Clinical Pharmacokinetics of Levornidazole in Elderly Subjects and Dosing Regimen Evaluation Using Pharmacokinetic/Pharmacodynamic Analysis

Beining Guo, PhD[1,2]; Gaoli He, MS[1,2]; Xiaojie Wu, PhD[1,2]; Jicheng Yu, BS[1,2]; Guoying Cao, MS[1,2]; Yi Li, MS[1,2]; Yaxin Fan, MS[1,2]; Yuancheng Chen, PhD[1,2]; Yaoguo Shi, BS[1,2]; Yingyuan Zhang, BS[1,2]; and Jing Zhang, PhD[1,2]

[1]*Institute of Antibiotics, Huashan Hospital, Fudan University, Shanghai, China; and* [2]*Key Laboratory of Clinical Pharmacology of Antibiotics, Ministry of Health, Shanghai, China*

ABSTRACT

Purpose: Levornidazole, the levo-isomer of ornidazole, is a third-generation nitroimidazole derivative newly developed after metronidazole, tinidazole, and ornidazole. An open-label, parallel-controlled, single-dose study was conducted for the investigation of the pharmacokinetic (PK) profile of levornidazole and its metabolites in healthy elderly Chinese subjects, and for the evaluation of 2 dosing regimens in the elderly.

Methods: Levornidazole was intravenously administered at 500 mg to healthy elderly (aged 60–80 years) or young subjects (aged 19–45 years). The PK profiles of levornidazole and its metabolites in elderly subjects were evaluated and compared with those in the young group. WinNonlin software was used for simulating the PK profile of levornidazole in the elderly population following the dosing regimens of 500 mg BID and 750 mg once daily for 7 days. Monte Carlo simulation was used for estimating the cumulative fraction of response and probability of target attainment of both dosing regimens against *Bacteroides* spp.

Results: The C_{max}, $AUC_{0–24}$, and $AUC_{0–\infty}$ values of levornidazole in the elderly group were 11.98 μg/mL, 131.36 μg · h/mL, and 173.61 μg · h/mL, respectively. The $t_{1/2}$, CL_t, and mean residence time from time 0 to infinity were 12.21 hours, 2.91 L/h, and 16.46 hours. The metabolic ratios of metabolites (M) 1, 2, 4, and 6 were $<3.0\%$, and that of M16 was 17.70%. The urinary excretion values of levornidazole, M1, M2, M4, M6, and M16 over 96 hours were 10.21%, 0.92%, ~0%, 2.69%, 0.54%, and 41.98%. The PK properties of levornidazole and the urinary excretion of all metabolites were not statistically different between the 2 groups. The cumulative fraction of response was $>90\%$ against *B fragilis* and other *Bacteroides* spp, and the probability of target attainment was $>90\%$ when the minimum inhibitory concentration was ≤ 1 μg/mL, in both groups.

Implications: No dosing regimen adjustment is suggested when levornidazole is used in elderly patients with normal hepatic functioning and mild renal dysfunction. The findings from the PK/PD analysis imply that both regimens may achieve satisfactory clinical and microbiological efficacy against anaerobic infections in elderly patients. Chinese Clinical Trial Registry (http://www.chictr.org.cn) identifier: ChiCTR-OPC-16007938. (*Clin Ther*. 2017;39:1336–1346)

Key words: dosing regimen evaluation, elderly subject, levornidazole, metabolite, pharmacokinetics.

INTRODUCTION

Levornidazole (*S*-1-[3-chloro-2-hydroxypropyl]-2-methyl-5-nitroimidazole), the levo-isomer of ornidazole, is a third-generation nitroimidazole derivative newly developed after metronidazole, tinidazole, and ornidazole. Ornidazole is the mixture of its levo- and dextro-isomers at a ratio of 1:1. Ornidazole has been found to have CNS toxicity resulting from dextrornidazole, the dextro-isomer of ornidazole.[1]

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Therefore, a new drug named *levornidazole** has been developed. An injectable formulation of levornidazole sodium chloride was approved by China Food and Drug Administration in 2009. The in vitro activity of levornidazole against most anaerobic species, such as *Bacteroides thetaiotaomicron*, *Clostridium difficile*, *Clostridium perfringens*, *Peptostreptococcus* spp, and especially *Bacteroides fragilis,* is similar to or slightly stronger than those of metronidazole, ornidazole, and dextrornidazole.[2,3] For the treatment of adult patients with infections caused by anaerobic bacteria, the drug label recommends a regimen of an intravenously administered loading dose of 500 to 1000 mg, followed by 500 mg q12h (ie, BID) for 5 to 10 days.

