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Pharmacokinetic interaction of flecainide and paroxetine in relation to the *CYP2D6*10* allele in healthy Korean subjects

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The only existing study of *CYP2D6*10*-associated alterations in flecainide pharmacokinetics was retrospective.
- Paroxetine has been known as a strong inhibitor of CYP2D6.

WHAT THIS STUDY ADDS

- This study reports that the extent of drug interaction between flecainide and paroxetine is influenced by the *CYP2D6*10* allele in healthy subjects, which is frequent in Asians.

AIMS
The objectives were to evaluate the effect of *CYP2D6* genetic polymorphism on the pharmacokinetics of flecainide, and also on the extent of drug interaction with paroxetine as a CYP2D6 inhibitor after a single oral administration in healthy subjects.

METHODS
An open-label, two-period, single-sequence, cross-over study was performed in 21 healthy Korean male volunteers (seven for *CYP2D6*1/*1* or **1/*2*, group 1; seven for *CYP2D6*1/*10*, group 2; seven for *CYP2D6*10/*10* or **10/*36*, group 3). Subjects were administered 200 mg of flecainide on day 1. After a 7-day wash-out period, subjects were administered 20 mg of paroxetine from day 8 to 14, and 200 mg of flecainide on day 15. Blood sampling was performed up to 72 h after flecainide administration.

RESULTS
Terminal elimination half-life and mean residence time (MRT) were significantly different among three genotype groups after a single oral administration of flecainide ($P = 0.021, 0.011$, respectively). Area under the concentration–time curve, terminal elimination half-life and MRT increased significantly after paroxetine co-administration only in groups 1 and 2.

CONCLUSIONS
This study reports that the extent of drug interaction between flecainide and paroxetine is influenced by the *CYP2D6*10* allele in healthy subjects, which is frequent in Asians.

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Introduction

There is a considerable variation between individuals regarding cytochrome P450 (CYP) 2D6 activity [1]. CYP2D6 protein and enzymatic activity is completely absent in subjects with two null alleles (e.g. *4 and *5), with a frequency of up to 10% in Caucasians and <1% in Asians [2]. Compared with these 'poor metabolizers' (PMs), a subgroup of individuals is termed 'intermediate metabolizers' (IMs) of CYP2D6, to reflect reduced protein activity. However, the most prevalent IM allele is different among different ethnic groups such as Caucasians, Africans and East Asians [3]. Yoon *et al.* reported that the frequency of the *CYP2D6*10* allele, one of the most common IM alleles in East Asians, is approximately 50% in Koreans [4]. Moreover, the magnitude of the effect of the *CYP2D6*10* allele varies between substrates [3]. Recently, Lim *et al.* reported that CYP2D6*10/*10 was associated with lower steady-state plasma concentrations of active tamoxifen metabolites and influenced the clinical outcome of tamoxifen in Korean breast cancer patients [5].

Flecainide acetate (Tambocor™; 3M Pharmaceuticals, St Paul, MN, USA) is a class Ic antiarrythmic agent indicated for paroxysmal supraventricular tachycardia and paroxysmal atrial flutter/fibrillation. It is metabolized by CYP2D6 [6], and the target therapeutic range is relatively narrow, i.e. 200–1000 ng ml^{-1} [7]. Increased adverse effects including proarrythmic potential are reported to be related to high plasma flecainide concentrations [8]. In a previous study, exposure to flecainide was increased after amiodarone coadministration to Caucasian healthy subjects, but the extent of the increase was not significantly different between CYP2D6 extensive metabolizers (EMs) and PMs [9]. In other studies, quinidine decreased total and nonrenal clearance of flecainide by 24 and 28%, respectively, in six nongenotyped or phenotyped healthy subjects [10] and decreased total clearance of flecainide by 15% in five EM patients [11]. Doki *et al.* recently reported that the pharmacokinetics (PK) of flecainide differs between subjects with the *CYP2D6* wild-type (**1* or **2*) allele and the **10* allele in Japanese patients with supraventricular tachyarrhythmia using routine therapeutic drug monitoring data [12], which might be clinically relevant in the East Asian population. However, paroxetine, known as a strong inhibitor of CYP2D6 [13], has not yet been reported to inhibit metabolism of flecainide.

