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Pharmacokinetics and bioequivalence evaluation of acamprosate calcium tablets in healthy Chinese volunteers

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ABSTRACT

Background: Few pharmacokinetic data of acamprosate were available in Chinese population and no medication is approved for alcohol dependence in China.
Purpose: 1. Investigate the pharmacokinetic properties of acamprosate calcium in healthy Chinese male volunteers on single- and multiple-dose administration. 2. Compare the bioequivalence of two formulations of acamprosate calcium tablets both under fasting and fed conditions.
Methods: This open-label, randomized study included 3 stages. In each stage, a 2-way crossover bioequivalence study was conducted to study the pharmacokinetic properties and bioequivalence of acamprosate calcium tablets on multiple dosing after standardized meals, single dosing under fasting conditions and fed conditions, respectively. The washout period between each treatment in a stage and between each stage was 1 week. Plasma acamprosate calcium was quantified by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Tolerability was evaluated by monitoring adverse events, physical examinations, 12-lead ECG, and laboratory tests.
Results: Totally, 36 male subjects were enrolled in the study and all of them completed the whole 3 study stages. Main pharmacokinetic parameters of test and reference formulations were as follows: multiple dosing, T_{max} 9.94 ± 6.59 and 9.47 ± 5.47 h, C_{max} 435.74 ± 348.10 and 346.54 ± 155.66 ng · mL^{-1}, $AUC_{0\text{-}t}$ 8600.52 ± 5264.77 and 9315.10 ± 6820.03 ng · mL^{-1} · h, $AUC_{0\text{-}\infty}$ 8845.38 ± 5838.18 and 9669.24 ± 7326.53 ng · mL^{-1} · h, $t_{1/2}$ 10.06 ± 8.83 and 9.87 ± 10.35 h; single dosing under fasting conditions, T_{max} 7.29 ± 4.87 and 6.57 ± 1.85 h, C_{max} 247.85 ± 110.05 and 244.64 ± 132.43 ng · mL^{-1}, $AUC_{0\text{-}t}$ 3385.41 ± 1418.92 and 3496.24 ± 1767.29 ng · mL^{-1} · h, $AUC_{0\text{-}\infty}$ 3781.53 ± 1556.96 and 3829.56 ± 1981.25 ng · mL^{-1} · h, $t_{1/2}$ 13.07 ± 17.24 and 10.26 ± 7.78 h; single dosing under fed conditions, T_{max} 17.72 ± 9.42 and 19.50 ± 9.84 h, C_{max} 183.90 ± 74.52 and 168.14 ± 60.67 ng · mL^{-1}, $AUC_{0\text{-}t}$ 3181.71 ± 1368.24 and 3575.11 ± 1416.39 ng · mL^{-1} · h, $AUC_{0\text{-}\infty}$3442.39 ± 2002.53 and 3624.44 ± 1418.12 ng · mL^{-1} · h, $t_{1/2}$ 8.76 ± 12.28 and 6.67 ± 4.84 h, respectively. In all three stages, 90% CIs for the test/reference ratio of $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were located within 80%–125%, 90% CI for C_{max} was within 70%–143%.
Conclusions: Similar pharmacokinetic results of acamprosate calcium tablets in healthy Chinese volunteers were found as those in Caucasic population. In all three stages, the two formulations met the regulatory criteria for bioequivalence.
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1. Introduction

Alcohol dependence is a severe problem worldwide. According to the World Health Organization, approximately 4% of all deaths in the world are caused by alcohol abuse (World Health Organization, 2011). In the United States, estimates of alcohol dependence is reported to be 12.5% and the price of the health care resulting from alcohol abuse is estimated at more than US$ 26 billion per year (Wright and Myrick, 2006; Saivin et al., 1998). In China, the rate of alcohol dependence is 3.7% in 1992, equivalent to approximately 50 million and the prevalence is increasing (Hao et al., 2004). However, by now, no medication is approved in China for alcohol dependence (Tang et al., 2012). Acamprosate is the newest approved drug in the United States for treatment of alcohol dependence. It is structurally similar to gamma-aminobutyric acid (GABA) and the inhibition of neuronal hyperexcitability mediated by antagonism or modulation of activity at the NMDA receptor may be one explanation of mechanism of action (Wright and Myrick, 2006; Saivin et al., 1998; Scott et al., 2005).

