Haloperidol plasma concentration in Japanese psychiatric subjects with gene duplication of CYP2D6

Tohru Ohnuma, Nobuto Shibata, Yoichiro Matsubara & Heii Arai

Department of Psychiatry, Juntendo Koshigaya Hospital, 560 Fukuroyama, Koshigaya-shi Saitama, 343-0032 Japan

Aims The cytochrome P-450 2D6 (CYP2D6) gene duplication/multiduplication producing an increase in enzyme activity, and the common Japanese mutation, CYP2D6*10A producing a decrease of enzyme activity were screened in a large number of Japanese psychiatric subjects ($n = 111$) in order to investigate whether these mutated alleles affected the plasma concentration of haloperidol.

Methods Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was performed to identify the CYP2D6*10A and CYP2D6*2 genotypes in subjects who had been taking haloperidol. For the screening of duplicated active CYP2D6 gene, allele-specific long PCR was performed. Plasma concentration of haloperidol was measured by the enzyme immunoassay, and expressed as 'plasma concentration dose ratio' to normalize individual differences.

Results The plasma concentration-dose ratio showed large interindividual differences of approximately 18-fold. PCR-RFLP methods revealed that 29 (26.1%), 10 (9.0%), 39 (35.1%), 0 (0%), seven (6.3%) and 26 (23.4%) cases possessed the CYP2D6 genotypes *1/*1, *1/*2, *1/*10A, *2/*2, *2/*10A and *10A/*10A, respectively. Six cases (5.4%) had duplicated CYP2D6 genes. There were no significant differences of plasma concentration-dose ratio between the groups classified by CYP2D6*10A and *2 genotypes (Kruskal-Wallis test; $P = 0.37$), even in those cases whose daily doses were lower than 20 mg ($n = 90$, $P = 0.91$). Subjects having duplicated genes ($n = 6$) did not show significant differences of plasma concentration-dose ratio by comparison with subjects who had no duplicated genes (Mann-Whitney U -test; $P = 0.80$).

Conclusions Gene duplication, and the common Japanese mutation CYP2D6*10A on CYP2D6 gene are not likely to be the main modulatory factors of plasma concentration of haloperidol in Japanese psychiatric subjects.

Keywords: CYP2D6, gene duplication, haloperidol, plasma concentration

Introduction

Haloperidol is one of the major neuroleptics for psychiatric patients, and clinically it is well known that the plasma concentration of haloperidol shows large interindividual differences independent of its dose amount [1, 2]. The enzyme, cytochrome P-450 2D6 (CYP2D6) is one of the possible factors which may affect the plasma concentration of haloperidol, because haloperidol is partly metabolized by this enzyme in the liver [3, 4]. The

CYP2D6 gene has already been sequenced and mapped to chromosome 22q13.1, which includes nine exons [5]. Until now, over 80 polymorphisms due to mutation have been reported and inherited as autosomal recessive traits (<http://www.imm.ki.se/CYPalleles/cyp2d6.htm>). Phenotypically, almost all these mutated genes cause decreased CYP2D6 activity (poor metabolizer), and may be associated with elevated plasma concentrations of drugs [6, 7]. Recently, we investigated the relation between plasma concentration of haloperidol and the Japanese common mutation CYP2D6*10A, which also produces decreased CYP2D6 activity, and obtained the results that CYP2D6*10A mutation does not affect the steady-state plasma concentration of haloperidol [8]. Someya *et al.* [9] also reported no association of the CYP2D6*10A allele with plasma concentrations of halo-

Correspondence: Tohru Ohnuma MD, PhD, Department of Psychiatry, Juntendo Koshigaya Hospital, 560 Fukuroyama, Koshigaya-shi Saitama, 343-0032 Japan. Tel.: +81 489 75 0321; Fax: +81 489 75 0322; E-mail: tohru.ohnuma@nifty.ne.jp

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peridol. However, some studies reported the possibility that CYP2D6*10A allele at least partly affected the plasma concentration of haloperidol [10, 11], especially in cases where daily doses <20 mg haloperidol were given [12]. Thus, the influence of decreased enzyme activity by CYP2D6*10A allele on the plasma concentration of haloperidol seems as yet unclear.