The objectives of this study were to evaluate the effect of *CYP2D6* genetic polymorphism on the PK of flecainide, and also on the extent of drug interaction with paroxetine as a CYP2D6 inhibitor, after a single oral administration in healthy Korean subjects.

Methods

Subjects and study design

Twenty-one healthy nonsmoking Korean male volunteers were enrolled in the study. None showed any abnormalities on physical examination, vital signs, routine laboratory tests, or 12-lead electrocardiograms, and none had any relevant medical disorders. All of the subjects denied any medication use within the period of 4 weeks before the study, and this was confirmed by urine drug screening using REMEDi HS® (Bio-Rad Laboratories, Hercules, CA, USA). Written informed consent was obtained from all subjects after the study procedures had been fully explained. The study was approved by the Institutional Review Board of Seoul National University Hospital.

This was an open-label, two-period, single-sequence, cross-over study. Subjects were administered 200 mg of rac-flecainide acetate (four 50-mg tablets) on day 1. After a 7-day wash-out period, subjects were administered 20 mg of paroxetine once a day from day 8 to 14, and 200 mg of flecainide on day 15. Blood samples for PK evaluation were collected at 0 (predose), 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48 and 72 h after flecainide administration, and additional safety evaluations, including serial 12-lead electrocardiograms, were performed.

CYP2D6 *genotyping*

Genomic DNA was extracted from the peripheral whole blood of each subject using a QIAamp DNA Blood mini kit (Qiagen GmbH, Hilden, Germany). In brief, the presence of the *CYP2D6*5* (*CYP2D6* gene deletion), **2N* (*CYP2D6* gene multiplication) or **36* (*CYP2D6* gene conversion to *CYP2D7P* in exon 9) allele was determined using amplification by polymerase chain reaction (PCR) [14, 15]. The presence of the *CYP2D6*10* (*100 C→T*) allele was determined using amplification by PCR-restriction fragment length polymorphism [16]. The presence of the *CYP2D6*2* (*285 C→T*), **4* (*1846 G→A*), **14* (*1758 G→A*), **21* (*2573 C* insertion) or **41* (*2988 G→A*) allele was determined using single base extension by SNaPshot analysis using an ABI PRISM® SNaPshot™ Multiplex Kit (Applied Biosystems, Foster city, CA, USA) [17].

Assay of flecainide levels in plasma

Following liquid–liquid extraction using methyl-*t*-butyl ether, plasma concentrations of flecainide were measured by tandem mass spectrometry (MS; API 4000, Applied Biosystems/MDS Sciex, Toronto, Canada) coupled with high-performance liquid chromatography (Agilent 1100 series; Agilent Technologies, Wilmington, DE, USA). Chromatographic separation was achieved under gradient conditions on a Luna CN 100A column (100 × 2.0 mm, 3 µm; Phenomenex, Torrance, CA, USA) with a mobile phase consisting of 10 mmol ammonium formate and acetonitrile. The MS/MS system was operated using an electrospray in positive ionization mode. For flecainide and the internal standard, haloperidol, the precursor-to-product ion reactions monitored were *m/z* 415.2→398.4 and 376.0→123.1, respectively. The lower limit of quantification

Table 1

Demographic characteristics of subjects

CYP2D6 genotype	Group 1 ($n = 7$)	Group 2 ($n = 7$)	Group 3 ($n = 7$)	*P*-value*
Age (years)	24.3 ± 3.3	25.3 ± 3.3	23.9 ± 2.5	0.647
Height (cm)	173.0 ± 4.5	172.4 ± 4.3	175.3 ± 5.0	0.401
Weight (kg)	66.3 ± 7.3	67.7 ± 8.2	73.3 ± 6.1	0.168

*Kruskal–Wallis test. Group 1, *CYP2D6*1/*1* ($n = 5$) or **1/*2* ($n = 2$); group 2, *CYP2D6*1/*10* ($n = 7$); group 3, *CYP2D6*10/*10* ($n = 6$) or **10/*36* ($n = 1$). Data are presented as arithmetic mean ± standard deviation.

for flecainide was 1.0 ng ml^{-1}. The day-to-day coefficient of variation was 4.40% at 2.5 ng ml^{-1}, 4.36% at 20 ng ml^{-1} and 5.77% at 400 ng ml^{-1}.

