ABCB1 Polymorphisms Influence Steady-State Plasma Levels of 9-Hydroxyrisperidone and Risperidone Active Moiety

Arzu Gunes, MD, PhD,* Edoardo Spina, MD, PhD,†‡ Marja-Liisa Dahl, MD, PhD,* and Maria Gabriella Scordo, MD, PhD*

**Abstract:** Risperidone is metabolized to its active metabolite, 9-hydroxyrisperidone, mainly by the cytochrome P450 enzymes CYP2D6 and 3A4. Its antipsychotic effect is assumed to be related to the active moiety, that is, the sum of risperidone and 9-hydroxyrisperidone. Both risperidone and 9-hydroxyrisperidone are substrates of P-glycoprotein (P-gp), a transport protein involved in drug absorption, distribution, and elimination. The aim of the present study was to evaluate the influence of polymorphisms in genes encoding CYP3A5 and P-gp (ABCB1) on the steady-state plasma levels of risperidone, 9-hydroxyrisperidone, and the active moiety, taking CYP2D6 genotype status into account. Forty-six white patients with schizophrenia treated with risperidone (1–10 mg/d) in monotherapy for 4–6 weeks were genotyped, and their plasma concentrations of risperidone and 9-hydroxyrisperidone were measured. Dose-corrected plasma concentrations (C/D) of risperidone, 9-hydroxyrisperidone, and active moiety showed up to 68-, 9-, and 10-fold interindividual variation, respectively. Six patients carried 1 CYP3A5*1 allele and therefore were likely to express the CYP3A5 enzyme. The CYP3A5 genotype did not influence risperidone, 9-hydroxyrisperidone, or active moiety C/Ds. The CYP2D6 genotype in these 46 patients was again associated with risperidone C/D (P = 0.001) but not with 9-hydroxyrisperidone C/D or active moiety C/D, as previously shown by our group in 37 of these patients. Patients homozygous for the ABCB1 3435T/2677T/1236T haplotype had significantly lower C/Ds of 9-hydroxyrisperidone (P = 0.026) and active moiety (P = 0.028) than patients carrying other ABCB1 genotypes. In conclusion, our results confirmed the significant effect of CYP2D6 genotype on the steady-state plasma levels of risperidone and showed that ABCB1 polymorphisms have a moderate effect on those of 9-hydroxyrisperidone and the active moiety.

**Key Words:** risperidone, 9-hydroxyrisperidone, ABCB1, CYP3A4, CYP3A5

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INTRODUCTION

Risperidone is a widely used atypical antipsychotic drug that is effective against positive and negative symptoms of schizophrenia.1,2 It is extensively metabolized in the liver to a pharmacologically active metabolite, 9-hydroxyrisperidone, mainly by cytochrome P450 2D6 (CYP2D6) and 3A4 (CYP3A4).3–5 The antipsychotic effect of risperidone is assumed to be related to the active moiety (ie, the sum of risperidone and 9-hydroxyrisperidone), of which 9-hydroxyrisperidone constitutes the major part in plasma.6 Although risperidone is considered to have a relatively low incidence of extrapyramidal side effects (EPS), the risk of developing EPS increases at higher doses and at higher plasma levels of the active moiety.7,8

CYP3A expression exhibits substantial interindividual variation, part of which is genetically determined. A number of allelic variants have been described in CYP3A4 and CYP3A5 coding genes. The CYP3A4*1B allele contains an A(−290)G substitution (−292A/G nucleotide change in the gene according to the nomenclature; http://www.cypalleles.ki.se/cyp3a4.htm) in the promoter region of the gene, potentially affecting the transcription efficiency and thus the overall enzymatic activity of CYP3A4 and has a frequency of 4%–5% among whites.9 The CYP3A4*3 allele, with a frequency of 1%–2% among whites, has a T1473C (23171T/C nucleotide change in the gene according to the nomenclature) change in exon 12, leading to a Met445Thr substitution, near the active site of the enzyme, thus causing altered substrate specificity.10 The CYP3A4*4 variant is characterized by a single nucleotide polymorphism (SNP) at position 352 (A352G) (13871A/G nucleotide change in the gene according to the nomenclature) change in exon 12, leading to a Met445Thr substitution, near the active site of the enzyme, thus causing altered substrate specificity.10 The CYP3A4*4 variant is characterized by a single nucleotide polymorphism (SNP) at position 352 (A352G) (13871A/G nucleotide change in the gene according to the nomenclature), leading to an Ile118Val substitution and a decrease in enzyme activity.11–13 These 3 CYP3A4 allelic variants have been reported to alter enzyme activity and to affect the in vivo metabolism of commonly used drugs, such as simvastatin, tacrolimus, and cyclosporine.11–13

