

# Effect of CYP2D6 Genotypes on the Metabolism of Haloperidol in a Japanese Psychiatric Population

**Toshiyuki Someya<sup>\*1</sup>, Kazutaka Shimoda<sup>2</sup>, Yutaro Suzuki<sup>1</sup>, Satoshi Sato<sup>1</sup>, Yoshiaki Kawashima<sup>1</sup>, Genta Hirokane<sup>3</sup>, Sachio Morita<sup>3</sup>, Aya Yokono<sup>3</sup>, Saburo Takahashi<sup>4</sup>**

<sup>1</sup>Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; <sup>2</sup>Department of Psychiatry, Dokkyo University School of Medicine, Mibuchi, Tochigi, Japan; <sup>3</sup>Department of Psychiatry, Shiga University of Medical Science, Otsu, Shiga, Japan; <sup>4</sup>Saitama Kounan Hospital, Kounancho, Saitama, Japan

We investigated the effect of CYP2D6 genotypes on plasma levels of haloperidol (HAL) and reduced haloperidol (RHAL) in 88 Japanese schizophrenic inpatients being treated with HAL. Some subjects carrying CYP2D6\*5 allele ( $CYP2D6^*1/CYP2D6^*5$ ,  $CYP2D6^*5/CYP2D6^*10$ ) showed extremely high concentrations of both HAL and RHAL, and the groups with CYP2D6\*5 allele seemed to have higher plasma concentrations of HAL ( $1.14 \pm 0.69$  ng/ml/mg) and RHAL ( $1.10 \pm 1.05$  ng/ml/mg) than the other groups. Among those without CYP2D6\*5 allele, there were no significant differences in plasma concentrations of HAL and RHAL between those without CYP2D6\*10 allele (HAL =  $0.68 \pm 0.31$  ng/ml/mg, RHAL =  $0.28 \pm 0.37$  ng/ml/mg), those with one CYP2D6\*10 (HAL =  $0.70 \pm 0.23$  ng/ml/mg, RHAL =  $0.31 \pm 0.16$  ng/ml/mg) and those with two CYP2D6\*10 alleles (HAL =  $0.69 \pm 0.14$  ng/ml/mg, RHAL =  $0.40 \pm 0.09$  ng/ml/mg), although there was a tendency of higher plasma concentration of RHAL in those with two CYP2D6\*10 alleles. At a lower daily dosage of HAL (<10 mg/day), the subjects with two or one CYP2D6\*10 allele(s) showed significantly higher plasma concentrations of RHAL ( $0.43 \pm 0.23$  ng/ml/mg,  $0.34 \pm 0.16$  ng/ml/mg) than those without CYP2D6\*10 allele ( $0.18 \pm 0.16$  ng/ml/mg). The results of this study indicate that CYP2D6\*10 allele plays significant but modest role in HAL metabolism in Japanese; nevertheless, we should not lump CYP2D6\*10 allele with CYP2D6\*5 allele because these two mutated alleles seem to have different impacts in the metabolism of HAL. *Neuropsychopharmacology* (2003) **28**, 1501–1505, advance online publication, 4 June 2003; doi:10.1038/sj.npp.1300213

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## INTRODUCTION

Haloperidol (HAL) is an antipsychotic drug, which is widely used in the treatment of schizophrenia and other psychiatric disorders. The plasma concentration of HAL varies widely among individuals (Someya *et al.*, 1990), which has been thought to have some clinical implications. Several metabolic pathways of HAL, including oxidative N-dealkylation (Gorrod and Fang, 1993), carbonyl reduction yielding reduced haloperidol (RHAL) (Inaba and Kovacs, 1989), and glucuronide conjugation (Oida *et al.*, 1989; Someya *et al.*, 1992) have been intensively studied. It has also been shown that RHAL is reversely oxidized to HAL (Tyndale *et al.*, 1991).

