RESEARCH PAPER

Influence of *ABCB1* genetic polymorphisms on the pharmacokinetics of risperidone in healthy subjects with *CYP2D6**10/*10

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BACKGROUND AND PURPOSE

The objective of this study was to investigate the combined influence of genetic polymorphisms in *ABCB1* and *CYP2D6* genes on risperidone pharmacokinetics.

EXPERIMENTAL APPROACH

Seventy-two healthy Korean volunteers receiving a single oral dose of 2 mg risperidone were included in this study.

KEY RESULTS

Significant differences were observed between the *ABCB1* 3435C>T genotypes for the pharmacokinetic parameters (peak serum concentration) of risperidone and the active moiety (risperidone and its main metabolite, 9-hydroxyrisperidone). There were no significant differences in the area under the serum concentration-time curves of risperidone and the active moiety among the *ABCB1* 2677G>T/A and 3435C>T genotypes. However, the peak serum concentration and area under the serum concentration-time curves were significantly different among the *ABCB1* 3435C>T genotypes in *CYP2D6**10/*10.

CONCLUSIONS AND IMPLICATIONS

These findings indicate that polymorphisms of *ABCB1* 3435C>T in individuals with *CYP2D6**10/*10, which has low metabolic activity, could play an important role in the potential adverse effects or toxicity of risperidone.

Abbreviations

ABCB1, ATP-binding cassette, sub-family B (MDR/TAP), member 1; AM, active moiety; AUC, area under the serum concentration-time curves; BE, bioequivalence; C_{max} , peak serum concentration; CYP, cytochrome P450; P-gp, P-glycoprotein; SNP, single nucleotide polymorphism

Introduction

Risperidone is an atypical antipsychotic drug and has potent antagonistic properties for dopamine D₂ and 5-HT₂ receptors

(Janssen *et al.*, 1988; Leysen *et al.*, 1988; Marder and Meibach, 1994). This drug is characterized by established therapeutic effects against positive and negative symptoms in the treatment of schizophrenia (Claus *et al.*, 1992; Carman *et al.*,

1995). Furthermore, it produces a slightly less favourable extrapyramidal side effect profile than conventional antipsychotic drugs (Leucht *et al.*, 1999).

Risperidone is primarily metabolized into the active metabolite 9-hydroxyrisperidone (9-OH-risperidone) via 9-hydroxylation. An *in vitro* study revealed that cytochrome P450 (CYP) 2D6 is involved in this metabolism (Fang *et al.*, 1999). CYP2D6 is considered the clinically important drug-metabolizing enzyme that modulates the plasma levels of risperidone and 9-OH-risperidone (Kang *et al.*, 2009). Oral risperidone is approximately twice as potent as oral 9-OH-risperidone (Wang *et al.*, 2004; de Leon *et al.*, 2010). Risperidone and its main metabolite, 9-OH-risperidone, form the active serum compound (termed 'active moiety'; AM). Approximately 7–10% of Caucasians and 1% of Asians are homozygous for non-functional CYP2D6 alleles. Despite the low frequency of poor metabolizers of CYP2D6 substrates in Asian populations, these people have been found to carry a high frequency (51%) of the 100C>T (exon 1) polymorphism, which causes a Pro₃₄→Ser amino acid substitution that leads to an unstable enzyme with lower metabolic activity (Bertilsson *et al.*, 1992; Johansson *et al.*, 1994). Indeed, the presence of CYP2D6*10 reduces CYP2D6-dependent metabolism of several substrates. The single nucleotide polymorphism (SNP) that defines the CYP2D6*10 allele is not as common in Caucasian populations as in Asians (3–5% vs. 35–54%) (Roh *et al.*, 2001a). Therefore, besides rare non-functional variants such as CYP2D6*4, *5 or *14b, the CYP2D6*10 allele seems to be the most clinically important allele in Asian populations (Gan *et al.*, 2002).

P-glycoprotein (P-gp) is a member of the ATP-binding cassette (ABC) superfamily of transporters (Higgins, 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immunosuppressants (Kuyper *et al.*, 2008), antiviral agents (Lee *et al.*, 1998), antipsychotics and antidepressants (Shinkai *et al.*, 2008; Uhr *et al.*, 2008; Cho *et al.*, 2010). According to *in vitro* studies, risperidone and quetiapine have a stronger affinity for P-gp than other atypical antipsychotic drugs, suggesting that risperidone and quetiapine are relatively good substrates for P-gp (Boulton *et al.*, 2002; Yasui-Furukori *et al.*, 2004). Treatment with a P-gp inhibitor, verapamil, increased the peak plasma concentrations ($C_{\max}$) and the area under the plasma concentration-time curves (AUC) of risperidone and 9-OH-risperidone after a single dose, suggesting that P-gp plays a role in the pharmacokinetics of risperidone and 9-OH-risperidone (Nakagami *et al.*, 2005; Gunes *et al.*, 2008). 9-OH-risperidone may have less ability to enter the brain because of its greater affinity for the transporter P-gp than risperidone (Wang *et al.*, 2004). Several SNPs exist in the ABCB1 gene and contribute to the bioavailability of drugs that are P-gp substrates (Chowbay *et al.*, 2003a). The silent 3435C>T (exon 26) and the 2677G>T/A (exon 21), which leads to an amino acid exchange (Ala893Ser/Thr), are common ABCB1 polymorphisms. It has been reported that 3435C>T and 2677G>T/A polymorphisms influence the duodenal expression of P-gp and alter the absorption and/or disposition of many drugs (Hoffmeyer *et al.*, 2000; Nakamura *et al.*, 2002; Rodrigues *et al.*, 2005). Because of the effects of the timing of cotranslational folding and insertion of P-gp into the membrane, the silent 3435C>T (exon 26) may influence the ABCB1 gene controlling expres-