Only subjects carrying at least 1 functional CYP3A5*1 allele express the CYP3A5 protein.14 The main cause of the absence of CYP3A5 expression in more than 70% of whites is an SNP at position 6986 (A6986G, CYP3A5*3), leading to alternative splicing of CYP3A5 transcript and absence of the protein.14 Other more rare allelic variants (1% and 0.01% frequency in whites) coding for an enzyme without activity are CYP3A5*2, characterized by an SNP at position 27289 (C27289A), leading to a T398N substitution, and CYP3A5*6, with an SNP at position 14690 (G14690A), causing a splicing defect.15

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From the *Department of Medical Sciences, Clinical Pharmacology, Uppsala University, Uppsala, Sweden; †Department of Clinical and Experimental Medicine and Pharmacology, University of Messina, Messina, Italy; and ‡IRCCS Centro Neurolesi “Bonino-Pulejo,” Messina, Italy.
Correspondence: Dr. Maria Gabriella Scordo, MD, PhD, Department of Medical Sciences, Clinical Pharmacology, Uppsala University, Uppsala SE-75185, Sweden (e-mail: gabriella.scordo@medsci.uu.se).
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628
Polymorphism. The G2677T and G2677A polymorphisms to be in close linkage disequilibrium with the C3435T polymorphism in exon 12, and G2677T/A in exon 21, were found during risperidone kinetics, the only positive finding has been in the few studies performed so far, evaluating the impact of CYP3A4/5 polymorphisms on 9-hydroxyrisperidone and risperidone after a single dose, suggesting that P-gp plays a role in risperidone pharmacokinetics. The gene encoding P-gp (ABCB1) is highly polymorphic. Hoffmeyer et al identified a polymorphism in the noncoding region, in exon 26, characterized by a silent C to T substitution (C3435T). Lower P-gp function and duodenal P-gp expression have been shown in subjects with the 3435T/T genotype compared with those with the 3435C/C genotype. Two other ABCB1 polymorphisms, C1236T, a silent polymorphism in exon 12, and G2677T/A in exon 21, were found to be in close linkage disequilibrium with the C3435T polymorphism. The frequency of 2677A/T variant is very low among whites (2%), whereas 3435T, 2677T, and 1236T variants are quite common (41%–56%).

Previously, the CYP2D6 genotype has been shown to have a significant impact on steady-state plasma levels of risperidone but not on those of 9-hydroxyrisperidone or the active moiety. In the few studies performed so far, evaluating the impact of CYP3A4/5 or ABCB1 polymorphisms on risperidone kinetics the only positive finding has been the lower plasma 9-hydroxyrisperidone levels and higher risperidone/9-hydroxyrisperidone ratios in patients with the ABCB1 2677T/T genotype compared with those with other genotypes. In another study, greater clinical improvement was reported in risperidone-treated Chinese patients who carried the 1236T/T genotype compared with those with 1236C/T and 1236C/C genotypes, whereas no influence of the C3435T or G2677T/A polymorphisms was observed.

The aim of the present study was to evaluate the influence of CYP3A5 and ABCB1 genotypes on the steady-state plasma levels of risperidone, 9-hydroxyrisperidone, and the active moiety in patients with schizophrenia on risperidone therapy, taking CYP2D6 genotype status into account. Patients were also evaluated for a number of CYP3A4 allelic variants (*1B, *3, and *4) to rule out the chance of these allelic variants affecting the result of the study.