Acamprosate tablets have been in clinical use for more than 10 years for the indication of maintaining abstinence in alcohol-dependent

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patients in USA and many European countries. Although the pharmacokinetic characteristics of acamprosate calcium have been studied previously (Saivin et al., 1998), few data in Chinese population were published.

The present study aimed to 1. Investigate the pharmacokinetic properties of acamprosate calcium in healthy Chinese male volunteers on single- and multiple-dose administration. 2. Compare the bioequivalence of two formulations of acamprosate calcium tablets both under fasting and fed conditions. This was a registered study approved by China Food and Drug Administration.

2. Subjects and Methods

2.1. Study Design and Drug Administration

This open-label, randomized study planning to enroll 36 healthy male Chinese subjects included 3 stages. In each stage, a 2-way crossover bioequivalence study was conducted. The washout period between each treatment in a stage and between each stage was 1 week. Fig. 1 shows the flowchart of the whole study.

In the first stage, each subject received test or reference formulation of 666 mg acamprosate calcium tablets randomly, three times per day (7:30 AM, 1:30 PM, and 7:30 PM) after standardized meals (total energy ~900 calories; 30% protein, 60% carbohydrate, 10% fat) till the 8th day morning. In the second stage, each subject received single dose of test or reference formulation of 666 mg acamprosate calcium tablets randomly, under fasting conditions (overnight fast for 12 h). In the third stage, each subject received single dose of test or reference formulation of 666 mg acamprosate calcium tablets randomly, under fed conditions (high-fat, high-calorie; total energy 1000 calories, 60% fat, 15% protein, 25% carbohydrate). The study drug was administered with 200 mL water. Additional water intake was permitted 2 h after dosing.

2.2. Study Population

Healthy male Chinese volunteers aged from 18 to 40 and with a body mass index between 19 and 24 kg/m^2 were eligible for recruitment. Additional inclusion criteria included a healthy status confirmed by medical history, physical examination, 12-lead ECG, and laboratory tests (hematology, blood biochemistry, hepatic function, urinalysis, hepatitis B surface antigen, tests for alcohol and other drugs of abuse) and nonsmoking status. Those with any allergic history or history of cardiac, pulmonary, renal, hepatic, gastrointestinal, or hematologic abnormality or any other acute or chronic disease were excluded.

The study protocol was approved by the Independent Ethics Committee of West China Hospital, Sichuan University (Chengdu, China). All subjects provided written informed consent.

2.3. Formulations

Acamprosate calcium enteric-coated tablets (CAMPRAL®, 333 mg; lot no. A174451, A206998; expiration date May 2013) purchased from Merck Santé s.a.s. and acamprosate calcium enteric-coated tablets (333 mg; lot no. 120401; expiration date Mar 2014) manufactured by Kelun Pharmaceuticals Co. Ltd.(Sichuan, People's Republic of China) were used as the reference and test formulations, respectively.

2.4. Sampling and Medical Supervision

Blood samples (~1.5 mL) were collected before and at 3, 4, 6, 8, 10, 12, 14, 16, 20, 24, 30, 36, 42, 48, 54, 60, 72, and 84 h after dosing in the third stage and last dosing of the first stage. At 7:30 AM and 7:30 PM on the 6th and 7th day of multiple-dosing stage, predose samples were collected to check the trough level. In the second stage, blood samples were collected before and at 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 32, 40, 48, 60, 72, and 84 h after dosing. Fig. 2 shows the administration and dosing schedule of one period in stage 1.

The subjects were under continuous medical supervision in the Phase I Unit of West China Hospital, Sichuan University, throughout the study. Tolerability was evaluated by monitoring adverse events, physical examinations, 12-lead ECG, and laboratory tests. All laboratory tests were performed at the laboratory of West China Hospital, Sichuan University, which was authenticated by College of American Pathologists (CAP).

