

Bioequivalence and Pharmacokinetic Profiles of Generic and Branded Obeticholic Acid in Healthy Chinese Subjects Under Fasting and Fed Conditions

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Objectives: This study was conducted to evaluate the bioequivalence (BE) of a generic form of obeticholic acid (OCA) and OcalivaTM under fasting and fed conditions and to determine the effects of food on the pharmacokinetic (PK) profiles of OCA in healthy Chinese subjects.

Methods: A randomized, single-dose, three-sequence, three-period, partial replicated crossover study was conducted with a 21-day washout interval between periods under fasting (n=48) and fed (n=48) conditions. Blood samples for OCA and its metabolites Glyco-OCA and Tauro-OCA were collected up to 168 hours after administration in each period. PK parameters were calculated using the non-compartmental method. Geometric mean ratios for PK parameters of the test to reference drug under fasting and fed conditions and their 90% confidence intervals were estimated. Safety evaluations were carried out all through the study.

Results: A total of 91 subjects completed the study with 45 in a fasted state and 46 receiving a high-fat diet. There were no serious or unexpected drug-related adverse events occurring during the study. There was no significant difference in the main PK parameters of the two preparations, irrespective of the fasting or fed conditions. Under fasting and fed conditions, the S_{WR} of $\ln C_{max}$, $\ln AUC_{0-t}$ and $\ln AUC_{0-\infty}$ were 0.445, 0.370, 0.448, 0.340, 0.168, and 0.180, respectively. Thus, the average BE or the reference-scaled average BE was used to verify that the two preparations were bioequivalent under fasting and fed conditions. Compared with the fasting state, the AUC_{0-t} of the test drug, the AUC_{0-t} , and $AUC_{0-\infty}$ of the reference drug were higher in the fed state.

Conclusion: The test drug and the reference drug were BE and well tolerated in Chinese healthy subjects under both fasting and fed conditions. Food-intake may cause a significant difference in the main PK parameters of the two preparations.

Keywords: obeticholic acid, bioequivalence, pharmacokinetics, food effect

Introduction

Primary biliary cholangitis (PBC) is a progressive cholestatic liver disease that leads to the gradual destruction of intrahepatic bile ducts resulting in periportal inflammation, cholestasis, and fibrosis and may potentially lead to cirrhosis in a proportion of patients.¹ The etiology of PBC remains unknown, and both environmental factors and genetic variants increase disease susceptibility.²⁻⁵ The number of patients with PBC in China has been increasing annually.⁶

Obeticholic acid (OCA, OcalivaTM), an oral potent selective agonist of farnesoid X receptor (FXR), is indicated for the treatment of PBC in ursodeoxycholic acid

(UDCA)-refractory or UDCA intolerant patients.^{3,7} The FXR is a nuclear receptor abundantly expressed in tissues that engage in the enterohepatic circulation of bile acid.⁸ Unlike UDCA which operates at a post-translational level, FXR-signaling directly regulates genes involved in bile acid synthesis, secretion, transportation, absorption, and detoxification.⁹ The time to peak plasma concentrations (T_{max}) of OCA has been reported to occur after 1.5 hours, and systemic exposures to OCA increased the dose proportionally.¹⁰ OCA metabolites glyco-obeticholic acid (Glyco-OCA) and tauro-obeticholic acid (Tauro-OCA) have similar pharmacological activities, which are secreted into bile and are absorbed in the small intestine leading to enterohepatic recirculation.¹¹ OCA is mainly excreted in feces through biliary secretion.¹⁰

The United States Food and Drug Administration (FDA) has recommended the implementation of a reference-scaled average bioequivalence (RSABE) approach scaled to the high variability of reference drugs to be administered to patients more than once.¹² The primary objective of the present partially replicated experimental study was to evaluate the bioequivalence (BE) of the generic and reference drug in healthy Chinese subjects under both fasting and fed conditions and to determine the effect of food intake on the pharmacokinetic (PK) profile, the secondary objective was to observe and evaluate the safety of the two formulations.

Methods

Ethics Statement of Human Rights

This study was reviewed and approved by the Institutional Review Board of the Third Xiangya Hospital of Central South University. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All subjects provided written informed consent and the study was registered at the Chinese Clinical Trial Registry [<http://www.chictr.org.cn>] (number ChiCTR1900026043).