On the other hand, the ultrarapid metabolizer having CYP2D6 active gene duplication/multiduplication (CYP2D6*2XN; CYP2D6*2 includes three point mutations: G1749C on exon 3, C2938T on exon 6, G4268C on exon 9, $N = 2, 3, 4, 5$ or 13) has shown increased CYP2D6 activity compared with CYP2D6*1 (wild-type allele) [13, 14]. Later, it was reported that duplicated alleles were not limited to only CYP2D6*2 allele, but also to other alleles (CYP2D6*1XN) [15]. If the metabolism of haloperidol is affected by CYP2D6 gene duplication, concentrations may be expected to be extremely low in subjects who have active CYP2D6 allele duplication/multiduplication. However, no study of this possibility has been reported in Japanese subjects, and the investigation of this aspect could clarify the relation between CYP2D6 genotypes and the plasma concentration of haloperidol.

In the present study therefore we focused on a common Japanese mutation CYP2D6*10A, and CYP2D6*2 mutation which is particularly concerned with gene duplication, in a relatively large number of Japanese psychiatric patients who had been taking haloperidol, and assessed whether these genotypes affect the plasma concentration of haloperidol.

Methods

Subjects who had been consistently taking the same oral dose of haloperidol for at least 2 weeks were randomly chosen from in-patients of Juntendo Koshigaya Hospital. Almost all patients had been taking other psychotropic agents simultaneously. The subjects who had been taking carbamazepine and antidepressants including selective serotonin reuptake inhibitor (SSRI) simultaneously were excluded from the present subjects, because these drugs were considered to influence CYP2D6 activity [16, 17]. Remaining subjects taking concomitants of anti-Parkinsonism drugs and benzodiazepine tranquillizers which have not been reported for evidence of major influence on CYP2D6 were included in the present study. Finally, 111 subjects (55 males/56 females; schizophrenia 91, affective disorder 16, organic mental disorder 4; mean age $\pm$ SD $43.1 \pm 0.516.5$ years; body weight $62.4 \pm 0.515.6$ kg) taking haloperidol (daily dose 1–45 mg, range 10.0 mg day⁻¹) were selected for the study. Among these, 56 cases had also been used in our previous study investigating the relation between plasma concentration of

haloperidol and CYP2D6 genotypes [8]. All patients had normal liver and renal function (we studied each case using glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, blood urea nitrogen and creatinine). The steady-state plasma concentration of haloperidol of each case was divided by each 'dose amount of haloperidol per body weight', and expressed finally as 'plasma concentration dose ratio' in order to normalize individual differences. This study was approved by the Ethics Committees of Juntendo University. Before extracting genomic DNA, the purpose and significance of this study were explained to each patient in detail, and all subjects gave written informed consent. Blood samples for measurements of plasma concentration of haloperidol were taken early in the morning (around 08.00 h), and plasma concentrations of haloperidol were measured by the enzyme immunoassay method using Markit-M *Haloperidol* II Kit (Dainippon Pharmaceutical Suitu-shi, Osaka, Japan). The specificity of this assay was as follows: the coefficients of variation from intra- and interday assay were 4.4 and 1.2%, limit of quantification was 1.25 ng mL⁻¹, and the cross reaction ratio was 5% for reduced haloperidol and <0.01% for other haloperidol metabolites. Genomic DNA was extracted from white blood cells using Nucleon II kit (Scottlabo, Shelton, CT, USA).