*In vitro* (Inaba *et al.*, 1985; Tyndale *et al.*, 1991) and *in vivo* (Gram *et al.*, 1989; Llerena *et al.*, 1992a,b) studies have suggested the involvement of CYP2D6 in the metabolism of HAL, and the disposition of HAL is related to the polymorphic debrisoquine oxidation phenotype, which represents the activity of CYP2D6. Llerena *et al.* (1992a,b) investigated the metabolism of HAL and RHAL after single doses of HAL in extensive metabolizers (EMs) and poor metabolizers (PMs) of debrisoquine, finding the clearance of HAL to be significantly lower in PMs than in EMs. Also, plasma levels of RHAL were significantly higher in PMs than in EMs. These results also suggested the involvement of CYP2D6 in the metabolism of HAL.

Recently, the molecular genetic basis for interethnic differences in the distribution of CYP2D6 activity has been revealed. The major defect CYP2D6 alleles causing absent enzyme activity in white patients are  $CYP2D6^*3$  (\*3),  $CYP2D6^*4$  (\*4), and  $CYP2D6^*5$  (\*5), with frequencies of 2.3%, 21.5%, and 4%, respectively (Bertilsson and Dahl, 1996). However, in Asian patients, the allele frequencies of \*3, \*4, and \*5 have been reported to be 0, 0.4, and 5.7%, respectively (Johansson *et al.*, 1994). On the other hand,  $CYP2D6^*10$  (\*10), which causes decreased enzyme activity,

\*Correspondence: Dr T Someya, Department of Psychiatry, Niigata University Graduate School of Medical and Dental Sciences, 757 Asahimachidori-ichibancho, Niigata 951-8510, Japan, Tel: +81 25 227 2209, Fax: +81 25 227 0777, E-mail: someya@med.niigata-u.ac.jp

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is found with a higher frequency in Asian populations (51%) (Johansson *et al*, 1994) compared to that in white populations (2.8%) (Bertilsson and Dahl, 1996). The high frequency of \*10 allele in Asian populations might be an important factor in the HAL metabolism of Asian patients.

There have been several studies on the impact of \*5 or \*10 alleles on plasma concentrations of HAL and RHAL in Japanese patients with schizophrenia. Suzuki *et al* (1997) investigated the effects of the number of \*5 or \*10 in Japanese schizophrenic patients in steady-state plasma concentrations of HAL and RHAL. The mean plasma concentrations of HAL were significantly ( $p < 0.05$ ) higher in patients with one mutated allele than in those with no mutated allele. The mean plasma concentrations of RHAL were significantly ( $p < 0.05$ ) higher in patients with one or two mutated allele(s) than in those with no mutated allele.

In our preliminary study (Someya *et al*, 1999), there was a significant tendency for the plasma concentrations of HAL to be higher in subjects who had the \*5 allele than in those with the CYP2D6\*1 (\*1)/\*1 genotype, and plasma concentrations of RHAL were significantly higher in those subjects with the \*5 allele than in those without \*5, including those with the \*10/\*10 genotype. Although our results and those of Suzuki *et al* (1997) suggest that CYP2D6 contributed to the HAL metabolism at least in part, Suzuki *et al* (1997) examined only the impact of the number of CYP2D6 mutated alleles. Unlike their study, we specifically examined patients with \*5 allele and suggest that \*5 and \*10 alleles should not be treated in a lump as mutated allele of same impact on the individual metabolic capacity for HAL.

On the other hand, previous results were not consistent regarding the impact of \*10 allele on plasma concentrations of HAL and RHAL; some studies have suggested that \*10 allele had a significant effect (Mihara *et al*, 1999), while others reported no significant effect of \*10 allele (Shimoda *et al*, 2000).

The present study investigated the effect of CYP2D6 mutated alleles on plasma levels of HAL and RHAL in 88 Japanese schizophrenic inpatients being treated with HAL.