Subjects

This study enrolled healthy Chinese subjects aged >18 years, weighing > 55 kg for males and >45 kg for females, with a body mass index (BMI) ranging from 19.0 to 26.0 kg/m², no pregnancy plan within 3 months after the end of the trial, both fasting and fed conditions were required. Exclusion criteria included history of circulatory disease, endocrine disease, or any other clinically significant diseases that could affect PK of the drug, history of

alcoholism or drug dependence, history of sensitivity to pharmaceutical products, taking any other medication within 14 days before the study, participation in other trials in the previous 3 months, surgery within the last 1 month, blood donation in the previous 3 months, pregnancy, breast-feeding or participation in high-performance athletics.

Sample Size

This study adopts a three-cycle partly repeated design. When S_{WR} is greater than or equal to 0.294 (that is, when the intra-individual CV_w \geq 30%), RSABE is used to evaluate BE. Assuming one-sided $\alpha=0.05$, $\beta=0.1$, Intra-CV=50%, and the geometric mean ratio (GMR) of the test drug to the reference drug is 0.95–1.05, the sample sizes that meets the FDA and EMA equivalence standard are 31 and 39 cases. Therefore, this study intends to enroll 48 healthy subjects, both male and female.

Study Design

This study was performed as a single-dose, randomized, open-label, 3-sequence, 3-period partial replicated cross-over trial design, including two parts: fasting and fed. A total of 96 healthy subjects were enrolled, 48 in the fasting study and 48 in the fed study. Eligible subjects were randomly assigned to three sequences (T-R-R, R-T-R, R-R-T, where T was the test drug, and R was the reference drug). Given that the effective elimination half-life ($t_{1/2eff}$) was 24 hours, the actual elimination half-life ($t_{1/2z}$) could not be calculated due to the significant enterohepatic circulation, a 21-day washout period was used between the periods.

The subjects in the fasting-condition study received a single oral dose (10-mg tablet) of the reference (Intercept Pharmaceuticals, Inc.) or test (Nanjing Zhengda Tianqing Pharmaceutical Co., Ltd) formulation of OCA with 240 mL of water after fasting overnight (\geq 10 hours) and accepting a thorough examination of the oral cavity and hand to guarantee administration compliance. The subjects were constrained from drinking for 2 hours before and after dosing. Light meals were served at 4 and 10 hours after each dose, which should be eaten within 30 minutes, with identical standardized diets provided across all dosing periods.

In total, 48 subjects participated in the fed-condition study. All the procedures were the same as those in the fasting condition, except for eating high-fat, high-calorie standard meals (approximately 150 kcal protein, 250 kcal

carbohydrates, and 500–600 kcal fat, a total of about 800–1000 kcal, three periods should ensure that the standard meal formula was consistent) 30 minutes before administration, to be finished within 30 minutes.

Blood Sampling and Determination of Concentration

A peripheral blood sample (5 mL) from each subject was collected in tubes containing sodium heparin at time 0 (within 60 minutes before dosing) and at 15, 30, 45 minutes and 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0, 120.0, and 168.0 hours after dosing in the study under both fasting and fed conditions. Plasma was obtained from the supernatants of the collected blood samples after centrifugation at $2150 \times g$ for 10 minutes and were stored at -60°C until use.

Briefly, the plasma concentration of OCA, Glyco-OCA and Tauro-OCA was measured by HPLC-MS/MS (Triple QuadTM 6500⁺; Sciex) after liquid-liquid extraction (cyclohexane:ethyl acetate=1:3, v/v), and separated on a Poroshell 120 EC-C18, 2.1 \times 50 mm column (Agilent, USA) with mobile phase A (water with 0.1% formic acid) and a mobile phase B (acetonitrile with 0.1% formic acid) for OCA, and mobile phase A (Water with 0.05% formic acid) and mobile phase B (100% acetonitrile) for Glyco-OCA and Tauro-OCA, gradient elution. Glimepiride was used as the internal standard (IS). Multiple reaction monitoring was employed, and transmission masses for OCA, Glyco-OCA, Tauro-OCA, and the IS were 465.3 to 419.3, 476.3 to 74.1, 526.3 to 123.9, and 489.3 to 224.8, respectively. The linear ranges of OCA, Glyco-OCA and Tauro-OCA were 0.15–100 ng·mL⁻¹, 1.00–120 ng·mL⁻¹, and 0.15–18.0 ng·mL⁻¹, respectively.

PK and BE Evaluation

A non-compartmental approach (Phoenix[®] WinNonlin 7.0) was used to calculate the PK parameters for OCA, and its metabolites Glyco-OCA and Tauro-OCA from the concentration-time profiles. The following PK parameters were evaluated: the peak plasma concentration (C_{\max}), time to reach the peak plasma concentration (T_{\max}), area under the plasma concentration-time (AUC) from dosing to the last measurable concentration (AUC_{last}), AUC from dosing to infinity ($\text{AUC}_{0-\infty}$), $t_{1/2z}$, apparent clearance, λ_z .