2.5. Assays of Acamprosate Calcium

Plasma acamprosate calcium was quantified by a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method developed and validated before the clinical study. API 3000 LC-MS/MS system and Gemini C_{18} analysis column (4.6 × 4.0 mm, 5 μm) were used. The protein of 150 μl plasma sample was precipitated with 500 μl acetonitrile. After evaporation of the supernatant, the residue was dissolved in 100 μl mobile phase, washed with 1.0 ml dichloromethane, and injected (15 μl) onto the column. The mobile phase of acetonitrile-0.2% ammonium water(10:90, v:v, adjusted pH 4.0 with formic acid) was pumped at 0.4 ml.min^{-1} through the column. Acetylate taurine calcium was internal standard (IS). Transitions for multiple reaction monitoring (MRM) were at m/z 180.2 → 79.9 and 166.1 → 79.9 for acamprosate calcium and IS, respectively. The MS parameters were optimized for the detection: curtain gas 7, ion spray voltage −4500 V, source temperature 500 °C, nebulizer gas 8, declustering potential −75 V, collision energy −35 V, FP −70 V, entrance potential −7 V, collision cell exit potential −11.6 V. Typical chromatograms are shown in Fig. 3. The retention time for acamprosate calcium and IS were 2.73 min and 2.72 min, respectively. The calibration curve was linear over the range of 2.0–1000 ng · mL^{-1}. The limit of quantification (LOQ) in plasma was 2.0 ng · mL^{-1}. The method recovery was 96%–114%; the intra-day RSD less than 5% and inter-day RSD less than 9%. Matrixes effect of acamprosate calcium was below 11%. The results of all stability studies were fit for requirement.

2.6. Pharmacokinetics and Bioequivalence Analysis

Pharmacokinetic parameters of acamprosate calcium were calculated with WinNonlin Version 6.1 (Pharsight Corporation, Mountain View,

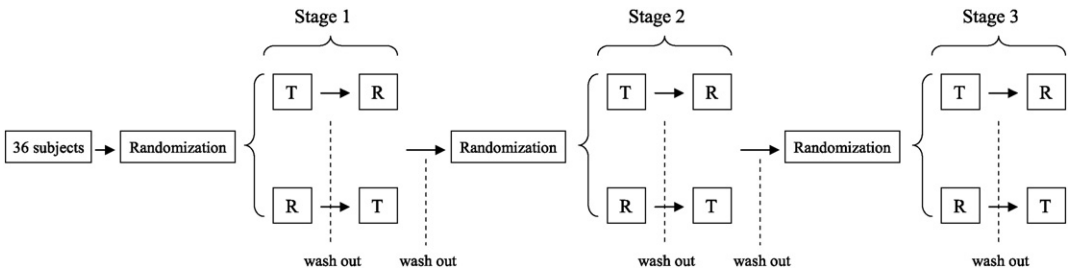

Fig. 1. Flowchart of the study. (The washout period = 1 week; T = Test formulation; R = Reference formulation.)

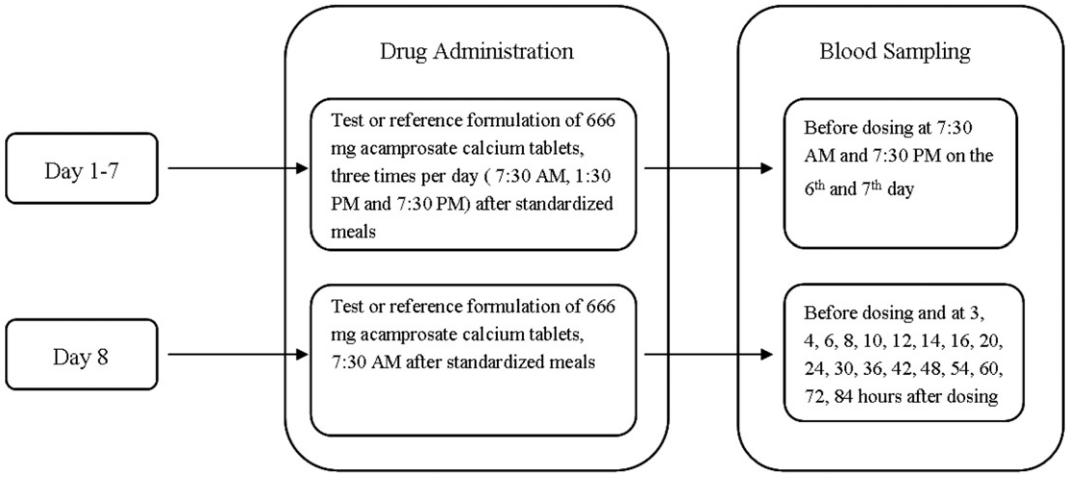

Fig. 2. Administration and dosing schedule of one period in stage 1.

