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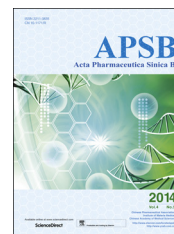


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ORIGINAL ARTICLE

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



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KEY WORDS

Levosulpiride;
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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.

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1. Introduction

Levosulpiride (Fig. 1A), *N*-[[*(2S)*-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, schizophrenia³, dyspepsia and emesis^{4,5}, vertigo and premature ejaculation⁶. Compared with the dextro enantiomer, levosulpiride has stronger pharmacological activities¹. 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 noted⁷. Studies suggest that compared with the enantiomers, lower doses of levosulpiride can produce identical or even higher efficacy¹, greatly diminishing the occurrence of adverse events⁸.

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 disposition⁹. The bioavailability of sulpiride is about 30% after oral administration¹⁰, 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 administration¹⁵ and oral administration¹⁰. 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 subjects¹⁴.

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.

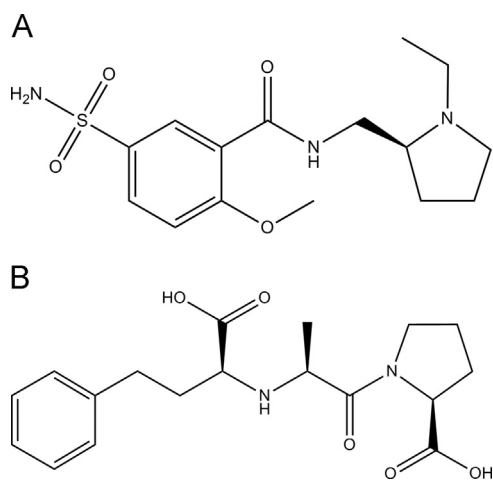


Figure 1 Chemical structures of levosulpiride (A) and enalaprilat (B, IS).

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/m², 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.

prior to the morning injections on day 3, 4, 5 and 5, 10, 15, 20, 25, 30, 40 min, 1, 2, 3, 5, 8, 12, 24 and 36 h after the morning injections on day 5. Plasma was isolated immediately by centrifugation at 4000 rpm for 5 min and stored at -20°C until analysis. The light diets were served 4 h and 10 h after the injections.

2.4. Sample preparation

Samples (blank plasma samples, standard working solutions) were first thawed at ambient temperature and vortex-mixed. An aliquot of 200 μL plasma was transferred into a centrifuge tube containing 20 μL IS working standard. This was vortex-mixed for 5 s, followed by addition of 800 μL methanol as protein precipitation agent. After vortex-mixing for 3 min, this tube was centrifuged for 10 min at 15,600 rpm and supernatant transferred to a sample vial for analysis. The injection volume was 5 μL .

2.5. Instrumentation

The Agilent series 1200 HPLC system and 6410B mass system (Agilent Technologies, Palo Alto, CA) included a binary pump, an autosampler, a temperature controlled column and a triple quadrupole MS. Chromatographic separation was performed on a Hanbon Hedera ODS-2 (150 mm \times 2.1 mm, 5 μm , Hanbon Sci & Tech Co., Ltd., China) with a gradient elution system of methanol (A) and water phase (B) (containing 0.002% formic acid and 5 mmol/L ammonium acetate) at a flow rate of 0.4 mL/min. The mobile phase program was 0–0.5 min: 10% A; 0.5–0.75 min: 10% A \rightarrow 80% A; 0.75–3 min: 80% A; 3–3.05 min: 80% A \rightarrow 100% A; 3.05–4 min: 100% A; 4–4.25 min: 100% A \rightarrow 10% A; 4.25–8 min: 10% A. The autosampler was maintained at 15°C , and the column at 35°C . Under these conditions, the total run time was 8 min and the injection volume was 5 μL .

