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Single-dose pharmacokinetics of paliperidone extended-release tablets in healthy Chinese subjects

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Objective Paliperidone is the active metabolite of risperidone. This single-center, double-blind, randomized, single-dose study characterized the pharmacokinetics of 3 mg and 9 mg of paliperidone ER OROS® in healthy Chinese subjects.
Methods 24 subjects (13 male, 11 female), aged 19–35 years, with a BMI of 19.0–24.6 kg/m^2 participated. Blood samples were collected immediately before and over 96 h following single oral doses of 3 mg and 9 mg paliperidone. Plasma paliperidone concentrations were determined, and pharmacokinetic parameters were analyzed.
Results Paliperidone's disposition after oral administration was characterized by a one-compartment pharmacokinetic model. Paliperidone was well absorbed (median t_{max}: 24 h after a 3-mg dose, and 26 h after a 9-mg dose). Apparent clearance and apparent volume of distribution were not significantly different between the two doses. C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ were dose-dependent. Pharmacokinetics was linear with respect to time; Geometric mean $t_{1/2}$ was 22.8 h and 21.4 h in 3-mg and 9-mg groups, respectively. No clinically significant safety issues were identified.
Conclusions The pharmacokinetic results obtained in Chinese subjects were similar to those obtained in Japanese and Caucasian subjects.

KEY WORDS — Chinese; paliperidone ER; pharmacokinetics; tolerability

INTRODUCTION

Paliperidone, the 9-OH-risperidone, is an new atypical psychotropic medication that is the active metabolite of risperidone, an established, efficacious, atypical antipsychotic (Ceskova and Svestka, 1993; Lindstrom *et al*., 1995; Peuskens, 1995; Moller *et al*., 1998; hHwang *et al*., 2003). The formation of paliperidone is predominantly catalyzed in the liver by cytochrome P450 isoenzymes (CYP) 2D6 and, to a lesser extent, CYP3A4 from risperidone (Fang *et al*., 1999; Spina *et al*., 2001). It has pharmacological activity at monoaminergic receptors similar to that of risperidone. In vitro, paliperidone has almost the same binding affinity as risperidone for both dopamine type 2 (D_2) and serotonin (5-hydroxytryptamine (Karlsson, *et al.*) type 2A (Karlsson, Dencker, Nyberg, Mannaert, Boom, Talluri, Rossenu, Eriksson, Eerdekens and Farde)) receptors, for α_1- and α_2-adrenoceptors, and for the H_1 receptor. Paliperidone extended-release (ER) tablet formulation was designed using OROS® (osmotic release oral systems) technology (ALZA Corporation, Mountain View, CA, USA) to provide consistent and continual drug delivery for periods of more than 24 h, thereby reducing the peak-to-trough fluctuations in plasma concentrations that are characteristic of immediate-release formulations (Karlsson *et al*., 2005). The gradually ascending release profile of paliperidone ER permits initiation of treatment with a therapeutically effective dose without the need for initial dose titration (Davidson *et al*., 2007; Kane *et al*., 2007; Marder *et al*., 2007).

Results from population pharmacokinetic analyses based on Phase I data indicate that the terminal half-life of paliperidone is approximately 24 h, which is unaffected by the formulation. Furthermore, preclinical studies demonstrate that paliperidone does not undergo significant hepatic metabolism (Vermeir *et al*., 2008), which may reduce the risk of hepatic drug–drug interactions. These features may offer particular benefits for schizophrenia patients, who frequently have comorbidities requiring additional medications (Goff *et al*., 2005). The data from three randomized, double-blind, controlled, 6-week clinical studies showed that all doses of paliperidone ER were consistently effective in significantly improving the symptoms of

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schizophrenia and personal and social functioning, and were generally well tolerated (Davidson *et al*., 2007; Kane *et al*., 2007; Marder *et al*., 2007). Long-term treatment with paliperidone ER has been demonstrated in a randomized, double-blind, placebo-controlled study to delay symptom recurrence, maintain symptom control and function in patients with schizophrenia, and was generally well tolerated (Kane *et al*., 2007). Paliperidone ER therefore offers a distinctive treatment profile and may provide a valuable new treatment option for patients with schizophrenia.

Most Phase I/II paliperidone ER studies were conducted in Caucasian, African, or Japanese subjects. This study was designed to evaluate the pharmacokinetic profile of paliperidone ER within the therapeutic dose range in healthy Chinese subjects.

