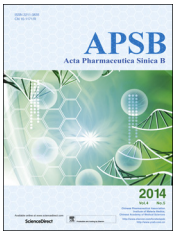
Acta Pharmaceutica Sinica B 2014;4(5):402–407

HOSTED BY

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



ORIGINAL ARTICLE

Pharmacokinetics of levosulpiride after single and multiple intramuscular administrations in healthy Chinese volunteers

Chuting Gong[a], Janvier Engelbert Agbokponto[a], Wen Yang[a], Ernest Simpemba[a], Xiaohong Zheng[a], Quanying Zhang[b], Li Ding[a,*]

[a]*Department of Pharmaceutical Analysis, China Pharmaceutical University, Nanjing 210009, China*
[b]*Organization for State Drug Clinical Trial, the Second Affiliated Hospital of Soochow University, Suzhou 215004, China*

Received 13 March 2014; revised 7 May 2014; accepted 9 June 2014

KEY WORDS

Levosulpiride;
Pharmacokinetics;
Intramuscular administration;
Safety and tolerability

Abstract The main purpose of this study was to evaluate the pharmacokinetics of levosulpiride in humans after single and multiple intramuscular injections. Six males and six females received single dose of either 25 mg or 50 mg levosulpiride, or multiple doses of 25 mg every 12 h for 5 consecutive days. In the single 25 mg study, the mean peak plasma concentration (C_{max}) was 441 ng/mL, the mean area under the concentration–time curve from 0 to 36 h (AUC_{0-36}) was 1724 ng h/mL, and the mean elimination half-life ($t_{1/2}$) was 7.0 h. In the single 50 mg study, the mean C_{max} was 823 ng/mL, the mean AUC_{0-36} was 3748 ng · h/mL, and the mean $t_{1/2}$ was 6.8 h. After multiple doses of 25 mg levosulpiride, the average plasma concentration (C_{av}) was 136 ng/mL, the fluctuation index (DF) was 3.60, and the accumulation ratio (R) was 1.2. Levosulpiride injections appeared to be well tolerated by the subjects, and can be used for successive administration.

*Corresponding author: Tel.: +86 025 83271485; fax: +86 025 83271485.
E-mail address: dinglihg@sina.com (Li Ding).

Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

http://dx.doi.org/10.1016/j.apsb.2014.06.001

1. Introduction

Levosulpiride (Fig. 1A), *N*-[[(2*S*)-1-ethylpyrrolidin-2-yl]methyl]-2-methoxy-5-sulfamoylbenzamide, the levorotatory form of sulpiride enantiomers, is a benzamide derivative, which specifically blocks dopamine D2- and D3-receptors both in the central and peripheral nervous system (CNS and PNS)[1,2]. Levosulpiride has therapeutic efficacy in psychiatric disorders like depression, somatoform disorders, schizophrenia[3], dyspepsia and emesis[4,5], vertigo and premature ejaculation[6]. Compared with the dextro enantiomer, levosulpiride has stronger pharmacological activities[1]. Since metabolic conversion at the chiral center of the drug has been observed in rats, no marked differences in pharmacokinetic parameters of the enantiomers has been noted[7]. Studies suggest that compared with the enantiomers, lower doses of levosulpiride can produce identical or even higher efficacy[1], greatly diminishing the occurrence of adverse events[8].

Levosulpiride mainly exists in ionic form at physiological pH because of its pK_a. Metabolites found in other species were all missing in human urine, indicating that the parent drug, rather than metabolites, plays an extremely important role in drug disposition[9]. The bioavailability of sulpiride is about 30% after oral administration[10], probably due to incomplete gastrointestinal absorption[10–13]. The value is nearly 100% after intramuscular (im) administration[14,15]. Following oral administration, intra-individual and inter-individual variabilities were high, with a coefficient of variation for all subjects above 25% in the pharmacokinetics parameters[10,14,16]. These differences, most likely attributable to variations in absorption, could be due to genetic polymorphisms or fluctuations in gastrointestinal pH. Pharmacokinetics of sulpiride in humans was linear over the test dose range after im administration[15] and oral administration[10]. Gender discrepancy was also investigated after intravenous (iv) administration. These results showed that the distribution of sulpiride was slightly slower, and area under the curve notably higher in male subjects[14].