## MATERIALS AND METHODS

### Patients

This study was approved by the ethics committee and the gene ethics committee of Niigata University School of Medicine. Informed consent was obtained from each subject before entry to the present study. Subjects were 88 (59 male, 29 female) Japanese schizophrenic inpatients diagnosed by DSM-IV. All were hospitalized at the Saitama Kounan Hospital and aged 27–73 years (mean  $\pm$  SD = 53.1  $\pm$  9.4). None of the subjects in the present study had obvious general medical conditions. The body weights of patients ranged from 33.0 to 84.0 kg (58.2  $\pm$  10.9). They were treated exclusively with HAL per os. Additional drugs were not allowed other than biperiden, trihexyphenidyl, and laxatives, which are not known to affect plasma HAL concentrations. Demographic data, medical histories, and laboratory data, including hematology, serology, electrolytes, and urine analysis, were collected from each patient. Patients who took other antipsychotic drugs such as phenothiazine were excluded from the study. Daily dosages

of HAL were titrated at 2.0–42.0 mg (12.5  $\pm$  8.7) according to each patient's clinical symptomatology. The nursing staff confirmed the compliance of patients at each medication.

### Blood Sampling

Patients were maintained on the same daily dosage of HAL for at least 2 months, which means that all of the patients in the present study had steady-state HAL concentrations. A measure of 7 ml of venous blood was collected at 06.00 am, that is, 12 h after the evening dose, into a Venoject<sup>®</sup> tube with EDTA-Na (Terumo Japan, Tokyo, Japan). Within 2 h after collection, blood samples were centrifuged at 3000g and aliquots of plasma were drawn out and stored at  $-80^{\circ}\text{C}$  to determine plasma levels of HAL and RHAL. After the plasma was drawn, the remaining cell fractions were frozen and also stored at  $-80^{\circ}\text{C}$  to analyze the CYP2D6 genotype.

### Measuring Plasma Levels of HAL and RHAL

The plasma concentrations of HAL and RHAL were measured using column-switching high-performance liquid chromatography with ultraviolet detection according to the method of Hikida *et al* (1989), which was originally developed to determine plasma levels of bromperidol, which is an analogue of HAL.

The plasma, to which trifluperidol had been added as an internal standard, was extracted with hexane-chloroform, and the extract was subjected to automated column-switching HPLC using a hydrophilic meta-acrylate polymer column for sample clean-up and a reversed-phase column for separation. The lowest limit of detection was 0.3 ng/ml, and the inter-assay coefficient of variation was less than 5% at concentrations of 1 ng/ml for both HAL and RHAL.

### Genotyping CYP2D6

To determine the CYP2D6 genotype, DNA was isolated from peripheral leucocytes using a QIAamp Blood Kit (QIAGEN Inc., CA, USA). The \*1 and \*10 alleles were identified as the C188 T mutation using a two-step polymerase chain reaction (PCR) analysis as described by Johansson *et al* (1994). A long-PCR analysis was used to detect the \*5 allele, as described by Steen *et al* (1995). \*3 and \*4 were screened by the method described by Heim and Meyer (1990).

### Statistical Analysis

The statistical analyses were performed using GraphPad Prism Ver. 3.0 (GraphPad Software, Inc., San Diego, CA, USA). The between-group differences were compared using one-way analysis of variance (ANOVA), and the Bonferroni test was used for *post hoc* analysis. The level of significance was set at less than 0.05.

## RESULTS

### Inter-Individual Variations of Plasma Concentrations of HAL and RHAL

There were significant correlations both between plasma concentration of HAL and dosages of HAL (HAL = 0.

$675 \times \text{Dosage} + 0.788$ ,  $r = 0.751$ ,  $p < 0.0001$ ) and between plasma concentrations of RHAL and dosages of HAL ( $\text{RHAL} = 0.412 \times \text{Dosage} - 0.145$ ,  $r = 0.523$ ,  $p < 0.0001$ ). For the following comparison, the plasma concentrations of HAL and RHAL were corrected for daily dosages. The ranges of plasma concentrations of HAL and RHAL corrected for daily dosages were  $0.21\text{--}3.18 \text{ ng/ml/mg}$  ( $\text{mean} \pm \text{SD} = 0.76 \pm 0.42$ ) and  $0.00\text{--}3.00 \text{ ng/ml/mg}$  ( $0.38 \pm 0.43$ ), respectively. There were approximately 15-fold interindividual variations in the plasma concentrations of HAL.

