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Effect of Probenecid on Pharmacokinetics and Tolerability of Olmesartan in Healthy Chinese Volunteers[☆]



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ABSTRACT

Background: Olmesartan is an angiotensin II receptor antagonist and is effective and well tolerated in the treatment of arterial hypertension. Probenecid is a well-established hypouricemic agent for the treatment of hyperuricemia and gout.

Objective: The goal of this study was to examine the impact of coadministration of probenecid on the pharmacokinetic parameters and tolerability of olmesartan in healthy volunteers.

Methods: In a randomized, open-label, 2-way crossover study, 12 volunteers received 2 oral treatments (olmesartan alone or olmesartan plus probenecid) separated by 4 days. Blood samples were obtained for a 48-hour pharmacokinetic evaluation after drug administration. Tolerability was assessed by monitoring vital signs and laboratory tests before and after administration of the study drug.

Results: Pharmacokinetic parameters were evaluated in 6 male and 6 female healthy volunteers (mean age, 22 [range, 20–25] years); weight, 56.0 [range, 51.0–60.0] kg). Probenecid coadministration increased olmesartan C_{ss-av} , $AUC_{0 \rightarrow \infty}$, and AUC_{0-48} by 40%, 50%, and 50%, respectively ($P = 0.018, 0.000, 0.000$, respectively), but there was no statistical significance for T_{max} , $t_{1/2}$, C_{ss-max} , and C_{ss-min} between olmesartan plus probenecid and olmesartan alone ($P = 0.697, 0.053, 0.521, \text{ and } 0.734$, respectively). No serious adverse event (AE) was reported during the study. The proportion of volunteers with AEs in the olmesartan plus probenecid period (5 of 12 [42%]) was higher than that in the olmesartan-alone period (1 of 12 [8%]). All of the AEs during the olmesartan plus probenecid period were abnormal routine urine test results. The AE in olmesartan-alone period was dizziness. All AEs were classified as mild and considered to be at least possibly related to treatment. All volunteers recovered from the AEs by 2 weeks after the end of the study.

Conclusions: Probenecid increases the exposure speed of olmesartan by increasing the AUC_{0-48} , $AUC_{0 \rightarrow \infty}$, and C_{ss-av} . The combined treatment of olmesartan medoxomil with probenecid may increase the occurrence of genitourinary side effects. ClinicalTrials.gov identifier: NCT01907373.

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Introduction

Hypertension and hyperuricemia are widespread conditions. There is significant overlap of the 2 conditions. Serum uric acid (SUA) is currently recognized as a risk factor for cardiovascular disease.¹ Thus, at some point in their therapy, hypertensive patients with hyperuricemia are likely to require concurrent treatment with antihypertensive and hypouricemic agents. For

this reason, it is important to determine whether there are any pharmacokinetic interactions resulting from the concomitant administration of such agents.

Probenecid is a well-established hypouricemic agent for the treatment of hyperuricemia and gout and is thought to act on urate transporter 1 (URAT1),^{2,3} a novel member of the organic anion transporter (OAT) family, thereby increasing uric acid excretion in the kidney by blocking urate reuptake and resulting in a decrease in SUA.⁴

Olmesartan is an angiotensin II receptor antagonist and is effective and well tolerated in the treatment of arterial hypertension.⁵ Olmesartan is orally administered in olmesartan medoxomil, the prodrug form.^{6,7} The recommended dose of olmesartan ranges from 20 to 80 mg once daily. There is no relationship between the dose and the occurrence of side effects of olmesartan

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medoxomil. The mean oral bioavailability of olmesartan medoxomil in healthy adult volunteers has been found to be 29%. C_{max} occurs at 2 hours (range, 1–4 hours). Distribution of olmesartan occurs over the first 8 hours after oral administration with an estimated volume of distribution of 29 L. Olmesartan is primarily excreted unchanged in the feces (up to 89%), with a small proportion (10%–16%) excreted unchanged in the urine. Because the rate of renal clearance (mean, 0.55 L/h) is substantially lower than the glomerular filtration rate, it was hypothesized that there is extensive tubular reabsorption of olmesartan. The mean elimination half-life was ~5 to 7 hours in Chinese patients and 12 to 18 hours in Western patients, with a duration of action of up to 24 hours.⁷ In vitro studies show that OAT polypeptides 1B1 and 1B3 are involved in hepatobiliary and renal transport of olmesartan.^{6,8} We know that probenecid interferes with the kidneys' OAT.^{2,3} Will probenecid have an effect on the pharmacokinetics of olmesartan, thereby resulting in changes in the antihypertensive effect and side effects of olmesartan? Until now, many clinical studies have shown that olmesartan has no pharmacokinetic interactions with other drugs; moreover, there is no research on the interactions between olmesartan and probenecid. In this study, we assess the involvement of probenecid in the pharmacokinetics and tolerability of olmesartan.