California) by noncompartmental analysis method. C_{max} and T_{max} were obtained directly from the concentration–time data. AUC_{0-t} was calculated using the linear trapezoidal rule. $AUC_{0-\infty}$ was calculated as the sum of AUC_{0-t} and Ct/λ. *Ct* was the last measured concentration and λ was the slope of linear regression of the log-transformed concentration–time curve, and $t_{1/2}$ was calculated as $0.693/\lambda$.

The relative bioavailability of the test formulation was calculated as $F = AUC_{0-t(test)}/AUC_{0-t(reference)} \times 100\%$. 90% CIs for the test/reference ratio of log-transformed C_{max} and AUC were evaluated by analysis of variance (ANOVA) using WinNonlin Version 6.1. T_{max} was tested by paired Wilcoxon test for significant differences. According to China Food and Drug Administration proposal, the formulations were considered to be bioequivalent if the 90% CI for AUC was located within 80%–125% and C_{max} within 70%–143% (State Food and Drug Administration, n.d.).

Other pharmacokinetic parameters were analyzed using SPSS Version 18.0 (SPSS Inc. Chicago, IL, USA). The paired T-test or paired Wilcoxon test was used to determine significant differences. For all the analyses, $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Study Population

We totally enrolled 36 male subjects and all of them completed the whole study. The demographic details (mean ± SD) were age 22.1 ± 1.6 years, weight 60.9 ± 5.7 kg, height 1.70 ± 0.05 cm, body mass index 21.0 ± 1.2 kg/m^2.

3.2. Pharmacokinetic Properties

The detailed pharmacokinetic parameters of the two formulations of acamprosate calcium tablets on multiple dosing after standardized meals, single dosing under fasting conditions and fed conditions are presented in Table 1. The mean plasma acamprosate calcium concentration–time curves of test and reference formulations are shown in Fig. 4.

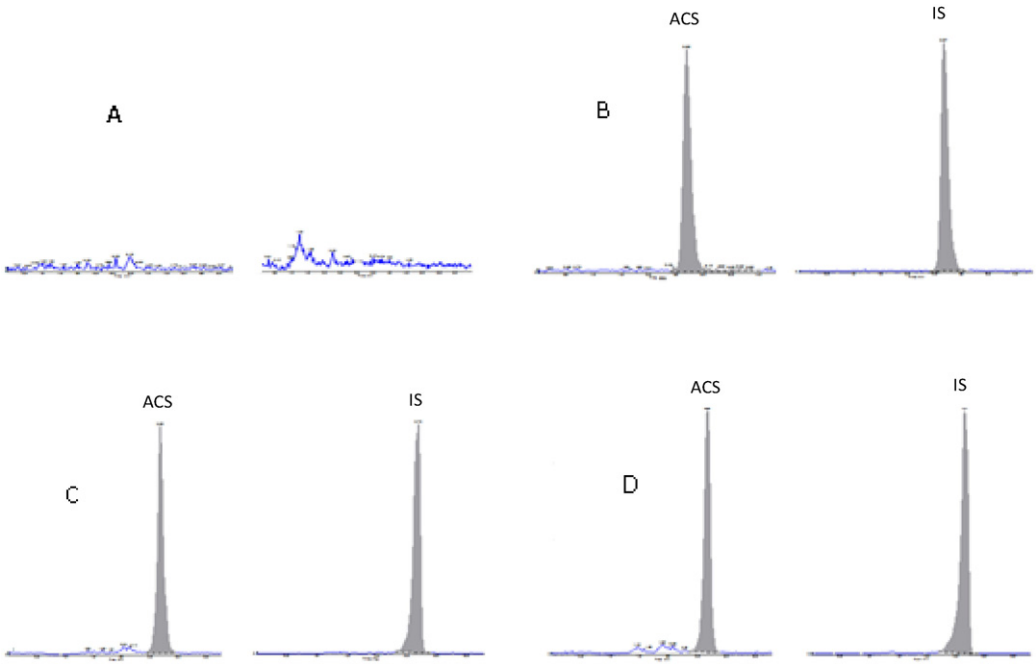

Fig. 3. LC-MS/MS of acamprosate of blank plasma solution (A), reference standards solution (B), blank plasma with reference standards solution (C), and subject plasma solution(D).

