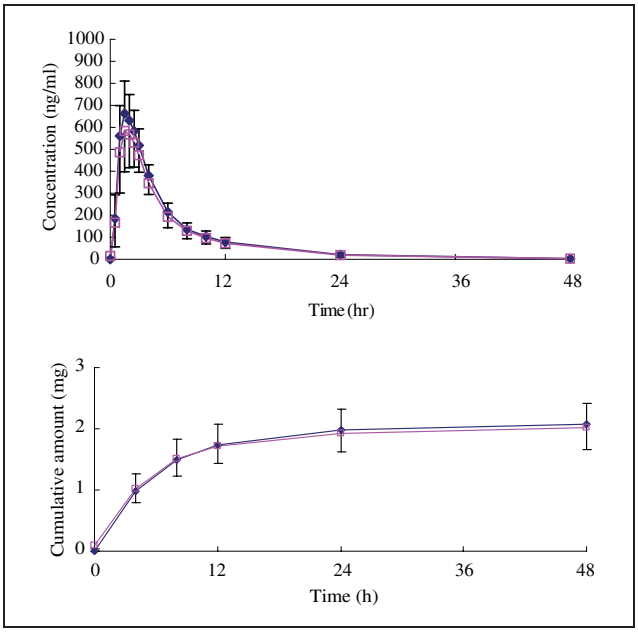

Fig. 1: The pharmacokinetic profile of olmesartan in Chinese subjects after single (◆) and multiple doses (□) of 20 mg olmesartan medoxomil. Upper panel: The concentration (arithmetic mean ± SD) – time curve of olmesartan in plasma, lower panel: The cumulative amount (arithmetic mean ± SD) – time curve of olmesartan in urine

20%) were found in males after a single dose, but these differences were minimized in steady state where the differences of AUCs and C_{max} were just to 3.5% and 11%,

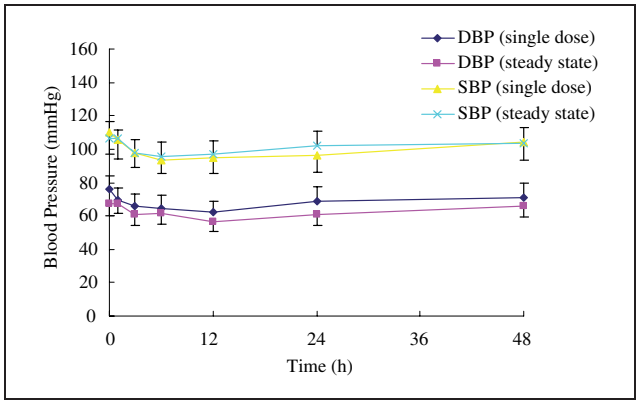

Fig. 2: The mean blood pressure (SD) – time curve in Day 1 and Day 9 in the study. SBP: systolic blood pressure; DBP: diastolic blood pressure

respectively. The elimination parameters, such as $t_{1/2,\lambda z}$ and CL_r, were comparable between male and female volunteers on Day 1 and Day 9.

2.2. *Safety evaluation*

The DBP and SBP fluctuation information at the Day 1 and Day 9 is shown in Fig. 2. The blood pressure at steady state is presented in Fig. 3. The fluctuation tendency by time was similar between the two blood pressure values and was consistent with the olmesartan concentration level in plasma except for a little time lag (about 4.5 h) of the pressure decreasing. Fortunately, the mean heart rate has little changed throughout the study.