Japanese common mutation CYP2D6*10A was screened by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis in order to search for a genuine CYP2D6*1 allele carrier. PCR-RFLP analysis for the detection of three mutations (C188T on exon 1, G1749C on exon 3, and G4268C on exon 9) included in CYP2D6*10A was performed according to Armstrong *et al.* [18] as we have previously reported [8]. For the detection of each mutation of CYP2D6*2 gene, PCR-RFLP analysis was performed according to Panserat *et al.* [7]. In short, every three exons containing a single nucleotide point mutation of 2D6*2 gene were amplified with respective primers, and digested with respective restriction enzyme (G1749C on exon 3; Alw26I, C2938T on exon 6; HhaI, G4268C on exon 9; BstEII). The digested patterns for each enzyme were electrophoresed on 1% agarose gel, and each genotype was determined.

For the determination of duplication/multiduplication of active CYP2D6 gene, allele-specific long PCR was performed by a recently published method [19]. Two sets of PCR primers were prepared. One set of primers (cyp-207f and cyp-32r) only amplifies a fragment spanning the potential cross-over sites of genomic DNA from subjects carrying a duplicated or multiduplicated CYP2D6 gene, but does not amplify in individuals lacking a duplicated CYP2D6 gene. The other set of primers (cyp-17f and cyp-32r) amplifies 2D6 in its entirety and was used to ensure that PCR amplification of the DNA samples used

was possible (for more detail on the principle and sequences of the primers, refer to Lovlie *et al.* and Steijns *et al.* [19, 20]).

The plasma concentration–dose ratio of haloperidol on each mutation/allelic combination was compared by means of nonparametric analysis (Kruskal–Wallis test was used for the comparison among more than three groups; Mann–Whitney *U*-test was used for the comparison between two groups). Allelic frequencies were compared by the χ^2 test. All tests were applied using StatView® 5.0 program. *P*-value <0.05 was considered statistically significant.

Results

PCR–RFLP methods revealed that 29 (26.1%), 10 (9.0%), 39 (35.1%), 0 (0%), seven (6.3%) and 26 (23.4%) cases possessed the CYP2D6 genotypes *1/*1, *1/*2, *1/*10A, *2/*2, *2/*10A and *10A/*10A, respectively. The allele frequency of CYP2D6*1 (0.482) was quite similar to that of *10A (0.441). The *2 allele (0.077) was found less frequently than that of *1 or *10A. There were no significant differences in the frequencies of *1, *2 and *10A between the present psychiatric subjects and a healthy Japanese population [21] for any allelic frequency studied here (χ^2 ; *1 = 0.035, *2 = 0.316, *10A = 0.660, all *P* > 0.05).

With a primer pair of cyp-17f/cyp-32r, the expected 5.2-kb PCR product was obtained from all 111 subjects, indicating a reliable long PCR DNA amplification in every subject. The 3.6-kb product, indicating the presence of two CYP2D6 genes on the same allele, was observed in six subjects (5.4%). Only these six subjects showed a 3.2-kb PCR product with the cyp-207f/cyp-32r primer pair, whereas no amplification was obtained in any other subject with this primer pair, as was expected (Figure 1). Genotypes of six duplication carriers were *1/*1, *1/*2, *1/*10A (three cases) and *10A/*10A, respectively.

The range of plasma concentrations of haloperidol was

1.5–38.0 ng mL⁻¹ (median 7.7 ng mL⁻¹), showing approximately 25-fold interindividual differences. The range of plasma concentration–dose ratios of haloperidol was 12.1–212.0 (median 51.3), still showing large interindividual differences, approximately 18-fold.