sion (Kimchi-Sarfaty *et al.*, 2007). Since 2677G>T/A is a missense SNP, it probably causes differences in P-gp expression (Tanabe *et al.*, 2001). Subjects carrying the 3435T/T genotype have remarkably lower duodenal P-gp expression and higher plasma digoxin levels than subjects with the CC or CT genotype (Rodrigues *et al.*, 2005). Therefore, SNPs in exon 26 (3435C>T) and exon 21 (2677G>T/A) of the ABCB1 gene cause differences in P-gp expression.

The respective effects of CYP2D6 and ABCB1 polymorphisms on the steady-state plasma levels in patients receiving risperidone and 9-OH-risperidone have been evaluated in some studies (Leon *et al.*, 2007; Gunes *et al.*, 2008; Jovanovic *et al.*, 2010), but the involvement of CYP2D6 and ABCB1 polymorphisms in the serum levels in humans has not been evaluated yet. Therefore, in this study we aimed to investigate the combined influence of genetic polymorphisms in CYP2D6*10 and ABCB1 (3435C>T and 2677G>T/A) on the pharmacokinetics of risperidone, 9-OH-risperidone and its AM after oral administration of a single dose of risperidone in healthy Korean subjects.

Methods

Subjects

A total of 80 healthy Korean male volunteers participated in this study. The subjects' ages and weights ranged from 19 to 30 years (mean $\pm$ SD, 23.4 $\pm$ 2.1 years) and from 51.1 to 89.0 kg (mean $\pm$ SD, 65.3 $\pm$ 7.5 kg), respectively, in the pharmacokinetic study. Based on medical history, physical examination and routine biochemical laboratory test results, all subjects were considered healthy. All subjects gave informed written consent to undergo genotype analysis and pharmacokinetic studies. The study protocol was approved by the Institutional Review Board of the Institute of Bioequivalence and Bridging Study, Chonnam National University, Gwangju, Korea. This study was performed according to the revised Declaration of Helsinki for biomedical research involving human subjects and the rules of Good Clinical Practice. Each subject was physically normal and had no previous history of significant illness or hypersensitivity to any drugs. Furthermore, the health status of subjects was judged normal on the basis of a physical examination that included screening of blood chemistries and urine analysis before the subjects were admitted to the study. Finally, the subjects were asked to refrain from taking alcohol, nicotine, caffeine and any other drugs for at least 1 week before and throughout the study period.

Study design

Subjects who participated in four separate risperidone bioequivalence (BE) studies having the same protocol design were included in this retrospective analysis; only data from the reference formulation were used for the current analysis. The BE studies were conducted as single-dose, randomized, two-way, open-label and crossover studies at the Institute of Bioequivalence and Bridging Study, College of Pharmacy, Chonnam National University. After an overnight fast, the subjects in each study received a single oral dose of 2 mg risperidone with 240 mL of water (Risperdal tablet in each study, 2 mg; lot no. 8487, Janssen Korea Ltd, Seoul, Korea).

Blood samples were collected in Vacutainer® tubes before dosing and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 and 48 h after drug administration. Following centrifugation (3000× *g*, 20 min, 4°C), serum samples were transferred to polyethylene tubes and immediately stored at –70°C until analysis. After a washout period of 7 days, each study was repeated in the same manner to complete the crossover design.

Simultaneous assay of risperidone and 9-OH-risperidone in serum

Concentrations of risperidone and 9-OH-risperidone in serum were analysed using a validated HPLC method as described previously (Llerena *et al.*, 2003). Briefly, frozen serum was allowed to thaw at room temperature. In total, 100 µL of internal standard working solution (azelastine 1 µg·mL⁻¹ in methanol), methanol (100 µL), 1 mol·L⁻¹ sodium hydroxide (500 µL) and ethyl acetate (4 mL) were added to 1 mL of serum in a glass tube. After shaking with a vortex mixer for 2 min and centrifugation at 3000× *g* for 10 min, the organic upper layer was transferred to a clean tube and back-extracted with 150 µL of 0.025 mol·L⁻¹ sulphuric acid by vortex-mixing for 1 min and centrifugation at 3000× *g* for 5 min. The aqueous layer was alkalized with 30 µL of 1 mol·L⁻¹ sodium hydroxide. Sample aliquots (50 µL) were injected directly into the HPLC system.

Analyses were performed with the following HPLC system: a Model LC-10Ai isocratic pump, a Model SPD-10Avp UV-VIS detector, a Model SCL-10Avp system controller (Shimadzu, Kyoto, Japan), Rheodyne 7725 injection valve (Rheodyne, Cotati, CA, USA), Security guard cartridge system and Luna C18(2) column (3 µm particle size, 150 × 3.0 mm I.D., Phenomenex, Torrance, CA, USA). The mobile phase consisted of 40 mmol·L⁻¹ ammonium acetate: methanol: acetonitrile (35:35:30, v/v/v) adjusted to pH 7.6 with 1 mol·L⁻¹ sodium hydroxide. The flow-rate was set at 0.3 mL·min⁻¹. The eluate was monitored at UV wavelength of 280 nm.