HPLC eluates were analyzed by triple quadrupole mass spectrometer, with an electrospray ion source (ESI). The tandem mass spectrometer was operated in ESI positive mode at a unit resolution using multiple reaction monitoring (MRM) data acquisition. The monitoring transitions for levosulpiride and the IS were 342.0 \rightarrow 112.0 and 349.1 \rightarrow 206.1, respectively. The MS conditions were: fragmentor 120 V, drying gas 12 L/min, drying gas temperature 350°C , and nebulizer pressure 45 psig. Collision energy was 25 V for levosulpiride and 15 V for the IS. Data were collected by using Agilent MassHunter.

2.6. Statistical analysis

All pharmacokinetic calculations of the study were carried out with the drug and statistics (DAS) 2.1.1 pharmacokinetic program authorized by the Chinese Pharmacology Society (Beijing, China), and statistical analyses were performed with SPSS 11.5 (LEAD Technologies Inc.). Key pharmacokinetic parameters were derived by noncompartmental methods and then compared by using SPSS statistical analysis software package. *P* value of less than 0.05 was considered statistically significant.

Peak plasma concentration at steady state (C_{ssmax}) and time to peak plasma concentration (T_{max}) were taken as the observed data. DAS was used to calculate the pharmacokinetic parameters, including C_{av} , $t_{1/2}$, DF, area under the concentration–time curve from time zero to time of the last quantifiable concentration (AUC_{0-t}), area under the concentration–time curve from 0 h to

12 h (AUC_{0-12}), area under the concentration–time curve from 0 h to 12 h at steady state (AUC_{ss}), mean residence time (MRT_{0-t}), apparent volume of distribution (V_z/F), apparent clearance (CL_z/F), and plasma concentration at steady state before injection on day 5 (C_{ssmin}). *R* was calculated as $\text{AUC}_{\text{ss}}/\text{AUC}_{0-t}$ or $C_{\text{ssmax}}/C_{\text{max}}$.

The C_{max} and AUC values were logarithmically transformed, and the normal distribution test was conducted using one-sample Kolmogorov–Smirnov test within-group in pharmacokinetic variables of levosulpiride except T_{max} (using nonparametric tests). The variables of levosulpiride were compared between the 25 mg dose and 50 mg dose groups using paired samples *t*-test. To confirm whether C_{max} and AUC_{0-t} for levosulpiride were dose proportional over the 25–50 mg dose range in healthy Chinese subjects, paired samples *t*-test was performed in dose corrected data $\ln(C_{\text{max}}/\text{dose})$ and $\ln(\text{AUC}_{0-t}/\text{dose})$. Body weight corrected AUC_{0-t} and C_{max} and untransformed parameter values of both sexes were compared using independent samples *t*-test to evaluate gender difference. To compare pharmacokinetic parameter values of 25 mg dose between single-dose study and multi-dose study, paired samples *t*-test was used. One-way analysis of variance was used to compare the lowest plasma concentrations on day 3–5.

3. Results and discussion

3.1. Plasma assay

The plasma assay method was fully validated. Retention times of levosulpiride and IS were 2.81 and 2.97 min, respectively. Levosulpiride and the IS were baseline separated with symmetrical narrow peaks. Standard curves for levosulpiride were linear over the concentration range 2–2000 ng/mL with correlation coefficients (r^2) > 0.9995 . Low (5 ng/mL), medium (300 ng/mL) and high (1600 ng/mL) quality control (QC) samples for levosulpiride were prepared. Within-run and between-run precisions of QC samples were 5.3% and 8.0% (relative deviation %), respectively. No carryover was observed in a blank plasma sample immediately following an injection of the highest levosulpiride calibration standard when the cycle was repeated four times. Matrix effect (from 97.4% to 107.9%) and recovery (from 87.7% to 102.0%) of QC samples at three levels (low, median, high) were sufficient for the analysis of levosulpiride in human plasma. Levosulpiride was stable in plasma for 13 h at room temperature, 2 months at -20°C , after three freeze–thaw cycles and in autosampler for 39 h at low and high QC levels.