Table 1: Olmesartan pharmacokinetic parameters (geometric mean and 95% CI) in healthy Chinese subjects

Parameter	Day 1 (Single-dose)*	Day 9 (Steady-state)	Day 9/Day 1 overall ratio 95% CI (P value)*
t_{max} (h)			
Male	1.5 (1.5, 3.0)	2.0 (1.5, 6.0)	
Female	1.5 (1.0,1.5)	1.5 (1.5,2.5)	p = 0.093
Overall	1.5 (1.0, 3.0)	1.75 (1.5, 6.0)	
C_{max} ($ng \cdot ml^{-1}$)			
Male	605 (516, 712)	559 (441, 726)	0.89
Female	764 (668, 871)	648 (554, 755)	0.75, 1.06
Overall	669 (605, 757)	596 (531, 697)	(p = 0.172)
AUC (0,24h) ($\mu g \cdot ml^{-1} \cdot h$)			
Male	3.51 (3.17, 3.90)	3.26 (2.68, 4.01)	0.89
Female	4.01 (3.60, 4.46)	3.44 (2.98, 3.96)	0.78, 1.03
Overall	3.72 (3.47, 4.02)	3.34 (3.02, 3.78)	(p = 0.106)
AUC $_{0\text{-}\infty}$ ($\mu g \cdot ml^{-1} \cdot h$)			
Male	3.77 (3.39, 4.20)	3.47 (2.83, 4.31)	0.89
Female	4.26 (3.78, 4.79)	3.66 (3.11, 4.27)	0.77, 1.03
Overall	3.97 (3.70, 4.31)	3.55 (3.19, 4.05)	(p = 0.111)
CLr (h^{-1})			
Male	528 (443, 632)	555 (451, 685)	0.97
Female	516 (357, 710)	521 (385, 692)	0.85, 1.24
Overall	523 (459, 613)	540 (476, 635)	(p = 0.721)
t1/2,z (h)			
Male	7.69 (6.75, 8.79)	7.41 (6.78, 8.12)	0.96
Female	7.41 (6.86, 7.98)	7.24 (6.59, 7.95)	0.89, 1.06
Overall	7.57 (7.06, 8.18)	7.34 (6.96, 7.79)	(p = 0.463)
R			
Male		0.93 (0.82, 1.05)	
Female	NA	0.86 (0.73, 1.01)	NA
Overall		0.90 (0.83, 0.99)	

*: The column shows the median (range) of t_{max}
**: The p-value of t_{max} is tested with nonparameter test
NA: Not applicable

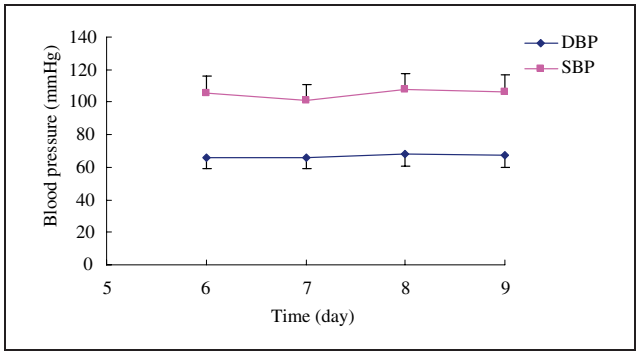

Fig. 3: The mean blood pressure (SD) – time curve at steady state between Day 6 and Day 9 in the study. SBP: systolic blood pressure; DBP: diastolic blood pressure.

Seven adverse events from six subjects occurred in the whole study and no serious adverse event was reported. All adverse events were mild to moderate in severity. The relationships of these adverse events to the study drug were rated as unlikely related or likely related. One subject was pharmacologically cured after the end of the clinical trial and the others recovered without medication.

3. Discussion

The present study clearly showed that there is no indication of continuous accumulation of olmesartan when olmesartan medoxomil is given at a dose of 20 mg once daily for 7 days. The AUC (0, 24 h) and C_{max} of olmesartan at steady states were slightly lower (about 10% and 11%) than its AUC (0, 24 h) and C_{max} calculated after a single dose with higher CL_r (about 3%). But these differences were not statistically significant.

The degree of exposure (both C_{max} and AUC) was similar in males and females although slightly higher estimates were found in females, which was probably due to the weight differences between male (average 59.8 kg) and female (average 52.4 kg) volunteers. The gender difference was minimized in steady state and was consistent with previous studies (data not published). The elimination PK parameters ($t_{1/2,z}$ and CLr) were almost not different between male and female.