The retention times for 9-OH-risperidone, risperidone and azelastine (IS) were 5.5, 7.0 and 10.0 min respectively. The peaks of these compounds were well resolved and free of interference from endogenous compounds in the serum. The calibration curves for serum samples were linear over the concentration range examined ($r^2 > 0.99$ for two analytes). The responses were linear in the range of 0.2–50 ng·mL⁻¹ ($y = 0.0598x - 0.00252$, $r^2 = 0.9998$, $n = 9$) for risperidone. In addition, the responses were linear in the range of 0.2–50 ng·mL⁻¹ ($y = 0.0626x + 0.00132$, $r^2 = 0.9998$, $n = 9$) for 9-OH-risperidone, where y is the ratio between the area of the standard and the area of the IS and x is the standard content (ng·mL⁻¹). The intra- and inter-assay coefficients of variation for the two analytes were lower than 15% at relevant concentrations ($n = 5$). The lower limit of quantification for both analytes was 0.2 ng·mL⁻¹. The mean relative recoveries of risperidone and 9-OH-risperidone were $89.2 \pm 4.7\%$ and $97.1 \pm 4.5\%$ (mean $\pm$ SD), respectively, indicating that the present method could achieve complete recoveries for the two compounds studied.

Pharmacokinetic analysis

Pharmacokinetic parameters were calculated by non-compartmental analysis of serum concentration-time curve

data using WinNonlin software (Pharsight Corporation, Mountain View, CA, USA). The peak concentration ($C_{\max}$) and area under the concentration-time curve from time zero to time infinity (AUC) for risperidone and 9-OH-risperidone were determined from individual serum concentration-time profiles. The AUC was calculated as $AUC_{0-t} + C_t \lambda_z^{-1}$, where C_t is the last measurable concentration and λ_z is the terminal rate constant. AUC_{0-t} was calculated by the linear trapezoidal rule from zero to the last measurable time point. The terminal half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$. Metabolic ratio (MR) was defined as the mean ratio of the serum concentration of risperidone and 9-OH-risperidone at each time point.

Genotype analysis

Blood samples were collected from 80 volunteers for genotype analysis. Genomic DNA was isolated from peripheral leucocytes using the Wizard Genomic DNA Purification Kit (Promega Co., Madison, WI, USA). The DNA was dissolved in 100 µL of DNA hydration solution and stored at –70°C.

Identifications of *CYP2D6* alleles

All subjects recruited in this study were genotyped by DNA sequencing analysis for *CYP2D6**2, *4, *10, *14A/B, *36 and *47, which are frequently found in Asians with clinical consequences (Lee *et al.*, 2009). For detection of *CYP2D6* genotypes, a 20 µL PCR reaction was performed. Primers were designed with the primer3 software (<http://frodo.wi.mit.edu/primer3>) (Rozen and Skaletsky, 2000). Primers used in this study are shown in Table 1. The PCR amplifications were performed with SolGent™ f-Taq DNA polymerase. The reaction mixture contained 14.5 µL water, 2.0 µL 10× f-taq buffer, 0.1 µL Enzyme Mix (5 U·µL⁻¹), 0.4 µL dNTP mixture (10 mmol·L⁻¹), 0.8 µL forward primer (10 mmol·L⁻¹), 0.8 µL reverse primer (10 mmol·L⁻¹) and 1.0 µL genomic DNA (50 ng·mL⁻¹), and the cycling conditions were as follows: 3 min at 94°C, followed by 35 cycles of 94°C for 20 s, 62°C for 30 s, 72°C for 20 min and a final extension of 5 min at 72°C. The PCR products were then analysed by direct sequencing using the ABI PRISM BigDye Terminator Cycle Sequencing Kit and an ABI Prism 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). The *CYP2D6**5 allele was identified using the Long-PCR methods with minor modifications as described previously (Lee *et al.*, 2009).

Identifications of *ABCB1* 2677G>T/A and 3435C>T

Candidate SNPs (2677G>T/A and 3435C>T) in the *ABCB1* gene were genotyped using PCR restriction fragment length polymorphism (PCR-RFLP) with minor modifications (Cascorbi *et al.*, 2001; Chowbay *et al.*, 2003b). The primer sequences for 3435C>T were obtained from published sequences, while mismatch primer sets were designed for identification of the allelic variant 2677G>T/A (Table 1). The PCR conditions consisted of an initial denaturation step for 2 min at 94°C, followed by 30 cycles consisting of denaturation at 94°C for 30 s, annealing at 59.8°C for 30 s and extension at 72°C for 30 s. The terminal extension was performed at 72°C for 5 min. The PCR products were digested with specific restriction enzymes: *Ban I*/*Rsa I* for 2677G>T/A and

Table 1

Primers used in this study

Genotype	SNP	Orientation	Sequence (5' to 3')
<i>CYP2D6</i>			
Exon 1	73C>T	Forward	CTGAGAGTGTCTGCCTGGT
	100C>T	Reverse	GTTTCACCCACCATCCATGT
Exons 3, 4	1758G>A	Forward	CAAGAAGTCGCTGGAGCAGT
	1846G>A	Reverse	GAGGGTCGTCGACTCGAAG
Exon 6	2850C>T	Forward	GGTGCAGAATTGGAGGTCAT
		Reverse	GGTGTCACAGCAAAGTTCAT
Exon 9	4180G>C	Forward	GGAGTCTTGCAGGGGTATCA
		Reverse	CTGAGGAGGATGATCCCAAC
<i>ABCB1</i>			
Exon 21	2677G>T/A	Forward	TGCAGGCTATAGGTTCCAGG
		Reverse	TTAGTTTGACTCACCTTCCCCG
Exon 26	3435C>T	Forward	TGTTTTCAGCTGCTTGATGG
		Reverse	AAGGCATGTATGTTGGCCTC

SNP, single nucleotide polymorphism.