Pharmacokinetics

Individual PK parameters were calculated by a noncompartmental method using WinNonlin® (version 5.1; Pharsight Co., Mountain View, CA, USA). The maximum drug concentrations in plasma (C_{max}) and the time at C_{max} (T_{max}) were determined directly from the observed values. Area under the concentration–time curve from time 0 to infinity ($AUC_{0-\infty}$) was calculated using the linear-up and log-down trapezoidal method in plasma concentration–time curves. Apparent clearance was calculated as dose administered over $AUC_{0-\infty}$. Elimination half-life was calculated from linear regression of log-transformed plasma concentration and time. Mean residence time (MRT) was calculated as area under the first-moment time curve over AUC.

Statistical analysis

The Kruskal–Wallis test was used for comparisons of demography and PK parameters among the three genotypic groups. Two-sided paired *t*-tests were used to compare PK parameters of the inhibited state with those of the basal state. For overall analysis, linear mixed models were used, including genotype and drug interaction as fixed effects, and with an interaction term between these fixed effects. S-PLUS® (version 6.2; Insightful Corp., Seattle, WA, USA) was used for statistical analysis, and the level of significance used was 0.05.

Results

Because the original plan was to enrol subjects who had the genotypes *CYP2D6*1/*1* or **1/*2*, *CYP2D6*1/*10* or *CYP2D6*10/*10*, we had planned to determine the presence or absence of *CYP2D6*2*, **2N*, **4*, **5*, **10*, **14*, **21* and **41* alleles among more than 80 alleles of *CYP2D6*, considering the frequencies already known in Koreans [4, 18]. However, after conducting the clinical study, it was reported that *CYP2D6*36* had been previously misclassified as *CYP2D6*10* [14]. After re-examination, one subject previously classified as *CYP2D6*10/*10* was revealed actually to be *CYP2D6*10/*36*. Therefore, the *CYP2D6*10/*10* group included one subject with the genotype *CYP2D6*10/*36*. None of the demographic characteristics was significantly different in the three *CYP2D6* genotypic groups (Table 1); group 1, *CYP2D6*1/*1* ($n = 5$) or **1/*2* ($n = 2$); group 2, *CYP2D6*1/*10* ($n = 7$); group 3, *CYP2D6*10/*10* ($n = 6$) or **10/*36* ($n = 1$).

Statistically significant differences were found in the elimination half-life and MRT of flecainide among the *CYP2D6* genotypic groups in the basal state ($P = 0.021$, 0.011, respectively, Table 2 and Figure 1). The results were similar even with the subject who had the *CYP2D6*10/*36* allele excluded from the analysis ($P = 0.034$, 0.015, respectively). There was an increasing tendency of the AUC as the number of variant alleles (*CYP2D6*10*) increased; however, the difference was not statistically significant (Table 2). Apparent clearance showed a decreasing tendency in groups 2 and 3 compared with group 1, but this also was not significant. C_{max} and T_{max} values showed no differences among the three genotypic groups.

During the paroxetine administration period, the AUCs of flecainide were increased to 128.5% (122.2–135.2%) and 116.6% (107.3–126.8%) of the basal values in groups 1 and 2, respectively (Table 2 and Figure 2). The apparent clearances were reduced to 77.8% (74.0–81.8%) and 85.7% (78.9–93.2%) of the basal values in groups 1 and 2, respectively. However, the AUC and apparent clearance in group 3 did not exhibit any changes after paroxetine administration (Table 2 and Figure 2). The changes of elimination half-life and MRT in the paroxetine-inhibited state displayed similar results (Table 2 and Figure 2). C_{max} and T_{max} values showed no remarkable changes in any of the three genotypic groups. No differences were found among the three genotypic groups in the paroxetine-inhibited state in terms of AUC, apparent clearance, elimination half-life, MRT, C_{max} or T_{max}.

