

Possible impact of the *CYP2D6*10* polymorphism on the nonlinear pharmacokinetic parameter estimates of paroxetine in Japanese patients with major depressive disorders

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Abstract: It has been suggested that the reduced function allele with reduced cytochrome P450 (CYP) 2D6 activity, *CYP2D6*10*, is associated with the interindividual differences in the plasma paroxetine concentrations, but there is no data presently available regarding the influence of the *CYP2D6*10* polymorphism on the pharmacokinetic parameters, eg, Michaelis–Menten constant (K_m) and maximum velocity (V_{max}), in Asian populations. The present study investigated the effects of the *CYP2D6* polymorphisms, including *CYP2D6*10*, on the pharmacokinetic parameters of paroxetine in Japanese patients with major depressive disorders. This retrospective study included 15 Japanese patients with major depressive disorders (four males and eleven females) who were treated with paroxetine. The *CYP2D6*2*, *CYP2D6*4*, *CYP2D6*5*, *CYP2D6*10*, *CYP2D6*18*, *CYP2D6*39*, and *CYP2D6*41* polymorphisms were evaluated. A total of 56 blood samples were collected from the patients. The K_m and V_{max} values of paroxetine were estimated for each patient. The allele frequencies of *CYP2D6*2*, *CYP2D6*4*, *CYP2D6*5*, *CYP2D6*10*, *CYP2D6*18*, *CYP2D6*39*, and *CYP2D6*41* were 6.7%, 0%, 10.0%, 56.7%, 0%, 26.7%, and 0%, respectively. The mean values of K_m and V_{max} were 50.5 ± 68.4 ng/mL and 50.6 ± 18.8 mg/day, respectively. Both the K_m and V_{max} values were significantly smaller in *CYP2D6*10* allele carriers than in the noncarriers (24.2 ± 18.3 ng/mL versus 122.5 ± 106.3 ng/mL, $P=0.008$; 44.2 ± 16.1 mg/day versus 68.3 ± 15.0 mg/day, $P=0.022$, respectively). This is the first study to demonstrate that the *CYP2D6*10* polymorphism could affect the nonlinear pharmacokinetic parameter estimates of paroxetine in Asian populations. The findings of this study suggest that the *CYP2D6*10* polymorphism may be associated with the smaller values of both the K_m and V_{max} in Japanese patients with major depressive disorders, and these results need to be confirmed in further investigations with a larger number of patients.

Keywords: pharmacokinetics, dose requirement, Michaelis–Menten constant, maximum velocity

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Introduction

Paroxetine is a selective serotonin reuptake inhibitor that is widely used in the treatment of mental disorders, including depression, panic disorders, and obsessive compulsive disorder.¹ Two previous studies suggested that the plasma drug concentration is associated with the therapeutic response to paroxetine.^{2,3} Gilles et al suggested an upper threshold of paroxetine serum concentrations (39.1 ng/mL) for the preferable response.² Another recent study suggested that the plasma paroxetine

concentrations of 64.2 ng/mL may distinguish responders from nonresponders and remitters from nonremitters, and low drug concentrations may be associated with preferable treatment.³

Paroxetine is extensively metabolized in humans and exhibits nonlinear kinetics.^{4,5} It is metabolized by oxidation and methylation in the liver to unstable metabolites that are further conjugated with glucuronic or sulfuric acid.^{4,6} Cytochrome P450 (CYP) 2D6 is most likely to be the major contributor to paroxetine metabolism in humans.⁶