The aims of this study were to evaluate the pharmacokinetics of levosulpiride for the first time in healthy Chinese volunteers after im administration of a single 25 mg dose, a single 50 mg dose and multiple 25 mg doses, and to compare these parameters with those from Caucasian and Korean populations.

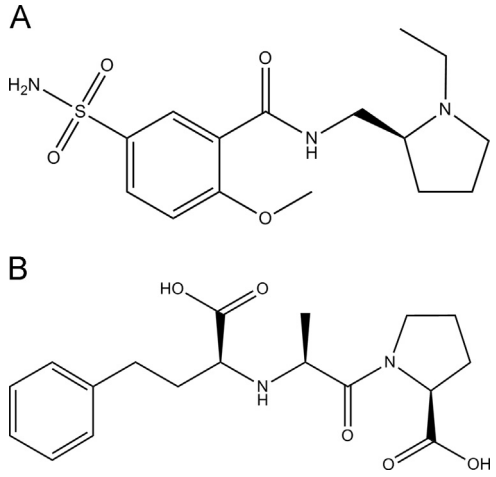


Figure 1 Chemical structures of levosulpiride (A) and enalaprilat (B, IS).

2. Materials and methods

2.1. Chemicals and reagents

Levosulpiride (reference standard, purity 100%) was provided by Shanghai Hotmed Sciences Co., Ltd. (Shanghai, China), and the internal standard enalaprilat (IS, purity 100%, Fig. 1B) was purchased from National Institutes for Food and Drug Control (Beijing, China). The test formulation levosulpiride injections (25 mg/2 mL, 50 mg/4 mL) were provided by Shanghai Hotmed Sciences Co., Ltd. (Shanghai, China). Methanol (HPLC-grade) was obtained from Merck KGaA (Darmstadt, German). Formic acid and ammonium acetate (analytical grade) were purchased from Nanjing Chemical Reagent Co., Ltd. (Nanjing, China).

2.2. Subjects

Twelve healthy Chinese volunteers (6 males and 6 females) were enrolled. All subjects provided written informed consent. All the experiments were approved by an Independent Ethics Committee and carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. All the volunteers met the selection criteria: a body mass index (BMI) between 19 and 24 kg/m^2, 18–31 years old, in good health as determined by screening; laboratory examination (including hematology, biochemical tests, urine routine tests, and electrocardiogram), medical history, vital signs and physical examination. The demographic data for all subjects are given in Table 1. All laboratory parameters were monitored during screening and after the study. Vital signs and adverse events were recorded before and throughout the study.

2.3. Study design

Single-dose pharmacokinetic study was carried out with an open-label, randomized, 2-way crossover study design. The 12 volunteers were randomly allocated to two groups (group 1 and group 2), and each group had 3 males and 3 females. They were required to fast overnight for at least 10 h, and were given breakfast 1 h before dose administration. Group 1 received a single im injection of 25 mg (2 mL) levosulpiride in gluteus muscle, then after a 1-week washout period, they were given a single im injection of 50 mg (4 mL) levosulpiride. Group 2 were given a 50 mg (4 mL) dose of levosulpiride, then after a washout period were given a 25 mg (2 mL) dose of levosulpiride. After the single-dose experiments, multi-dose (25 mg dose) pharmacokinetic study was assessed with im administration of levosulpiride every 12 hours on the five consecutive days. In the single-dose studies, a catheter was placed in the forearm vein, and venous blood samples (4 mL) were collected in heparinized tubes immediately before and 5, 10, 15, 20, 25, 30, 40 min, 1, 2, 3, 5, 8, 12, 24 and 36 h after each injection. In the multi-dose study, plasma samples were drawn

Table 1 Demographic data for the subjects.

Sex	Age (year)	Weight (kg)	Height (cm)	BMI (kg/m^2)
Male	24.8±1.9	62.5±6.3	172±7	21.2±1.9
Female	25.3±4.4	54.3±5.4	160±5	21.3±1.6

Data are mean±standard deviation. n=6 for males and females.