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A comparison of haloperidol plasma levels among Japanese, Korean and Swedish psychiatric patients

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ABSTRACT

Purpose: The purpose of this study is to compare the steady-state plasma levels of HAL between Japanese, Koreans and Swedes who were treated with HAL monotherapy *per os*.
Method: The steady-state plasma levels of haloperidol (HAL) in 75 Japanese, 120 Korean, and 50 Swedish psychiatric patients treated orally with HAL were compared.
Results: Significantly higher doses of HAL were used in the Koreans (mean dose = 21 mg/day) than in the Japanese (15 mg/day) or Swedes (9 mg/day) (one-way analysis of variance (ANOVA) ($p<0.0001$), Bonferroni's post test ($p<0.001$)). The mean concentration/daily dose ratio (C/D ratio) of HAL was 2.2 times higher in Korean patients (2.78 nmol/L/mg/day) and 1.5 times higher in Japanese patients (1.88 nmol/L/mg/day) than that in Swedish patients (1.24 nmol/L/mg/day). A significant difference in the C/D ratio was observed among the 3 ethnic groups (one-way ANOVA; $p<0.0001$).
Discussion: The higher C/D ratio of HAL in Asians might be partly due to the higher frequency of the *CYP2D6*10* allele in Asians; however, interethnic differences in the activity of other enzymes, such as CYP3A4, might have caused the differences in the present study, especially at the higher doses of HAL.

Keywords: haloperidol, ethnic difference, steady-state plasma concentration

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INTRODUCTION

Although second-generation antipsychotics have become the main pharmacotherapeutic tool for various psychiatric disorders all over the world, first-generation antipsychotics such as haloperidol (HAL) have not lost their clinical value [1].
Interethnic differences in concentrations of HAL

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have been observed between Caucasian and Asian populations. In those studies, the numbers of subjects were relatively small, especially in the Caucasian groups [2-5], and the majority of the Asian subjects were Chinese [2, 3, 6]. These limited reports taken together seem to indicate that plasma HAL levels are higher in Asians than in Caucasians.

Roh and colleagues [7] showed that the steady-state plasma levels of HAL at doses lower than 20 mg were significantly different in the three main *CYP2D6* genotype groups in Asians; specifically, patients with *CYP2D6*10/CYP2D6*10* had significantly higher HAL C/D ratios than patients with *CYP2D6*1/CYP2D6*1* or *CYP2D6*1/CYP2D6*10*. Two reports showed similar results in Japanese patients [8, 9].

The aim of this study was to compare the steady-state plasma concentrations of HAL in Swedish, Korean, and Japanese psychiatric patients treated with oral HAL.

SUBJECTS AND METHODS

The data from 245 patients who took HAL orally were analyzed. Descriptive statistics of each ethnic group are shown in Table 1. For Japanese samples, the ethical committee of Shiga University of Medical Science approved this study and written informed consent was obtained from each subject after the procedure was fully explained. Korean samples were collected at the Seoul National Mental Hospital after informed consent was obtained from each subject. Korean samples were subjected to analysis with high performance liquid chromatography (HPLC) for determination of plasma levels of HAL in Karolinska University Hospital, Sweden; however, at the time of study, there was no ethical committee at Seoul National Mental Hospital, so the study protocol was approved by the ethics committee at Karolinska University Hospital, Sweden.

Swedish patients

Plasma levels of HAL have been analyzed at the therapeutic drug monitoring (TDM) laboratory at Karolinska University Hospital. A total of 1121 consecutive request forms for analysis in 723 patients treated with HAL during the period 1991-2000 were screened. Fifty of these patients, whose daily doses of HAL, dosing schedules, treatment durations, and time intervals between the last doses and blood sampling collection time points were available, were included in this study. Only patients who took the same dosage of HAL for more than 7 days were included in order to get appropriate steady-state HAL concentrations. Thirty-seven patients took HAL twice a day, nine patients took HAL three times a day, and four patients took HAL before bedtime. Thirty-five of the patients (70%) were inpatients and fifteen (30%) were outpatients. If there were several HAL concentration measurement results from the same patient, priority was given to the first. Non-barbiturate hypnotics (benzodiazepines, zopiclone), antiparkinson drugs (biperiden, orphenadrin), and lithium carbonate were allowed as concomitant therapies. No other drugs were allowed. Thirteen patients took 2-6 mg/day of biperiden and eight patients took 50-200 mg/day of orphenadrin to control the extrapyramidal side effects of HAL, and twenty patients took benzodiazepines to control sleep disturbance or anxiety. Six patients took 84-294 mg/day of lithium carbonate.