The PK profiles of Glyco-OCA and Tauro-OCA were also calculated, but no BE analysis was performed. The within-subject standard deviation (S_{WR}) of the log-

transformed values of C_{\max} , AUC_{0-t} and $\text{AUC}_{0-\infty}$, were calculated. The BE analysis method selection was based on the S_{WR} : the average bioequivalence (ABE) method was adopted when $S_{\text{WR}} < 0.294$, while the RSABE method was adopted when $S_{\text{WR}} \geq 0.294$. The BE acceptance limits were scaled to the variability of the reference formulation as directed by the RSABE approach.

BE was determined by ABE method when the 90% confidence interval (CI) of the test preparation/reference preparation GMR of C_{\max} , AUC_{0-t} , and $\text{AUC}_{0-\infty}$ of OCA was within 80.00%-125.00%.

The RSABE can be applied to a BE measure, when the test and reference formulations are considered bioequivalent, calculated as:

$$95\% \quad \text{upper} \quad \text{confidence} \quad \text{limit} \\ \text{for } (\bar{Y}_T - \bar{Y}_R)^2 - \theta \times S_{\text{WR}}^2 \leq 0$$

Where \bar{Y}_T and \bar{Y}_R are the means of the log-transformed PK endpoints for the test formulation and that for the reference formulation, θ is $\left(\frac{\ln(1.25)}{\sigma_{\text{w0}}}\right)$, σ_{w0} is the regulatory limit (FDA set σ_{w0} at 0.25). Point estimates of test/reference GMR and 90% CIs of the GMR of test to reference were also calculated. BE conducted by RSABE method need to meet both the BE limits and the GMR constraints (0.80–1.25).

Safety Evaluation

The safety and tolerability of the two formulations were assessed based on the occurrence of adverse events (AEs), vital signs, clinical laboratory tests, electrocardiogram, and physical examination throughout the study period. The severity of AEs was classified as mild, moderate, and severe. The causality of AEs was evaluated as five categories: unrelated, unlikely, possibly, probably, or definitely related. Among them, AEs determined by the trial doctor to be possibly, probably, or definitely related to the treatment were recorded as adverse reactions (ADRs).

Statistical Analysis

Statistical description methods were used to identify the demographic characteristics, the occurrence of AEs and PK parameters. Based on the above two methods of assessing BE, if the 90% CI of the GMR (test drug/reference drug) of C_{\max} , AUC_{0-t} and $\text{AUC}_{0-\infty}$ was within 80.00%-125.00% under fasting or fed conditions, we should consider the two preparations to be bioequivalent. In addition, we also used analysis of variance (ANOVA) to compare the PK parameters (C_{\max} , AUC_{0-t} , $\text{AUC}_{0-\infty}$, and $t_{1/2z}$) under fasting

and fed conditions to explore the effects of food on the PK profiles of the test/reference drug. The Mann–Whitney *U*-test was used to perform statistical analysis on T_{max} .

Results

Subjects

A total of 96 subjects were enrolled and randomized to one of two groups: a fasting group ($n=48$) and a fed group ($n=48$). The gender, average age, height, weight and BMI of the subjects were similar for the two parts of the study (Table 1). Of the 96 subjects, 5 subjects discontinued the study (fasting group: 3 subjects; fed group: 2 subjects). In the fasting group, one subject discontinued the study before the period 1, two subjects discontinued because of personal reasons before period 3. In the fed group, one subject withdrew because of AE and the other one discontinued because of personal reasons before period 2.

Safety Evaluations

In the fasting group, 29 AEs were reported from 19 (41.3%) of 46 subjects included in the safety evaluation in the test drug part; of these, 14 AEs in 10 subjects were defined as ADRs. One subject experienced a severe AE (diarrhea), one subject experienced moderate AE (abdominalgia), and all other AEs were of mild severity. Overall, 21 AEs were reported from 16 (34.0%) of 47 subjects in the R1 part (ie, first time taking the reference drug); among them, 10 AEs in eight subjects were defined as ADRs. Except for one severe AE (presyncope), the others were mild AEs. A total of 38 AEs

were identified in 24 (52.2%) of 46 subjects in the R2 part (ie, the second time taking the reference drug); 16 AEs in 15 subjects were ADRs. All AEs were of mild severity. In the fasting-condition study, elevated triglycerides, acne, diastolic hypotension and low high-density lipoprotein cholesterol were the most common AEs.