CYP2D6 is one of the most widely investigated CYPs in relation to its genetic polymorphisms.^{7,8} To date, more than 100 allelic variants have been reported for *CYP2D6*.⁹ A combination of polymorphisms, including single nucleotide polymorphisms, duplications, insertions/deletions, and/or gene conversions has been reported to cause either increased or reduced activity levels.^{7,8} Despite the low frequency of nonfunctional *CYP2D6* alleles (eg, *CYP2D6*4*, **5*, **18*) in Asian populations, the *CYP2D6*10* allele that causes intermediate enzyme activity is present at a high frequency of about 50% in Asian populations.^{7–11} Additionally, the *CYP2D6*39* allele is also common in Asian populations, and it may reduce the expression level of CYP2D6 protein, but it does not alter the CYP2D6 activity.¹¹ Among these alleles, it has been suggested that the *CYP2D6*10* allele has a significant impact on the plasma paroxetine concentrations in Asians.^{11–14} Therefore, the therapeutic drug monitoring of paroxetine can substantially contribute to preventing an overdose, especially in the Asian patients with the *CYP2D6*10* allele. Because knowing the pharmacokinetic parameters is necessary to optimize the dose administered to each patient, several previous studies have been performed in Caucasian and African-American subjects.^{15–17} These studies demonstrated that the pharmacokinetic parameters of paroxetine were associated with the *CYP2D6* polymorphisms.^{15–17} Although there are large interethnic differences in the frequencies of the *CYP2D6* genotypes, as described above, there is presently no data available regarding the influence of the *CYP2D6* polymorphisms on the nonlinear pharmacokinetic parameters, eg, the Michaelis–Menten constant (K_m) and maximum velocity (V_{max}), in Asian populations.

The aim of the present study was thus to investigate the effects of the *CYP2D6* polymorphisms, including *CYP2D6*10*, on the nonlinear pharmacokinetic parameter estimates of paroxetine in Japanese patients with major depressive disorders using the Michaelis–Menten method.

Material and methods

Subjects and protocol

This retrospective study was conducted at Hirosaki University Hospital (Hirosaki, Japan). The patients with major depressive disorders were recruited from the participants of previous studies.^{3,18} A dose of 20 mg/day of paroxetine (Paxil®; GlaxoSmithKline, Brentford, UK) was administered at around 8 pm for the first week; thereafter, the dose of paroxetine was increased to 40 mg/day from the 2nd to the 6th weeks. When mild side effects were observed, the dose was maintained. The dose of paroxetine was decreased when moderate side effects were observed. During the paroxetine treatment period, blood samples (10 mL) were collected. The patients were included if they fulfilled all of the following conditions: having received paroxetine for 2 weeks or longer and not taking any drugs that may alter the pharmacokinetics of paroxetine; having normal renal and hepatic functions; and having data available from at least three therapeutic drug monitoring time points at different paroxetine doses. A total of 15 patients were included in the study (four males, eleven females). The mean \pm standard deviation age, body weight, the daily paroxetine dose, the time after the last paroxetine dose, and the number of blood samples collected for the pharmacokinetic analysis are shown in Table 1. The mean time after the last paroxetine dose was 13.5 ± 3.4 hours (range: 10–20 hours). A total of 56 blood samples were collected for the pharmacokinetic analyses of paroxetine, and the mean number of blood samples collected per patient was 3.7 ± 0.7 samples (range: 3–5 samples). The range of the daily dose was 10–40 mg/day. The study protocol was approved by the Ethics Committee of the Hirosaki University School of Medicine, and written informed consent was obtained from the patients or their families before the study.

Assays of paroxetine

The plasma paroxetine concentrations were measured using a high-performance liquid chromatography method, as reported previously.^{3,18}

Cytochrome P450 2D6 genotype determination

Genomic DNA was extracted from 5 mL of whole blood via manual extraction using the QIAamp DNA Blood Maxi Kit (QIAGEN, Venlo, the Netherlands). The *CYP2D6*5* (deleted) allele was identified using a long polymerase chain reaction (PCR) analysis.¹⁹ Genotyping for *CYP2D6*2* (rs16947), *CYP2D6*4* (rs3892097), *CYP2D6*10* (rs1065852), *CYP2D6*18* (GTGCCCACT insertion), *CYP2D6*39* (rs1135840), and *CYP2D6*41*