Sau3A I for 3435C>T. The digested PCR products were subsequently analysed on a 2.5% agarose gel with ethidium bromide staining.

Statistical analysis for the influence of genetic polymorphisms

Multiple analyses were performed to test for associations under dominant, recessive and co-dominant models. The pharmacokinetic parameters from three or more different genotype groups were compared with the Kruskal–Wallis test, a nonparametric one-way ANOVA. The differences between the pharmacokinetic parameters of the two genotypic groups were determined by the Mann–Whitney test. Two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS 12.0 K for Windows (version 12.0.1; SPSS Inc., Chicago, IL, USA).

Materials

AccuPower™ PCR PreMix, primers, 100-bp DNA ladder, 50X TAE buffer, 5X TBE buffer (Bioneer Co., Cheongwon-Kun, Chungbuk, Korea), Wizard Genomic DNA Purification Kit (Promega Co., Madison, WI, USA), SolGent™ f-Taq DNA polymerase, ABI PRISM BigDye Terminator Cycle Sequencing Kit, an ABI Prism 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA), *Ban I*, *Rsa I* and *Sau3A I* (New England Biolabs, Inc., Beverly, MA, USA), agarose (USB™, Cleveland, OH, USA) were used in the experiments. Risperidone, 9-OH-risperidone and azelastine HCl (I.S.) were kindly supplied by Whanin Pharma. Co., Ltd. (Seoul, Korea), Janssen Pharmaceutica N.V. (Beerse, Belgium) and KyungDong Pharm. Co., Ltd. (Seoul, Korea), respectively. HPLC-grade acetonitrile and methanol were purchased from Fisher Scientific (Fair Lawn, NJ, USA). All reagents and buffer solutions were prepared with analytical-reagent grade chemicals.

Results

Genotype analysis

In the 80 subjects analysed, the allele frequencies of *CYP2D6**1, *2, *5 and *10 were 32.4%, 12.1%, 0.5% and 54.4%, respectively. This result was similar to the previous study (Lee *et al.*, 2009). The *CYP2D6**4, *14A/B, *36 and *47 alleles were not detected in any of the subjects of this study. *CYP2D6* genotyping revealed that 11 (13.8%) were homozygous for the wild-type allele (*1/*1), nine (11.3%) were heterozygous for the *2 allele (*1/*2), three (3.8%) were homozygous for the *2 allele (*2/*2), 18 (22.5%) were heterozygous for the *10 allele (*1/*10), 31 (38.8%) were homozygous for the *10 allele (*10/*10) and one (1.3%) was heterozygous for the *5 allele (*1/*5). To investigate the effect of the *CYP2D6* genotypes on the pharmacokinetics of risperidone, subjects were classified based on their level of *CYP2D6* enzyme activity (<http://www.imm.ki.se/CYPalleles/cyp2d6.htm>) (Lee *et al.*, 2006). On the basis of genotype, 23 (31.9%) subjects that were *CYP2D6**1/*1, *1/*2 and *2/*2 were defined as Group 1, who could be categorized as extensive metabolizers. In addition, 18 (25.0%) subjects that were *CYP2D6**1/*10 were defined as Group 2, heterozygous intermediate metabolizers, while 31 (43.1%) subjects that were *CYP2D6**10/*10 were defined as Group 3, homozygous intermediate metabolizers. However, rare variants [eight subjects including *CYP2D6**1/*5 (one subject) and non-classified genotypes] in Koreans were excluded from this study.

ABCB1 2677G>T/A genotyping revealed that 29 (36.3%) were homozygous wild-type (G/G), 32 (40.0%) were heterozygous type (G/A or G/T) and 19 (23.8%) were mutant type (T/T, T/A or A/A). *ABCB1* 3435C>T genotyping revealed that 27 (33.8%) were homozygous wild-type C/C, 38 (47.5%) were heterozygous C/T and 15 (18.8%) were homozygous T/T (Table 2).

Table 2

Genotype and allele frequencies for the studied variant genes

Genotype		No. (frequency,)	
CYP2D6	*1/*1, *1/*2 or *2/*2	23 (31.9)	
	*1/*10	18 (25.0)	
	*10/*10	31 (43.1)	
ABCB1	2677G>T/A (exon 21)	G/G	29 (36.3)
		G/T, G/A	32 (40.0)
		T/T, T/A, A/A	19 (23.8)
	3435C>T (exon 26)	C/C	27 (33.8)
		C/T	38 (47.5)
		T/T	15 (18.8)

Effect of genetic polymorphisms on risperidone pharmacokinetics

We examined the association between the *CYP2D6* genotypes and the pharmacokinetic parameters of risperidone and 9-OH-risperidone. Significant differences ($P < 0.05$) were observed between the *CYP2D6* genotype groups for the pharmacokinetic parameters ($C_{\max}$ and AUC) of risperidone and 9-OH-risperidone. MR had significant differences ($P < 0.001$) among the *CYP2D6* genotypes. However, no significant differences were found in $C_{\max}$, AUC and $t_{1/2}$ of AM among the *CYP2D6* genotypes (Table 3).

