Original Research

Pharmacokinetic Properties and Tolerability of Cycloserine Following Oral Administration in Healthy Chinese Volunteers: A Randomized, Open-Label, Single- and Multiple-Dose 3-Way Crossover Study

Huili Zhou, MS; Guolan Wu, MS; Xingjiang Hu, MS; Meixiang Zhu, PhD; You Zhai, MS; Jian Liu, MS; Jianzhong Shentu, MD, PhD; and Lihua Wu, MD, PhD

Research Center of Clinical Pharmacy, State Key Laboratory for Diagnosis and Treatment of Infectious Disease, First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

ABSTRACT

Purpose: A new generic formulation of cycloserine has been developed in China but the pharmacokinetic properties of cycloserine in the Chinese population have not been reported. The aim of our study was to evaluate the pharmacokinetic properties and tolerability of single and multiple oral administrations of cycloserine capsules in healthy Chinese volunteers.

Methods: This open-label, single- and multiple-dose 3-way crossover study was conducted in healthy Chinese volunteers. Subjects were randomized to receive a single dose of cycloserine (250, 500, or 1000 mg) in separate trial periods, with a 1-week washout between periods. Those allocated to the 250-mg dose continued into the multiple-dose phase, in which they received 250 mg BID for 5 consecutive days. During the single-dose phase, blood samples were collected at regular intervals from 0 to 72 hours after drug administration and the concentrations of cycloserine were determined using LC-MS/MS. During the multiple-dose phase, blood samples were obtained before drug administration on Days 4, 5, and 6 to determine the C_{min} at steady state. On Day 6, blood samples were also collected from 0 to 72 hours after drug administration. Pharmacokinetic parameters were estimated using noncompartmental methods. Tolerability was determined using clinical evaluation and monitoring of adverse events.

Findings: The study enrolled 12 healthy Chinese volunteers (6 men: mean [SD] age = 23.0 [2.6] years, weight = 60.2 [6.2] kg, height = 170.0 [3.0] cm, and body mass index = 20.7 [1.7]; 6 women: mean [SD] age = 25.3 [1.4] years, weight = 51.5 [3.3] kg, height = 160.0 [4.0] cm, and body mass index = 20.1 [0.9]). After administration of a single dose, cycloserine was rapidly absorbed, reaching peak plasma concentrations approximately 0.84 hours after oral administration, and $t_{½}$ in plasma was about 13.0 hours. The geometric mean (SD) C_{max} value increased in proportion to cycloserine dose, from 19.42 (5.89) to 84.76 (21.74) mg/L, and the geometric mean (SD) $AUC_{0–72h}$ value increased from 264.16 (133.37) to 1153.87 (522.16) mg · h/L in the range of a 250- to 1000-mg dose. After administration of multiple doses of cycloserine 250 mg BID, the mean (SD) $t_{½}$ was 13.56 (4.38) hours, the apparent total clearance of the drug from plasma after oral administration was 1.02 (0.42) L/h, and the apparent volume of distribution was 18.22 (5.25) L, which were comparable with those after single dosing. The accumulation index was 2.19 (0.51), and the fluctuation was 1.05 (0.35). Results of the *t* tests of C_{max} and AUC found no significant differences between the male and female groups. No serious adverse events were reported, and there were no discontinuations due to adverse events.

Implications: The pharmacokinetic properties of cycloserine were linear at doses from 250 mg to 1000 mg. After multiple doses, the pharmacokinetic properties of cycloserine were consistent with those after single doses. At the doses studied, cycloserine appears to be well tolerated in these healthy volunteers. Chinese Clinical Trials registration: ChiCTR-TTRCC-13003982. (*Clin*

Accepted for publication March 11, 2015.
http://dx.doi.org/10.1016/j.clinthera.2015.03.015
0149-2918/$ - see front matter

© 2015 Published by Elsevier HS Journals, Inc.

Ther. 2015;▮:▮▮▮–▮▮▮) © 2015 Published by Elsevier HS Journals, Inc.

Key words: Chinese, cycloserine, LC-MS/MS, pharmacokinetic, tolerability.