In the fed group, 16 AEs were observed in 13 (28.3%) of 46 subjects in the test drug part; among them, 11 AEs in eight subjects were judged as ADRs. All AEs were mild. Four AEs were found in 4 (8.3%) of 48 subjects in R1 part; of these, two AEs in two subjects were defined as ADRs. Except for one case of moderate AEs (urinary tract obstruction), the rest were mild. Overall, 29 AEs were observed in 20 (43.5%) of 46 subjects in R2 part, of which, 13 AEs in 12 subjects were defined as ADRs. All AEs were moderate (elevated bilirubin, urinary tract obstruction, and eczematous) and mild in severity. Common AEs in this fed-condition study were low high-density lipoprotein cholesterol, increased radial pulse and elevated bilirubin.

All ADRs were mild or moderate in severity, see Table 2 for details.

BE Studies and Effect of Food on PK

The mean concentration-time curves of the test drug was similar to the reference drug in both the fasting-condition study and the fed-condition study (Figures 1 and 2). According to the actual blood collecting time, the main PK parameters of OCA, Glyco-OCA and Tauro-OCA were calculated by non-atrioventricular model in the two groups (Table 3). There was no significant difference in the PK profile of the test drug and the reference drug, irrespective of the fasting group or the fed group.

The S_{WR} of C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ of OCA in healthy subjects after a single oral administration of 10 mg test drug or reference drug under fasting condition were 0.445, 0.370, and 0.448 respectively, which were all higher than 0.294. Using the RSABE for BE assessment, the point estimation values of GMR (test drug/reference drug) of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were 1.009, 1.015, and 0.983 respectively, which all fell within the interval (0.80–1.25), and the cutoff standards were -0.110 , -0.078 , -0.115 respectively, which were all less than 0 (Table 4).

After a single 10 mg dose of the test drug or reference drug under the fed condition, the S_{WR} of C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ were 0.340, 0.168, and 0.180, respectively, in which the S_{WR} of the C_{max} was higher than 0.294. The RSABE method was used to evaluate BE of the C_{max} , the point

Table 1 Demographic Data of the Subjects Under Fasting and Fed Conditions

Variable	Fasting (n = 47)	Fed (n = 48)
Age (years) mean \pm SD (range)	27.8 \pm 5.85 (18.0 ~ 40.0)	27.1 \pm 5.15 (19.0 ~ 37.0)
Gender, n (%)		
Male	37 (78.7)	38 (79.2)
Female	10 (21.30)	10 (20.8)
Weight (kg) mean \pm SD (range)	61.2 \pm 7.32 (45.1 ~ 75.9)	58.8 \pm 6.69 (46.7 ~ 80.1)
BMI (kg/m ²) mean \pm SD (range)	22.1 \pm 1.90 (19.0 ~ 26.0)	21.8 \pm 1.71 (19.1 ~ 25.9)
Race, n (%)		
Han	40 (85.1)	43 (89.6)
Others	7 (14.9)	5 (10.4)

Abbreviations: BMI, body mass index; SD, standard deviation.

Table 2 Adverse Reaction of Subjects After Study Drug

ADR, n (%)	Fasting			Fed			All (N=95)
	Test (n=46)	Reference 1 (n=47)	Reference 2 (n=46)	Test (n=46)	Reference 1 (n=48)	Reference 2 (n=46)	
All ADRs	10 (21.7)	8 (17.0)	15 (32.6)	8 (17.4)	2 (4.2)	12 (26.1)	42 (44.2)
Low high-density lipoprotein cholesterol	1 (2.2)	0 (0)	5 (10.9)	2 (4.3)	0 (0)	7 (15.2)	15 (15.8)
Elevated ALT	1 (2.2)	0 (0)	2 (4.3)	1 (2.2)	0 (0)	0 (0)	4 (4.2)
Elevated bilirubin	1 (2.2)	0 (0)	2 (4.3)	4 (8.7)	0 (0)	1 (2.2)	8 (8.4)
Hyperthyroidism	0 (0)	0 (0)	1 (2.2)	0 (0)	0 (0)	0 (0)	1 (1.1)
Hypothyroidism	0 (0)	0 (0)	0 (0)	2 (4.3)	0 (0)	0 (0)	2 (2.1)
Autoimmune thyroiditis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	1 (1.1)
Elevated AST	0 (0)	0 (0)	1 (2.2)	0 (0)	0 (0)	0 (0)	1 (1.1)
Toothache	1 (2.2)	1 (2.1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2.1)
Abdominalgia	1 (2.2)	1 (2.1)	1 (2.2)	0 (0)	0 (0)	0 (0)	2 (2.1)
Constipation	2 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2.1)
Chest discomfort	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	1 (1.1)
Abdominal discomfort	0 (0)	2 (2.1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.1)
Pruritus	3 (6.5)	3 (6.4)	1 (2.2)	1 (2.2)	1 (2.1)	0 (0)	5 (5.3)
Ecematous	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	1 (1.1)
Fever	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	1 (1.1)
Oropharyngeal pain	1 (2.2)	0 (0)	2 (4.3)	0 (0)	0 (0)	0 (0)	3 (3.2)
Hypersomnia	1 (2.2)	1 (2.1)	0 (0)	0 (0)	1 (2.1)	0 (0)	2 (2.1)
Dizzy	1 (2.2)	0 (0)	0 (0)	1 (2.2)	0 (0)	1 (2.2)	2 (2.1)
Temporomandibular syndrome	0 (0)	1 (2.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.1)
Hypodynamia	0 (0)	0 (0)	1 (2.2)	0 (0)	0 (0)	0 (0)	1 (1.1)

