Pharmacokinetics of Pilsicainide Hydrochloride for Injection in Healthy Chinese Volunteers: A Randomized, Parallel-Group, Open-Label, Single-Dose Study

Qi Qiu, PhD; Wenfang Liu, MM; Jing Li, BS; Yongxiang Wei, MD; Kexu Yang, MM; Wei Suo, MS; Wei Wu, BS; Haiyan Du, PhD; Yingchao Zhang, BS; Guiping Zhao, BS; Zijie Zhou, BS; Yingming Zheng, BS; and Yang Lin, PhD

Clinical Pharmacology of Capital Medical University–Affiliated Beijing Anzhen Hospital, Beijing, People's Republic of China

ABSTRACT

Background: Pilsicainide hydrochloride is a class IC antiarrhythmic agent used for the treatment of supraventricular and ventricular arrhythmias and atrial fibrillation.

Objective: The objective of the present study was to determine the pharmacokinetics (PK) of a pilsicainide hydrochloride injection in healthy Chinese adults. The study was conducted to meet China State Food and Drug Administration requirements for the marketing of the new generic formulation of pilsicainide hydrochloride.

Methods: This Phase I, randomized, parallel-group, open-label, single-dose PK study was conducted in healthy Chinese volunteers. Subjects were randomized to receive a single dose of 0.25-, 0.50-, and 0.75-mg/kg pilsicainide hydrochloride with a 10-minute intravenous infusion. Serial blood and urine samples were collected up to 24 hours after dosing; drug concentrations in plasma and urine were then determined by using LC-MS/MS. The PK parameters of pilsicainide were calculated from the plasma concentration–time data according to noncompartmental methods. Safety profile was evaluated by monitoring adverse events, clinical laboratory parameters, and the results of 12-lead ECGs.

Results: Thirty healthy volunteers (mean [SD] age, 28.0 [4.95] years; weight, 59.3 [6.51] kg; height, 165.0 [7.25] cm; body mass index, 21.7 [1.94] kg/m^2) were randomly divided into 3 groups, each consisting of 5 men and 5 women. After single-dose intravenous administration of 0.25, 0.50, and 0.75 mg/kg of pilsicainide hydrochloride, mean C_{max} was 0.34 (0.11), 0.54 (0.15), and 1.05 (0.19) μg/mL, respectively; $AUC_{0–24}$ was 0.76 (0.12), 1.61 (0.37), and 2.61 (0.46) h · μg/mL; and $AUC_{0–\infty}$ was 0.79 (0.13), 1.71 (0.46), and 2.72 (0.50) h · μg/mL. The ranges for $t_{½z}$, CL, and V_z were 5.19 to 5.98 hours, 4.73 to 5.44 mL/min/kg, and 2.23 to 0.58 L/kg, respectively. The mean urinary recovery rate within 24 hours was 75.0% (12.0%), 65.0% (19.2%), and 66.4% (14.1%). Men and women had significantly different $AUC_{0–24}$ values in the 0.50-mg/kg dose group ($P = 0.044$), and V_z showed significant differences between men and women in all 3 dose groups ($P = 0.001$). According to ECG parameters, PR intervals were significantly prolonged after administration at all 3 doses ($P = 0.034$, $P < 0.001$, and $P = 0.034$); no significant changes were seen in QRS width, QTc interval, or other parameters.

Conclusions: Pilsicainide hydrochloride demonstrated linear PK, and the increase in the exposure of pilsicainide ($AUC_{0–24}$ and $AUC_{0–\infty}$) was dose proportional after single doses of 0.25, 0.50, and 0.75 mg/kg. All 3 pilsicainide hydrochloride doses were well tolerated in these Chinese volunteers. ChiCTR-ONC-13003546. (*Clin Ther.* 2014;36:255–263)

Key words: Chinese, healthy volunteer, injection, pharmacokinetics, pilsicainide hydrochloride.