Table 1
Pharmacokinetic parameters of two formulations of acamprosate calcium tablets on multiple dosing after standardized meals, single dosing under fasting conditions and fed conditions in healthy Chinese volunteers. All values are mean ± SD (n = 36).

PK parameter	Multiple dosing		Single dosing (fasting conditions)		Single dosing (fed conditions)	
	Test	Reference	Test	Reference	Test	Reference
T_{max}, h	9.94 ± 6.59	9.47 ± 5.47	7.29 ± 4.87	6.57 ± 1.85	17.72 ± 9.42	19.50 ± 9.84
C_{max}, ng · mL^{-1}	435.74 ± 348.10	346.54 ± 155.66	247.85 ± 110.05	244.64 ± 132.43	183.90 ± 74.52	168.14 ± 60.67
AUC_{0-t}, ng · mL^{-1} · h	8600.52 ± 5264.77	9315.10 ± 6820.03	3385.41 ± 1418.92	3496.24 ± 1767.29	3181.71 ± 1368.24	3575.11 ± 1416.39
$AUC_{0-\infty}$, ng · mL^{-1} · h	8845.38 ± 5838.18	9669.24 ± 7326.53	3781.53 ± 1556.96	3829.56 ± 1981.25	3442.39 ± 2002.53	3624.44 ± 1418.12
$t_{1/2}$, h	10.06 ± 8.83	9.87 ± 10.35	13.07 ± 17.24	10.26 ± 7.78	8.76 ± 12.28	6.67 ± 4.84
MRT_{0-t}, h	18.19 ± 6.10	17.92 ± 6.44	16.80 ± 5.74	16.77 ± 6.41	25.21 ± 9.06	26.26 ± 8.11
C_{min}, ng · mL^{-1}	211.48 ± 110.03	222.87 ± 148.72	—	—	—	—
C_{avg}, ng · mL^{-1}	294.48 ± 154.91	293.25 ± 154.01	—	—	—	—
V/F, L	1364.02 ± 1210.64	1239.11 ± 1050.95	2773.04 ± 2066.18	2818.69 ± 2009.58	2308.73 ± 1595.85	2141.96 ± 1976.71
Cl/F, L/h	102.65 ± 54.87	107.81 ± 74.86	198.94 ± 72.97	221.16 ± 111.64	239.82 ± 108.12	220.08 ± 107.43

3.3. Bioequivalence

The 90% CIs for the test/reference ratio of log-transformed C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ were shown in Table 2. In all three stages, 90% CIs of AUC_{0-t} and $AUC_{0-\infty}$ were located within 80%–125%, 90% CI for C_{max} was within 70%–143%. The two formulations were considered to be bioequivalent on multiple dosing, single dosing under fasting conditions and fed conditions.