Table 1 The clinical characteristics of the plasma paroxetine concentrations and the observed pharmacokinetic parameters in all patients, *CYP2D6*10* allele carriers, and *CYP2D6*10* noncarriers

	All patients (n=15)	<i>CYP2D6*10</i> allele carriers (n=11)	<i>CYP2D6*10</i> allele noncarriers (n=4)	P-value ^a
Age (years)	43.4±18.3	36.5±14.9	62.5±12.7	0.010
Sex (M, male; F, female)	M=4, F=11	M=2, F=9	M=2, F=2	0.516
Body weight (kg)	58.1±11.8	60.3±11.3	52.3±12.7	0.733
Daily paroxetine dose (mg)	29.1±11.3	31.5±9.9	28.4±11.7	0.392
Blood sampling time after the last paroxetine dose (hour)	13.5±3.4	13.5±3.1	13.5±3.5	0.922
The number of blood samples collected per patient	3.7±0.7	3.9±0.7	3.3±0.5	0.144
Plasma paroxetine concentration (ng/mL)	74.4±73.7	116.6±124.5	61.7±44.3	0.122
Plasma paroxetine concentration corrected for dose (ng/mL/mg)	2.4±1.9	3.5±3.1	2.1±1.2	0.159
K _m (ng/mL)	50.5±68.4	24.2±18.3	122.5±106.3	0.008
V _{max} (mg/day)	50.6±18.8	44.2±16.1	68.2±15.0	0.022

Note: ^aCompared between the *CYP2D6*10* allele carriers and the noncarriers by the Mann–Whitney *U*-test or by Fisher's exact test.

Abbreviations: K_m, Michaelis–Menten constant; V_{max}, maximum velocity.

(rs28371725) was performed using real-time PCR with 5'-nuclease allele discrimination assays (ABI PRISM® 7000 Sequence Detection System; Life Technologies, Carlsbad, CA, USA) according to the manufacturer's protocol (assay identification numbers: C_27102425_10, C_27102431_D0, C_11484460_40, C_32407220_60, C_27102414_10, and C_34816116_20, respectively).

Data analyses and statistics

The K_m and the V_{max} values of the paroxetine concentrations were estimated by nonlinear regression using the Michaelis–Menten kinetic equation,

$$\text{Dose} = \frac{V_{\max} \times \text{Conc}}{K_m + \text{Conc}} \quad (1)$$

where the Dose and Conc are the daily dose and the plasma paroxetine concentration, respectively, in each patient. The comparisons of the patients' characteristics and the pharmacokinetic parameters associated with the *CYP2D6* genotypes were made using the Mann–Whitney *U*-test or by Fisher's exact test. Additionally, we determined the associations of the *CYP2D6* genotypes with the concentration to dose ratios or pharmacokinetic parameters of paroxetine using a multiple linear regression model with an adjusted regression coefficient (β). The model was developed using the time after the last paroxetine dose or the number of blood samples collected as a random effect. Correlations between the patients' characteristics and the pharmacokinetic parameters were also assessed using Spearman's rank correlation coefficient (*r*). A *P*-value <0.05 was considered to be statistically significant.

The relationships between the daily doses and the plasma concentration of paroxetine were plotted based on the mean values of the observed pharmacokinetic parameters. All statistical analyses were performed with the R software program (version 3.0.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

Six genotypes were identified in the 15 subjects studied: *CYP2D6*2/*10* (n=2), *CYP2D6*10/*39* (n=2), *CYP2D6*39/*39* (n=2), *CYP2D6*10/*10* (n=6), *CYP2D6*5/*39* (n=2), and *CYP2D6*5/*10* (n=1). None of the subjects was identified as a homozygote for the defective *CYP2D6* alleles (ie, *CYP2D6*4*, *CYP2D6*5*, and *CYP2D6*18*). The allele frequencies of *CYP2D6*2*, *CYP2D6*4*, *CYP2D6*5*, *CYP2D6*10*, *CYP2D6*18*, *CYP2D6*39*, and *CYP2D6*41* were 6.7%, 0%, 10.0%, 56.7%, 0%, 26.7%, and 0%, respectively. The subjects were grouped into two groups according to the combination of these alleles: extensive metabolizers (*CYP2D6*2/*10*, **10/*39*, and **39/*39*) and intermediate metabolizers (**10/*10* and **5/*10*); the *CYP2D6*10/*10* genotype and the other genotypes; or *CYP2D6*10* allele carriers and noncarriers.