Subjects and Methods

Study design

This study had an open-label, randomized-sequence, multiple-dose, 2-treatment, 2-period design. The protocol was approved by the Ethics and Research Committee of the Hunan Provincial Tumor Hospital, and the study was performed in accordance with the current revision of the Declaration of Helsinki⁹ concerning medical research in humans and with current Good Clinical Practice (the European Union) guidelines¹⁰ and the Technical Guideline for Chemical Drug Clinical Pharmacokinetic Study (China Food and Drug Administration).¹¹ The study was conducted in August 2009. The national study registration number for the study was 2005L01077. The dose of 20 mg/d for olmesartan medoxomil and 500 mg/time for probenecid were chosen for this study according to the recommended doses in clinic.^{12,13} Subjects underwent 2 consecutive 4-day treatment periods (period I: olmesartan medoxomil, 20 mg once daily for 4 days; period II, olmesartan medoxomil 20 mg once daily for 4 days plus probenecid 500 mg twice daily on the last day). The first dose of probenecid was administered with olmesartan medoxomil in the morning of the last day in period II. The second dose of probenecid was administered alone 6 hours after the first administration. The treatment periods were separated by a washout period of 4 days. Subjects arrived at the hospital the day before the study. A table of random numbers was used to assign the sequence for subjects to receive multiple doses (administered with 200 mL of water) of olmesartan medoxomil tablets (Lot: 070901; expiration: September 2009, TianQuan Pharmaceutical Co., Ltd, Fujian, China), with or without a probenecid tablet together (Lot: 081201; expiration: December 2010, Shanghai Sine Pharmaceutical Co., Ltd.). Subjects could not consume anything other than water for 12 hours before and 2 hours after administration of the study drug. The drug administration schedule is shown in Table I.

Subjects

Healthy female and male Chinese subjects were recruited through the Phase I Trial Unit at the Hunan Provincial Tumor Hospital (Affiliated Tumor Hospital of Xiangya Medical School of

Table I
Drug administration schedule.

| Treatment | Period I | | | |
|--------------------------|-----------|-------|-------|-------|
| | Day 1 | Day 2 | Day 3 | Day 4 |
| Olmesartan medoxomil, mg | 20 | 20 | 20 | 20 |
| Blood sample | ▲ | ▲ | ▲ | ▲* |
| Washout time (4 days) | | | | |
| Treatment | Period II | | | |
| | Day 1 | Day 2 | Day 3 | Day 4 |
| Olmesartan medoxomil, mg | 20 | 20 | 20 | 20 |
| Probenecid, mg | — | — | — | 500 |
| Blood sample | ▲ | ▲ | ▲ | ▲* |

▲, Venous blood samples (5 mL) were collected pre-dose.

*Venous blood samples (5 mL/time) were obtained at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, and 48 hours after olmesartan medoxomil administration.

Central South University) via advertisement. Written informed consent was obtained from all of the subjects after an explanation of the aim and the risks of the study before study initiation. The main information in the informed consent included the details of the tested drugs, the purpose and the length of the study, the number of visits required, and the medical procedures and medications included. It also provided expected outcomes, potential benefits, and possible risks. Subjects were compensated for study participation. Subjects were eligible based on the following criteria: age 18 to 40 years and a body mass index between 19 and 25 kg/m². Additional inclusion criteria were nonsmoking status and an unremarkable clinical history. No volunteers could have a history or evidence of a renal, gastrointestinal, hepatic, or hematologic abnormality; any acute or chronic disease; or an allergy to any drugs. These subjects were excluded to ensure that the degrees of variation were not due to the influence of illness or other medications. Chest radiography, electrocardiography, biochemistry, hematology, and routine urine test results were used to confirm subject history. Subjects were required to have negative HIV and hepatitis B and C test results.

Blood sampling and assaying

A 20-gauge catheter was placed in a forearm vein. The schedule for drawing the blood samples is shown in Table I. The blood samples were drawn into vacuum tubes with heparin sodium as an anticoagulant and centrifuged at 1500g ($r = 0.03$ m) for 10 minutes. The separated plasma was stored at -40°C until analyzed by ultraperformance LC-MS/MS. The concentrations of olmesartan in plasma samples were determined as described previously.¹⁴ Briefly, Strata-X SPE (solid-phase extraction) cartridges (Phenomenex, Torrance, California) were used to extract olmesartan from plasma. Olmesartan was analyzed in the ultraperformance LC-MS/MS system (10.0-cm column length, 2.1-mm inner diameter, 3.0- μm particle size; Welchrom XB-CN, Welch Materials, Ellicott City, Maryland). The LC system (ACQUITY UPLC, Waters, Manchester, United Kingdom) was coupled with a Waters Quattro Premier XE triple quadrupole with an ion-source electrospray probe (Waters Corporation, Milford, Massachusetts). The method was validated over the concentration range of 2 to 1600 ng/mL for olmesartan. The limit of quantification was 2 ng/mL. The intraday precision and interday precision were < 7% and 8%, respectively. The intraday accuracy and interday accuracy were 90.5% to 101.8% and 91.3% to 100.4% respectively.