By comparing previous data studied in the US (Schwocho and Masonson 2001), EU (Laeis et al. 2001) and Japan (Takanori et al. 2003) (Table 2), we found that absorption rate and exposure parameters in Chinese were higher than in others, and also elimination was faster in Chinese after single dose. Although there were obvious differences between Chinese people and other three races after a single dose, fortunately, these differences were minimized in steady state. There was no difference of PK parameters between Japanese and Caucasian according to Yoshihara (2005). A reason of the obvious differences between Japanese and Chinese could not be identified so far.

Because the main aim of the study was to evaluate the pharmacokinetics and safety of olmesartan in Chinese healthy subjects, so the study was designed to a non-controlled trial and no time-blood pressure curve in baseline was obtained. To observe the blood pressure of healthy subjects after treatment with olmesartan medoxomil, we compared the blood pressure change at the same time point between Day 0 and Day 9. Through comparing the blood pressure and olmesartan concentration level in plasma (Fig. 1), the anti-hypertensive action of olmesartan medoxomil was closely correlated with olmesartan concentration levels in plasma. The anti-hypertension effect had an about 4.5 h lag time and had no effect on the heart rate in healthy subjects. In previous studies in healthy Caucasian and Japanese (data not published), the lowest blood pressure was reached 6 h after dosing olmesartan medoxomil, which was consistent with the present study.

In conclusion, when 20 mg oral dose of Olmesartan medoxomil once daily were given to Chinese healthy subjects, the steady state was reached after 3 continuous repeated doses. There was no indication of drug accumulation with olmesartan medoxomil in the given regimen for 7 days. There were no significant differences for most of PK parameters between single-dose and steady state.

Administration of olmesartan medoxomil (20 mg once daily for 7 days) is found to be safe and well tolerated in healthy Chinese subjects.

4. Experimental

4.1. Volunteers

Fourteen healthy Chinese subjects (8 males/6 females) were enrolled. The average ± standard deviation of age, height and weight of subjects was 31.7 ± 3.75 years old, 1.61 ± 0.08 m and 56.6 ± 5.0 kg, respectively. Their healthy status was determined by regular medical assessments. Subject testing positive for HIV, HBV, HCV, serum pregnancy test (females only) and TPHA within 2 weeks prior to dosing in the study were excluded. Participants were required to abstain from smoking, alcoholic and caffeine-containing beverages during the study.

4.2. Methods

This was an open-label, two-phase and single-centre study. Study protocol and subject informed consent forms (ICF) were approved by Ethics Committee of Peking Union Medical College Hospital and the written ICFs were obtained from subjects prior to their participation in the study.

Subjects were assigned to treatment with a single 20 mg oral dose followed 48 h later by repeated 20 mg oral dose once daily for 7 days. On Day 1, a 20 mg tablet of olmesartan medoxomil was given to each subject after an overnight fast. Venous blood samples (5 ml) were obtained predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24 and 48 h post-dose. Urine samples were collected before dosing and over the following post-dose intervals: 0–4 h, 4–8 h, 8–12 h, 12–24 h and 24–48 h. On Day 3, the repeated administration with the same dose level was started and kept on performing for 7 days. On Day 6, 7 and 8, venous blood samples (5 ml) were also collected to determine the trough concentration. And, on Day 9, the same procedure as the Day 1 was conducted.

The concentrations of olmesartan in plasma and urine samples were determined as described previously (Liu et al. 2007). Briefly, Solid-phase extraction (SPE) was used to isolate olmesartan from biological matrix. Olmesartan was separated on a C_{18} column with isocratic elution and analyzed by API 3000 triple-quadrupole mass spectrometer. The method was validated over the concentration range of 0.2–1000 ng/mL and 5–10000 ng/mL for olmesartan in human plasma and urine, respectively.

