Pharmacokinetic and Pharmacodynamic Properties of Cinacalcet (KRN1493) in Chinese Healthy Volunteers: A Randomized, Open-label, Single Ascending–dose and Multiple-dose, Parallel-group Study

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ABSTRACT

Purpose: The aim of this study was to assess the pharmacokinetic (PK) and pharmacodynamic (PD) properties and safety of single and multiple doses of cinacalcet in Chinese healthy volunteers (HVs) for the purposes of a New Drug Application package for the Chinese Food and Drug Administration.

Methods: In this randomized, open-label, single ascending–dose and multiple-dose, parallel-group study, 42 Chinese HVs were randomized to receive a single oral dose of 25, 50, or 100 mg of cinacalcet and multiple doses of 50 mg of cinacalcet once daily for 7 days. Plasma cinacalcet concentrations were analyzed by HPLC-MS/MS. The PK parameters were assessed with noncompartmental analysis. Plasma intact parathyroid hormone, serum calcium, and phosphorus concentrations were measured for PD evaluation. The safety profile was also assessed. Adverse events (AEs) were noted during the study.

Findings: Of the 42 randomized HVs, 41 completed the study per protocol; 1 prematurely discontinued the study because of AEs. Cinacalcet has nonlinear PK properties over a dose range of 25 to 100 mg after a single dose. Mean (SD) C_{max} values were 7.68 (4.25), 17 (6.33), and 31.3 (16.42) ng/mL with single doses of 25, 50, and 100 mg of cinacalcet, respectively. Mean (SD) $AUC_{0-\ last}$ values were 58.4 (25.38), 187 (70.7), and 367 (180.03) hr•ng/mL with single doses of 25, 50, and 100 mg of cinacalcet, respectively. Steady state was attained within 7 doses of successive daily administration of 50 mg of cinacalcet. At steady state, the mean (SD) C_{max} and AUC_{0-last} values were 20.6 (9.63) ng/mL and 297 (146.15) ng•h/mL. The accumulation ratios of C_{max} and AUC (AUC_{τ}/AUC_{0-24}) were 1.21 and 1.32. Plasma intact parathyroid hormone and serum calcium concentrations had similar patterns, both decreased after administration of cinacalcet, whether after single dose or multiple doses. A total of 52 AEs were reported in 20 HVs (47.6%). The most frequently reported AEs after single-dose and multiple-dose cinacalcet administration were hypocalcemia, numbness, dizziness, and muscle soreness. No serious AEs were reported.

Implications: Cinacalcet was well tolerated and effective after administration of a single oral dose up to 100 mg and multiple doses of 50 mg of cinacalcet once daily for 7 days. Cinacalcet has nonlinear PK properties over a dose range of 25 to 100 mg after a single dose. PK profiles after multiple doses were similar to those after a single dose with no accumulation. Cinacalcet had similar PK and safety profiles between Chinese and Western HVs at the same dose levels. (*Clin Ther*. 2016;38:348–357)

Key words: Chinese healthy volunteers, cinacalcet, pharmacodynamic properties, pharmacokinetic properties, secondary hyperparathyroidism.

INTRODUCTION

Secondary hyperparathyroidism is a common complication in patients with chronic kidney disease.[1,2] This condition is characterized by an increased level of circulating parathyroid hormone (PTH) and derangements in calcium and phosphorus metabolism.[3]

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If not adequately controlled, secondary hyperparathyroidism contributes to an increased risk of mortality,[4,5] vascular calcification,[6,7] and metabolic bone disease, causing disability and a risk of skeletal fracture.[8]

Traditional therapies for secondary hyperparathyroidism frequently involve the use of phosphate binders and vitamin D sterols.[9] However, these conventional therapies may contribute to hypercalcemia and/or hyperphosphatemia. Therefore, few patients achieve treatment targets for calcium, phosphate, calcium-phosphorus product, or PTH. Thus, there is a significant unmet medical need in the treatment of secondary hyperparathyroidism.

Cinacalcet (KRN1493) is a calcimimetic approved for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease and for the treatment of hypercalcemia in patients with parathyroid carcinoma.[10] Cinacalcet increases the sensitivity of the calcium-sensing receptor to extracellular calcium, which leads to a decrease of PTH secretion and subsequently to lower serum calcium concentrations. Cinacalcet has been successfully used in dialysis patients[11] and in patients with primary hyperparathyroidism.[12] The pharmacokinetic (PK) and pharmacodynamics (PD) properties of cinacalcet have been investigated in Westerners, including healthy volunteers (HVs),[13] patients with chronic kidney disease,[14] patients after renal transplantation,[15] and patients with hepatic impairment.[16] After oral administration, peak plasma concentrations of cinacalcet occur within 2 to 6 hours. The absolute bioavailability is 20% to 25%. The terminal $t_{½}$ is 30 to 40 hours, and steady-state concentrations are achieved within 7 days. The PK properties of cinacalcet are dose proportional over the dose range of 30 to 180 mg.[10] Differences in the PK and PD properties among ethnic groups have been reported with several drugs, with one of the major causes of differences being related to ethnic-specific genetic polymorphisms in drug-metabolizing isozymes, such as cytochrome P450 (CYP) 3A4, 1A2, and 2D6.[17,18] The drug is extensively metabolized primarily by the CYP3A4, CYP2D6, and CYP1A2 to *N*-dealkylation and β-oxidation derivatives that have little or no pharmacologic activity.[19] The PK and PD properties of cinacalcet have also been investigated in healthy male Korean populations[20] and Japanese populations,[21] but they have not ever been investigated in Chinese populations.

The objective of the present study was to evaluate the PK and PD properties and safety of a single ascending dose of 25, 50, and 100 mg of cinacalcet and multiple doses of 50 mg of cinacalcet once daily for 7 days in Chinese HVs for the purposes of a New Drug Application package for the Chinese Food and Drug Administration.

METHODS

Subjects

Forty-two Chinese HVs (30 for single dose and 12 for multiple doses) between the ages of 20 and 36 years with a body mass index (BMI) in the range of 18.8 to 24.4 kg/m^2 were enrolled in this study. The percentage of male to female is 50/50. Before enrollment, subjects were examined to confirm that they were of good physical and mental health. Subjects who consumed any medicine, food, or beverage known to be CYP2D6, CYP1A2, or CYP3A4 inducers or inhibitors within 2 weeks before the study initiation were excluded from the study.

Study Design

This was a randomized, open-label, single ascending–dose and multiple-dose, parallel-group study. Thirty HVs were randomly assigned to receive a single dose of 25, 50, or 100 mg of oral cinacalcet. After the single-dose study was finished, other 12 HVs were assigned to receive multiple doses of 50 mg of oral cinacalcet once daily for 7 days. All study medications were provided as 25-mg or 75-mg tablets. The HVs were admitted to the Peking Union Medical College Hospital (PUMCH) Clinical Pharmacology Research Centre 1 day before dosing. On the day of dosing, HVs received study medication together with 240 mL of water in the overnight-fasted state.

This study was sponsored by Kyowa Hakko Kirin China Pharmaceutical Co, Ltd. All study procedures were conducted in accordance with Chinese Good Clinical Practice and the Declaration of Helsinki.[22] The Independent Ethics Committee of PUMCH (Beijing, China) approved the study protocol. All participants provided written informed consent before any study procedures, including screening tests, were conducted.

PK Assessments

Blood samples (4 mL each) were taken to determine plasma cinacalcet concentrations before dosing and at