In terms of the *ABCB1* 3435C>T genotypes, which were not combined with the *CYP2D6* genotypes, significant differences were observed in $C_{\max}$ of risperidone and AM ($P = 0.049$ and $P < 0.001$, respectively) among the *ABCB1* 3435C>T genotypes. In addition, $C_{\max}$ of risperidone was significantly higher ($P = 0.001$) in *ABCB1* 3435T/T compared with that in 3435C/C. There was also a trend towards a higher AUC in subjects with variant alleles in exon 26. However, no significant differences were found in the AUC and $t_{1/2}$ of risperidone, 9-OH-risperidone and AM among *ABCB1* 3435C>T genotypes (Table 4).

Among the single *ABCB1* G2677T/A genotypes, which were not combined with the *CYP2D6**10 genotypes, there were no significant differences between the *ABCB1* 2677G>T/A genotypes in terms of the pharmacokinetic parameters of risperidone, 9-OH-risperidone and AM. However, there was a trend towards higher $C_{\max}$ and AUC in subjects with variant alleles in exon 21 (2677T/T, T/A or A/A) compared with those in subjects who were homozygous 2677G/G (Table 5).

In addition to the single and isolated effects of the *CYP2D6* and *ABCB1* 3435C>T genotypes, we also examined the association between the pharmacokinetic parameters of risperidone, 9-OH-risperidone, AM and MR and the different combinations of the *CYP2D6* and *ABCB1* 3435C>T genotypes. Nine different combinations of the *CYP2D6* and *ABCB1* 3435C>T genotypes were observed. The pharmacokinetic parameters in relation to the combination of the

Table 3

Pharmacokinetic parameters of risperidone, 9-hydroxyrisperidone and the active moiety in *CYP2D6* genotype groups

<i>CYP2D6</i>	Risperidone		9-Hydroxyrisperidone		Active moiety		$t_{1/2}$ (h)	Metabolic ratio (Risperidone/9-OH-risperidone)
	$C_{\max}$ (ng·mL ⁻¹)	AUC (ng·h ⁻¹ ·mL ⁻¹)	$C_{\max}$ (ng·mL ⁻¹)	AUC (ng·h ⁻¹ ·mL ⁻¹)	$C_{\max}$ (ng·mL ⁻¹)	AUC (ng·h ⁻¹ ·mL ⁻¹)		
Group 1 (n = 23)	7.62 ± 0.89	24.39 ± 3.09	2.86 ± 0.24	8.08 ± 1.85	11.75 ± 2.57	97.39 ± 22.11	10.73 ± 1.52	0.59 ± 0.08
Group 2 (n = 18)	8.78 ± 0.48	35.27 ± 3.08	3.49 ± 0.44	7.55 ± 0.61	13.98 ± 0.98	130.50 ± 8.57	7.91 ± 1.83	1.39 ± 0.48
Group 3 (n = 31)	11.29 ± 0.64	93.75 ± 5.79	7.47 ± 0.52	4.75 ± 0.25	12.89 ± 0.80	153.37 ± 9.30	9.84 ± 1.01	3.08 ± 0.40
P	0.001*	<0.001*	<0.001*	<0.001*	0.632	0.081	0.084	<0.001*
	0.005*†	<0.001*†	<0.001*†	<0.001*†				<0.001*†
	0.001**	<0.001**	<0.001**	<0.001**				<0.001**

Data are shown as mean ± SD.

Group 1 (*CYP2D6**1/*1, *1/*2 or *2/*2); Group 2 (*CYP2D6**1/*10); Group 3 (*CYP2D6**10/*10).

Co-dominant model by Kruskal–Wallis test among three genotypes.

* $P < 0.05$ was considered statistically significant.

†Dominant and ‡recessive model by Mann–Whitney test between two genotypes.

AUC, area under concentration-time curve; $C_{\max}$, peak plasma concentration.

Table 4

Pharmacokinetic parameters of risperidone, 9-hydroxyrisperidone and the active moiety in *ABCB1* 3435C>T genotype groups

<i>ABCB1</i> C3435C>T	Risperidone		9-Hydroxyrisperidone		Active moiety	
	C_{max} (ng·mL ⁻¹)	AUC (ng·h ⁻¹ ·mL ⁻¹)	$t_{1/2}$ (h)	C_{max} (ng·mL ⁻¹)	AUC (ng·h ⁻¹ ·mL ⁻¹)	$t_{1/2}$ (h)
C/C (n = 27)	8.27 ± 0.56	43.83 ± 4.70	5.01 ± 0.66	6.54 ± 0.71	87.63 ± 11.10	23.20 ± 4.94
C/T (n = 38)	9.06 ± 0.54	52.12 ± 5.93	4.94 ± 0.47	6.42 ± 0.63	65.38 ± 5.85	21.89 ± 4.64
T/T (n = 15)	11.82 ± 1.22	58.40 ± 12.12	4.55 ± 0.57	8.56 ± 1.25	103.91 ± 10.06	13.05 ± 1.75
P	0.049*	0.873	0.895	0.150	0.056*	0.235
	0.030**				0.017**	
					<0.001*	<0.001*
					0.014*†	0.014*†
					<0.001**	<0.001**

Data are shown as mean ± SD.

Co-dominant model by Kruskal–Wallis test among three genotypes.