Discussion

In this study, we have shown that elimination half-life and MRT were significantly different among the three genotypic groups; elimination half-life and MRT of *CYP2D6*1/*10* subjects were longer than in those with the

Table 2

Pharmacokinetic parameters of flecainide according to *CYP2D6* genotypes and periods

CYP2D6 genotype	*1/*1 (*n* = 5) or *1/*2 (*n* = 2)	*1/*10 (*n* = 7)	*10/*10 (*n* = 6) or *10/*36 (*n* = 1)
Period 1 (basal)			
AUC (h ng ml^{-1})	5717.5 ± 1795.1	6719.2 ± 1478.5 (120.7; 91.3, 159.5)	7034.9 ± 1939.0 (123.6; 93.5, 163.4)
CL/*F* (l h^{-1})	38.6 ± 13.9	31.0 ± 6.5 (82.9; 62.7, 109.5)	31.3 ± 12.6 (80.9; 61.2, 106.9)
$t_{1/2}$ (h)	10.0 ± 1.0	11.6 ± 1.0 (115.5; 97.7, 136.3)	12.5 ± 3.0 (120.9; 102.4, 142.9)
MRT (h)	15.2 ± 1.2	17.6 ± 1.1 (116.2; 100.5, 134.2)	18.4 ± 4.1 (118.8; 108.1, 137.2)
C_{max} (ng ml^{-1})	391.2 ± 97.4	425.4 ± 123.7 (108.2; 85.5, 137.0)	402.6 ± 89.1 (104.0; 82.1, 131.7)
T_{max} (h)	1.5 [1.0, 3.0]	1.0 [1.0, 3.0]	2.0 [1.0, 3.0]
Period 2 (paroxetine-inhibited)			
AUC (h ng ml^{-1})	7317.5 ± 2230.6 (128.5; 122.2, 135.2)	7828.2 ± 1592.3 (116.6; 107.3, 126.8)	6925.7 ± 1472.9 (100.6; 90.2, 112.2)
CL/*F* (l h^{-1})	29.8 ± 9.8 (77.8; 74.0, 81.8)	26.6 ± 5.9 (85.7; 78.9, 93.2)	30.1 ± 6.9 (99.4; 89.2, 110.9)
$t_{1/2}$ (h)	12.1 ± 2.0 (119.2; 108.6, 130.7)	13.5 ± 2.3 (115.8; 100.4, 133.7)	12.1 ± 2.5 (98.1; 89.8, 107.1)
MRT (h)	18.0 ± 2.3 (118.0; 111.3, 125.0)	19.8 ± 2.6 (112.0; 103.2, 121.7)	17.4 ± 2.9 (95.7; 88.9, 103.1)
C_{max} (ng ml^{-1})	477.3 ± 121.4 (122.5; 97.1, 154.6)	474.0 ± 130.0 (111.9; 99.9, 125.4)	467.6 ± 105.1 (115.9; 104.9, 128.0)
T_{max} (h)	1.0 [1.0, 4.0]	1.0 [1.0, 1.5]	1.5 [1.0, 3.0]

Data are presented as arithmetic mean ± standard deviation, except for T_{max}, median [range]; values in parentheses indicate percentages compared with genotypic group 1 (period 1) or compared with basal values (period 2), expressed as geometric mean ratio and 90% confidence interval. AUC, area under the concentration–time curve from 0 to infinity; CL/*F*, apparent clearance; MRT, mean residence time; $t_{1/2}$, elimination half-life.