The plasma concentration–dose ratio of haloperidol was compared between the groups classified by genotype (Table 1). There were no significant differences of plasma concentration–dose ratio of haloperidol between the genotypic groups from total subjects (Kruskal–Wallis test, *P* = 0.37). According to the finding of Roh *et al.* [12] that the CYP2D6*10A genotypes influenced the plasma concentration of haloperidol in the case of low doses (< 20 mg), but not in high doses (≥ 20 mg), we classified the total subjects into two groups, low dose (< 20 mg, *n* = 90) and high dose (≥ 20 mg, *n* = 21). However, our results showed no significant differences of plasma concentration–dose ratio in any group (Table 1; *P* = 0.91). Furthermore, we classified total subjects into two classes using median dose (10.0 mg), and again the results failed

Figure 1 Long polymerase chain reaction (PCR) assay for detection of alleles with duplicated CYP2D6 genes. Lanes 1–4 show the results of DNA amplification using entire 2D6-specific primers (cyp-17f and cyp-32r). Subjects who have no duplication show only the 5.2-kb PCR product, and subjects who have duplication/multiduplication show 5.2-kb and 3.6-kb products. Lane 5–8 show the results of DNA amplification using duplication specific primer (cyp-207f and cyp-32r) with the same subjects as lanes 1–4, lined up in numerical order. The 3.2-kb PCR product was recognized only in subjects who had duplicated gene, and showed 3.6-kb PCR product with entire 2D6 specific primers (cyp-17f and cyp-32r). M, λ .5 *Hind*III DNA marker.

Table 1 Comparison of plasma concentration–dose ratio of haloperidol by genotypes.

Genotypes	Total subjects (n = 111)	Plasma concentration dose ratio of haloperidol	
		Dose < 20 mg (n = 90)	Dose ≥ 0.520 mg (n = 21)
*1/*1	49.4 (23.4–212.0) (29)	53.9 (23.4–212.0) (23)	45.6 (27.0–91.0) (6)
*1/*2	42.3 (17.2–116.1) (10)	53.5 (28.0–116.1) (6)	30.3 (17.2–47.8) (4)
*1/*10A	50.2 (15.3–137.1) (39)	52.7 (15.3–137.1) (34)	29.7 (18.4–69.4) (5)
*2/*2	– (0)	– (0)	– (0)
*2/*10A	53.9 (12.1–186.2) (7)	84.5 (12.1–186.2) (5)	23.8 (19.5–28.1) (2)
*10 A/*10A	53.9 (17.7–106.1) (26)	59.6 (18.0–106.1) (22)	25.1 (17.7–66.3) (4)

Data are shown as median (range).

to show a significant influence of analysed CYP2D6 genotypes on plasma concentration–dose ratio in any group (< 10 mg, $n = 48$, $P = 0.140$; ≥ 10 mg, $n = 63$, $P = 0.437$; raw data not shown).

The duplication/multiduplication carrier did not show a significant difference of plasma concentration–dose ratio again by comparison with subjects who had no duplication/multiduplication (Mann–Whitney U -test; $P = 0.80$, Table 2). Cases with gene duplication showed slightly higher daily doses of haloperidol [16 mg (3–30)] than those without duplication [10 mg (1–45)], but this did not reach statistical significance ($P = 0.30$).

Discussion

The allelic frequencies of Japanese common allele (CYP2D6*10A) and CYP2D6*2 were similar to those in the Japanese healthy population [21]. These findings might suggest that the CYP2D6 polymorphisms studied here are not involved in a genetic risk factor for Japanese psychiatric disorders, especially schizophrenia.

The plasma concentration–dose ratio of haloperidol was compared between the groups classified by genotypes. However, no significant differences between any classified groups were revealed. In regard to CYP2D6*10A allele, Yokota *et al.* have reported that this allele encodes an enzyme having lower rates of sparteine metabolism [22]. Therefore, if as previously reported haloperidol is partly metabolized by CYP2D6 *in vitro* [3, 4] and *in vivo* [23, 24], its plasma concentration should have been higher in the present subjects having this allele. However, similar to our previous results obtained in 56 subjects [8], the present results using a larger number of subjects again failed to show a higher plasma concentration of haloperidol in subjects having both heterozygous and homozygous CYP2D6*10A allele than that found in homozygous CYP2D6*1 subjects, even in subjects whose daily doses were lower than 20 mg. This contrasts