3.2. Safety and tolerability

The most common adverse events reported during levosulpiride treatment are dizziness, drowsiness and endocrine effects; rare adverse events are cardiovascular and extrapyramidal effects^{4,18–19}. In our study, there were no serious adverse events like extrapyramidal symptoms, and the only clinically significant abnormality was the mildly elevated serum alanine aminotransferase concentration in two male volunteers. This adverse event started 13 h after the last sample collection in multiple 25 mg dose study. Ten days later, the two male volunteers were reexamined, and this effect disappeared without any medication during this period. The adverse event was not observed in female volunteers, and did not couple with elevated aspartate aminotransferase. Thus, more attention should be paid to patients with drinking habits and

other potential hepatic dysfunction. Previous studies noted the occurrence of adverse reactions following doses greater than 50 mg^{8,20–21}. Sulpiride-treated patients with extrapyramidal

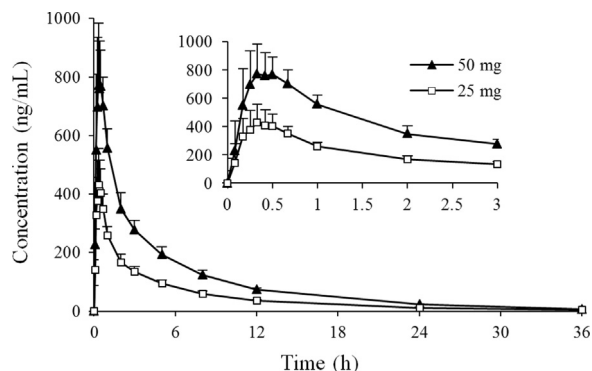


Figure 2 Concentration–time profiles of levosulpiride after single intramuscular doses of 25 mg (–□–) and 50 mg (–▲–) injections. Data are mean \pm standard deviation, $n=12$ (6 males and 6 females).

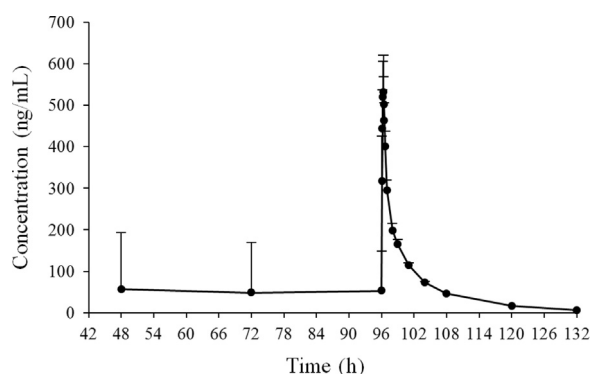


Figure 3 Concentration–time profiles of levosulpiride after multiple intramuscular doses of 25 mg (–●–) injections every 12 h for 5 days. Data are mean \pm standard deviation, $n=12$ (6 males and 6 females).

adverse events had significantly higher drug concentrations in serum⁸. All these clinical results suggested that adverse events are associated with high doses and elevated plasma concentrations. The doses in our study are much lower, consistent with the very low incidence of adverse events. Overall, single-dose and multi-dose im administration of levosulpiride were well tolerated by healthy volunteers.

3.3. Single-dose pharmacokinetics

Fig. 2 shows the mean levosulpiride concentration–time profiles of 12 subjects after single 25 mg and 50 mg im administration. No statistical differences were noted between the 25 and 50 mg single dose results for the $\ln(C_{\max}/\text{dose})$ or the $\ln(\text{AUC}_{0-t}/\text{dose})$ parameters. Furthermore, values for T_{\max} , $t_{1/2}$ and CL_z/F were independent of levosulpiride dose. Levosulpiride was absorbed rapidly, with a T_{\max} less than 0.5 h after im administration, consistent with the results from a previous study in Caucasians^{10,15}. The AUC after im injections of levosulpiride in our study were much larger than those after oral administration of the same levosulpiride dose in Korean volunteers^{16,22,23}, but similar to values after im administration of sulpiride in Caucasians^{10,14}. The V_z/F was 146 ± 33 L (25 mg dose study) and 143 ± 28 L (50 mg dose study), suggesting that levosulpiride was widely distributed all over the body or distributed largely in a specific tissue. The $t_{1/2}$ of levosulpiride in Chinese volunteers after im administration was about 7 h, which was consistent with that of enantiomers of sulpiride in Caucasians^{10,14}. The CL_z/F was about 14.5 L/h in our study.