MATERIALS AND METHODS

Study subjects

A total of 24 healthy Han Chinese subjects were to be enrolled in the study. The eligibility criteria included: (i) age 18–55 years, inclusive, with a body weight of at least 50 kg and a BMI of 19–24 kg/m^2; (ii) healthy on the basis of a pre-study physical examination, medical history, ECG, serum chemistry, hematology, and urinalysis performed within 21 days before the first dose; and (iii) normotensive. The exclusion criteria included: (i) known drug allergy to any compound used in the study, or a relevant history or presence of any physical disorders; (ii) less than one bowel movement on average every other day or more than two bowel movements per day, or inability to swallow solid oral dosage forms whole with the aid of water; (iii) use of any prescription or nonprescription medication (including vitamins and herbal supplements) within 14 days before the first dose of study drug; and (iv) history of smoking or use of nicotine-containing substances within the last 2 months, or consuming more than 450 mg of caffeine per day. Subjects had to agree to refrain from using caffeine or nicotine throughout the study. The eligible subjects were assigned to either the 3 mg or the 9 mg treatment group based on a computer-generated randomization schedule prepared before the study.

Study design

This was a double-blind, randomized, single-period study. Twenty-four subjects were enrolled and randomly assigned in a 1:1 ratio to receive either paliperidone ER 3 mg or 9 mg. Paliperidone ER 3 mg (given as one paliperidone OROS® tablet, 3 mg) and two tablets of matching placebo were supplied by Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) and ALZA Corporation (Mountain View, CA, USA). Paliperidone ER 9 mg was given as three paliperidone OROS® tablets. All study medications were taken with 200 mL water, at about 8:00 am in the fasted condition on Day 1. The patients were instructed to swallow the medication whole, without chewing, dividing, or crushing it. Sequential blood samples were obtained by venipuncture from the antecubital vein immediately before and 2, 5, 8, 12, 16, 18, 20, 22, 24, 26, 29, 32, 36, 48, 60, 72, 84, and 96 h after dosing.

Food or beverages containing alcohol, grapefruit juice, methylxanthine or caffeine, Seville oranges, or quinine were restricted from 24 h (3 days for grapefruit juice or Seville oranges) before the first dose of study drug through completion of the study to minimize dietary effects on CYP1A2.

Analytical methods

Plasma samples were analyzed by a validated HPLC/tandem mass spectrometry (LC/MS/MS) method. The lower limit of quantification was 0.1 ng/mL, and the upper limit was 200.0 ng/mL. Samples above the upper limit of quantification were diluted and reanalyzed to yield results within the calibrated range. The inter-assay accuracy, expressed as percentage relative error during validation, was $\leq$9.1%. The inter-assay precision, expressed as percentage relative standard deviation during validation, was $\leq$6.1%.

Pharmacokinetic analysis

Plasma paliperidone concentration-time data obtained from individual subjects were analyzed with non-compartmental pharmacokinetic methods using Drug and Statistics Software 2.1 (DAS, Mathematical Pharmacology Professional Committee of China). Pharmacokinetic parameters determined for paliperidone included the maximum plasma concentration (C_{max}), time to maximum concentration (t_{max}), the area under the concentration-time curve ($AUC_{0\text{-}\infty}$), apparent clearance (CL/F), apparent volume of distribution (Vs/F), and the terminal half-life ($t_{1/2}$).

Statistical analysis

Pharmacokinetic parameters obtained following a single dose were evaluated for statistical difference using a mixed effect model with ''dose'' (single-) as a fixed effect and ''subject'' as a random effect. For each treatment, descriptive statistics for all pharmacokinetic parameters of paliperidone, including arithmetic mean, SD, coefficient of variation (CV), median, minimum,

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and maximum were calculated for the paliperidone plasma concentrations at each sampling time.

In addition, ANOVA was performed on the paliperidone ER pharmacokinetic parameters to investigate statistical differences between Chinese subjects and those previously reported in Caucasian and Japanese subjects.

Safety and tolerability evaluations

Safety data were collected in the form of clinical examinations, clinical laboratory testing, and vital signs (body temperature, supine blood pressure, and pulse rate), and adverse events were monitored throughout the study.

Ethical considerations

The study was approved by the Independent Ethics Committee of Peking University Institute of Mental Health, China, and was performed in accordance with the Declaration of Helsinki.