Abbreviations: ADR, adverse reaction; Reference 1, the first time taking the reference drug; Reference 2, the second time taking the reference drug; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

estimation of the GMR (test drug/reference drug) of C_{max} was 1.093, which fell within the range of 0.80–1.25, and the cutoff standard was -0.050 , which was less than 0. The ABE method was used to evaluate BE of the AUC_{0-t} and $AUC_{0-\infty}$, the GMR (90% CI) for AUC_{0-t} and $AUC_{0-\infty}$ were 99.86% (94.85–105.13%) and 100.41 (94.39–104.81%) between the test drug and reference drug in the fed group. The corresponding 90% CI were completely contained within the equivalence margin of 80–125% (Table 4).

The ANOVA results showed that the AUC_{0-t} of the test drug and the AUC_{0-t} , $AUC_{0-\infty}$ of the reference drug were significantly different between fasting and fed conditions. In addition, food had no significant effect on other PK parameters (Table 5).

Discussion

This random, three-period, three-sequence, partial replicated crossover, Phase I study under fasting and fed conditions was performed to evaluate the similarity of the PK, tolerability and safety between OCA and re-OCA formulations with a 10-mg oral administration dose. OCA passes through the enterohepatic circulation and is a highly

variable drug, intra-individual variability in the C_{max} , AUC_{0-t} may exceed 30%, therefore the partial replicated crossover design was selected.^{10,13} Subjects were given the reference drug for two cycles to obtain an accurate intra-individual coefficient of variation. As for the number of subjects, we assumed that the geometric mean ratio of AUC_{0-t} and C_{max} was from 0.95 to 1.05, setting the power (1- β) at 90%, the individual CV%=50%, and the one-sided test level $\alpha=0.05$. Considering the 20% shedding rate, a total of 48 subjects were enrolled in each group.¹⁴ According to the label of the branded formulation of OCA,¹⁵ it can be taken before and after meals, so fasting and fed groups were set up for the BE study.

OCA is mainly metabolized by OCA combined with glycine or taurine in the liver and excreted into the bile. These conjugates are absorbed through the small intestine and then circulate enterohepatically.¹⁶ The main active metabolites are Glyco-OCA and Tauro-OCA.¹⁷ The $AUC_{0-\infty}$ of OCA could not be calculated completely because OCA is subject to enterohepatic circulation, the PK parameters of the active metabolites, Glyco-OCA and Tauro-OCA were used as supporting data in this

