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QT prolongation of the antipsychotic risperidone is predominantly related to its 9-hydroxy metabolite paliperidone

Yutaro Suzuki[1], Naoki Fukui[1], Junzo Watanabe[1], Shin Ono[1], Takuro Sugai[1], Nobuto Tsuneyama[1], Mami Saito[1], Yoshimasa Inoue[2] and Toshiyuki Someya[1]*

[1]*Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan*
[2]*MP-Technopharma Corporation Technology Department, Fukuoka, Japan*

Objective A dose-dependent increase in risk of sudden cardiac death for the antipsychotic drug risperidone was reported. However, few reports have so far addressed QT prolongation associated with the use of risperidone or its major active metabolite, which is also used as a separate antipsychotic drug, paliperidone.
Methods The present study evaluated associations between risperidone metabolism and QT interval in 61 psychiatric patients who had been receiving risperidone for ≥4 weeks at an average dosage of 4.7 mg/day. Plasma risperidone and paliperidone levels were measured and electrocardiographic measurements were also obtained.
Results There was no correlation between risperidone dosage and QTc or plasma risperidone levels and QTc. However, there was a significant positive correlation between plasma paliperidone levels and QTc ($r = 0.361$; $p = 0.004$). There was no correlation between age and dose-corrected plasma risperidone levels or between age and QTc. There was a significant positive correlation between age and dose-corrected plasma paliperidone levels ($r = 0.290$; $p = 0.023$).
Conclusion Clinically, paliperidone is considered to play a more important role in QT prolongation than risperidone. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS—risperidone (RIS); paliperidone; QT interval; pharmacokinetics; pharmacodynamics

INTRODUCTION

Most antipsychotic agents can cause QT prolongation, which is a surrogate marker for the ability of a drug to cause *torsades de pointes* and ventricular fibrillation. For instance, a dose-dependent increase in risk of sudden cardiac death for antipsychotic drug risperidone was reported (Ray *et al*., 2009); Hennessy *et al*. (2002) also reported that risperidone was associated with higher rates of cardiac arrest, ventricular arrhythmia, and death in a cohort study using administrative data. However, few reports have so far addressed QT prolongation associated with the use of risperidone. Paliperidone (9-OH-risperidone) is the major active metabolite of risperidone, which has also been developed as a separate antipsychotic drug. We and others reported that plasma levels of paliperidone were significantly higher than those of risperidone and that plasma prolactin levels, which are often elevated in patients taking antipsychotics, correlated with paliperidone levels, but not with those of risperidone in psychiatric patients (Knegtering *et al*., 2005; Melkersson, 2006; Suzuki *et al*., 2010). Therefore, when one investigates side effects induced by antipsychotic drug risperidone, the plasma level of paliperidone cannot be disregarded.

Drugs associated with prolongation of QT interval and *torsades de pointes* are thought to cause blockade of repolarizing potassium currents, particularly, the rapid component of the delayed rectifier current (IKr; Haverkamp *et al*., 2000). In addition, the human ether-a-go-go-related gene (HERG) channel carries IKr in the heart (Sanguinetti *et al*., 1995), and its inhibition causes drug-related QT prolongation. *In vitro* study showed that paliperidone, similar to the parent compound risperidone, prolongs cardiac repolarization by selectively blocking the HERG channel (Vigneault *et al*., 2011). However, the effects of paliperidone on QT interval are still unclear.

We evaluated associations of plasma risperidone and paliperidone levels on QT interval in psychiatric patients treated with risperidone.

*Correspondence to: T. Someya; Professor and Chair, Department of Psychiatry Niigata University Graduate School of Medical and Dental Sciences, 1–757 Asahimachi-dori, Chuo-ku, Niigata 951–8510, Japan. Tel: +81-25-227-2209; Fax: +81-25-227-0777. E-mail: psy@med.niigata-u.ac.jp

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METHODS

Subjects

Sixty-one subjects treated with risperidone were enrolled in the present study. Fifty-eight patients were diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria, two with psychotic disorder not otherwise specified, and one with delusional disorder. We excluded subjects if they met the following criteria: atrial fibrillation or bundle-branch block, pre-existing cardiac disease, family history of congenital QT syndrome, obesity, hypertension, diabetes, and dyslipidemia. Only benzodiazepines were allowed to be included as concomitant drugs. To evaluate psychotic symptoms, the Brief Psychiatric Rating Scale was completed. The body mass index of each patient (BMI: body weight in kilograms divided by the square of the individual's height in meters) was also calculated. The current study was approved by the Ethics Committee on Genetics of the Niigata University Graduate School of Medical and Dental Sciences. Informed consent was obtained from all patients after they received a thorough explanation of the study.