All subjects had to be able to read and understand the purpose of and procedures required for the study and be willing to participate in the study. Written informed consent was obtained from the participants before study commencement.

RESULTS

Demographics

Figure 1 shows the subject disposition. A total of 24 subjects (13 men, 11 women) received paliperidone ER 3 mg or 9 mg ($n = 12$ for each group). The average age, screening bodyweight, screening height and body mass index were 23 years (range 19–35 years), 59 kg (range 50–76 kg), 167 cm (range 155–179 cm) and 21.2 kg/m^2 (range 19.0–24.6 kg/m^2). The demographics data of the two dose groups were comparable. All subjects completed the study.

Pharmacokinetics

Following single-dose administration, maximal paliperidone concentrations were achieved at approximately 22.2 h and 24.8 h for 3 mg and 9 mg dosings, respectively. The geometric mean $MRT_{0\text{-}t}$ and $t_{1/2}$ were 33.7 h and 22.8 h, respectively, for 3 mg dosing, and

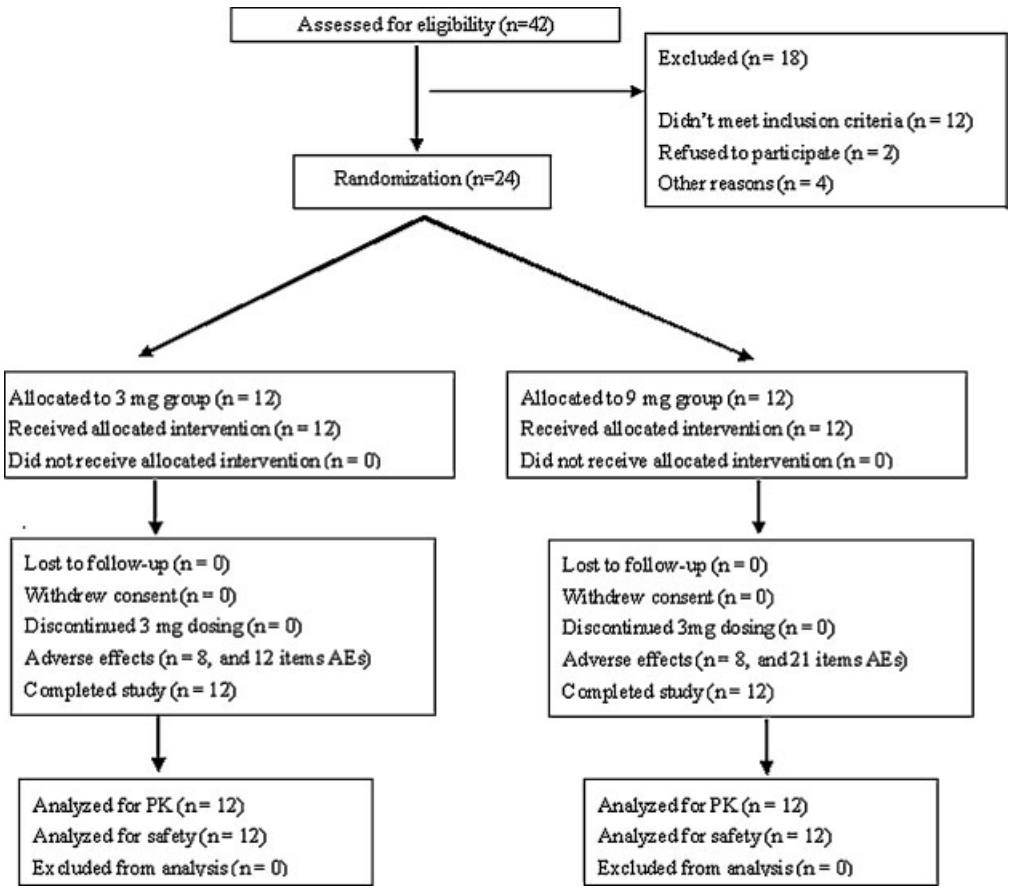

Figure 1. Trial profile.