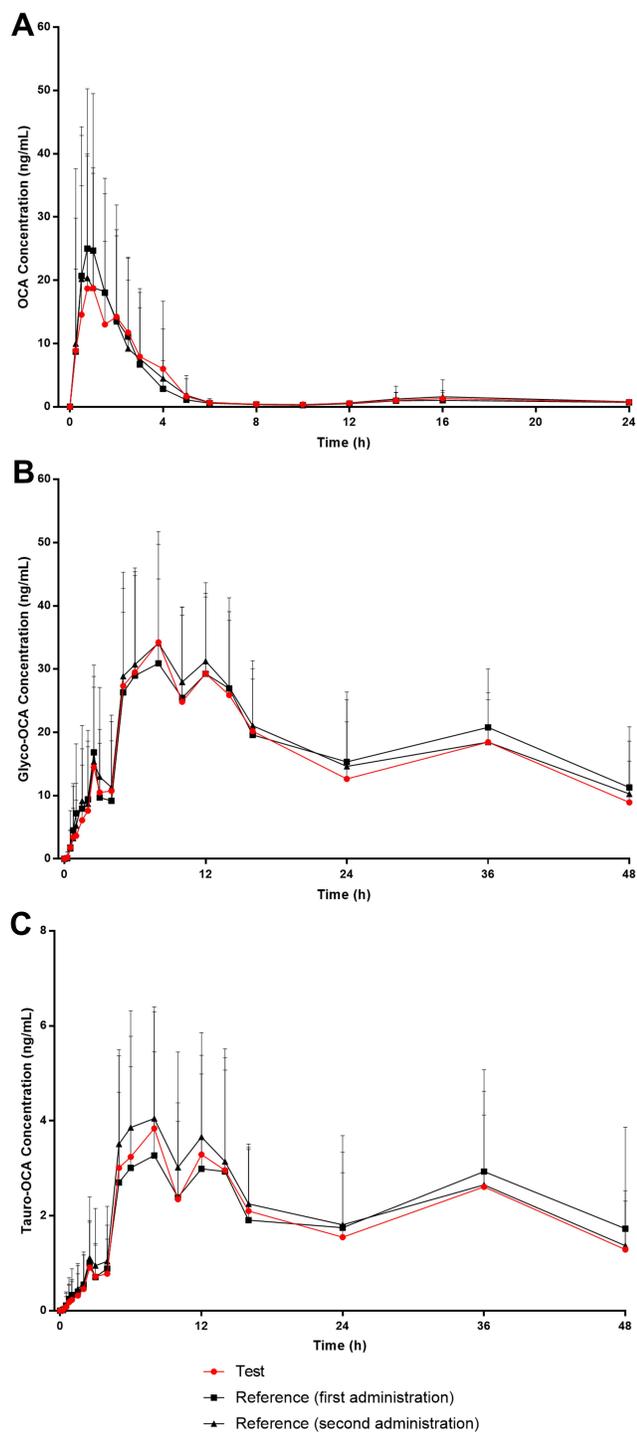


Figure 1 Mean plasma concentration-time curves of OCA, Glyco-OCA and Tauro-OCA after a single 10 mg dose of the test/reference drug in healthy subjects under fasting conditions. (A) OCA. (B) Glyco-OCA. (C) Tauro-OCA.

Abbreviations: OCA, obeticholic acid; Glyco-OCA, glyco-obeticholic acid; Tauro-OCA, tauro-obeticholic acid.

study. The PK results showed that the test drug had similar PK characteristics to the reference drug, and overlapped with the drug-time curve of the reference drug, with similar trends under fasting and fed