INTRODUCTION

Pilsicainide hydrochloride was approved in Japan in 1991 as a class IC antiarrhythmic agent that exhibits antiarrhythmic properties exclusively through sodium

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channel effects.[1] It has been used for the treatment of supraventricular and ventricular arrhythmias.[2,3] In preclinical research, pilsicainide significantly decreased conduction velocity and lengthened wavelength by increasing the effective refractory period (ERP) during atrial fibrillation.[4] In a clinical study, pilsicainide suppressed paroxysmal atrial fibrillation more effectively and safely than disopyramide.[1] Mechanistically, pilsicainide treatment prolongs the atrial ERP without increasing the action potential duration, resulting in an increase in the ERP/action potential duration.[5–7] This effect is more noticeable during quick myocardial excitement, referred to as rate-dependent blockade.[8,9]

A single-dose pilsicainide hydrochloride pharmacokinetics (PK) study in healthy Japanese adults found that C_{max} was 0.22 to 1.40 μg/mL, AUC was 0.40 to 3.24 g · h/mL, and $t_{½β}$ was 2.36 to 6.59 hours for the 0.25-, 0.50-, and 0.75-mg/kg pilsicainide hydrochloride 10-minute complete injections, respectively.[10] Pilsicainide hydrochloride is mainly distributed in the liver and kidneys and then excreted by the kidneys. In 11 healthy Japanese subjects, it was reported that 75% to 86% of pilsicainide was recovered in urine without change,[11] and the mean (SD) serum protein-binding rate was 26.8% (2.9%) in subjects with normal renal function after oral administration of a 50-mg single dose.[12]

The objective of the present study was to determine the PK of pilsicainide hydrochloride injection in healthy Chinese adults. The study was conducted to meet China State Food and Drug Administration requirements for the marketing of the new generic formulation of pilsicainide hydrochloride.

SUBJECTS AND METHODS

Subjects

Participants were healthy nonsmokers. Each subject underwent a detailed health screening, including a medical history, complete physical examination, 12-lead ECG, and a series of laboratory tests including hematology (red and white blood cell counts, lymphocyte percentage, neutrophil percentage, monocyte percentage, platelet count, and hemoglobin levels), blood chemistry (alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase, total protein, albumin, total bilirubin, urea, creatinine, uric acid, creatine kinase, L-lactate dehydrogenase, triglyceride, cholesterol, HDL-C, LDL-C, glutamate, sodium, potassium, and chloride levels), and urinalysis (pH, glucose, hemoglobin, blood, bilirubin, ketone bodies, specific gravity, and protein levels). Women of childbearing potential were required to have a negative pregnancy test result at screening.

Subjects who demonstrated abnormalities on testing at screening were excluded from the study. Other exclusions included a history of clinically significant cardiovascular, renal, hepatic, pulmonary, gastrointestinal, endocrine, hematologic, vascular, or collagen disease; a history of neurologic diseases, muscle disease, or a psychiatric disorder that might hinder compliance with the study protocol; any alcohol or drug abuse; drug allergies; testing positive for hepatitis B virus or HIV; blood donations within the past 3 months; participation in any study of another investigational drug within the past 3 months; and being under treatment for an illness in the past 2 weeks. Women who were breastfeeding, menstruating, or receiving hormone replacement therapy were also excluded.

Study Design

This was a single-center, randomized, parallel-group, open-label study and was conducted to determine the PK of a generic pilsicainide hydrochloride formulation after single-dose intravenous administration in healthy Chinese volunteers. The drug used in the study (lot 110901) was provided by Beijing Jialin Pharmaceutical Co Ltd (Beijing, China). The protocol was approved by the independent ethics committee of Capital Medical University–affiliated Beijing Anzhen Hospital (Beijing, China). The study was conducted in accordance with the China State Food and Drug Administration,[13] the Good Clinical Practice Guideline of the International Conference on Harmonisation,[14] and the Declaration of Helsinki (revised, Seoul, 2008).[15] All subjects provided written informed consent before undergoing any study procedures.

Subjects were randomly assigned to receive a single pilsicainide hydrochloride dose of 0.25, 0.50, or 0.75 mg/kg with a 10-minute intravenous infusion. All 3 groups consisted of equal numbers of men and women. Subjects were hospitalized the day before administration. All subjects received the assigned dose of pilsicainide hydrochloride at 8:00 AM the next morning, after having a standard medium-fat breakfast (40 g egg, 100 g bread, and a 200-mL glass of