The mean plasma concentrations, the concentrations corrected for dose, and the K_m and the V_{max} values of paroxetine among all patients enrolled are shown in Table 1. The mean values of K_m and V_{max} were 50.5±68.4 ng/mL and 50.6±18.8 mg/day, respectively (Table 1). The individual and mean values of the K_m and V_{max} in *CYP2D6*10* allele carriers and noncarriers, respectively, are shown in Figure 1. Both the

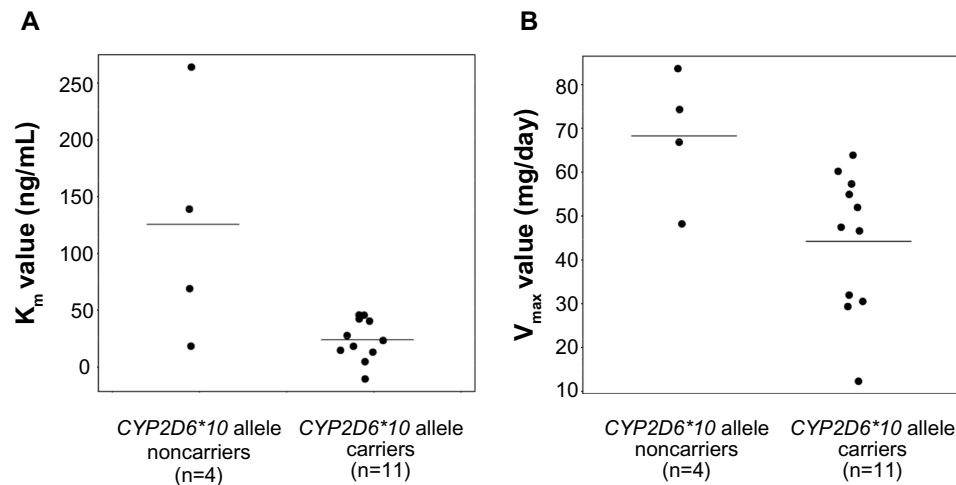


Figure 1 Individual and mean values of the nonlinear pharmacokinetic parameters, K_m (A) and V_{max} (B), of paroxetine in the *CYP2D6*10* allele carriers and the noncarriers, respectively.

Abbreviations: K_m , Michaelis–Menten constant; V_{max} , maximum velocity.

K_m and V_{max} values were significantly smaller in *CYP2D6*10* allele carriers than in the noncarriers (Table 1 and Figure 1). Figure 2 shows the simulated relationships between the plasma concentration and the daily dose based on the observed mean values of the K_m and V_{max} in the *CYP2D6*10* allele carriers and the noncarriers.

Carrying a *CYP2D6*10* allele was associated with a lower concentration to dose ratio ($\beta = -1.80$, $P=0.015$) compared with that observed in the *CYP2D6*10* allele noncarriers using a multiple linear regression model, which was adjusted for the time after the last paroxetine dose. In *CYP2D6*10* allele carriers, the K_m value was significantly smaller ($\beta = -84.2$, $P=0.041$), and the V_{max} value tended to be smaller ($\beta = -17.1$, $P=0.075$) than that in noncarriers as determined using a multiple linear regression model that was adjusted for the number of blood samples collected.

