Tolerability and Pharmacokinetic Comparison of Oral, Intramuscular, and Intravenous Administration of Levosulpiride After Single and Multiple Dosing in Healthy Chinese Volunteers

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ABSTRACT

Purpose: The aim of this study was to characterize the pharmacokinetic (PK) properties and assess the safety profiles of different formulations of levosulpiride in healthy Chinese volunteers.

Methods: Levosulpiride was administered to 42 healthy male and female (1:1) subjects in tablet (PO) and injectable (IM and IV) dosage forms. Blood samples were collected at regular intervals after single and multiple drug administration. The concentration of levosulpiride in plasma was determined by a validated liquid chromatography tandem mass spectrometry method. Noncompartmental analysis was performed to estimate PK parameters. One-way ANOVA was used to test for linearity and assess the effect of sex on the PK properties of the drug. Adverse effects were monitored using investigators' questionnaires and subjects' spontaneous reports, vital sign measurements, hematology, clinical chemistry, and electrocardiography.

Findings: Levosulpiride exhibited linear pharmacokinetic properties over the dose range of 25 to 100 mg by PO route and 25 to 75 mg by IM route. The corresponding mean AUC_{0-t} increased from 449 to 1443 ng/h/mL and from 2874 to 7559 ng/h/mL, respectively. After repeated PO and IM administration, steady state was reached on day 4 of multiple dosing with accumulation index of 1.8 and on day 2 of multiple dosing with accumulation index of 1.3, respectively. The bioavailability of levosulpiride via IM and PO routes was 96.8% and 23.4%, respectively. No significant differences were observed on PK properties between male and female subjects. More than half (23 of 42 [54.8%]) of healthy volunteers experienced one or more adverse events in total, including constipation, diarrhea, drowsiness, skin rash, and extrapyramidal reactions.

Implications: The regimen of 50-mg levosulpiride tablets 3 times daily and 50-mg levosulpiride injection (IM) twice daily provided similar accumulation coefficient, and the former reached steady state much more slowly. The bioavailability of levosulpiride after oral administration was poor and the absorption rate was slower compared with IM administration, which imply delayed clinical efficacy for patients with dyspepsia or neuropsychiatric disorders. On multiple dosing, levosulpiride exhibited poor tolerability with high incidence of adverse reactions. There was no need to adjust administration regimen based on sex. ClinicalTrials.gov Identifier: NCT02481583. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮)

Key words: adverse effects, bioavailability, levosulpiride, pharmacokinetics.

INTRODUCTION

Sulpiride (N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-sulfamoyl-o-anisamide), a substituted benzamide with high selectivity for D2-like dopamine receptors, is widely

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used in the treatment of psychiatric and gastroenterological disorders.[1–4] The recommended oral dose of sulpiride for the treatment of mental disorders of senescence, depression, and schizophrenia is 200 to 800 mg. It is also used to treat gastric or duodenal ulcers at doses of 50 to 150 mg.[5,6] Sulpiride is characterized by a low incidence of extrapyramidal side effects with long tradition since going on the market[1,7] Since it was developed in France in 1967, there has been much interest in studying this powerful drug.

For sulpiride, both a racemic form and a pure enantiomer (levosulpiride, L-SULP) form are on the market, and it is used currently in most countries as the racemate. However, earlier studies proposed that L-SULP is clinically more effective with lower acute toxicity than the racemate or D(+) enantiomer.[8–10] Thus, L-SULP has the same pharmacologic effect as sulpiride, but at about 50% of the dosage because of its higher affinity to dopamine receptor compared with D-SULP.[11] Different levosulpiride formulations have been developed (eg, tablet, injection, and oral solution) and approved for clinical use since 1987 and are available worldwide (eg, Italy, Spain, Germany, Belgium, and South Korea).[12] The pharmacokinetic (PK) parameters of levosulpiride have been studied in healthy volunteers and show a linear relationship with dose. Although Gong et al[13] investigated the PK properties of levosulpiride in Chinese healthy volunteers, the number of subjects was small (n = 12). Previous literature[14–16] also reported the PK properties of sulpiride in human beings. According to the literature, the mean elimination half-life ($t_{½z}$) of sulpiride was 6.47 hours after IV administration, and the renal clearance (119.5 mL/min) was very close to total clearance (127.8 mL/min). The values of all these parameters were very close to those obtained after IM administration. Müller et al[17] pointed out that the concentration of sulpiride had a positive correlation with side effects at the range of 0−1200 ng/mL. Cho et al[18] reported that genetic polymorphisms of the ABCB1 gene can affect levosulpiride disposition in humans, which contributes to the substantial inter-individual differences in the disposition and antipsychotic effects of levosulpiride.[18] To optimize treatment with levosulpiride, it is necessary to study the PK parameters and safety profile of L-SULP and the differences between multiple formulations of L-SULP. For this purpose, we conducted an open-label, single- and multiple-dose study in healthy Chinese subjects to investigate the PK profile and differences in PK properties between levosulpiride tablet and injection formulations; safety profiles were also evaluated.

METHODS

Subjects

The protocol for this Phase I, open-label, single- and multiple-dose PK properties study was reviewed and approved by the ethics committee at Huazhong University of Science and Technology. Study procedures were performed in accordance with ethical principles based on the Declaration of Helsinki.[19] A total of 42 healthy Chinese volunteers participated in this study. Volunteer-screening procedures included written informed consent, inclusion and exclusion criteria assessment, collection of demographic data, medical history, medication history, complete physical examination, chest x-ray, 12-lead ECG and laboratory test results (hematology [red blood cell count, total and differential leukocyte counts, platelet count, and hemoglobin], blood chemistry [creatinine, glucose, alanine and aspartate aminotransferase, alkaline phosphatase, and direct and total bilirubin], and urinalysis [pH, glucose, specific gravity, blood, and protein]).

Eligible participants were healthy adults (inclusive range, 19−45 years) with a weight ≥ 50 kg for men and ≥ 45 kg for women. Women of childbearing potential were required to have a negative pregnancy test during screening. Subjects were not enrolled if they had a history of clinically significant cardiovascular, renal, hepatic, pulmonary, gastrointestinal, or nervous system diseases; participation in another investigational drug study or blood donation within the previous 3 months; and treatment with any drug during the previous 2 weeks. The volunteers were instructed to abstain from smoking, alcohol, and caffeine-containing food and beverages for at least 48 hours before the study period.

Study Designs

All 42 subjects were randomly assigned to 1 of 2 parts according to the order of enrollment. The sequential dose-escalating and multiple-dose trials were conducted on each part. Part 1 consisted of 12 subjects (6 men and 6 women) who received levosulpiride tablet via PO administration. Part 2 consisted of 30 subjects (15 men and 15 women) who received levosulpiride injection via IM and IV infusion. Subject disposition was described in Figure 1.