**MATERIALS AND METHODS**

**Patients and Study Design**

Forty-six white patients (35 males and 11 females, aged 26–64 years) from Southern Italy, who were diagnosed with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria and in therapy with risperidone (1–10 mg/d) for 4–6 weeks were included in the study. Most of the patients (n = 37) had participated in a previous study designed to assess the relationship between plasma risperidone and 9-hydroxyrisperidone concentrations and CYP2D6 genotype. The risperidone doses prescribed were in the normal recommended range when the study was performed. No other psychotropic medication, except benzodiazepines as sedative/hypnotic, was given to the patients. Compliance to treatment was confirmed by their families or the nursing staff. Blood samples for the determination of risperidone and 9-hydroxyrisperidone concentrations were obtained between 8:00 and 9:00 AM, approximately 12 hours after the bedtime dose, after a minimum of 4 weeks of risperidone treatment at a stable dose. The study was approved by the Local Ethics Committee at the Centre of Mental Health, Azienda USL 5, Messina (Italy), and written informed consent was obtained from the patients before inclusion in the study.

**Genotyping**

Genomic DNA was isolated from peripheral leukocytes with Qiagen Blood and Cell Culture kit (Qiagen, Hilden, Germany). CYP3A4 alleles were identified by allele-specific polymerase chain reaction (PCR) followed by digestion with restriction enzymes. The CYP3A4*1B was investigated with the method described by van Schaik et al. The CYP3A4*3 allele was identified according to van Schaik et al, whereas the presence of the CYP3A4*4 allele was investigated according to Wang et al. The CYP3A5*2 and CYP3A5*6 alleles were identified by PCR, followed by digestion with restriction enzymes, whereas the presence of the CYP3A5*3 allele was investigated by TaqMan allelic discrimination in the ABI PRISM 7000 Sequence Detection System. The CYP2D6 genotype was available for most of the patients from the previous study. The newly included patients were genotyped with the methods previously described.

The ABCB1 polymorphisms were analyzed with realtime PCR by TaqMan kits purchased from Applied Biosystems: for C1236T (rs1128503) assay ID C___7586662_10, for C3435T (rs1045642) assay ID C___7586665_1, and for G2677T/A (rs2032582), forward primer GTA AGC AGT AGG GAG TAA CAA AAT AAC ACT, reverse primer GAC AAG CAC TGA AAG ATA AGA AAG AAC T, 2677G probe FAM-CTT CCC AGA ACC AGG GAG TAA CAA AAT AAC ACT, 2677T probe VIC-CCT TCC CAG CAC CT, 2677A probe FAM-CCT CCC AGT ACC TTC, and 2677T probe FAM-CCT CCC AGA ACC TT were used according to the guidelines of the manufacturer.

**Drug Analysis**

Plasma concentrations of risperidone and 9-hydroxyrisperidone were measured in duplicate by high-performance liquid chromatography, as previously described. The interday coefficient of variation was less than 8.2% for risperidone and less than 6.5% for 9-hydroxyrisperidone, and the limit of quantitation was 2 nmol/L for both analytes.

**Statistical Analysis**

The Mann–Whitney test was used to compare the genotype groups with respect to drug plasma levels, using GraphPad Prism 4 (GraphPad Software, Inc., San Diego,
CA). Haplotype and multiple model analyses were performed using Statistical Analyses Software (SAS), version 9.1. P values <0.05 were considered as statistically significant.

RESULTS

The plasma concentrations of risperidone varied 74-fold (range 2–148 nmol/L, median 10 nmol/L), and those of 9-hydroxyrisperidone varied 33-fold (12–384 nmol/L, 142 nmol/L), whereas those of the active moiety showed a 23-fold variation (21–480 nmol/L, 188 nmol/L). The ratio of risperidone to 9-hydroxyrisperidone varied 129-fold (0.01–1.16, 0.15). Dose-corrected plasma levels (C/Ds) of risperidone, 9-hydroxyrisperidone, and active moiety showed a 68-fold (0.3–22 nmol L\(^{-1}\) mg\(^{-1}\), median 3 nmol L\(^{-1}\) mg\(^{-1}\)), a 10-fold (6–64 nmol L\(^{-1}\) mg\(^{-1}\), 27 nmol L\(^{-1}\) mg\(^{-1}\)), and a 10-fold (7–70 nmol L\(^{-1}\) mg\(^{-1}\), 32 nmol L\(^{-1}\) mg\(^{-1}\)) variation, respectively. The plasma levels of 9-hydroxyrisperidone and active moiety were strongly correlated (\(r_s = 0.90, P < 0.0001\)).