3.4. Multi-dose pharmacokinetics

Fig. 3 reveals that after 25 mg im doses of levosulpiride every 12 h for 5 consecutive days in 12 subjects, the mean C_{\max} increased from 441 ng/mL (single 25 mg dose) to 539 ng/mL (C_{ssmax} , multiple 25 mg doses). The AUC_{0-t} increased from 1340 ng \cdot h/mL (AUC_{0-t} , single 25 mg dose) to 1635 ng \cdot h/mL (AUC_{ss} , multiple

Table 2 Levosulpiride pharmacokinetic parameters following single-dose and multi-dose intramuscular studies.

Parameter	Single-dose		Multi-dose on day 5 25 mg	P value
	25 mg	50 mg		
C_{\max} (ng/mL)	441 \pm 134	823 \pm 218	539 \pm 103	0.013*
AUC_{0-36} (ng \cdot h/mL)	1724 \pm 304	3478 \pm 585	2146 \pm 449	0.000*
T_{\max} (h)	0.37 \pm 0.08	0.44 \pm 0.14	0.33 \pm 0.08	0.054
$t_{1/2}$ (h)	7.0 \pm 1.0	6.8 \pm 0.6	7.6 \pm 1.1	0.009*
MRT_{0-t} (h)	6.9 \pm 0.9	6.8 \pm 0.8	7.1 \pm 0.7	0.083
CL_z/F (L/h)	14.6 \pm 2.7	14.5 \pm 2.7	15.9 \pm 3.3	0.002*
V_z/F (L)	146 \pm 33	143 \pm 28	174 \pm 38	0.001*
C_{av} (ng/mL)	–	–	136 \pm 28	–
C_{ssmin} (ng/mL)	–	–	53.2 \pm 12.8	–
AUC_{0-t} (ng \cdot h/mL)	1340 \pm 247	–	–	–
AUC_{ss} (ng \cdot h/mL)	–	–	1635 \pm 334	–
R_1	–	–	1.220	–
R_2	–	–	1.222	–
DF	–	–	3.60 \pm 0.47	–

Data are from 6 male and 6 female volunteers and are given as mean \pm standard deviation. The pharmacokinetic parameter differences between single 25 mg dose and multiple 25 mg dose are listed with P values.

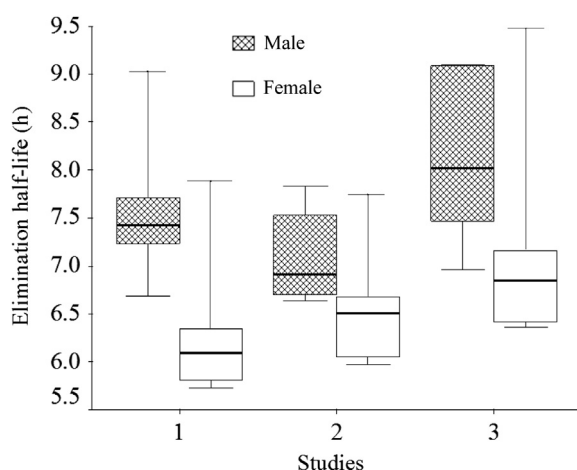
* $P < 0.05$ means there is a statistical difference (95% confidence interval). –Not applicable.

Table 3 Gender differences following a single im dose of 25 mg levosulpiride.