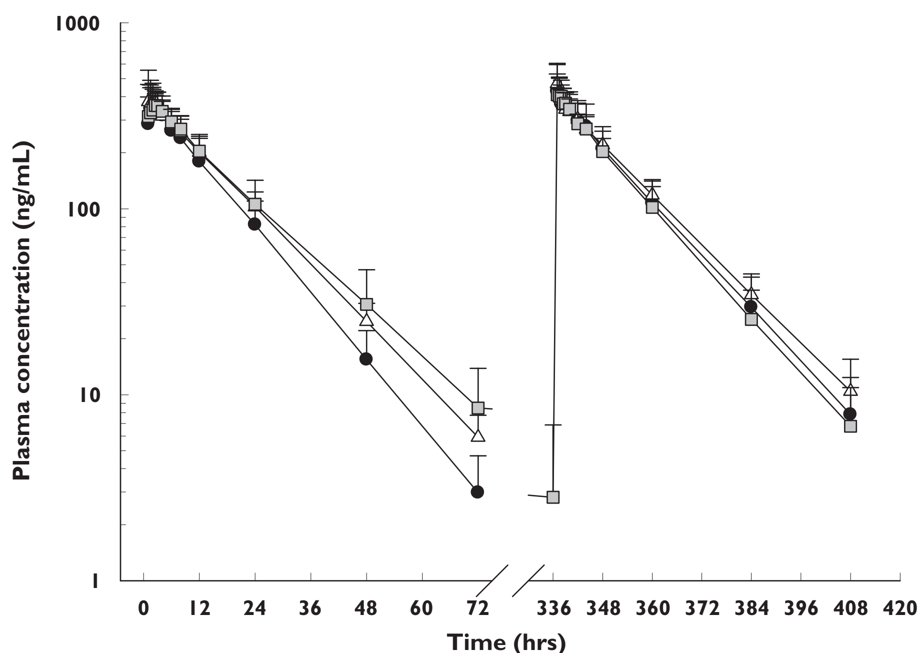

Figure 1

Plasma concentration–time profiles of flecainide by three genotypic groups. Values are presented as arithmetic mean + standard deviation. Left, basal state; right, paroxetine-inhibited state. *1/*1 or *1/*2 (N = 7) (●); *1/*10 (N = 7) (△); *10/*10 or *10/*36 (N = 7) (■)