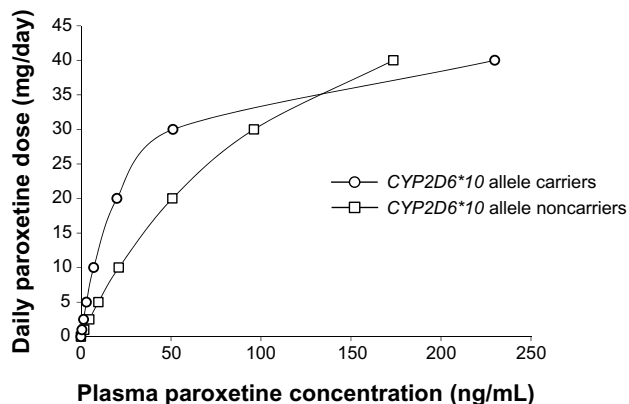


Figure 2 The simulation of the relationships between the plasma concentrations and the daily doses of paroxetine between the *CYP2D6*10* allele carriers and the noncarriers based on the pharmacokinetic parameters observed in this study.

Figure 3 shows the plots of the daily dose versus plasma concentration of paroxetine in *CYP2D6*10* allele carriers and the noncarriers. When we compared the plasma paroxetine concentrations between the *CYP2D6* genotypes using the Mann–Whitney U -test, the plasma concentrations did not differ significantly between the *CYP2D6*10* allele carriers and the noncarriers among the patients treated with 20 mg/day, 30 mg/day, or 40 mg/day of paroxetine ($P=0.673$,

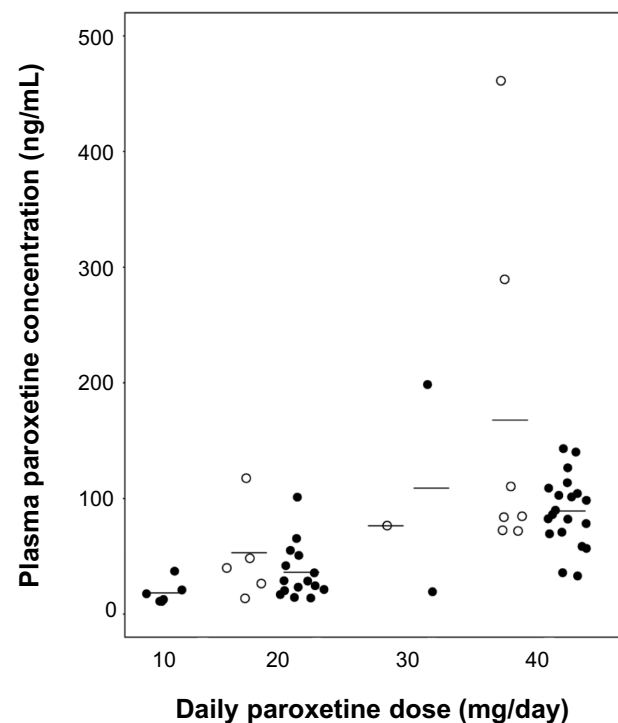


Figure 3 Individual and mean values of the plasma concentration in each daily dose of paroxetine among the *CYP2D6*10* allele carriers (solid circles) and the noncarriers (open circles).

$P=1.000$, and $P=0.400$, respectively) while no *CYP2D6*10* allele noncarrier was treated with 10 mg/day of paroxetine (Figure 3).

On the other hand, the K_m and V_{max} values did not differ between the *CYP2D6* intermediate and extensive metabolizers (25.7 ± 16.7 ng/mL versus 72.1 ± 89.3 ng/mL, $P=0.189$ and 46.8 ± 12.1 mg/day versus 54.0 ± 23.5 mg/day, $P=0.336$, respectively) and between the *CYP2D6*10*/10* genotype and the other genotypes (27.5 ± 17.5 ng/mL versus 65.8 ± 85.7 ng/mL, $P=0.388$ and 49.3 ± 11.2 mg/day versus 51.5 ± 23.2 mg/day, $P=0.607$, respectively).