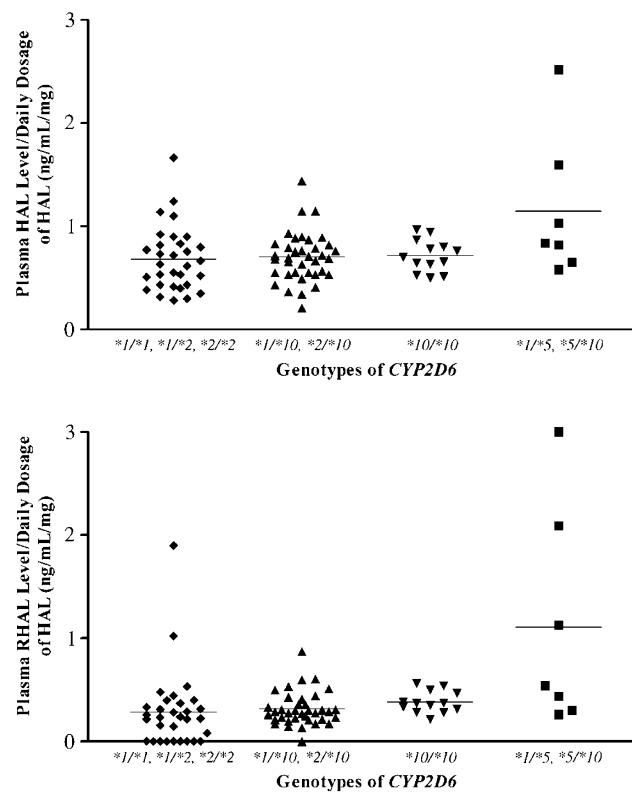
### Relation between CYP2D6 Genotypes and Plasma Concentrations of HAL and RHAL

Eight CYP2D6 genotypes were identified in the subjects studied:  $*1/*1$  ( $n = 17$ ),  $*1/\text{CYP2D6}^*2$  ( $*2$ ) ( $n = 12$ ),  $*1/*5$  ( $n = 4$ ),  $*1/*10$  ( $n = 23$ ),  $*2/*2$  ( $n = 2$ ),  $*2/*10$  ( $n = 14$ ),  $*5/*10$  ( $n = 3$ ), and  $*10/*10$  ( $n = 13$ ).  $*3$  or  $*4$  alleles were not found. The allele frequencies of  $*1$ ,  $*2$ ,  $*5$ , and  $*10$  alleles were 41.5, 17.0, 4.0, and 37.5%, respectively.

It is known that the debrisoquine metabolic ratio of subjects carrying one copy of the  $*2$  gene did not significantly differ from that of subjects with the wild-type gene (Dahl *et al*, 1995; Johansson *et al*, 1993). On the contrary, multiple copies of  $*2$  gene result in increased activity of CYP2D6 and clearance of nortriptyline. The apparent oral clearances of nortriptyline were increased in the subjects with two or three functional CYP2D6 genes (Dalén *et al*, 1998). However, those with  $*2$  allele did not result in increased or decreased activity of CYP2D6 at least in our data. So we categorized  $*2$  allele as the normal function allele in the present study, although we have not identified the multiplication of  $*2$ .