None of the patients carried the CYP3A4*1B, *3, or *4 alleles, whereas 6 patients carried 1 CYP3A5*1 allele (CYP3A5*1*3 genotype) and the rest had CYP3A5*3*3 genotype. Three patients carried extra copies (more than 2) of CYP2D6 alleles, whereas 6 patients carried 1 CYP2D6*1 alleles (CYP2D6*1*1 genotype), and 34 patients carried the 1236T and 33 also the 3435T alleles. There was no variant allele. Of the 35 patients who carried the 1236T allele, 11 patients carried the 2677G/T, 22 the 2677G/T, and 13 the 2677G/G genotype, whereas 11 patients carried the 2677G/T, 18 the 2677G/G, and 17 the 2677G/T genotype. None of the patients carried the 2677A allele (ultrarapid metabolizers), 39 had the 1236C/C, 23 the 1236C/T, and 12 the 1236T/T genotype. Eleven patients carried the ABCB1 1236C/C genotype, 23 the 1236C/T, and 12 the 1236T/T genotype. Eleven patients carried the 2677G/G, 22 the 2677G/T, and 13 the 2677T/T genotype, whereas 11 patients carried the 3435C/C, 18 the 3435C/T, and 17 the 3435T/T genotype. None of the patients carried the 2677A variant allele. Of the 35 patients who carried the 1236T allele, 34 carried the 2677T and 33 also the 3435T alleles. There was thus close linkage disequilibrium between the ABCB1 polymorphisms (Fig. 1). Six ABCB1 haplotypes were observed in our study group. A haplotype including the 1236T, 2677T, and 3435T alleles was the most frequent (Table 1).

Plasma Levels of Risperidone,
9-Hydroxyrisperidone, and Active Moiety in
Relation to CYP3A5, CYP2D6 and
ABCB1 Genotypes

The CYP3A5 genotype did not influence C/Ds of risperidone, 9-hydroxyrisperidone, or active moiety, or the risperidone/9-hydroxyrisperidone ratio (\(P > 0.05\)).

As already shown in the previous study in 37 of the patients included in the present study,\(^{29}\) the CYP2D6 genotype associated significantly with risperidone C/D (\(P = 0.0082\)) and risperidone/9-hydroxyrisperidone ratio (\(P = 0.003\)) but not with 9-hydroxyrisperidone or active moiety C/D (\(P > 0.05\)).

Risperidone, 9-hydroxyrisperidone, and active moiety C/Ds in ABCB1 genotype groups are summarized in Table 2. Risperidone C/D was not influenced by ABCB1 polymorphisms (\(P > 0.05\)). On the other hand, 9-hydroxyrisperidone and active moiety C/Ds were significantly lower in ABCB1 1236T/T carriers compared to other genotype groups (\(P = 0.021\) and 0.033, respectively). Similarly, subjects with ABCB1 2677T/T genotype had lower 9-hydroxyrisperidone (\(P = 0.012\)) and active moiety (\(P = 0.021\)) C/D than those carrying 2677G/T or 2677G/G. A trend for an effect of the ABCB1 3435T/T genotype was also observed (Table 2).

Consistently, patients homozygous for the ABCB1 1236T/2677T/3435T haplotype (n = 11) had significantly lower C/Ds of 9-hydroxyrisperidone (\(P = 0.026\)) and active moiety (\(P = 0.028\)) than those with other genotypes, whereas no significant influence of this haplotype was observed on risperidone C/D or risperidone/9-hydroxyrisperidone ratio (Fig. 2).

As shown in Table 3, there was no difference in patients’ characteristics between the subjects homozygous for the ABCB1 3435T/2677T/1236T haplotype and patients carrying other haplotypes, but for a slight underrepresentation of females in the former group. Exclusion of CYP2D6 poor metabolizer subjects from this analysis did not influence the results; patients homozygous for the 1236T/2677T/3435T still having significantly lower C/Ds of 9-hydroxyrisperidone (\(P = 0.038\)) and active moiety (\(P = 0.030\)) than those with other genotypes.