Determination of plasma risperidone, paliperidone, and QTc

The patients took different daily doses of risperidone, and blood samples were collected from the 61 patients after more than 4 weeks of treatment with the same daily dosage of risperidone to ensure that all patients had steady-state plasma risperidone levels. The patients took risperidone tablets once (before sleep) or twice (morning and before sleep) daily. Forty-three subjects took risperidone once daily, and blood samplings were performed before the morning dose. The subjects awoke at 6:00 AM, and fasting blood samples (7 ml) were collected 1 h later in blood collection tubes containing sodium-ethylenediaminetetraacetic acid as an anticoagulant to examine the plasma drug levels, electrolytes, and fasting plasma glucose. Samples were centrifuged at $3000 \times g$ for 10 min, and the plasma and cellular fractions were stored at $-80\,^{\circ}C$ until the analyses. The plasma risperidone and paliperidone levels were measured using a previously-described liquid chromatography-tandem mass spectrometry method (Nakagami *et al*., 2005). Electrocardiographic measurements were also obtained between 9:00 and 10:00 AM on this day. The QT interval was corrected using Bazett's correction formula (QTc = QT/RR1/2) (Bazett, 1920).

Statistical analyses

Statistical Package for the Social Sciences version 19.0 software program (IBM Japan, Ltd., Tokyo, Japan) was used for all statistical calculations. Correlations among risperidone dosage, plasma risperidone levels, plasma paliperidone levels, and QTc were analyzed by Pearson's correlation coefficient. Differences with p-values <0.05 were considered statistically significant.

RESULTS

Relationship between risperidone dosage and the plasma levels of risperidone or paliperidone

Data on the dosage of risperidone, plasma drug levels, and QTc are presented in Table 1. In the 61 patients, there were significant positive correlations between risperidone dosage and plasma risperidone levels ($r = 0.406$; $p = 0.002$) and between risperidone dosage and plasma paliperidone levels ($r = 0.555$; $p < 0.001$).

Effect of plasma risperidone or paliperidone levels on QT interval

There was no correlation between risperidone dosage and QTc or plasma risperidone levels and QTc (Figure 1a). However, there was a significant positive correlation between plasma paliperidone level and QTc ($r = 0.361$; $p = 0.004$) (Figure 1b). Among male and female patients one of 37 and zero of 24, respectively, exhibited a maximum QTc exceeding upper limit of normal for each sex (430 and 450 ms, respectively) (Goldenberg *et al*., 2006).

Table 1. Demographic characteristics, plasma risperidone/paliperidone levels, and QTc

Parameter	Mean ± SD (or *n*)
Sex (M/F), *n*	37/24
Age, years	32.4 ± 12.4
BPRS	25.5 ± 8.0
BMI, kg/m^2	24.1 ± 4.0
Risperidone dose, mg	4.4 ± 2.3
Plasma risperidone level, ng/ml	6.5 ± 4.4
Plasma paliperidone level, ng/ml	33.1 ± 22.7
QTc, ms	396.0 ± 21.7
Plasma electrolyte, mEq/l	
Na (138–146)*	140.2 ± 2.2
K (3.6–4.9)*	4.2 ± 0.3
Mg (1.6–2.0)*	2.3 ± 0.1