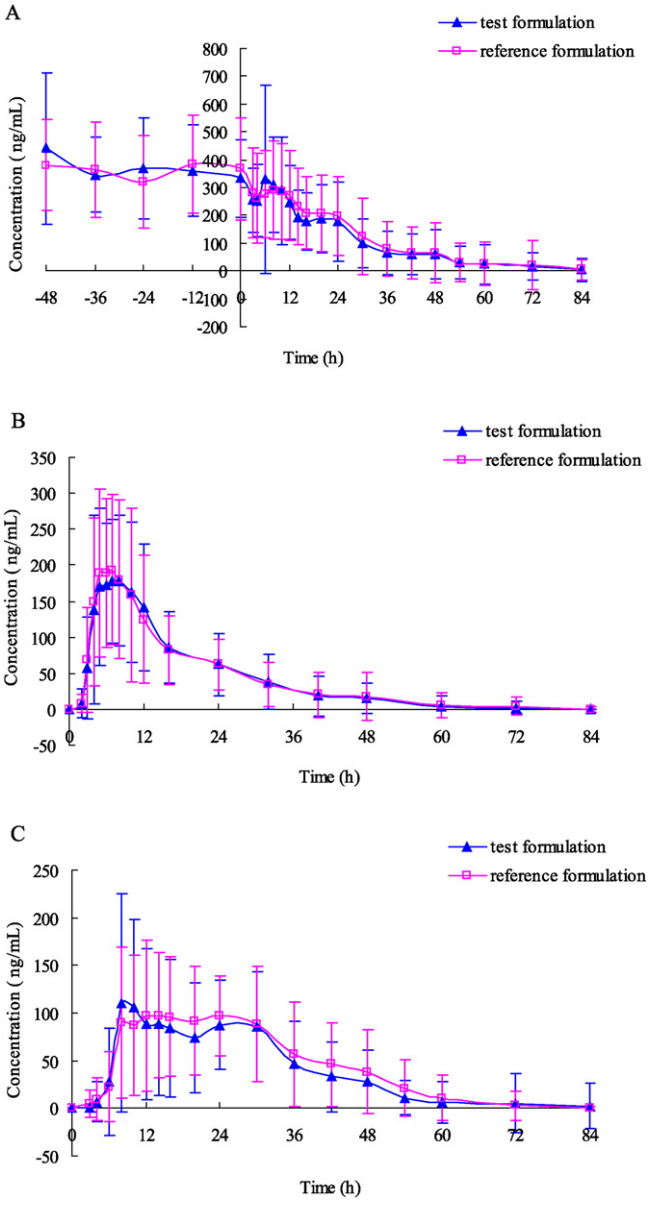

Fig. 4. Mean plasma concentration–time curves of test and reference formulations of acamprosate calcium tablets on multiple dosing after standardized meals (A), single dosing under fasting conditions (B) and fed conditions (C).

3.4. Tolerability

Among the 36 subjects, 3 of them reported looser stools, which happened during the multiple-dosing stage, both after administration of test and reference formulations. One subject reported abdominal pain after administration of test formulation during the multiple-dosing stage. One subject reported skin rash after administration of reference formulation during the multiple-dosing stage. The above adverse events were rated as mild and considered possibly associated with the study drug. No other adverse events were observed or reported. Physical examination, electrocardiograms, and laboratory tests did not suggest any clinically significant abnormality.

4. Discussion

Although acamprosate has been clinically used for decades, few data on the pharmacokinetic properties of acamprosate were openly published. To our knowledge, the pharmacokinetic data of acamprosate were mainly based on the internal reports of Lipha company, which have been reviewed previously (Saivin et al., 1998). The present study investigated the pharmacokinetic properties of acamprosate calcium in healthy Chinese male volunteers on single- and multiple-dose administration and compared the bioequivalence of two formulations of acamprosate calcium tablets both under fasting and fed conditions.

Acamprosate is available in 333 mg enteric-coated tablets and the recommended dosage is two 333 mg tablets taken orally three times daily (Lipha, 1995). After oral administration, acamprosate is poorly absorbed, with an average bioavailability of about 11% under fasting conditions (Fourtillan, 1990). Considering the pharmacokinetic properties and dosage form of tested formulations (European Medicines Agency, n.d.; FDA Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies, 2002), we designed this 3-stage study to evaluate the PK properties and bioequivalence of acamprosate calcium tablets under different conditions.

Previous studies indicated that after administration of single oral dose of 666 mg acamprosate calcium tablets in healthy volunteers, C_{max} ranged from 162 ± 22 to 212 ± 83 ng · mL^{-1}, $AUC_{0-\infty}$ from 1988 ± 431 to 4110 ± 442 ng · mL^{-1} · h, and T_{max} was between 4.3 ± 1.2 and 15.3 ± 2.2 h (Saivin et al., 1998; Fourtillan, 1992; Sennesael, 1992; Dewland, 1995). After multiple-dose administration, Steady-state plasma concentrations of acamprosate were reached within 5 days, ranging from 370 ± 145 to 644 ± 386 ng · mL^{-1}. Acamprosate is not metabolized in the liver and approximately 90% of the drug is excreted unchanged in the urine. The terminal half-life ranges from 13.0 to 32.7 h after oral dosing of 666 mg of acamprosate calcium tablets (Saivin et al., 1998; Fourtillan, 1992; Sennesael, 1992;

Table 2
Bioequivalence evaluation of two formulations of acamprosate calcium tablets in healthy Chinese volunteers (n = 36).