Tolerability

Tolerability was assessed by monitoring vital signs (blood pressure, heart rate, and respiratory rate at baseline [0] and at 1, 2, 3, 6, 12, 36, and 48 hours) after administration of the study drug

in each period. Laboratory tests, as mentioned in the Subjects section, were performed at baseline and 24 hours after administration of the study drug in each period. Subjects were interviewed during the study by the physician concerning the occurrence of adverse events (AEs). The tolerability information of all subjects was recorded in detail on the case-report forms.

Data and statistical analyses

The pharmacokinetic parameters of olmesartan were obtained by noncompartmental analysis with the Drug and Statistics Program Package (DAS, Version 2.0.1, Wannan Medical College, Wuhu, China). The elimination rate constant (λ_z) was obtained as the slope of the linear regression of the log-transformed concentration values versus time data in the terminal phase. The $t_{1/2}$ was calculated as $0.693/\lambda_z$. T_{max} , C_{max} , and C_{min} were read directly from the observed concentration versus time profiles. AUC_{0-t} was calculated by the linear trapezoidal rule. $AUC_{0-\infty}$ was calculated as $AUC_{0-t} + C_t/\lambda_z$, where C_t was the last measurable concentration. The log-transformed parameters, including $AUC_{0-\infty}$, AUC_{0-48} , C_{min} , $t_{1/2}$, and C_{max} , were subjected to analysis of paired-sample t tests. ANOVA was used to analyze log-transformed C_{min} for the intraperiod on 3 different days (days 2, 3, and 4). A nonparametric test (Wilcoxon signed rank test) was performed for T_{max} . Statistical significance was set at $P < 0.05$.

Results

Demographic characteristics

Twenty volunteers were assessed for eligibility. Of them, 6 male and 6 female healthy Chinese subjects (mean age, 22 [range, 20–25] years of age; weight, 56.0 [range, 51.0–60.0] kg) were enrolled in the study. All volunteers completed the study.

Pharmacokinetic properties

The plasma pharmacokinetic parameters of olmesartan-alone (period I) and olmesartan plus probenecid (period II) are summarized in Table II.

Log-transformed concentration-time curves are shown in the Figure.

Olmesartan mean plasma concentrations in period II were 40% higher than that in period I ($P = 0.018$). There was statistical significance for $AUC_{0-\infty}$ and AUC_{0-48} between the 2 periods ($P = 0.000$ and 0.000 , respectively). The $AUC_{0-\infty}$ and AUC_{0-48} in period II increased nearly 50% of that in period I, but there was no statistical significance for T_{max} , $t_{1/2}$, C_{ss-max} , and C_{ss-min} between the 2 periods ($P = 0.697$, 0.053 , 0.521 , and 0.734 , respectively). There was also no statistical significance for C_{min} on 3 different days (days 2, 3, and 4) between the intraperiod (period II [$P = 0.998$] and period I [$P = 0.919$]).

Table II
Pharmacokinetic parameters of olmesartan.

| Period | AUC_{0-48} (ng/mL/h) | $AUC_{0-\infty}$ (ng/mL/h) | $t_{1/2}$ (h) | T_{max} (h) | C_{ss-max} (ng/mL) | C_{ss-min} (ng/mL) | C_{ss-av} (ng/mL) |
|--------|------------------------|----------------------------|---------------|---------------|----------------------|----------------------|---------------------|
| I | | | | | | | |
| Mean | 4849.703 | 4927.619 | 6.392 | 1.458 | 894.409 | 37.604 | 185.562 |
| SD | 1845.364 | 1887.675 | 1.239 | 0.396 | 300.610 | 25.282 | 68.155 |
| II | | | | | | | |
| Mean | 7007.432 | 7192.630 | 7.697 | 1.625 | 805.253 | 29.773 | 261.309 |
| SD | 2865.966 | 3064.606 | 1.757 | 0.433 | 219.337 | 16.415 | 90.349 |
| P | 0.000 | 0.000 | 0.053 | 0.697 | 0.521 | 0.734 | 0.018 |