INTRODUCTION

Tuberculosis continues to pose a massive threat to global health due to increasing drug resistance and exacerbating coexisting conditions such as HIV and diabetes.[1,2] Control of drug-susceptible tuberculosis is largely dependent on a standard 6-month chemotherapy regimen and new treatment-shortening regimens remain under development.[3–5] Cycloserine, a structural analogue of D-alanine amino acid, was recommended by World Health Organization guidelines as 1 of the 4 second-line drugs and it is used in conjunction with other tuberculostatic drugs to treat multidrug-resistant tuberculosis.[6,7] It acts by competition, inhibiting the enzymes indispensable for the synthesis of the peptidoglycan, which confers rigidity and stability to the mycobacteria tuberculosis cell membrane.[8] When given orally, cycloserine is rapidly absorbed at t_{max} of 0.75 hours in the fasting state.[9,10] Only a small proportion of cycloserine is metabolized in the liver, and most of the dose (70%) is excreted by the kidney.[8] The terminal half-life of cycloserine is 8 to 12 hours.[9,10]

A literature search of MEDLINE was conducted using the following terms: *cycloserine, pharmacokinetics, bioequivalence*, and *Chinese*. Although there were several pharmacokinetic studies in white,[10] Korean,[9] and Indian[11] populations, no reports were identified concerning the pharmacokinetic properties of cycloserine in a Chinese population. Therefore, the objective of our single- and multiple-dose study was to determine the pharmacokinetic properties and tolerability of a generic formulation of cycloserine in healthy Chinese adult volunteers. The effect of sex on the pharmacokinetic properties of cycloserine was evaluated as a secondary objective. The study was conducted to meet China Food and Drug Administration requirements for marketing of the new generic formulation.

SUBJECTS AND METHODS

Study Design

The protocol of this open-label, single- and multiple-dose 3-way crossover study was approved by the ethics committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (approval No. 2010-EC-96). The study was performed in accordance with the principles of the current revision of the Declaration of Helsinki concerning medical research in humans,[12] the International Conference on Harmonization Guideline for Good Clinical Practice,[13] the Guideline for Good Clinical Practice, and the Guideline for Pharmacokinetics Studies recommended by the China Food and Drug Administration.[14,15]

The study was conducted at the Phase I Clinical Research Center of the First Affiliated Hospital from September 2010 to June 2011. Subjects were admitted into the hospital at 7:00 pm the day before the study and fasted 10 hours before each drug administration. Treatments were administered with 240 mL water. Fasting was continued for an additional 4 hours after study drug administration. Water was allowed as needed up 2 hours before drug intake and from 2 hours after intake. A standardized lunch and dinner (920 [20] kcal; 65% carbohydrate, 20% protein, and 15% fat) were provided at 4 and 10 hours after administration. The consumption of alcohol, coffee, or grapefruit-containing drinks during the trial was forbidden. Intense physical activity and smoking were not allowed during the study period. According to the randomization plan, subjects were divided into 3 groups. The drug-intake sequence was determined by a randomization schedule.

Inclusion and Exclusion Criteria

Healthy Chinese men and women aged 18 to 40 years with body mass index between 19 and 25 were eligible for participation. The volunteers had been informed about the details, including the risks and benefits of this study, and they were free to withdraw at any time with any reason. Each volunteer provided written informed consent for participation before the study. Medical history, physical examination, 12-lead ECG, and various laboratory tests (eg, hematology, blood biochemistry, and urinalysis) were carried out before the beginning of the study. Women with childbearing potential were required to have a negative pregnancy test at screening.

Exclusion criteria included known hypersensitivity to any ingredient in this tablet; the presence of heart, kidney, neurologic, or metabolic disease; any acute or chronic disease; and the use of other drugs within 14 days before or during the trial.

Study Drugs

According to the randomization schedule generated using SAS version 9.0 (SAS Institute Inc, Cary,

Download English Version:

https://daneshyari.com/en/article/5825305

Download Persian Version:

https://daneshyari.com/article/5825305

Daneshyari.com