The completed Phase I clinical study of levornidazole showed that a single dose of 500 to 1500 mg was well tolerated, and that consecutive administration could cause drug accumulation in adult subjects.[4] Our previous study found that accumulation can be reduced if the dosing regimen is changed from 500 mg q12h (ie, BID) to 750 mg q24h (ie, once daily).[5] Our in vitro pharmacokinetic/pharmacodynamic (PK/PD) study indicated that both dosing regimens might achieve satisfactory clinical and microbiological efficacy against most anaerobic bacteria.[6]

The metabolic studies of ornidazole have indicated that ornidazole is metabolized mainly by liver. The main elimination pathway of the parent drug and its metabolites is via the kidney. Early PK and metabolic studies of ^{14}C-labelled ornidazole identified 5 metabolites in urine: 2 oxidative products of ornidazole (M1, M2), 1 hydrolytic dechlorination product of ornidazole (M4), and 2 cleavage products of the imidazole ring (M3, M5). The studies displayed that the major route of excretion of radioactivity was via the urine, and the recovery from urine was between 43% and 63% of the dose, of which <4% was recovered unchanged.[7,8] Recent metabolic investigations by UPLC-quadrupole/time-of-flight MS found 19 and 12 metabolites in human urine and bile, respectively. It was concluded that stereoselective glucuronidation followed by renal excretion was the principal metabolic pathway of ornidazole in humans, and that only 6% of drug was excreted unchanged in urine.[9,10] The metabolism and excretion pathway of levornidazole, the isomer of ornidazole, are not well studied. Our previous PK study monitored the concentrations of 5 phase 1 metabolites (M1–M5) in plasma and urine samples from healthy young subjects, and indicated that mean urinary recoveries of M1 and M4 were <3% after single-dose administration of 500 mg of levornidazole. The concentrations of M2 in plasma and urine samples were lower, and those of M3 and M5 could not be determined.[5] The result of <15% of drug dose recovered from urine (including the parent drug and the 5 metabolites) implied that there are other important metabolites. Referring to the metabolic result of ornidazole, 2 possibly more abundant phase 2 metabolites were additionally traced in this PK study. Furthermore, the exposure of levornidazole in elderly patients might be different due to age-related decreased renal and hepatic functioning. To the best of our knowledge, no PK information on levornidazole in the elderly population is available. The objectives of this PK study were to compare the PK profile and the urinary excretion of levornidazole and its phase 1 and 2 metabolites between elderly and young Chinese volunteers, and to evaluate the recommended dosing regimen in elderly patients using PK/PD analysis.

SUBJECTS AND METHODS

Study Design

This open-label, parallel-controlled, single-dose study was conducted at a single study site—Huashan Hospital, Fudan University (Shanghai, China). The study is registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cnidentifierChiCTR-OPC-16007938).

Levornidazole was administered intravenously at a single dose of 500 mg in 100 mL of sodium chloride injection in healthy elderly or young subjects after breakfast in 2 periods. The infusion duration was 60 ± 10 minutes. The dose and infusion duration were based on the recommendations in the drug labeling for the treatment of anaerobic infections. The PK samples (blood and urine samples) were collected until 96 hours after administration. The PK profiles of levornidazole and its 5 metabolites and drug disposition were evaluated. The toleraility of levornidazole was also assessed during the study.

The study was performed in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guideline. Prior to study initiation, the final protocol and amendments were reviewed and approved by an independent ethics committee (institutional review board) at Huashan Hospital. All subjects provided written informed consent before participating in any study-related activity. Candidates were informed about the nature and purpose of the trial,

*Sanhome Pharmaceutical Co, Ltd (Nanjing, China).