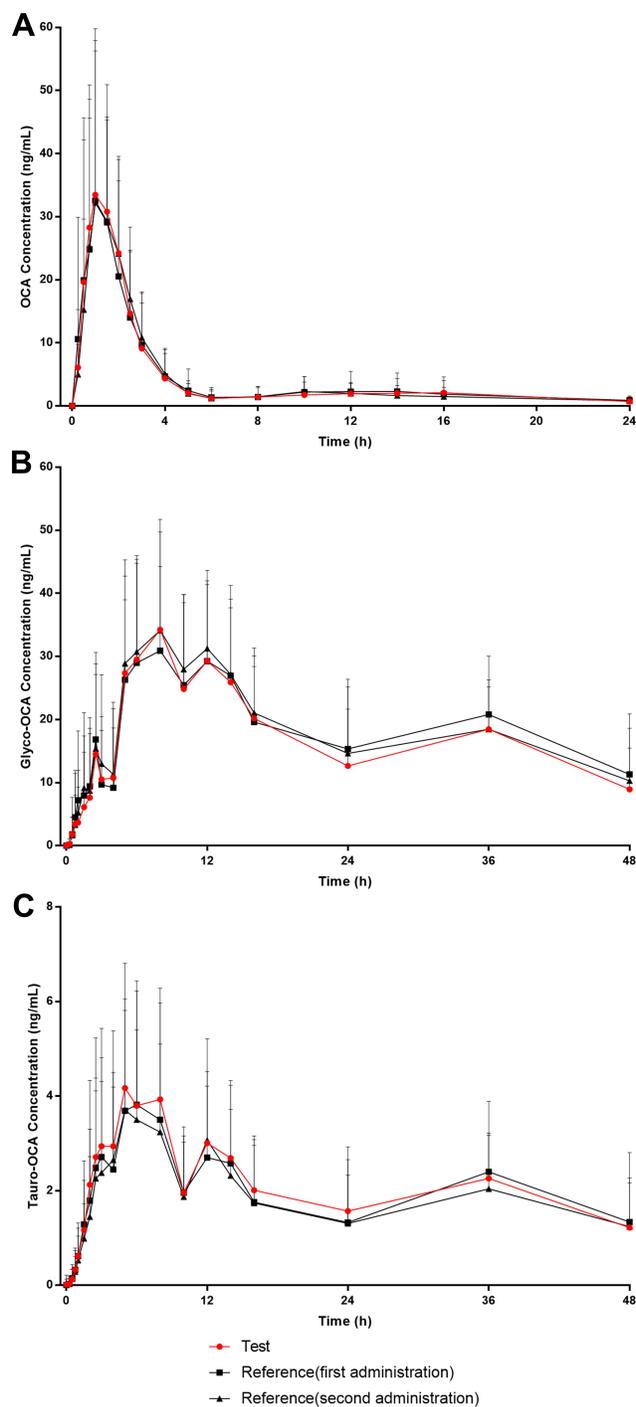


Figure 2 Mean plasma concentration-time curves of OCA, Glyco-OCA and Tauro-OCA after a single 10 mg dose of the test/reference drug in healthy subjects under fed conditions. (A) OCA. (B) Glyco-OCA. (C) Tauro-OCA.

Abbreviations: OCA, obeticholic acid; Glyco-OCA, glyco-obeticholic acid; Tauro-OCA, tauro-obeticholic acid.

conditions. The BE results proved that the test drug was equivalent to the reference drug in fasting group and fed group. Moreover, food had an influence on the PK of the OCA. The AUC_{0-t} of the test drug, and

Table 3 PK Parameters of the Test and Reference Formulations Under Fasting And Fed Conditions

Parameter	Fasting				Fed			
	Test (n = 46)		Reference (n = 47)		Test (n = 46)		Reference (n = 48)	
	Mean ± SD	%CV	Mean ± SD	%CV	Mean ± SD	%CV	Mean ± SD	%CV
OCA								
T _{max} (h)	1.50 (0.25, 5.00)	–	1.50 (0.50, 4.00)	–	1.00 (0.50, 3.00)	–	1.19 (0.50, 3.50)	–
C _{max} (ng/mL)	47.13 ± 27.24	57.8	47.72 ± 18.99	39.8	52.64 ± 23.75	45.1	49.34 ± 18.98	38.5
AUC _{0-t} (h ng/mL)	140.73 ± 71.77	51.0	134.01 ± 60.31	45.0	173.62 ± 68.51	39.5	173.12 ± 52.71	30.4
AUC _{0-∞} (h ng/mL)	170.89 ± 85.61	50.1	166.02 ± 70.20	42.3	202.84 ± 78.78	38.8	201.56 ± 66.31	32.9
t _{1/2z} (h)	63.51 ± 90.16	142.0	67.44 ± 45.47	67.4	56.30 ± 43.90	78.0	59.54 ± 42.02	70.6
Glyco-OCA								
T _{max} (h)	8.00 (0.75, 24.00)	–	8.00 (1.75, 29.00)	–	6.00 (2.00, 24.00)	–	6.00 (1.75, 25.00)	–
C _{max} (ng/mL)	42.58 ± 18.67	43.8	40.78 ± 15.06	36.9	39.38 ± 19.15	48.6	38.26 ± 16.41	42.9
AUC _{0-t} (h ng/mL)	1528.99 ± 599.25	39.2	1570.35 ± 707.57	45.1	1402.03 ± 638.05	45.5	1400.75 ± 669.39	47.8
AUC _{0-∞} (h ng/mL)	1925.90 ± 975.47	50.7	1855.66 ± 898.88	48.4	1683.03 ± 829.13	49.3	1619.88 ± 772.13	47.7
t _{1/2z} (h)	64.29 ± 49.22	76.6	48.71 ± 19.62	40.3	47.16 ± 24.86	52.7	45.68 ± 17.01	37.2
Tauro-OCA								
T _{max} (h)	8.00 (5.00, 48.00)	–	11.00 (5.00, 38.50)	–	6.00 (2.00, 72.00)	–	6.50 (3.00, 72.00)	–
C _{max} (ng/mL)	4.79 ± 3.10	64.7	4.90 ± 2.75	56.2	5.36 ± 3.11	57.9	4.77 ± 2.26	47.4
AUC _{0-t} (h ng/mL)	217.81 ± 146.02	67.0	224.98 ± 147.77	65.7	200.20 ± 104.45	52.2	203.54 ± 136.17	66.9
AUC _{0-∞} (h ng/mL)	319.28 ± 285.38	89.4	404.11 ± 437.18	108.2	339.87 ± 512.58	150.8	250.43 ± 160.72	64.2
t _{1/2z} (h)	90.17 ± 124.35	137.9	126.61 ± 225.93	178.5	79.17 ± 99.75	126.0	57.70 ± 29.49	50.2

Notes: Values are presented as mean ± SD, except T_{max}, which is the median (min, max).