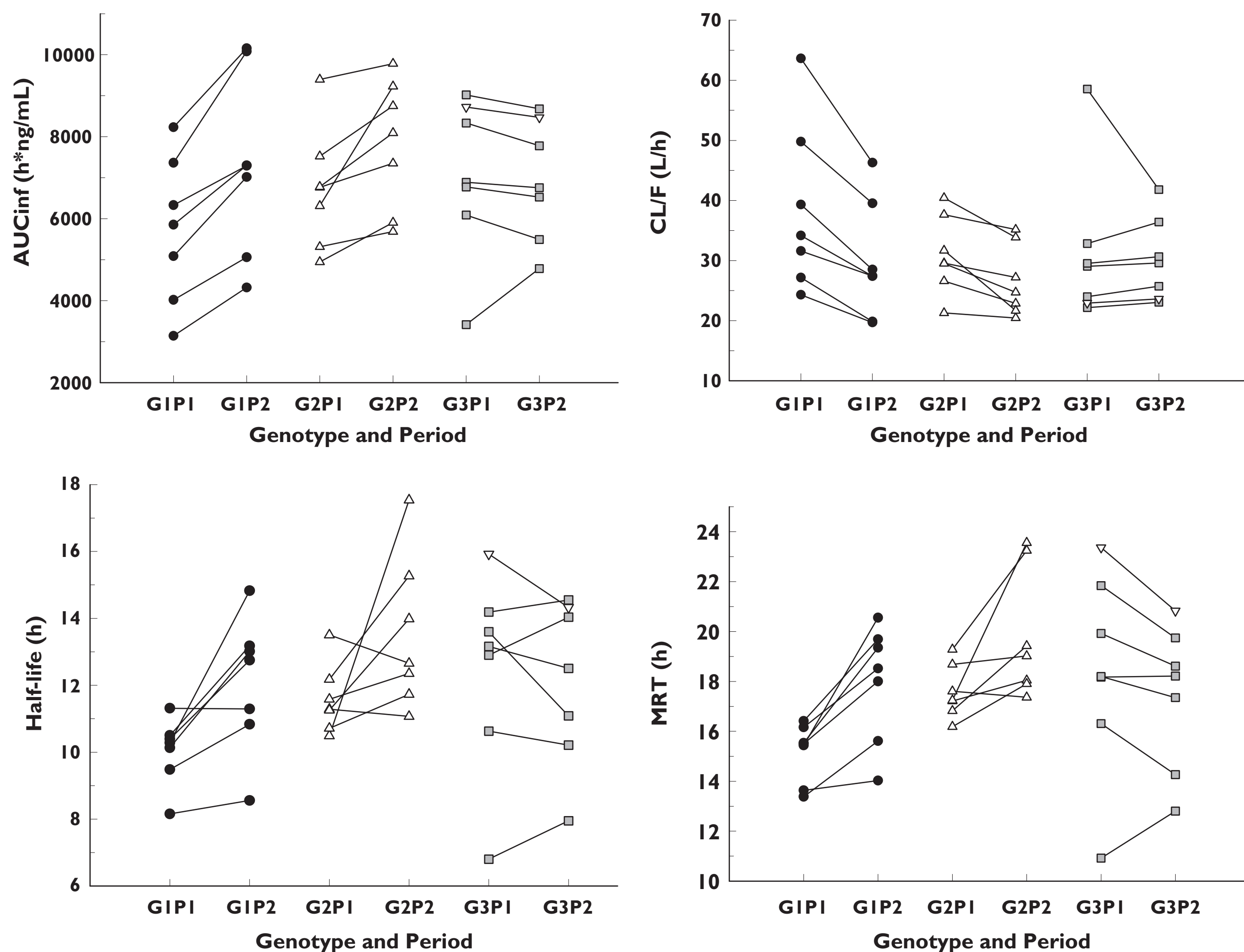

Figure 2

Area under the concentration–time curve (left upper panel), apparent clearance (right upper panel), elimination half-life (left lower panel) and mean residence time (right lower panel) of flecainide according to *CYP2D6* genotypes and periods. G1P1, group 1 (*CYP2D6*1/*1* or **1/*2*) and period 1; G1P2, group 1 and period 2; G2P1, group 2 (*CYP2D6*1/*10*) and period 1; G2P2, group 2 and period 2; G3P1, group 3 (*CYP2D6*10/*10* or **10/*36*) and period 1; G3P2, group 3 and period 2. Reverse triangle represents *10/*36 subject.

*CYP2D6*1/*1* or **1/*2* allele, and those with *CYP2D6*10/*10* were longer than in those with the *CYP2D6*1/*10* allele. Also, AUC, elimination half-life and MRT were increased and apparent clearance was decreased after paroxetine co-administration in only groups 1 and 2. To our knowledge, this is the first report that paroxetine inhibited metabolism of flecainide and that this interaction was different among *CYP2D6* genotypes, namely in subjects with the *CYP2D6*10* allele. Interestingly, one subject with *CYP2D6**10/*10 exhibited a remarkable decrease in apparent clearance after paroxetine administration (Figure 2). This subject showed a relatively high clearance in the basal state, allowing for the effect of paroxetine on the inhibition of CYP2D6 metabolism to be great. Findling *et al.* observed similar phenomena in children and adolescents with various *CYP2D6* genotypes; the largest decreases in paroxetine clearance were seen in those patients with the greatest clearance at the initial dose level [19].

