Pharmacokinetics and Tolerability of Minodronic Acid Tablets in Healthy Chinese Subjects and Food and Age Effects on the Pharmacokinetics

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ABSTRACT

Purpose: Minodronic acid is a third-generation bisphosphonate being developed for the treatment of osteoporosis. The aim of this study was to evaluate the pharmacokinetic profiles and tolerability of minodronic acid in healthy subjects, as well as to assess the effects of food and age on the pharmacokinetics.

Methods: This single-center, open-label, Phase I study was conducted in 4 parts. In part 1, minodronic acid tablets were administered to young volunteers at doses of 1, 2, and 4 mg. In part 2, after a single dose, young volunteers in the 1-mg dose group received repeated oral doses of minodronic acid once daily for 7 days. In part 3, a single oral dose of minodronic acid 1 mg was administered to elderly volunteers. In part 4, after a washout period of 8 days, volunteers in the 4-mg group received a single dose of 4-mg minodronic acid under fed conditions (administrated 30 minutes before a high-fat breakfast). Plasma samples were collected, and plasma concentrations of minodronic acid were analyzed by using a LC-MS/MS method. Tolerability was assessed throughout the study by physical examinations, measurement of vital signs, laboratory analyses, and monitoring of adverse events.

Findings: Thirty-six young volunteers (mean age, 22.1 years; mean weight, 58.6 kg) and 12 elderly volunteers (mean age, 62.3 years; mean weight, 62.4 kg) were enrolled in the study. After single doses of 1, 2, and 4 mg of minodronic acid, the dose-normalized AUC exhibited dose linearity over the range of 1 to 4 mg in the young subjects. The plasma concentration of minodronic acid reached a steady state on day 7 after oral administration once daily for 7 days, with a mean accumulation ratio of 1.3. After a single dose of minodronic acid 1 mg, plasma C_{max} and $AUC_{0-\infty}$ were both 1.8-fold higher compared with those of the young subjects. In the 4-mg dose group, minodronic acid C_{max} and $AUC_{0-\infty}$ were reduced by 55% and 72%, respectively, with a high-fat breakfast compared with fasted conditions. No clinically meaningful changes in vital signs, laboratory values, or ECGs were observed.

Implications: Single dosing of minodronic acid exhibited linear pharmacokinetics over the range of 1 to 4 mg; there was no accumulation after repeated administration. Food, especially high-fat food, reduced the bioavailability of minodronic acid. In addition, the exposure of the drug was increased with age. Minodronic acid seemed to be well tolerated throughout the study. ClinicalTrials.gov Identifier: NCT02295436. (*Clin Ther.* 2015;37:869–876)

Key words: age, Chinese subjects, food, minodronic acid, pharmacokinetics, tolerability.

INTRODUCTION

Osteoporosis, a disease that weakens bone structure and increases the risk of fractures, has probably existed throughout human history but has only

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recently become a major clinical problem in the aging society.[1] The ultimate purpose of prevention and treatment of osteoporosis is to reduce the incidence of fractures. Drugs currently used in the clinic for osteoporosis treatment include calcium, vitamin D, estrogens, calcitonin, and bisphosphonates (BPs).

BPs are structural analogues of inorganic pyrophosphate that suppress bone resorption, maintain bone mass, and prevent bone fractures.[2] First-generation BPs (eg, etidronate) inhibit calcification and bone resorption. Second-generation BPs (eg, alendronate) exhibit a significant difference in the extent of inhibition of calcification and bone resorption compared with the first-generation BPs.[3] Third-generation BPs, including minodronic acid hydrate, are even more powerful inhibitors of bone resorption.[2] Minodronic acid hydrate is 1000 times more effective than etidronate and 10 to 100 times more effective than alendronic acid.[4] Owing to its powerful suppression of bone resorption, minodronic acid has been approved for the treatment of osteoporosis and has been used clinically in Japan since 2009.

Minodronic acid, the same as other BPs, specifically accumulates in the bone after administration and is then separated from the bone by acid released by osteoclasts during the bone resorption process and selectively taken up by osteoclasts. Conventional BPs are believed to inhibit bone resorption through the induction of osteoclast apoptosis after being taken up by these cells. Recent research on minodronic acid, however, suggests that this drug has a metabolic pathway different from that of the existing BPs because the number of osteoclasts decreased without the induction of osteoclast apoptosis when minodronic acid was administrated to rat models with type II collagen–induced arthritis.[5,6] It is still under study as a new third-generation BP.

Nonclinical studies have shown that minodronic acid is a strong inhibitor of bone resorption at low doses.[7,8] In addition, clinical studies conducted to date indicate that minodronic acid is considered effective for improving bone density and preventing fractures.[9,10] Because osteoporosis is common in postmenopausal women and in the elderly population, minodronic acid would be widely used in these populations. However, thus far, no articles about the pharmacokinetic (PK) characteristics of minodronic acid have been published. The present study was designed to evaluate the PK properties, tolerability, and safety profile of minodronic acid tablets after single and multiple dosing in healthy Chinese volunteers. Secondary goals were to assess the effects of food and age on the PK profile of minodronic acid.

SUBJECTS AND METHODS

Study Design

This single-center, Phase I, open-label, single- and multiple-dose study was conducted at the Institute of Clinic Pharmacy, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology in Wuhan, People's Republic of China. The study protocol and conformance were approved by the medical ethical committee of Tongji Medical College, Huazhong University of Science and Technology. The study was conducted in accordance with the Declaration of Helsinki and the Guideline for Good Clinical Practice.[11] All subjects provided written informed consent after hearing a detailed explanation of the study schedule, procedures to be performed, and possible adverse events (AEs).

Inclusion and Exclusion Criteria

Subjects were included based on the following criteria: male or female subjects aged 19 to 35 years for young subjects or aged 60 to 65 years for elderly subjects; body mass index between 19 and 24 kg/m^2; thorax radiography and ECG with no abnormalities; normal blood pressure values, heart rate, and laboratory test results (hematology, blood biochemistry, hepatic function, and urinalysis); and negative test results for HIV and hepatitis B. Subjects were excluded if they had a heart disease or disorder or a hepatic, renal, respiratory, immune system, or nervous system disorder. They were also excluded for any of the following reasons: if they were pregnant or breastfeeding; were hypocalcemic; had taken prescription or over-the-counter medications (including herbal products) within 2 weeks before the initiation of the study; had donated blood or participated in other clinical trials within 3 months before study enrollment; abused alcohol or drugs; smoked >10 cigarettes a day; or had clinically significant allergies to drugs or foods, sitting blood pressure $<80/50$ mm Hg or $>140/100$ mm Hg, or a ventricular rate <60 beats/min or >100 beats/min at rest. All study subjects were required to abstain from drinking any alcoholic beverage for at least 1 week before enrollment.