Figure 1 shows the relation between CYP2D6 genotypes and plasma concentrations of HAL and RHAL corrected for daily dosage. As shown in Figure 1, some subjects with the genotype carrying  $*5$  allele ( $*1/*5$ ,  $*5/*10$ ) showed extremely high concentrations of both HAL and RHAL, and the groups of subjects with  $*5$  allele seemed to have higher plasma concentrations of HAL ( $1.14 \pm 0.69 \text{ ng/ml/mg}$ ) and RHAL ( $1.10 \pm 1.05 \text{ ng/ml/mg}$ ) than the other groups. However, because of the small number of subjects with  $*5$  allele ( $*1/*5$  ( $n = 4$ ),  $*5/*10$  ( $n = 3$ )), only the data from subjects without  $*5$  allele were subjected to statistical analysis. The 81 subjects without  $*5$  allele were categorized into three groups according to the number of  $*10$  allele as shown in Figure 1. There were no significant differences in plasma concentrations of HAL and RHAL between those without  $*10$  allele ( $\text{HAL} = 0.68 \pm 0.31 \text{ ng/ml/mg}$ ,  $\text{RHAL} = 0.28 \pm 0.37 \text{ ng/ml/mg}$ ), those with one  $*10$  ( $\text{HAL} = 0.70 \pm 0.23 \text{ ng/ml/mg}$ ,  $\text{RHAL} = 0.31 \pm 0.16 \text{ ng/ml/mg}$ ), and those with two  $*10$  alleles ( $\text{HAL} = 0.69 \pm 0.14 \text{ ng/ml/mg}$ ,  $\text{RHAL} = 0.40 \pm 0.09 \text{ ng/ml/mg}$ ), although there was a tendency of higher plasma concentration of RHAL in those with two  $*10$  alleles (one-way ANOVA:  $F = 0.635$ ,  $df = 2,80$ , NS;  $F = 0.081$ ,  $df = 2,80$ , NS).

Since different contributions of CYP2D6 have been reported to the metabolism of HAL between low daily dosage and high daily dosage of HAL (Roh *et al*, 2001), the subjects in the present study were divided into two groups according to the median daily dosage of HAL ( $< 10 \text{ mg/day}$

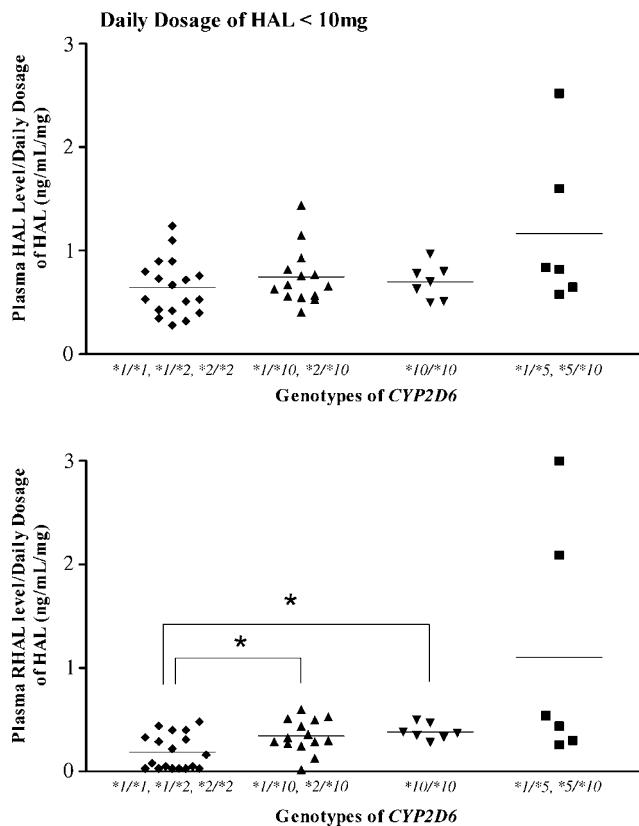


**Figure 1** Relations between CYP2D6 genotypes and steady-state plasma concentrations of HAL and RHAL corrected for daily dose of HAL.

( $n = 45$ ) or  $\geq 10 \text{ mg/day}$  ( $n = 43$ )), and the impact of CYP2D6 genotypes on the HAL and RHAL plasma levels were investigated. Roh *et al* (2001) used  $20 \text{ mg/day}$  as the cutoff point; however,  $20 \text{ mg/day}$  is apparently a high daily dosage of HAL in a recent clinical situation. So we set the median daily dosage of  $9 \text{ mg/day}$  as the cutoff point.