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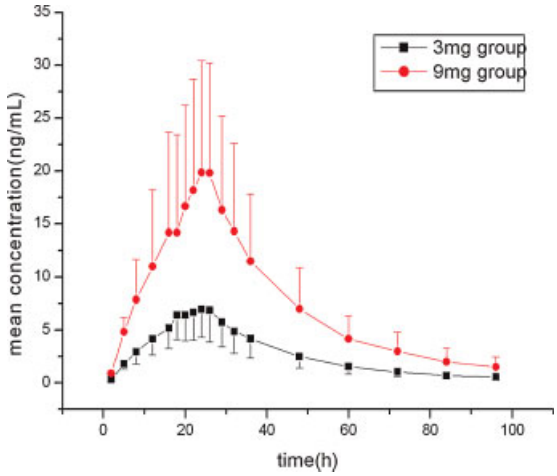

Figure 2. The time course of the mean (SD) paliperidone concentration in plasma following oral administration of 3 mg or 9 mg as single dose in healthy Chinese subjects. Standard deviations are represented as error bars.

34.2 h and 21.4 h, respectively, for 9 mg dosing. The time course of the mean paliperidone concentration demonstrated the characteristics of a one-compartment pharmacokinetic model (Figure 2). The mean pharmacokinetic parameters for paliperidone after 3 mg and 9 mg dosing are summarized in Table 1.

The pharmacokinetic parameters of paliperidone, including t_{max}, $t_{1/2}$, $MRT_{0\text{-}t}$, $MRT_{0\text{-}\infty}$, CL/F, and V/F, were not statistically significantly different following 3 mg or 9 mg dosing (Table 1). The differences in Cmax, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ for 3 mg and 9 mg were significantly different ($p = 0.001$) in a dose-dependent manner (correlation coefficient = 0.64, $p = 0.001$). After correcting for dose, no statistical significant differences in C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ between 3 mg and 9 mg were observed (Figure 2). Comparison of paliperidone oral clearance in men and women after correcting for dose, there is no significant difference. The inter-individual variation of pharmacokinetic parameters was large, up to 60%. The CL/F, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ of paliperidone were similar in women and men following single doses of 3 mg and 9 mg paliperidone ER (Figure 3).

Comparison of paliperidone ER pharmacokinetics in Chinese, Japanese, and Caucasian subjects

Statistical analyses revealed no significant differences across the three ethnic groups for all paliperidone ER pharmacokinetic parameters following single dosing (Table 2).

Safety and tolerability

Sixteen subjects (8 from 3 mg and 8 for 9 mg dosing) of the 24 subjects, experienced treatment-related adverse effects. The most common adverse events (≥5%) were somnolence, dizziness, asthenia, headache, feeling

Table 1. Pharmacokinetic parameters for paliperidone ER following 3 mg or 9 mg single dosing

PK parameters	3 mg ($N = 12$)		9 mg ($N = 12$)	
	Geometric mean (SD) CV%	90% CI	Geometric mean (SD) CV%	90% CI
t_{max} (h)	22.2 (16.1) *20%*	(20.6, 24.4)	24.8 (7.2) *10%*	(23.9, 25.8)
C_{max} (ng/mL)	7.5 (33.8) *30%*	(6.5, 9.4)	18.3 (51.7) *50%*	(15.0, 26.0)
$AUC_{0\text{-}t}$ (ng•h/mL)	240.4 (38.3) *40%*	(207.9, 311.0)	634.7 (55.1) *60%*	(508.4, 915.2)
$AUC_{0\text{-}\infty}$ (ng•h/mL)	257.3 (38.4) *40%*	(222.2, 332.8)	673.5 (55.4) *60%*	(538.4, 972.8)
$MRT_{0\text{-}t}$ (h)	33.7 (6.4) *10%*	(32.7, 34.9)	34.2 (5.6) *10%*	(33.3, 35.3)
$MRT_{0\text{-}\infty}$ (h)	40.3 (11.2) *10%*	(38.2, 42.9)	40.1 (7.8) *10%*	(38.6, 41.8)
$t_{½}$ (h)	*22.8 (21.8)* *20%*	(20.7, 26.0)	21.4 (12.4) *10%*	(20.2, 23.0)
CL/F (L/h)	*11.7 (46.1)* *50%*	(9.7, 15.7)	13.4 (45.9) *50%*	(11.3, 18.3)
V/F (L)	384.4 (60.0) *60%*	(302.8, 576.2)	412.8 (50.4) *50%*	(342.4, 584.9)
C_{max} /dose (ng/mL)	2.65 (0.92)	(2.17, 3.13)	2.28 (1.17)	(1.67, 2.89)
$AUC_{0\text{-}t}$ /dose (ng•h/mL)	86.50 (33.15)	(63.31, 103.68)	79.01 (43.59)	(56.49, 101.69)
$AUC_{0\text{-}\infty}$ /dose (ng•h/mL)	92.5 (35.56)	(74.07, 110.94)	83.95 (46.56)	(59.82, 108.09)