Since the mean age was significantly lower in *CYP2D6*10* allele carriers than in the noncarriers (Table 1), we analyzed the association of the pharmacokinetic parameters with subjects' age separately in the *CYP2D6*10* allele carriers and noncarriers. The K_m values did not correlate with the age in *CYP2D6*10* allele carriers ($r=-0.119$, $P=0.728$) and noncarriers ($r=0.400$, $P=0.750$), and the V_{max} values also did not correlate with age in the *CYP2D6*10* allele carriers ($r=0.005$, $P=0.989$) and noncarriers ($r=-0.600$, $P=0.417$).

Discussion

In this study, we found that the *CYP2D6*10* polymorphisms were associated with smaller values of K_m and V_{max} in Japanese patients with major depressive disorder. Two previous studies reported that the *CYP2D6* genotypes could influence the pharmacokinetic parameters of paroxetine in patients with major depressive disorder or obsessive-compulsive disorder, but these studies included mainly Caucasian patients.^{16,17} Findling et al reported that the oral clearance and volume of distribution were highly associated with the *CYP2D6* polymorphisms.¹⁶ In the study by Findling et al the decreased oral clearance associated with an increase in the paroxetine dose, ie, the saturation of the clearance, was more pronounced in the *CYP2D6* extensive metabolizers than in the intermediate and poor metabolizers.¹⁶ Another population pharmacokinetic study revealed that the V_{max} values were significantly smaller in the *CYP2D6* intermediate and poor metabolizers than those in the extensive metabolizers.¹⁷ Since the frequency of the *CYP2D6* genotypes exhibits a large interethnic variability, and because the *CYP2D6*10* allele is the most common in Asian populations,⁷⁻¹¹ we focused on the influence of the *CYP2D6*10* polymorphism on the pharmacokinetic parameters of paroxetine in the present study. To the best of our knowledge, this is the first study to demonstrate that the *CYP2D6*10* polymorphism could have an impact on the nonlinear pharmacokinetic

parameter estimates of paroxetine in Japanese patients with major depressive disorders.

The *CYP2D6.10* enzyme has a P34S substitution that results in an unstable enzyme with reduced affinity for *CYP2D6* substrates.^{7,8} In vitro studies demonstrated that paroxetine showed an approximately 13-fold greater inhibition constant, ie, K_i , value in *CYP2D6.10* than in *CYP2D6.1*.²⁰ In this study, we observed smaller V_{max} values in the *CYP2D6*10* allele carriers (Table 1 and Figure 1). The results of this study are in line with the findings of the previous Korean and Japanese studies showing that the plasma paroxetine concentrations at doses of 30~40 mg/day were higher in the carriers of the defective or reduced function alleles, including *CYP2D6*10*, than the homozygotes for the wild type allele.^{12,14} The results of this study also suggest that the paroxetine metabolism could become saturated at a lower dose in the *CYP2D6*10* allele carriers compared to the noncarriers (Figure 2).

A recent study of Japanese patients indicated that the plasma paroxetine concentrations at doses of 10~20 mg/day were not associated with the defective or reduced function alleles, mainly *CYP2D6*10*,¹⁴ although the results were not confirmed in another previous study.¹³ Paroxetine is extensively metabolized via high affinity *CYP2D6* to unstable intermediate metabolites,⁶ and mechanism-based inhibition of *CYP2D6* by these metabolites has been observed.^{14,21} The present study demonstrated that the values of K_m , which is the paroxetine concentration at the dose of $V_{max}/2$, were significantly smaller in the *CYP2D6*10* allele carriers compared to the noncarriers (Table 1, Figures 1 and 2), suggesting that the rate of the paroxetine metabolism at a low dose could be greater in the *CYP2D6*10* allele carriers. We speculate that the lower formation of the unstable metabolite in the *CYP2D6*10* allele carriers might be associated with the decreased inhibitory effect on *CYP2D6*, thus resulting in smaller K_m values in the *CYP2D6*10* allele carriers.