No gene–gene interactions were observed in the present study. In multiple model analysis, including CYP2D6 genotype and ABCB1 haplotypes as covariants, the influence of the CYP2D6 genotype on risperidone C/Ds remained highly significant (\(P = 0.0002\)), whereas the effect of ABCB1 haplotype on 9-hydroxyrisperidone (\(P = 0.049\)) and active moiety (\(P = 0.062\)) C/Ds was marginal. In the multiple model analysis, CYP2D6 and ABCB1 genotypes explained variation of 33% and 1%, respectively, in plasma risperidone C/D, 4% and 9% in the 9-hydroxyrisperidone C/D, and 5% and 11% in the active moiety C/D.

DISCUSSION

Our results suggest that in addition to the previously shown influence of CYP2D6 genotype on the steady-state C/D

| TABLE 1. ABCB1 Haplotype Frequencies in the Study Population |
|-----------------|-----------------|-----------------|------------------|-------------------|
| C1236T Exon 12 | C2677T/A Exon 21 | C3435T Exon 26 | Frequency       |
| T               | C               | T               | 0.478            |
| C               | G               | T               | 0.402            |
| C               | G               | T               | 0.076            |
| T               | T               | C               | 0.022            |
| T               | G               | C               | 0.011            |
| C               | T               | T               | 0.011            |

FIGURE 1. Pairwise linkage disequilibrium analysis (\(r^2\)) between ABCB1 polymorphisms 1236C/T (rs1128503), 2677G/T (rs2032582), and 3435C/T (rs1045642).
of risperidone, ABCB1 genotype has an effect on the C/Ds of 9-hydroxyrisperidone and the active moiety. The small number of subjects is the main limitation; therefore, results of the present study should be interpreted with caution. However, the association of ABCB1 polymorphisms with 9-hydroxyrisperidone and active moiety levels might have potential clinical importance.

In vitro studies have shown a minor stereoselective contribution of the CYP3A4 enzyme in addition to the major role of CYP2D6 in the biotransformation of risperidone to its active metabolite 9-hydroxyrisperidone. Moreover, concomitant use of drugs inducing or inhibiting CYP3A activity has been shown to influence risperidone plasma concentrations. Due to the lack of patients carrying any of the possible haplotypes, the impact of ABCB1 variants on the extent of drug metabolism observed here needs to be confirmed in larger studies.

### TABLE 2. Dose-Corrected Plasma Concentrations (C/D, nmol L\(^{-1}\) mg\(^{-1}\), Median and Range) of Risperidone, 9-Hydroxyrisperidone, and Active Moiety, and the Risperidone/9-Hydroxyrisperidone Ratio in ABCB1 Genotype Groups

<table>
<thead>
<tr>
<th>Polymorphisms</th>
<th>Genotype Groups (n)</th>
<th>Risperidone C/D</th>
<th>9-Hydroxyrisperidone C/D</th>
<th>Active moiety C/D</th>
<th>Risperidone/9-hydroxyrisperidone</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1236T</td>
<td>C/C (11) and C/T (23)</td>
<td>5 (0.3–22)</td>
<td>31 (6–64)</td>
<td>37 (7–70)</td>
<td>0.2 (0.01–1)</td>
<td>0.841</td>
</tr>
<tr>
<td></td>
<td>T/T (12)</td>
<td>3 (0.8–17)</td>
<td>20 (7–51)</td>
<td>28 (8–56)</td>
<td>0.2 (0.1–1)</td>
<td>0.021</td>
</tr>
<tr>
<td>G2677T/A</td>
<td>G/G (11) and G/T (22)</td>
<td>3 (0.3–22)</td>
<td>31 (6–64)</td>
<td>38 (7–70)</td>
<td>0.1 (0.01–1)</td>
<td>0.696</td>
</tr>
<tr>
<td></td>
<td>T/T (13)</td>
<td>3 (0.8–17)</td>
<td>18 (7–51)</td>
<td>28 (8–56)</td>
<td>0.2 (0.04–1)</td>
<td>0.012</td>
</tr>
<tr>
<td>C3435T</td>
<td>C/C (11) and C/T (18)</td>
<td>3 (0.4–22)</td>
<td>30 (6–57)</td>
<td>38 (7–65)</td>
<td>0.2 (0.01–1)</td>
<td>0.873</td>
</tr>
<tr>
<td></td>
<td>T/T (17)</td>
<td>3 (0.3–17)</td>
<td>18 (7–64)</td>
<td>28 (8–70)</td>
<td>0.1 (0.01–1)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