Parameter	Male	Female	P
C_{\max} (ng/mL)	383 ± 135	499 ± 116	0.446
T_{\max} (h)	0.36 ± 0.07	0.39 ± 0.10	0.589
AUC_{0-36} (ng · h/mL)	1671 ± 299	1778 ± 326	0.328
$t_{1/2}$ (h)	7.6 ± 0.8	6.3 ± 0.8	0.021*
MRT_{0-t} (h)	7.5 ± 0.8	6.3 ± 0.5	0.011*
CL_r/F (L/h)	14.9 ± 2.8	14.3 ± 2.8	0.696
V_z/F (L)	163 ± 32	130 ± 27	0.082

Body weight corrected C_{\max} , AUC_{0-36} and the other parameters in the table were compared between genders. The data come from 6 male and 6 female volunteers and are given as mean ± standard deviation. The P values are listed and

* $P < 0.05$ means there is a statistical difference (95% confidence interval).

**Figure 4** Elimination half-life of levosulpiride in 12 healthy Chinese volunteers (6 males and 6 females) after intramuscular administration of single 25 mg dose (study 1), single 50 mg dose (study 2) and multiple 25 mg doses (study 3) levosulpiride injections.

25 mg doses). Consistent with the single-dose data, T_{\max} was 20 ± 5 min. Compared with the results at single dose studies, the V_z/F was increased by 19.2%, the $t_{1/2}$ was increased by 8.6%, and the CL_r/F was increased by 8.9% at steady state. These differences were about 10% and were smaller than the experimental errors. Thus, they can be ignored. The accumulation ratios expressed as AUC_{ss}/AUC_{0-t} (R_1) and C_{ssmax}/C_{\max} (R_2) were 1.220 and 1.222. The drug was almost completely eliminated 36 h after the last dose. Plasma concentrations at steady state before morning injections on day 3, 4, 5 showed no significant differences among the three days, meaning steady state was achieved within 48 h. The DF was 3.60 ± 0.47 . In the present study, inter-individual pharmacokinetic variability (evaluated as the coefficient of variation of the pharmacokinetic parameters) was 10% and 30% (average 20%). These results show that after im administration of 25 mg levosulpiride every 12 h, steady state is reached after two days. Multiple doses of levosulpiride increased the drug exposure by 22%. The levosulpiride pharmacokinetic parameters after single-dose and multi-dose studies are shown in Table 2.

3.5. Gender differences in pharmacokinetics

Gender differences of pharmacokinetics were evaluated in six males and six females for single-dose and multi-dose studies. The results are displayed in Table 3. In the single 25 mg dose study, the mean $t_{1/2}$ was 17% smaller (Fig. 4), and the V_z/F was 20% smaller in females than in males. Earlier reports of the pharmacokinetics of sulpiride¹⁴ found that the disposition rate of drug in male is slightly slower than in female Caucasians after iv administration. These gender differences are similar to the results in the single 50 mg dose and the multi-dose studies.

4. Conclusions

Our findings showed that after im administration of levosulpiride in healthy Chinese volunteers, C_{\max} and AUC_{0-t} for levosulpiride were dose proportional over the 25–50 mg dose range, and steady state was reached within 2 days after im administration of 25 mg dose every 12 h. There was a slight accumulation of drug at steady state, but the drug was almost completely eliminated 36 h after the last dose. These results showed that im administration of levosulpiride was well tolerated by healthy Chinese volunteers.