CL/F = apparent oral clearance; C_{max} = maximum plasma concentration; $t_{1/2}$ = elimination half-life; t_{max} = time to reach C_{max}; $AUC_{0\text{-}\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; $AUC_{0\text{-}t}$ = area under the plasma concentration-time curve to time t; $MRT_{0\text{-}t}$ = mean residence time-to-time t; $MRT_{0\text{-}\infty}$ = mean residence time extrapolated to infinity; V/F = apparent distribution volume.

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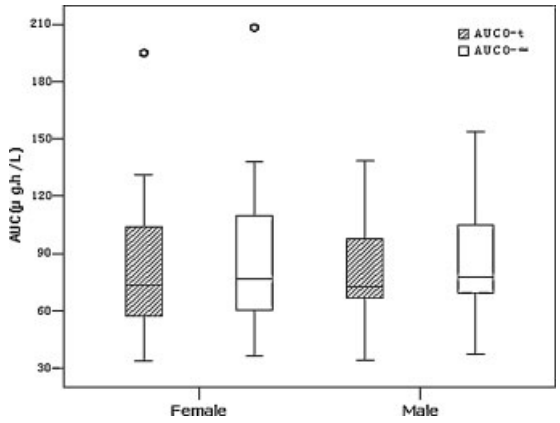

Figure 3. Comparison of paliperidone $AUC_{0-\infty}$ and AUC_{0-t} in men and women after converting the 3 mg or 9 mg single dose paliperidone into 1 mg dosing. The box plots illustrate the medians and interquartile ranges (25th–75th percentiles), and the whiskers represent the 10th and 90th percentiles.

flustered, and nausea. The somnolence and dizziness were dose-related. All adverse events were of mild severity and had resolved spontaneously by the time of study completion. No subject discontinued from the study because of adverse effects. One subject experienced a single episode of galactorrhea, about 84 h after receiving 9 mg paliperidone ER. During the course of the study there were no clinically significant changes in laboratory values and vital signs values.

DISCUSSION

The present study is the first to report the pharmacokinetics of paliperidone ER in healthy Chinese subjects. The study was conducted to evaluate the pharmacokinetics of paliperidone ER following single-dose, oral administration at 3 mg and 9 mg. The pharmacokinetics of paliperidone ER in Chinese subjects can be adequately described by a one-compartment pharmacokinetic model, consistent with those reported in Caucasian and Japanese subjects. The mean pharmacokinetic parameters, such as CL/F, V/F, and $t_{1/2}$, in Chinese subjects were also similar to those reported for Caucasian and Japanese subjects.

The pharmacokinetics of paliperidone ER are linearly related to dose, as there were no statistically significant differences in t_{max}, $t_{1/2}$, CL/F, and V/F after 3 mg or 9 mg dosing, and, after correcting for dose, no statistically significant differences in C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ between 3 mg and 9 mg were observed. Gender had no effect on the pharmacokinetics of paliperidone ER in this study. Data from preclinical and clinical studies demonstrate that paliperidone was not extensively metabolized in the liver, and renal excretion was the major route of elimination; 59% of an oral liquid dose was excreted unchanged in the urine. Other than renal excretion, four metabolic pathways, with possible involvement of CYP3A4 and CYP2D6 enzymes, were identified as being involved in the elimination of paliperidone, each of which accounted for up to 6.5% of the administered dose. No differences were observed in the overall plasma pharmacokinetics of paliperidone between poor and extensive CYP2D6 metabolizers. There is no relationship between the genotypic expression of metabolizing enzymes UGT1A1 and UGT1A6 and paliperidone pharmacokinetics(Vermeir *et al*., 2008). The characteristics of paliperidone's metabolism may reduce the risk of hepatic drug–drug interactions, and also may explain the similarity of paliperidone's pharmacokinetics across the various ethnic populations (Caucasian, Japanese, and Chinese).