**FIGURE 2.** Dose-corrected steady-state plasma levels (C/D, nmol L\(^{-1}\) mg\(^{-1}\)) of risperidone (A), 9-hydroxyrisperidone (B), and active moiety (C), and the risperidone/9-hydroxyrisperidone ratio (D) in patients homozygous for ABCB1 1236T/2677T/3435T haplotype compared with patients carrying other genotypes. \(*P = 0.026\) and \(**P = 0.028\). Lines indicate the median.
CYP3A4 variant alleles analyzed in this study, the influence of CYP3A4 polymorphisms could not be evaluated. Additionally, we did not observe any significant influence of CYP3A5 genotype on risperidone, 9-hydroxyrisperidone, or active moiety concentrations. Although the small number of patients heterozygous for the CYP3A5*1*A allele (n = 6), and the lack of subjects carrying the CYP3A5*1*A1 genotype might have prevented us from observing the influence of this polymorphism, our results are consistent with previous findings.32

Most of the patients (37 of 46) had participated in a previous study evaluating the influence of CYP2D6 polymorphisms on steady-state plasma levels of risperidone.29 The impact of CYP2D6 genotype on risperidone C/D and risperidone/9-hydroxyrisperidone ratio but not on 9-hydroxyrisperidone or active moiety C/D was confirmed in the present study by Leon et al.32 However, in the present study, patients homozygous for the ABCB1 haplotype 1236T/2677T/3435T had lower 9-hydroxyrisperidone and active moiety C/Ds. Thus, our findings do not support the hypothesis of an increased intestinal absorption of risperidone or decreased excretion of 9-hydroxyrisperidone in patients carrying this haplotype.

Reduced expression and/or activity of P-gp seems to occur in the presence of 2677T and 3435T alleles. Studies evaluating the functional significance of ABCB1 polymorphisms have, however, led to conflicting results for kinetic parameters of different P-gp substrates.22,23,41 Decreased P-gp function might be expected to lead to decreased renal and biliary excretion and increased intestinal absorption and central nervous system penetration, resulting in increased plasma and central nervous system concentrations of P-gp substrates. However, in the present study, patients homozygous for the ABCB1 haplotype 1236T/2677T/3435T had lower 9-hydroxyrisperidone and active moiety C/Ds. Thus, our findings do not support the hypothesis of an increased intestinal absorption of risperidone or decreased excretion of 9-hydroxyrisperidone in patients carrying this haplotype.

Adverse effects induced by risperidone such as EPS and hyperprolactinemia have been found to correlate with plasma 9-hydroxyrisperidone and active moiety concentrations.8,42 Therefore, the impact of an ABCB1 haplotype on risperidone active moiety concentrations found in the present study could have implications for the risk to develop adverse effects.

**CONCLUSIONS**

Among the polymorphisms evaluated, CYP2D6 genotype was confirmed to have the strongest influence on steady-state plasma levels of risperidone, whereas ABCB1 polymorphisms contributed to a certain extent to the interindividual variation in steady-state plasma levels of 9-hydroxyrisperidone and active moiety.

**ACKNOWLEDGMENTS**

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**REFERENCES**


**TABLE 3. Characteristics of the Patients Homozygous for ABCB1 1236T/2677T/3435T Haplotype Compared With Patients Carrying Other Genotypes**

<table>
<thead>
<tr>
<th>Subjects Homozygous for 1236T/2677T/3435T (n = 11)</th>
<th>Other Genotypes (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>10/1</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>40 (11)</td>
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<tr>
<td>Body weight (kg)</td>
<td>75 (5)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Paranoid schizophrenia</td>
<td>6</td>
</tr>
<tr>
<td>Disorganized schizophrenia</td>
<td>2</td>
</tr>
<tr>
<td>Undifferentiated schizophrenia</td>
<td>3</td>
</tr>
<tr>
<td>Risperidone daily dose (mg/d)</td>
<td>5.5 (1)</td>
</tr>
</tbody>
</table>

Age, body weight, and risperidone daily dose are given as mean (SD). F, female; M, male.