* $P < 0.05$ was considered statistically significant.

†Dominant and ‡recessive model by Mann–Whitney test between two genotypes.

AUC, area under concentration-time curve; C_{max} , peak plasma concentration.

Table 5

Pharmacokinetic parameters of risperidone, 9-hydroxyrisperidone and the active moiety in *ABCB1* 2677G>T/A genotype groups

<i>ABCB1</i> 2677G>T/A	Risperidone		9-Hydroxyrisperidone		Active moiety	
	C_{max} (ng·mL ⁻¹)	AUC (ng·h ⁻¹ ·mL ⁻¹)	$t_{1/2}$ (h)	C_{max} (ng·mL ⁻¹)	AUC (ng·h ⁻¹ ·mL ⁻¹)	$t_{1/2}$ (h)
G/G (n = 29)	8.15 ± 0.57	42.24 ± 4.47	5.00 ± 0.66	7.17 ± 0.82	82.60 ± 7.96	23.21 ± 4.12
G/T, G/A (n = 32)	9.62 ± 0.58	54.39 ± 6.71	5.01 ± 0.50	6.59 ± 0.65	67.65 ± 7.36	21.92 ± 5.36
T/T, T/A, A/A (n = 19)	10.55 ± 1.10	56.09 ± 9.83	4.51 ± 0.52	7.17 ± 1.16	99.83 ± 12.54	13.80 ± 2.20
P	0.113	0.623	0.865	0.984	0.142	0.110
	0.039*†					
					0.107	0.058*
					0.037*†	0.026*†

Data are shown as mean ± SD.

Co-dominant model by Kruskal–Wallis test among three genotypes.

* $P < 0.05$ was considered statistically significant.

†Dominant and ‡recessive model by Mann–Whitney test between two genotypes.

AUC, area under concentration-time curve; C_{max} , peak plasma concentration.

CYP2D6 and *ABCB1* 3435C>T genotypes are summarized in Table 6. Significant differences ($P < 0.05$) were observed in $C_{\max}$ and AUC of risperidone and AM among the *ABCB1* 3435C>T genotype groups with *CYP2D6**10/*10. MR also

Figure 1

The mean ($\pm$ SD) serum risperidone concentration-time profiles in three *ABCB1* 3435C>T genotypes with *CYP2D6**10/*10 after a single oral administration of risperidone (2 mg). Vertical bars represent SD. Wild-type (C/C) of *ABCB1* 3435C>T ($n = 12$); heterozygous type (C/T) of *ABCB1* 3435C>T ($n = 13$); homozygous type (T/T) of *ABCB1* 3435C>T ($n = 5$).

showed significant differences ($P = 0.004$) among the *ABCB1* 3435C>T genotype groups with *CYP2D6**10/*10. Serum concentration-time curves of risperidone in three *ABCB1* 3435C>T genotypes combined with *CYP2D6**10/*10 are shown in Figure 1. When *ABCB1* 3435C/C and 3435T/T genotypes with *CYP2D6**10/*10 were compared, the $C_{\max}$ and AUC of risperidone ($P = 0.001$ and $P = 0.001$, respectively) and AM ($P = 0.003$ and $P = 0.039$, respectively) were significantly higher in *ABCB1* 3435T/T than in *ABCB1* 3435C/C with *CYP2D6**10/*10 (Figures 2 and 3).

Discussion and conclusions

The first and major metabolic step in risperidone metabolism is 9-hydroxylation, which is catalysed by *CYP2D6* (Mannens *et al.*, 1993). Previous studies have reported the pharmacokinetics of risperidone and 9-OH-risperidone after an oral dose of risperidone in a panel of extensive metabolizers and poor metabolizers of *CYP2D6* (Huang *et al.*, 1993). These studies clearly showed decreased 9-hydroxylation of risperidone in poor metabolizers of *CYP2D6*. Also, the steady-state plasma concentrations of risperidone and MR (risperidone:9-OH-risperidone) are highly dependent on the *CYP2D6* genotype (Scordo *et al.*, 1999; Roh *et al.*, 2001b; Jovanovic *et al.*, 2010).

In the present study, significant differences were observed among *CYP2D6* genotype groups in the pharmacokinetic parameters ($C_{\max}$ and AUC) of risperidone and 9-OH-risperidone. However, no significant differences were found between *CYP2D6* genotype groups in terms of the pharmacokinetic parameters of AM. The AM, which consists of both

Figure 2

The peak serum concentration ($C_{\max}$) and area under the serum concentration-time curves (AUC) of risperidone in the combined *ABCB1* 3435C>T and *CYP2D6* genotypes after a single oral administration of risperidone (2 mg). The results were compared by Kruskal–Wallis test among three or more genotypes and by Mann–Whitney test between two genotypes.