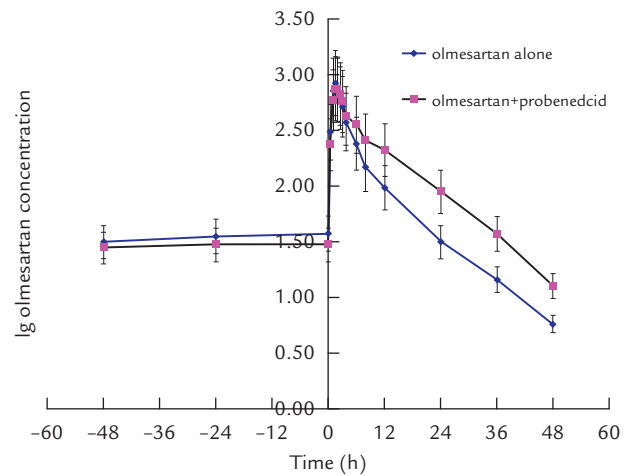


Figure. Log-transformed concentration-time curves after administration of olmesartan alone and olmesartan plus probenecid.

Tolerability assessments

No serious AE was reported during the study, and no volunteer withdrew from the study. The proportion of volunteers with AEs in period II (5 of 12 [42%]) was higher than that in period I (1 of 12 [8%]). All of the AEs in period II were abnormal routine urine test results 24 hours after olmesartan plus probenecid administration. The abnormal results were as follows: for volunteer 3, protein (3+), red blood cells (3+), white blood cells (1+), glucose (1+); for volunteer 5, protein (3+), glucose (1+); for volunteer 10, white blood cells (1+), glucose (2+); for volunteer 11, red blood cells (1+), white blood cells (1+); for volunteer 12: glucose (2+). The AE in olmesartan-alone period was dizziness. All AEs were classified as mild and considered to be at least possibly related to treatment. All volunteers recovered from the AEs by 2 weeks after the end of the study.

Discussion

In the current study, C_{min} , C_{ss-max} , T_{max} , and $t_{1/2}$ did not change significantly when olmesartan is combined with probenecid. As we know, olmesartan medoxomil is converted to olmesartan by intestinal wall esterases. Olmesartan undergoes virtually no further metabolism.¹³ Thus, the pharmacokinetics of olmesartan were considered less likely to be affected by the drugs metabolized or to have effects on the CYP450 isoenzyme system,^{15–17} for example, probenecid. At the same time, the tubular excretion with which probenecid interferes plays a small role in the excretion of olmesartan.

The changes in AUC_{0-48} , $AUC_{0-\infty}$, and C_{ss-av} in the study have statistical significance when olmesartan is combined with probenecid in healthy subjects. C_{ss-av} for the olmesartan plus probenecid period was 40% higher than that for the olmesartan-alone period.

The $AUC_{0 \rightarrow \infty}$ and AUC_{0-48} for the olmesartan plus probenecid period increased by nearly 50% of that of the olmesartan-alone period. The increase in olmesartan exposure may or may not increase the antihypertensive efficacy; this is not yet clear. More basic and clinical studies are needed to answer these questions.

There is another interesting result in that olmesartan exposure (AUC) is increased 40%, but the increase in exposure has no effect on either absorption (T_{max} , C_{max}) or elimination ($t_{1/2}$). In the study, we only studied the concentration of olmesartan in blood. In fact, the drug does not only distribute blood but in tissue as well. Sometimes the AUC may change without absorption or elimination may change if the distribution balance between blood and tissue is changed. Unfortunately, we did not obtain body tissue to study the drug concentrations. So our study is underpowered in some sense.

In this study, 42% of the volunteers in the olmesartan plus probenecid period had abnormal routine urine test. The urine tests are performed at baseline, 24 hours after olmesartan administration alone in period I, and 24 hours after olmesartan plus probenecid administration in period II. The AEs are considered to be at least possibly related to treatment. The genitourinary side effects including urinary tract infection with olmesartan were reported in only 0.5% to 1% of patients. Hematuria was reported in > 1% of patients, but at the same or greater incidence than with placebo.¹⁸ The genitourinary side effects of probenecid including bloody urine, difficult or painful urination, cloudy urine, sudden decrease in the amount of urine, and frequent urge to urinate are < 1%.¹⁹ The occurrence of AEs may not be increased by the increase in olmesartan exposure because there is no relationship between the dose and the occurrence of side effects with olmesartan medoxomil.¹³ We suspect the combined treatment of olmesartan medoxomil with probenecid may be not safe. Is there any additive or increased effect on AEs when olmesartan medoxomil and probenecid are administered together? More studies are needed to determine this.

Conclusions

In this small study of healthy Chinese volunteers, probenecid increases the exposure speed of olmesartan by increasing the AUC_{0-48} , $AUC_{0 \rightarrow \infty}$, and C_{ss-av} , but has no effects on other pharmacokinetic parameters of olmesartan. The combined treatment of olmesartan medoxomil and probenecid may increase the occurrence of genitourinary side effects.

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Conflicts of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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