Abbreviations: PK, pharmacokinetic; C_{max}, maximum plasma concentration; AUC_{0-t}, area under the concentration curve from 0 time to the last time point; AUC_{0-∞}, area under the concentration curve from 0 time to infinity; t_{1/2z}, terminal elimination half-life; T_{max}, time to C_{max}; SD, standard deviation; OCA, obeticholic acid; Glyco-OCA, glyco-obeticholic acid; Tauro-OCA, tauro-obeticholic acid.

Table 4 BE Statistics Under Fasting and Fed Conditions by Using RSABE or ABE

Parameter	Point Estimate	90% CI	S _{WR}	Critical Bound Value	Method	Outcome
Fasting						
C _{max} (ng/mL)	1.009	0.865 ~ 1.177	0.445	-0.110	RSABE	BE
AUC _{0-t} (h ng/mL)	1.015	0.926 ~ 1.113	0.370	-0.078	RSABE	BE
AUC _{0-∞} (h ng/mL)	0.983	0.878 ~ 1.101	0.448	-0.115	RSABE	BE
Fed						
C _{max} (ng/mL)	1.093	0.998 ~ 1.196	0.340	-0.050	RSABE	BE
AUC _{0-t} (h ng/mL)	0.999	0.949 ~ 1.051	0.168	–	ABE	BE
AUC _{0-∞} (h ng/mL)	1.004	0.944 ~ 1.068	0.180	–	ABE	BE

Abbreviations: PK, pharmacokinetic; C_{max}, maximum plasma concentration; AUC_{0-t}, area under the concentration curve from 0 time to the last time point; AUC_{0-∞}, area under the concentration curve from 0 time to infinity; CI, confidence intervals; S_{WR}, within-subject standard deviation.

AUC_{0-t}, AUC_{0-∞} of the reference drug in the fed group were higher than that of the fasting group, and the T_{max} of OCA were lower, which explained why food may increase the absorption of OCA.

As for safety, the main ADRs occurred in the subjects taking 10 mg of OCA tablets (test or reference drug) under fasting condition were pruritus (7 cases), low high-density lipoprotein cholesterol (6 cases), while the main ADRs in

the fed group were low high-density lipoprotein cholesterol (9 cases) and elevated bilirubin (5 cases). These main ADRs were consistent with those reported in previous studies.^{18–20} Comparing the incidence of ADRs between reference drug and test drug in the fasting and fed groups, there was no significant difference in the incidence between the two drugs, indicating that the safety of the two drugs was similar.

Table 5 Effects of Fasting and Fed Conditions on the PK Profile of Obeticholic Acid

Parameter	Test Drug		Reference Drug	
	ANOVA	Mann-Whitney U-test	ANOVA	Mann-Whitney U-test
C _{max} (ng/mL)	0.304	–	0.675	–
AUC _{0–t} (h ng/mL)	0.027*	–	0.000*	–
AUC _{0–∞} (h ng/mL)	0.066	–	0.004*	–
t _{1/2z} (h)	0.627	–	0.354	–
T _{max} (h)	–	0.074	–	0.692

Note: *P<0.05.

Abbreviations: PK, pharmacokinetic; C_{max}, maximum plasma concentration; AUC_{0–t}, area under the concentration curve from 0 time to the last time point; AUC_{0–∞}, area under the concentration curve from 0 time to infinity; t_{1/2z}, terminal elimination half-life; T_{max}, time to C_{max}; SD, standard deviation.

Conclusion

In this paper, we successfully verified that the test preparation is BE to the reference preparation in Chinese healthy subjects under both fasting and fed conditions. We also determined that food may affect the PK profiles of the two drugs. In addition, both preparations were safe with no serious or unexpected ADRs.

Data Sharing Statement

The raw data of this study will not be shared because of agreements.

Ethical Approval

This study was approved by the Medical Ethics Committee of the Third Xiangya Hospital of Central South University and was performed according to the ethical standards laid down in the 1964 Declaration of Helsinki.

Informed Consent

Informed consent was obtained by all individual participants included in the study.

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Author Contributions

All authors contributed to data analysis, drafting and revising of the article, gave final approval of the version to be

published, agreed on the journal to which the article was submitted and agreed to be accountable for all aspects of the work.

Disclosure

Hai-Tao Yu is an employee of Nanjing Chia Tai Tianqing Pharmaceutical Co., Ltd. The authors report no other potential conflicts of interest in this work.

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