	Multiple dosing		Single dosing (fasting conditions)		Single dosing (fed conditions)	
	Test/reference ratio	90% CI	Test/reference ratio	90% CI	Test/reference ratio	90% CI
AUC_{0-t}	98.85%	85.19%–113.70%	102.99%	91.27%–116.22%	89.19%	80.76%–98.49%
$AUC_{0-\infty}$	98.30%	84.49%–113.96%	105.84%	92.36%–121.29%	91.97%	82.73%–102.24%
C_{max}	115.26%	97.91%–135.69%	103.94%	92.41%–116.9%	108.57%	96.11%–122.63%

Dewland, 1995). In the present study, steady state of acamprosate plasma concentrations was reached around the 5th day of multiple dosing, which accorded with the previous studies. Other pharmacokinetic properties, including C_{max}, AUC, T_{max}, and $t_{1/2}$ were in the same range as in the previously reported studies (Saivin et al., 1998; Fourtillan, 1992; Sennesael, 1992; Dewland, 1995). Our study showed that the accumulation ratio between day 8 and 1 was 2.48 in test formulation and 2.66 in reference formulation, both corroborating the earlier results (Pelc, 1993). The present study indicated similar pharmacokinetic results of acamprosate calcium tablets in healthy Chinese volunteers as those found in Caucasic population.

Previous studies indicated that co-administration of acamprosate with food decreases bioavailability as measured by C_{max} and AUC, by approximately 42% and 23%, respectively, while T_{max} was not significantly modified (Fourtillan, 1992). However, the food effect on absorption is not clinically significant and no adjustment of dose is necessary (Saivin et al., 1998; Lipha, 1995). In the present study, C_{max} of both test and reference formulations were decreased by 25%–30% in accordance to previous studies. However, our study indicated that T_{max} were prolonged from 7.29 to 17.72 h (test formulation) and 6.57 to 19.50 h (reference formulation) under fed conditions compared with those under fasting conditions. Furthermore, AUC were not significantly modified. The possible reason of such discordance between results might be the food conditions of the test meals. In the previous study, standard meals (total energy 900 calories; 30% protein, 60% carbohydrate, 10% fat) were used; however, in the present study, we used high-fat, high-calorie meals (total energy 1000 calories, 60% fat, 15% protein, 25% carbohydrate). Our study suggested that the food effect on acamprosate absorption may be influenced by food conditions.

In the present study, double-peak phenomenon was observed in the concentration–time curves of many subjects, especially under fed conditions. The double-peak phenomenon may be attributed to the formulation being enteric coated and multiple absorption sites in the gut. The tested enteric-coated tablets formulations in the present study could be absorbed in multiple sites, including duodenum, jejunum, and ileum. Furthermore, as discussed above, the mean time to reach maximum plasma drug concentration was prolonged under fed conditions, suggesting that high-fat, high-calorie meals could delay gastic emptying of acamprosate, which made the double-peak phenomenon more obvious. In two previous pharmacokinetic studies of acamprosate solution formulation (Dewland, 1991; Fourtillan, 1989), no double-peak phenomenon was observed, which suggested that enterohepatic recycling may be ruled out for the reasons of double-peak phenomenon. In previously reported data of acamprosate enteric-coated tablets, double-peak phenomenon was observed in Caucasian people, too (Fourtillan, 1990).

In a study by Anders etc. in 2010 (Hammarberg et al., 2010), an LC-MS method was used to examine the levels of acamprosate both in human plasma and cerebrospinal fluid (CSF). The calibration curve was linear over the range of 50–1000 ng · mL^{-1} and the author estimated the level of acamprosate in CSF to be between 9 and 33 ng/mL, which was below the LOQ. In the present study, the use of LC-MS⁄ MS appeared to increase the sensitivity for measurement. Furthermore, we used acetylate taurine calcium as internal standard and increased the sensitivity as compared with the previously reported methods (Rhee et al., 2008; Burattini et al., 2008). The LOQ of the present method was 2.0 ng · mL^{-1}. The method validation results of specificity, precision, accuracy, recovery, and stability suggested that our method was suitable for the assay of acamprosate in human plasma.

A limitation of the present study is that we did not examine the levels acamprosate in the human central nervous system as the above-mentioned study because we failed to get the approval of the Ethics Committee about the sampling of cerebrospinal fluid of subjects.

5. Conclusions

Similar pharmacokinetic results of acamprosate calcium tablets in healthy Chinese volunteers were found as those in Caucasic population. In all three stages, the two formulations met the regulatory criteria for bioequivalence.

Conflict of Interest

The authors have declared that no financial relationships with any organizations that might have an interest in the submitted work; no any other relationships or activities that could appear to have influenced the submitted work.

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