In this study, there were no significant differences in the K_m and V_{max} values between the *CYP2D6* intermediate (ie, *CYP2D6*10*/10* or **5*/10* genotypes) and extensive metabolizers or between the *CYP2D6*10*/10* genotype and the other genotypes. These results may be in line with another recent study showing that the average area under the concentration-time curves of paroxetine in the homozygous *CYP2D6*10*/10* carriers was not different from that in the subjects heterozygous for *CYP2D6*10*.¹² Therefore, the effects of the *CYP2D6*10*/10* genotype or the intermediate metabolizers on the paroxetine pharmacokinetics might be comparable to those of the heterozygotes for the

*CYP2D6*10* allele. The findings of this study may suggest that the effects of the *CYP2D6*10*/10* or **5*/10* genotype might not be associated with the interindividual differences in the K_m and V_{max} values in Japanese patients with major depressive disorders. Nevertheless, further studies of a larger number of subjects are required to elucidate whether the *CYP2D6*10*/10* or **5*/10* genotype can affect the nonlinear pharmacokinetic parameters of paroxetine.

CYP2D6 activity has been reported to be lower in elderly subjects than in young subjects. For example, Schulz et al reported a reduction in amitriptyline metabolism (young versus elderly half-life: mean 16.2 versus 21.7 hours; clearance: mean 10.8 versus 12.5 mL/min/kg, respectively) in a group of elderly healthy males (mean age: 71 years) compared with younger healthy males (mean age: 22 years).²² In this study, the mean age was significantly lower in *CYP2D6*10* allele carriers than in the noncarriers (Table 1). However, the mean ages in *CYP2D6*10* allele carriers and the noncarriers represent younger and older adults, respectively (Table 1), but not elderly subjects, and we did not observe any correlation between the patient's age and the K_m or V_{max} in the *CYP2D6*10* allele carriers and noncarriers in the present study. These results suggest that age might not have affected the associations between the *CYP2D6*10* polymorphism and pharmacokinetic parameters of paroxetine in this study. However, the findings were obtained from a small sample of patients, and therefore the effects of age (younger versus older adults) on the nonlinear pharmacokinetic parameters of paroxetine remain unknown.

A major limitation of this study was that the number of subjects was small. Since we assessed the impact of different *CYP2D6* genotypes on the pharmacokinetic parameters of paroxetine, the sample sizes were small when the patients were stratified by the genotypes. Additionally, the observed pharmacokinetic parameters showed large interindividual variations (Table 1 and Figure 1), and we could not observe any significant effect of the *CYP2D6*10* polymorphism on the relationship between the plasma concentrations and the daily dose of paroxetine (Figure 3). Therefore, the associations between the pharmacokinetic parameters and the *CYP2D6*10* polymorphism might be overestimated, and the possibility of a Type 1 error cannot be excluded. Moreover, although two previous studies suggested that the plasma drug concentration is associated with the therapeutic response to paroxetine,^{2,3} other previous studies have failed to find any correlation of the plasma paroxetine concentration with the efficacy or adverse events.^{23,24} Therefore, the findings of the present study should be replicated with a larger number of subjects, and future studies are needed to elucidate the impact of the *CYP2D6*10*

polymorphism on the pharmacokinetic parameters as well as the dose requirement of paroxetine, after incorporating the clinical efficacy and adverse effects.

Conclusion

We herein provide findings showing that the *CYP2D6*10* polymorphism may be associated with smaller values of both the K_m and V_{max} in Japanese patients with major depressive disorders, suggesting that our results may be helpful for obtaining appropriate blood paroxetine concentrations based on the *CYP2D6*10* genotypes. Since the findings of this study were based on a small sample size, these results need to be confirmed in further investigations with a larger number of patients.

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Disclosure

The authors report no conflicts of interest in this work.

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