Figure 2 shows the relation between CYP2D6 genotypes and plasma concentrations of HAL and RHAL when the daily dosage of HAL is less than  $10 \text{ mg/day}$ . For the same reason as described above, only data from the subjects without  $*5$  alleles ( $n = 39$ ) were subjected to statistical analysis. The 39 subjects without  $*5$  alleles were categorized into three groups according to the number of  $*10$  allele. There were no significant difference in plasma levels of HAL corrected for daily dosage ( $< 10 \text{ mg/day}$ ) among the three groups (ANOVA;  $F = 0.621$ ,  $df = 2,38$ , NS), while significant differences were observed in plasma levels of RHAL corrected for daily dosage between genotypes (ANOVA;  $F = 5.954$ ,  $df = 2,38$ ,  $p < 0.005$ ). Bonferroni *post hoc* test revealed that subjects with two or one  $*10$  allele(s) had significantly higher plasma concentrations of RHAL ( $0.43 \pm 0.23$ ,  $0.34 \pm 0.16 \text{ ng/ml/mg}$ ) than those without  $*10$  allele ( $0.18 \pm 0.16 \text{ ng/ml/mg}$ ). The groups of subjects with  $*5$  allele seemed to have higher plasma concentrations of HAL ( $1.16 \pm 0.75 \text{ ng/ml/mg}$ ) and RHAL ( $1.10 \pm 1.15 \text{ ng/ml/mg}$ ) than the other three groups.

Figure 3 shows the relation between CYP2D6 genotypes and plasma concentrations of HAL and RHAL when the daily dosage of HAL is more than  $10 \text{ mg/day}$ . No significant differences were observed in plasma levels of HAL or RHAL among three groups (ANOVA;  $F = 0.267$  and  $0.983$ ,  $df = 2,41$ , NS, respectively).

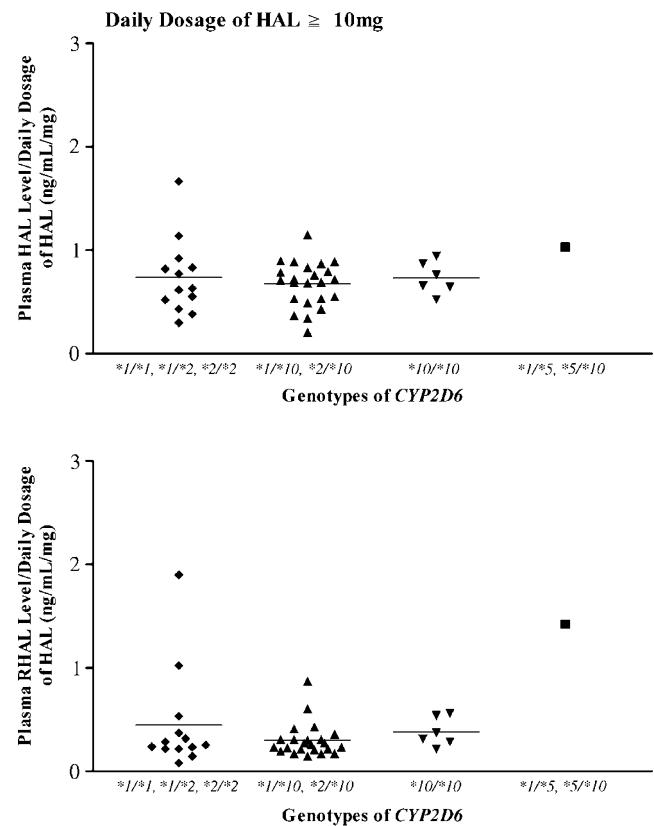


**Figure 2** Relations between CYP2D6 genotypes and steady-state plasma concentrations of HAL and RHAL corrected for daily dose of HAL with a lower daily dosage of HAL (< 10 mg/day).