4.3. Statistical analysis

The PK parameters of olmesartan were derived using noncompartmental calculation performed with WinNonlin version 4.0.1 (Pharsight C.o., California, USA). CL_r was calculated as $Ae_{48}/AUC_{(0,48h)}$, where Ae_{48} denotes the amount of olmesartan excreted in urine during the interval from 0 to 48 h. Accumulation ratio was estimated as $AUC_{\tau\ (steady\ state)}/AUC_{t\ (single\ dose)}$ ($\tau = t = 24$ hr).

All statistical analyses were conducted using JMP software version 5.1 (SAS Institute Inc. Cary, NC). Pharmacokinetic parameters were presented as the geometric mean and 90% confidence intervals (90% CI) for each of the following groups: males, females and combined as an overall statistic as well as between Day 1 and Day 9. The $\log_e$-transformed parameter estimates, including AUC_τ, $t_{1/2}$, CL_r and C_{max}, were subjected to analysis of variance, including the terms for day and gender as fixed effects. The point estimates and 90% CIs for the relative differences between Day 1 and Day 9 as the representative of single-dose versus steady-state in each subject were constructed and were then back transformed to give the estimates of the ratio of the geometric means and the corresponding 90% CIs for PK parameters. A nonparametric test (Wilcoxon signed rank test) was performed for t_{max} between Day 1 and Day 9.

Table 2: Olmesartan pharmacokinetic parameters (mean and SD) in healthy Chinese, US, Japanese and EU subjects

Single Dose	Chinese Study	US Study		Japanese Study		EU Study**
		Study 1	Study 2	Study 1	Study 2	
C_{max} (ng · ml^{-1})	681 ± 132	419 ± 56	479 ± 210	480 ± 117	469 ± 72.4	393 ± 82.5
T_{max} (h)	1.5*	2.5 ± 0.9	1.7 ± 0.8	2.2 ± 0.4	2.4 ± 0.9	1.00*
$T_{1/2}$ (h)	7.62 ± 0.97	12.1 ± 3.8	NA	11.0 ± 3.8	5.0 ± 0.7	12.3 ± 0.98
AUC (0, 24 h) (μg · ml^{-1} · h)	3.97 ± 0.623	NA	2.61 ± 0.675	2.88 ± 0.906	2.90 ± 0.688	NA
$AUC_{0-\infty}$ (μg · ml^{-1} · h)	4.00 ± 0.530	2.68 ± 0.479	NA	2.90 ± 0.915	3.01 ± 0.717	1.97 ± 0.296

Multiple Dose	Chinese Study (day 9)	US Study (day 10)	Japanese Study (day 7)	EU Study** (day 9)
C_{max} (ng · ml^{-1})	614 ± 143	507 ± 58	546 ± 108	376 ± 105
T_{max} (h)	1.5	1.7 ± 0.5	2.5 ± 1.1	1.5
$T_{1/2}$ (h)	7.37 ± 0.72	14.9 ± 5.9	6.7 ± 1.4	10.7 ± 1.93
AUC (0, 24 h) (μg · ml^{-1} · h)	3.59 ± 0.731	2.95 ± 0.378	3.35 ± 0.547	2.01 ± 0.542
AUC $_{0-\infty}$ (μg · ml^{-1} · h)	3.62 ± 0.739	NA	3.53 ± 0.558	NA

*: median
**: geometric mean
NA: Not available

4.4. Safety evaluation

Physical examination and 12-lead ECG were performed at the screening Day and the follow-up Day. Besides the screening Day and the follow-up Day, laboratory tests, including hematology, blood chemistry and urinalysis, were also performed at Day 0 and Day 6. Additionally, to observe partially the anti-hypertension action of the drug in healthy subjects, the systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate were determined at the time 0 hour from day 6 to day 8 and at the time 0, 1, 3, 6, 12, 24 and 48 hours after dosing in day 1 and day 9. All adverse events were recorded.

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