Few studies have investigated the metabolism of risperidone in Chinese subjects. One study (Zhou *et al*., 2006) was conducted in 23 Chinese female inpatients with schizophrenia. The subjects were tested after 17 days of treatment with 2 mg risperidone twice daily. The results showed that the t_{max} was 1.6 h for risperidone and 2.5 h for 9-hydroxy-risperidone (paliperidone); the half-life was 3.2 h for risperidone and 24.7 h for 9-hydroxy-risperidone. In our study, the t_{max} of paliperidone was 22.2 h and 24.8 h in the

Table 2. Comparison of paliperidone ER pharmacokinetic parameters in Chinese, Japanese and Caucasian subjects

Parameter	Chinese		Caucasian		Japanese
	3 mg dose	9 mg dose	3 mg dose	9 mg dose	3 mg dose
No. of subjects (*n*)	12	12	24	30	23
Bodyweight (kg)	59.0 ± 6.0	59.5 ± 8.4	69.2 ± 9.6	77.5 ± 8.4	59.6 ± 8.3
t_{max} (h)	22.2 ± 16.1	24.8 ± 7.2	25.02 ± 2.90	24.9 ± 12.4	22.68 ± 4.27
C_{max} (ng/mL)	7.5 ± 33.8	18.3 ± 51.7	5.59 ± 2.84	16.8 ± 33.1	6.60 ± 2.19
CL/F (mL/min)	211 ± 97	246 ± 113	306 ± 194	-	237 ± 97.2
$AUC_{0-\infty}$ (ng h/mL)	257 ± 38.4	673 ± 55.4	218 ± 114	711 ± 34.6	241 ± 84.2
$t_{½}$ (h)	22.8 ± 21.8	21.4 ± 12.4	20.8 ± 4.52	24.5 ± 12.3	19.6 ± 3.45

CL/F = apparent oral clearance; C_{max} = maximum plasma concentration; $t_{1/2}$ = elimination half-life; t_{max} = time to reach C_{max}; $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity. Data for Japanese and caucasian subjects from Janssen Pharmaceutical Company.

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3 mg and 9 mg groups, respectively, which is nearly equal to its half-life of 22.8 and 21.4 h, respectively. The only difference between these two studies was the t_{max} of paliperidone. This difference is due to the use of OROS® osmotic drug-releasing technology of paliperidone ER, which provides sustained drug release over a 24-hour period. The ''gradually ascending'' controlled delivery profile of paliperidone ER allows treatment to begin at a potentially therapeutically effective dose without the need for initial dose titration for tolerability. Theoretically, this pharmacokinetic profile provides a small 24-hour peak-to-trough fluctuation in paliperidone plasma concentrations at steady state (Karlsson *et al*., 2005) and may attenuate the potential deleterious effects of the occasional missed dose by removing the risk of excessively low plasma levels.

Evaluation of the safety and tolerability suggested that oral administration of a single dose of 3 mg and 9 mg paliperidone ER was well tolerated in the healthy Chinese subjects studied, which are consistent with previous data on paliperidone ER (Davidson *et al*., 2007; Kane *et al*., 2007). The number of treated subjects in this pharmacokinetic study was small. Phase III studies with a large number of Chinese subjects will provide more conclusive information on the safety and tolerability of paliperidone ER in Chinese subjects.

Paliperidone, which is pharmacologically similar to risperidone (Karlsson *et al*., 2005), is a known antagonist of dopamine D_2, serotonin 5-HT_{2A}, histamine H_1, and α_1- and α_2-adrenoceptors. As the most commonly used atypical antipsychotic (Owens, 1994; Peuskens, 1995), risperidone is associated with an increased incidence of extrapyramidal side effects, particularly for healthy volunteers at higher doses. In the present study, single doses of 3 mg and 9 mg paliperidone ER had few extrapyramidal side effects. This might be due to the 'gradually ascending' controlled delivery profile of paliperidone ER, which provides consistent and continual drug delivery, thereby avoiding the rapid increase in peak plasma concentration and D_2 receptor occupancy in the brain (Owen, 2007; Arakawa *et al.*, 2008) typically seen with immediate-release formulations of paliperidone (Zhou *et al*., 2006). Indeed, tolerability is a key factor in treatment adherence, which in turn, is vital to obtaining good long-term outcomes for patients with schizophrenia (Masand and Narasimhan, 2006), and poorer treatment adherence increases the risk of relapse (Weiden and Olfson, 1995).

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