with the results of Roh *et al.*, who found a significant influence of CYP2D6*10A genotype in this condition from Korean subjects [12]. With regard to this discrepancy, other ethnic differences in CYP2D6 polymorphisms might be involved between Korean and the present Japanese schizophrenic subjects. In a Japanese population, the present results are consistent with the findings of Someya *et al.* that CYP2D6*10 did not affect the plasma concentration of haloperidol, and only CYP2D6*5 mutation causing 'deficiency' (not decrease) of enzyme activity affects it [9]. Thus, the decrease of CYP2D6 enzyme activity caused by CYP2D6*10A might not be sufficient to affect the clinical plasma concentration of haloperidol.

According to the literature, CYP2D6 active gene duplication/multiduplication shows extremely increased CYP2D6 activity, and makes the plasma concentration of metabolized drugs quite low compared with subjects without active gene duplication [13–15]. Plasma concentrations of haloperidol should be lower in subjects who have only one duplicated CYP2D6 gene than in subjects without duplication, as has been reported in the case of other drugs [25, 26]. However, it should be noted that subjects who had active CYP2D6 gene duplication/multiduplication failed to show a lower plasma concentration of haloperidol than subjects without duplication/multiduplication, although the daily doses of haloperidol were slightly higher than in those without duplication. Recently, Brockmoller *et al.* showed significant differences in haloperidol clearance (serum concentration of haloperidol/reduced haloperidol) between the CYP2D6 gene duplicated subjects and poor/intermediate metabolizers (subjects with no active gene or one active gene) [27]. Subjects classified as 'poor metabolizers' mainly have CYP2D6*4, a common Caucasian mutation causing a 'deficiency' in enzyme activity. Compared with the CYP2D6*4 (deficiency), the genotype that we studied was a common Japanese genotype, CYP*10A, which causes only a 'decrease' in enzyme activity, and this decrease may not be sufficient to affect the plasma concentration of haloperidol. The different results between our group and those of Brockmoller *et al.* may be caused by ethnic differences in CYP2D6 genotypes. Taken together, the present findings suggest that CYP2D6 is not likely to be the main modulatory factor of plasma concentration of haloperidol in Japanese psychiatric subjects. Recently, another CYP isoform, CYP3A4, was considered to be involved in the metabolism of haloperidol [28–31]. Recent studies suggest the possibility that haloperidol might be metabolized not only by CYP2D6, but also by CYP3A4. In addition, it has been suggested that other metabolic enzymes, carbonyl reductase [32, 33] and glucuronyl-transferase [34], may be related to haloperidol metabolism. The main modulatory factor of

Table 2 Comparison of plasma concentration–dose ratio of haloperidol between CYP2D6 gene duplication/multiduplication carrier and noncarrier.

	n	Plasma concentration– dose ratio of haloperidol
Duplication/multiduplication	6	53.3 (20.4–93.5)
(*1/*1)	1	69.3
(*1/*2)	1	37.2
(*1/*10A)	3	82.3 (24.8–93.5)
(*10A/*10A)	1	20.4
Duplication (–)	105	51.3 (12.1–212.0)

Median (range) of plasma concentration–dose ratio of haloperidol from six duplication/multiduplication carriers.

plasma concentration of haloperidol might be included among these candidates.

In conclusion, the Japanese common mutation, CYP2D6*10A, causing a decrease of enzyme activity, and CYP2D6 gene duplication/multiduplication causing an increase of enzyme activity were screened in a large number of Japanese psychiatric subjects to investigate whether these mutated alleles affect the plasma concentration of haloperidol. However, these alleles did not show any influence on the plasma concentration of haloperidol, and could not explain the large interindividual differences revealed in the present subjects. Further genetic studies of the above-mentioned CYP isoforms and other metabolic enzymes should be carried out in order to verify interindividual differences of plasma concentration of haloperidol.

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