Table 6

Pharmacokinetic parameters of risperidone, 9-hydroxyrisperidone and the active moiety in the combination effect of the CYP2D6 and ABCB1 3435C>T genotype groups

CYP2D6		ABCB1 3435C>T		Risperidone		AUC		$t_{1/2}$ (h)		9-Hydroxyrisperidone		AUC		$t_{1/2}$ (h)		Active moiety		AUC		$t_{1/2}$ (h)		Metabolic ratio (Risperidone/9-OH-risperidone)	
				C _{max} (ng·mL ⁻¹)	AUC (ng·h ⁻¹ ·mL ⁻¹)					C _{max} (ng·mL ⁻¹)	AUC (ng·h ⁻¹ ·mL ⁻¹)					C _{max} (ng·mL ⁻¹)	AUC (ng·h ⁻¹ ·mL ⁻¹)						
Group 1		C/C (n = 7)		7.79 ± 1.24	28.55 ± 6.03	3.19 ± 0.37	8.31 ± 2.06	102.26 ± 7.29	40.33 ± 24.61	14.39 ± 2.25	148.33 ± 21.04	27.28 ± 10.80	0.68 ± 0.17										
		C/T (n = 9)		6.18 ± 1.42	15.14 ± 3.13	2.41 ± 0.36	7.79 ± 1.46	59.88 ± 11.23	14.68 ± 3.07	12.35 ± 2.08	95.45 ± 17.23	9.78 ± 1.51	0.54 ± 0.11										
		T/T (n = 7)		9.29 ± 1.90	27.75 ± 5.41	3.10 ± 0.54	9.42 ± 2.05	99.78 ± 14.90	12.53 ± 3.22	18.19 ± 2.42	163.71 ± 28.55	8.51 ± 2.49	0.53 ± 0.17										
P				0.401	0.084	0.401	0.913	0.140	0.354	0.210	0.107	0.060	0.794										
Group 2		C/C (n = 5)		8.45 ± 0.82	28.56 ± 2.91	2.70 ± 0.37	7.06 ± 1.18	76.39 ± 16.93	17.74 ± 5.63	13.20 ± 1.45	119.18 ± 20.90	8.85 ± 4.20	0.67 ± 0.09										
		C/T (n = 10)		8.57 ± 0.71	38.80 ± 5.53	3.87 ± 0.75	6.61 ± 0.82	80.13 ± 6.42	18.30 ± 1.93	13.39 ± 1.04	139.23 ± 6.21	8.65 ± 1.87	1.68 ± 0.80										
		T/T (n = 4)		9.93 ± 1.20	31.61 ± 3.94	3.80 ± 1.12	8.59 ± 1.95	91.85 ± 15.34	13.15 ± 2.69	16.48 ± 2.68	143.19 ± 22.12	6.52 ± 2.84	1.32 ± 0.61										
P				0.580	0.348	0.412	0.741	0.673	0.488	0.458	0.760	0.717	0.415										
Group 3		C/C (n = 12)		8.41 ± 0.89	58.09 ± 6.82	6.93 ± 1.05	4.87 ± 0.63	92.96 ± 32.81	22.98 ± 3.26	10.87 ± 1.01	145.59 ± 16.21	10.00 ± 1.77	2.08 ± 0.17										
		C/T (n = 13)		10.61 ± 0.64	82.55 ± 8.00	6.98 ± 0.67	4.26 ± 0.35	39.08 ± 3.05	38.96 ± 19.59	13.79 ± 1.12	157.95 ± 9.88	8.68 ± 1.36	3.73 ± 0.88										
		T/T (n = 5)		16.75 ± 0.43	128.35 ± 11.73	7.19 ± 0.25	5.33 ± 0.08	129.00 ± 1.40	18.52 ± 3.79	18.35 ± 0.81	225.10 ± 25.48	7.60 ± 1.68	4.19 ± 0.69										
P				<0.001*	0.002*	0.720	0.230	0.401	0.606	0.018*	0.038*	0.575	0.004*										
				0.021*†	0.003*†					0.018*†			0.001*†										
				<0.001**	<0.001**					0.005**			0.031**										

Data are shown as mean ± SD.

Group 1 (CYP2D6*1/*1, *1/*2 or *2/*2); Group 2 (CYP2D6*1/*10); Group 3 (CYP2D6*10/*10).

Co-dominant model by Kruskal–Wallis test among three genotypes.

**P* < 0.05 was considered statistically significant.

†Dominant and ‡recessive model by Mann–Whitney test between two genotypes.

AUC, area under concentration-time curve; C_{max}, peak plasma concentration.

Figure 3

The peak serum concentration (C_{max}) and area under the serum concentration-time curves (AUC) of the active moiety in the combined *ABCB1* 3435C>T and *CYP2D6* genotypes after a single oral administration of risperidone (2 mg). The results were compared by Kruskal–Wallis test among three or more genotypes and by Mann–Whitney test between two genotypes.

risperidone and 9-OH-risperidone, could be important for estimating the clinical effects of risperidone. The observed *CYP2D6* polymorphisms may not contribute to altered clinical efficacy, but rather affect risperidone:9-OH-risperidone ratios.

Numerous reports comparing the *ABCB1* variants in different populations have appeared in the literature. Subjects with 3435T/T genotypes had higher steady-state maximum plasma concentrations of digoxin and reduced *ABCB1* intestinal expression compared with subjects who were homozygous 3435C/C (Hoffmeyer *et al.*, 2000). *In vitro* studies have reported that risperidone, 9-OH-risperidone and quetiapine have a stronger affinity for P-gp than other atypical antipsychotic drugs (Hoffmeyer *et al.*, 2000; Boulton *et al.*, 2002). Brain concentrations of AM were 10-fold higher in knockout than in wild-type animals. The variants of *ABCB1* also affected the antipsychotic actions of risperidone in patients receiving drugs that are substrates of *ABCB1* (Kirschbaum *et al.*, 2008; Uhr *et al.*, 2008). The *ABCB1* 2677T/T and 3435T/T genotypes had similar strong effects on steady-state plasma concentrations of AM (Jovanovic *et al.*, 2010). Other studies reported that *ABCB1* polymorphisms had a moderate effect on 9-OH-risperidone and AM (Gunes *et al.*, 2008). Meanwhile, *ABCB1* variants have been found to be not associated with steady-state plasma concentrations of risperidone or 9-OH-risperidone (Yasui-Furukori *et al.*, 2004). Therefore, the effect of the *ABCB1* variant allele on the metabolism of risperidone is still controversial. The main reason for these discrepancies is thought to be the combined influence of genetic polymorphisms in *ABCB1* and *CYP2D6* genes on the pharmacokinetics of risperidone.