BPRS, Brief Psychiatric Rating Scale; BMI, body mass index.
*Normal range

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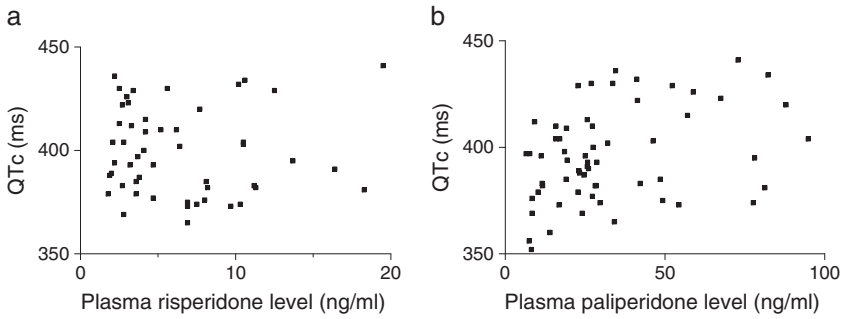

Figure 1. Scatter plot of plasma risperidone levels versus QTc (a) and plasma paliperidone levels versus QTc (b). QTc positively correlated with plasma paliperidone levels (b) (r=0.361; p=0.004) but not with those of risperidone (a)

Effect of age on risperidone metabolism or QT interval

There was no correlation between age and dose-corrected plasma risperidone levels or age and QTc. However, there was a significant positive correlation between age and dose-corrected plasma paliperidone level ($r = 0.290$; $p = 0.023$).

DISCUSSION

The present study suggests that QTc is significantly, positively, correlated with plasma levels of paliperidone but not with those of risperidone. To the best of our knowledge, this is the first study to report an impact of plasma paliperidone levels on QTc in psychiatric patients.

Although Gluais *et al.* (2002) previously reported that risperidone significantly prolonged QT interval in a concentration-dependent manner in rabbit myocytes, several clinical studies gave conflicting results (Tran *et al.*, 1997; Conley and Mahmoud, 2001; Harrigan *et al.*, 2004). Another *in vitro* study showed that paliperidone, similar to the parent compound risperidone, prolonged cardiac repolarization by selectively blocking HERG current (Vigneault *et al.*, 2011). We and others reported that plasma levels of paliperidone were significantly higher than those of risperidone and that plasma prolactin levels, which are often elevated in patients taking antipsychotics, correlated with paliperidone levels, but not with those of risperidone in psychiatric patients (Knegtering *et al.*, 2005; Melkersson, 2006; Suzuki *et al.*, 2010). The main compound risperidone seems to affect QT interval as shown in experimental studies, but, clinically, paliperidone is considered to play more important roles in QT prolongation than risperidone.

According to *in vivo* and *in vitro* studies, cytochrome P450 (CYP) 2D6 is responsible for metabolism of risperidone to paliperidone (Fang *et al.*, 1999; Jovanović *et al.*, 2010), and it has been suggested that several mutated alleles of the *CYP2D6* gene may decrease (CYP2D6*10) or eliminate (CYP2D6*5) its activity. Therefore, plasma risperidone levels are predictable by detecting CYP2D6 mutated alleles to a certain extent. However, paliperidone is eliminated mainly by the kidney, and nearly 60% of an oral dose of paliperidone is excreted unchanged in the urine (Chwieduk and Keating, 2010). In this study, the dose-corrected plasma paliperidone levels were correlated with age; this result is consistent with a previous report that steady-state clearance of paliperidone is 20% lower in subjects aged >65 years than in those aged 18–45 years (Chwieduk and Keating, 2010). Therefore, because plasma paliperidone level correlates with QT interval, QT interval may be extended in older patients.

There is a methodological limitation to the present study. Although healthy female subjects have been reported to have longer QT intervals than their male counterparts (Smetana *et al.*, 2002; Sredniawa *et al.*, 2005), this study did not analyze QT interval separated by sex because of the small sample size. Further research analyzing the differential effects of antipsychotic agents on QT interval in female and male subjects would be an important step to extend the current findings.

CONCLUSION

A concentration-dependent effect of paliperidone but not of risperidone on QT interval was observed. This phenomenon may account for the dose-dependent increase in risk of sudden cardiac death for reported risperidone therapy.

CONFLICT OF INTEREST

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All authors fulfill the criteria of authorship based on their substantial contribution to the conception and design, analysis and interpretation of data, drafting the article, or revising it critically for important intellectual content, and final approval of the submitted version. No one who fulfilled these criteria has been excluded as an author. Dr. Toshiyuki Someya is the guarantor for the present manuscript; this author accepts full responsibility for the finished article, had access to all data, and instigated the decision to submit for publication.

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