References

- O'Connor SE, Brown RA. The pharmacology of sulpiride—a dopamine receptor antagonist. *Gen Pharmacol* 1982;13:185–93.
- Rossi F, Forgione A. Pharmacotoxicological aspects of levosulpiride. *Pharmacol Res* 1995;31:81–94.
- Mucci A, Nolfi G, Maj M. Levosulpiride: a review of its clinical use in psychiatry. *Pharmacol Res* 1995;31:95–101.
- Corazza DGR, Tonini M. Levosulpiride for dyspepsia and emesis. *Clin Drug Investig* 2000;19:151–62.
- Lozano R, Concha MP, Montealegre A, de Leon L, Villalba JO, Esteban HL, et al. Effectiveness and safety of levosulpiride in the treatment of dysmotility-like functional dyspepsia. *Ther Clin Risk Manag* 2007;3:149–55.
- Hussain SJ, Hameed A, Nazar HS, Javid A, Shah Y, Hameed W, et al. Levosulpiride in premature ejaculation. *J Ayub Med Coll Abbottabad* 2010;22:124–6.
- Kamizono A, Inotsume N, Fukushima S, Nakano M, Okamoto Y. Disposition of enantiomers of sulpiride in humans and rats. *Biopharm Drug Dispos* 1993;14:475–81.
- Alfredsson G, Bjerkenstedt L, Edman G, Hamryd C, Oxenstierna G, Sedvall G, et al. Relationships between drug concentrations in serum and CSF, clinical effects and monoaminergic variables in schizophrenic patients treated with sulpiride or chlorpromazine. *Acta Psychiatr Scand* 1984;311:49–74.
- Sugnaux FR, Benakis A. Metabolism of sulpiride: determination of the chemical structure of its metabolites in rat, dog and man. *Eur J Drug Metab Pharmacokin* 1978;3:235–48.
- Bressolle F, Bres J, Faure-Jeantis A. Absolute bioavailability, rate of absorption, and dose proportionality of sulpiride in humans. *J Pharm Sci* 1992;81:26–32.
- Watanabe K, Sawano T, Terada K, Endo T, Sakata M, Sato J. Studies on intestinal absorption of sulpiride (1): carrier-mediated uptake of sulpiride in the human intestinal cell line Caco-2. *Biol Pharm Bull* 2002;25:885–90.
- Watanabe K, Sawano T, Endo T, Sakata M, Sato J. Studies on intestinal absorption of sulpiride (2): transepithelial transport of sulpiride across the human intestinal cell line Caco-2. *Biol Pharm Bull* 2002;25:1345–50.

13. Watanabe K, Sawano T, Jinriki T, Sato J. Studies on intestinal absorption of sulpiride (3): intestinal absorption of sulpiride in rats. *Biol Pharm Bull* 2004;**27**:77–81.
14. Bres J, Bressolle F. Pharmacokinetics of sulpiride in humans after intravenous and intramuscular administrations. *J Pharm Sci* 1991;**80**:1119–24.
15. Bressolle F, Bres J, Blanchin MD, Gomeni R. Sulpiride pharmacokinetics in humans after intramuscular administration at three dose levels. *J Pharm Sci* 1984;**73**:1128–36.
16. Cho HY, Yoo HD, Lee YB. Influence of ABCB1 genetic polymorphisms on the pharmacokinetics of levosulpiride in healthy subjects. *Neuroscience* 2010;**169**:378–87.
17. Qian WJ, Ding L, Wen AD, Gong B, Leng Y, Yun CH, et al. Establishment of HPLC–ESI–MS method for the determination of eplerenone in human plasma and its pharmacokinetics. *Acta Pharm Sin* 2009;**44**:771–7.
18. Guslandi M. The clinical use of levosulpiride. *Curr Ther Res Clin Exp* 1993;**53**:484–501.
19. Wagstaff AJ, Fitton A, Benfield P. Sulpiride. *CNS Drugs* 1994;**2**:313–33.
20. Shin HW, Kim MJ, Kim JS, Lee MC, Chung SJ. Levosulpiride-induced movement disorders. *Mov Disord* 2009;**24**:2249–53.
21. Garg S, Goyal N, Sinha VK. Levosulpiride-induced rabbit syndrome. *Aust N Z J Psychiatry* 2013;**47**:288–9.
22. Paek IB, Moon Y, Ji HY, Kim HH, Lee HW, Lee YB, et al. Hydrophilic interaction liquid chromatography–tandem mass spectrometry for the determination of levosulpiride in human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci* 2004;**809**:345–50.
23. Cho HY, Moon JD, Lee YB. Pharmacokinetics and bioequivalence evaluation of 2 levosulpiride preparations after a single oral dose in healthy male Korean volunteers. *Int J Clin Pharmacol Ther* 2004;**42**:174–80.