In the present study, there were no significant differences in the AUC of risperidone and AM in the *ABCB1* 3435C>T genotypes. But, the C_{max} of risperidone and AM differed significantly ($P = 0.049$ and $P < 0.001$, respectively) in the *ABCB1* 3435C>T genotypes (Table 4). Our results showed that *ABCB1* 3435C>T genotypes, which were not combined with the *CYP2D6**10 genotypes, seemed to be associated with RIS substrate specificity for P-gp. Therefore, the *ABCB1* 3435C>T variants probably have clinical implications based on significant changes in the C_{max} of risperidone and AM.

Although there was a trend towards higher C_{max} and AUC in subjects with variant alleles in exon 21 (2677T/T, T/A or A/A), there were no significant differences between the *ABCB1* 2677G>T/A genotypes in the pharmacokinetic parameters of risperidone, 9-OH-risperidone and AM (Table 5).

To more clearly represent the effect of *ABCB1* 3435C>T or 2677G>T/A on the metabolism of risperidone, we determined the association between *ABCB1* 3435C>T or 2677G>T/A genotype groups with the *CYP2D6* genotypes on the pharmacokinetic parameters of risperidone. Among the different *ABCB1* 2677G>T/A genotypes with the *CYP2D6* genotypes, there were no significant differences between the *ABCB1* 2677G>T/A genotypes in terms of the pharmacokinetic parameters of risperidone, 9-OH-risperidone and AM as in the case of the single *ABCB1* 2677G>T/A genotypes (data not shown). Meanwhile, unlike the single *ABCB1* 3435C>T genotypes, *ABCB1* 3435C>T genotypes in individuals with the *CYP2D6**10/*10 genotype were associated with statistically significant differences ($P < 0.01$) in the pharmacokinetic parameters (C_{max} , AUC and MR) of risperidone (Table 6). The

$C_{\max}$ and AUC of risperidone were significantly ($P = 0.001$) higher in *ABCB1* 3435T/T subjects than in 3435C/C subjects who were *CYP2D6**10/*10 (Figure 2). These results could indicate that the relative contribution of an efflux transporter such as P-gp to the metabolism of risperidone was greater in the *CYP2D6**10/*10 subjects than in the *CYP2D6* Group 1 or 2 subjects. On the other hand, if the P-gp transporter and *CYP2D6* enzyme sequentially and independently affect the metabolism of risperidone, the pharmacokinetic parameters of risperidone will be mostly dependent on the enzymatic activity of *CYP2D6*, and the MR of risperidone will not be changed with the P-gp activity. The MRs of risperidone were significantly ($P = 0.004$) associated and changed with *ABCB1* 3435C>T genotype groups with the *CYP2D6**10/*10 (Table 6). Moreover, the MRs of risperidone were significantly ($P = 0.006$) higher in *ABCB1* 3435T/T than in *ABCB1* 3435C/C with *CYP2D6**10/*10. These results show that the effects of genetic polymorphisms in *ABCB1* and *CYP2D6* genes on the pharmacokinetics of risperidone are combined and that the relative contributions of P-gp and *CYP2D6* enzyme may play an important role in the metabolism of risperidone.

With regard to 9-OH-risperidone, there were no significant differences in $C_{\max}$ and AUC of 9-OH-risperidone among *ABCB1* 3435C>T subjects with *CYP2D6**10/*10. Risperidone is metabolized to 9-OH-risperidone mostly after the absorption phase. Thus, the absorption of 9-OH-risperidone may only be slightly affected by P-gp.

The $C_{\max}$ and AUC of AM differed significantly ($P < 0.05$) in the three *ABCB1* 3435C>T genotypes combined with *CYP2D6**10/*10 (Figure 3). Thus, *ABCB1* 3435C>T and *CYP2D6**10/*10 genotypes could be clinically important in controlling the adverse effects of risperidone and 9-OH-risperidone *in vivo*. For example, temporary side effects, that is, somnolence and headache, were observed in all healthy subjects according to the case record form. However, subjects with 3435T/T in *CYP2D6**10/*10 genotypes had long-lasting side effects (data not shown). A single-dose study using a 2 mg dose may therefore underestimate side effects and repeated dosing with clinical doses may be associated with greater side effects.

This study was limited by the inclusion of only healthy young male volunteers and by studying the pharmacokinetics of a single dose of risperidone. In a previous report (Xuan *et al.*, 2008), no significant differences were found among independent variables, such as age, age of onset, gender or risperidone concentrations and the improvement of total Brief Psychiatry Rating Scale scores. Thus, these results could be extrapolated to healthy female subjects. Studies in a more diverse patient population (especially with poor metabolizers of *CYP2D6* substrates), which would include patients receiving chronic therapy, may allow a more meaningful examination of the influence of *CYP2D6* on pharmacokinetic parameters.

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Conflict of interest

The authors state no conflict of interest.

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