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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,

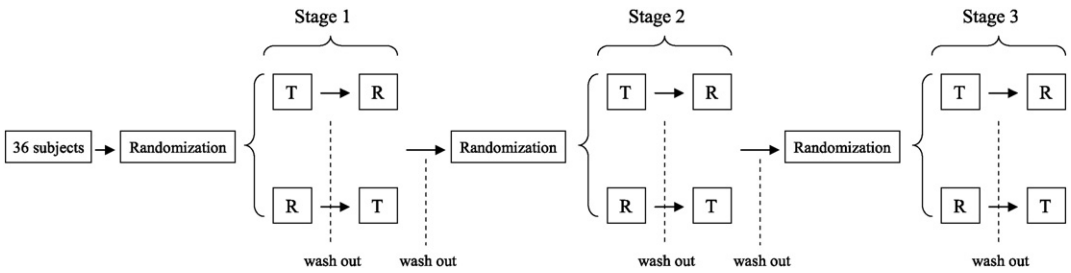

Fig. 1. Flowchart of the study. (The washout period = 1 week; T = Test formulation; R = Reference formulation.)

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