However, although subjects with *CYP2D6*1/*10* or *10/*10 allele did show a trend for increased AUC and decreased apparent clearance compared with subjects with the wild-type alleles, AUC and apparent clearance in the basal state did not exhibit statistically significant differences among three genotypic groups. This may be explained by the fact that approximately 30% of flecainide is excreted in urine in an unchanged form, and although R-flecainide is metabolized mainly by CYP2D6 [7], the metabolic pathway of S-flecainide is not yet clarified. Therefore, these factors are also thought to contribute to the individual variability in flecainide PK.

In a previous study with Caucasian subjects, Funck-Brentano *et al.* have reported that flecainide PK was not

significantly different between seven EM and five PM subjects with CYP2D6, and also reported that co-administration of amiodarone decreased the apparent total clearance and nonrenal clearance of both the EM and PM groups [9]. The same investigators reported that there was no significant difference of flecainide PK between 20 EM and four PM subjects with CYP2D6 [20]. However, in these studies the subjects' genotypes were not reported; only phenotypes based on the metabolic ratio of urinary dextromethorphan (DM) were used. It is known that the DM metabolic ratio displays consistency in distinguishing *CYP2D6* PM from EM subjects [2]. However, Evans *et al.* have reported that DM metabolic ratios overlapped extensively between the homozygous EMs and heterozygous EMs of the *CYP2D6* genotype, so it did not distinguish these two groups reliably [21]. Gaedigk A *et al.* have replicated these findings in a separate analysis using African-American and Caucasian populations [22]. It might be possible that subjects classified as EMs using DM metabolic ratios in the above-mentioned studies comprised heterozygous EMs in addition to homozygous wild-type subjects. Furthermore, they did find some tendencies of PK differences (e.g. $P = 0.08$ for nonrenal clearance [9]), although statistically significant differences were not detected, probably due to the small number of subjects studied (four to five PMs). Doki *et al*. also found that *CYP2D6* genotype affected the apparent clearance of flecainide significantly (11, 16, 21 and 27% reduction in EM/IM, EM/PM, IM/IM and IM/PM, respectively) [12].

There are several limitations of the current study that suggest caution in how these results are interpreted. First, this was a single-dose study in healthy volunteers, and genotypic effects by *CYP2D6* might be different after repeated dosing of flecainide, because a small extent (approximately 10–15%) of nonlinearity was seen in the multiple-dose study in patients with ventricular arrhythmia [7, 23]. Because this study was conducted in healthy volunteers, a usual daily dosage (200 mg) of flecainide was used, resulting in plasma drug concentrations within therapeutic range for all genotypic groups. However, situations may be considered in which higher doses might be administered to patients with arrhythmia, and drug exposure may be even greater in patients with hepatic or renal impairment. Second, dosing of paroxetine was stopped on day 14, whereas dosing of the substrate flecainide was done on day 15. This could potentially result in underestimation of the magnitude of interaction, although paroxetine has a relatively long half-life (longer than that of flecainide) and is importantly a mechanism-based inactivator of CYP2D6. In addition, the differences in magnitudes of drug interaction among genotypic groups might be greater when using other substrates that are metabolized entirely by CYP2D6. Third, although the therapeutic range of flecainide is relatively narrow, it needs to be further evaluated whether a 30% increase of flecainide exposure after paroxetine co-administration would influence the efficacy or safety of flecainide in the clinical setting. Not including pharmacodynamic analysis obtained from serial electrocardiographic measurements may also be a limitation of this study. However, some cases of flecainde-induced QT prolongation and torsade de pointes have been reported in clinical settings even with daily flecainide doses of 200 mg [24, 25]. Also, in some cases therapeutic drug monitoring is being performed for flecainide due to large interindividual PK variability of flecainide [12]. Therefore, caution should be exercised in patients with higher doses of flecainide, with hepatic or renal impairments or in patients using CYP2D6 inhibitors including paroxetine.

In summary, this study reports that the extent of drug interaction between flecainide and paroxetine is influenced by the *CYP2D6*10* allele in healthy subjects, which is frequent in Asians. The clinical significance of possible associations between increases in the QTc interval and the *CYP2D6*10* allele should be further evaluated in relevant patient populations.

Competing interests

None to declare.

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