## DISCUSSION

Suzuki *et al* (1997) investigated the effect of CYP2D6 mutated allele numbers on the plasma concentrations of HAL and RHAL. They reported that the group with one mutated allele had a higher plasma concentration of HAL than the subjects with no mutated allele ( $27.3 \pm 11.8$  vs  $18.4 \pm 8.5$  nM), and the subjects with one or two mutated allele(s) had higher plasma concentrations of RHAL than the group without mutated alleles (Suzuki *et al*, 1997), which suggests that CYP2D6 genotype is one of the major determinants of the metabolism of HAL.

In our previous study, we studied the effects of \*5 and \*10 alleles on the steady-state plasma concentrations of HAL and RHAL in 32 schizophrenic subjects, and reported that the group with the \*5 allele had higher plasma concentrations of HAL and RHAL than the subjects with \*1/\*1, \*1/\*10, or \*10/\*10 genotypes (Someya *et al*, 1999). Also in the present study, significant differences were observed in plasma levels of HAL and RHAL between genotypes, in the subjects treated with HAL < 10 mg/day. The subjects with \*5 allele ( $1.16 \pm 0.75$  ng/ml/mg) had significantly higher plasma concentrations of HAL than those without \*10 or \*5 allele ( $0.64 \pm 0.27$  ng/ml/mg), which is compatible with the result in our previous study. These results suggest that the \*5 allele is a significant determinant of plasma levels of HAL, especially in Japanese subjects treated with HAL < 10 mg/day. However, further investigation is still needed for clarifying the effect of genotype carrying \*5 allele(s) because of the sample size limitation.



**Figure 3** Relations between CYP2D6 genotypes and steady-state plasma concentrations of HAL and RHAL corrected for daily dose of HAL with a higher daily dosage of HAL (≥ 10 mg/day).

Regarding the impact of \*10 allele, no significant differences were observed in the plasma levels of HAL or RHAL among the subjects with no, one, and two \*10 allele(s) (see Figure 1). On the other hand, significant differences were observed in the plasma levels of RHAL between the subjects without \*10 allele and those with \*10 allele(s) (see Figure 2). Previous results were not consistent on the impact of \*10 allele on the plasma concentrations of HAL and RHAL. Mihara *et al* (1999) studied the effects of \*10 allele on the steady-state plasma concentrations of HAL and RHAL. The subjects were 67 Japanese schizophrenic inpatients who had only \*1 or \*10 alleles. The mean plasma concentration of HAL was significantly ( $p < 0.05$ ) higher in patients with one \*10 allele than in those without \*10 alleles. The mean plasma concentrations of RHAL were significantly ( $p < 0.05$ ) higher in patients with one and two \*10 allele(s) than in those without \*10 allele. On the other hand, Shimoda *et al* (2000) studied the impact of \*10 alleles on the plasma concentrations of HAL in 66 Japanese inpatients with schizophrenia without \*3, \*4, or \*5 alleles. No significant difference was observed in plasma concentrations of HAL among subjects with no, one, and two \*10 allele(s) in the subgroup of < 0.3 mg/kg of HAL and in another subgroup of ≥ 0.3 mg/kg of HAL. In addition to these discrepancies, it is somewhat strange that Mihara *et al* (1999) did not find any significant difference in plasma concentrations of HAL between those with two \*10 alleles and those without \*10 alleles, although they found significant difference between those with one \*10 allele

and those without \*10 alleles. It is just the same with the result of Suzuki *et al* (1997) that they did not identify the significant difference between the group with two mutated alleles and the subjects with no mutated allele, although they reported that the group with one mutated allele had a higher plasma concentration of HAL than the subjects with no mutated allele. All these discrepancies might be explained by the weak impact of \*10 alleles on the enzymatic activity of CYP2D6, that is, \*10 allele results in only reduced activity of CYP2D6 while \*5 allele is a defective allele. Additional explanation is that the involvement of CYP2D6 in the metabolism of HAL may not be as strong as in those of RHAL.

In conclusion, \*10 allele plays a significant but modest role in HAL metabolism in Japanese psychiatric population; nevertheless, \*5 allele possibly have a more important role in determining plasma HAL concentration. So we should not lump \*10 allele with \*5 allele because these two mutated alleles seem to have different impacts in the metabolism of HAL.

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