Body weight was documented in only 14 patients (28%), and no information on smoking habits was available for the Swedish subjects. The time interval between the last dose and blood sampling was 12.0 ± 3.8 (mean ± S.D.) hours.

Korean patients

Data from a previous study by Roh and colleagues [7] on steady-state plasma levels of HAL were used. In that study, 120 native Korean patients treated orally with HAL for at least two weeks were included. They were all inpatients who had been admitted to Seoul National Mental Hospital in Seoul, Republic of Korea. Sixty-eight patients were receiving 1 to 6 mg/day of benztropine in order to control extrapyramidal side effects of HAL, and 16 patients were receiving benzodiazepines in order to control sleep disturbance or anxiety. They took HAL twice a day (12 hours apart), and blood samples were taken just before the morning dose to determine the plasma concentrations of HAL.

Japanese patients

Seventy-five Japanese patients (66 inpatients and 9 outpatients) who had been treated orally with HAL monotherapy were investigated. The data from forty-five of the patients investigated in this study were from our previously published report [10], and the data from 30 patients that have not been previously published have been added.

Sixty-eight patients were receiving antiparkinson drugs in order to control the extrapyramidal side effects of HAL. Biperiden (2-11 mg/day) was given

to 64 patients, and trihexyphenidyl (3-20 mg/day) to 9 patients. Five patients received both biperiden (3-6 mg/day) and trihexyphenidyl (3-20 mg/day). Standard doses of benzodiazepines were allowed in cases where patients complained of sleep disturbance. Patients took HAL three times a day and were maintained on the same dose of HAL for at least 14 days before blood sampling. Blood samples were drawn before the morning dose. The time interval between the last dose and blood sampling was 12.5 ± 1.3 hours. If several samples had been taken from the same patients, priority was given to the first sample.

Analytical methods

Plasma levels of HAL in Korean and Swedish patients were determined by HPLC. The intra- and inter-assay coefficients of variation were 4.7% and 5.9%, respectively, for Karolinska University Hospital. In Japanese patients, the plasma levels of HAL were determined by HPLC at the Department of Psychiatry, Shiga University of Medical Science in Japan. The intra- and inter-assay coefficients of variation were 5.1% and 5.9%, respectively, for Shiga University of Medical Science.

To investigate the possible differences in the analytical results between the two institutions, identical frozen plasma samples to which HAL had been added were analyzed separately both in Japan and later in Sweden. The concentrations of HAL determined in Huddinge were approximately 10% lower than in Shiga. There was a close linear relationship between the values determined in the two laboratories for HAL (HAL [Karolinska, nmol/L] = 0.91 × HAL [Shiga, nmol/L] + 0.81, ($r = 0.99$, $p<0.0001$, $N = 18$) [equation 1].

Statistical analysis

To compare the means of the three ethnic groups, one-way analysis of variance (ANOVA) was employed. Where appropriate, direct pairwise comparisons of ethnic groups were conducted using Bonferroni's test.

Statistical analyses were performed using Prism (Version 2.0, Graphpad, Inc., San Diego, CA). Linear multiple regression analysis was performed using SPSS (SPSS Inc, Chicago, IL, USA) to see the impact of ethnicity and of concomitant drug usage.

Table 1. Descriptive statistics in three ethnic groups

	Koreans	Japanese	Swedes
Number of patients	120	75	50
Gender (male/female)	71/49	32/43	21/29
Smoker/Non-smoker	NA	15/59[a]	NA
Age (yr)***	34 ± 7 (19-54)	33 ± 11 (15-64)	40 ± 16 (16-80)[§,†]
Weight (kg)*	60 ± 9 (39-87)[†]	56 ± 9 (41-84)	71 ± 24 (45-135)[b,†]
Daily dose (mg)****	21 ± 11 (3-60)[†]	15 ± 13 (2-80)	9 ± 7 (1-32)[§,†]
HAL concentration (nmol/L)****	57.9 ± 42.2 (4.5-230)[†]	27.8 ± 25.5 (3.2-135)	10.2 ± 12.2 (1.0-63)[§,†]
Concentration/daily dose of HAL(nmol/L per mg)****	2.78 ± 1.39 (0.91-8.6)[†]	1.88 ± 0.64 (0.62-3.7)	1.24 ± 0.71 (0.25-3.9)[§,†]

Data given are mean ± SD (range). HAL: haloperidol; NA: information not available.
a: Data from 74 patients; b: Data from 14 patients;*: $p<0.05$; *** : $p<0.0001$; **** : $p<0.0001$ (one-way ANOVA in three ethnic groups)
§: $p<0.05$ compared to Koreans; †: $p<0.05$ compared to Japanese (Bonferroni's post test)

RESULTS

A significant positive correlation was observed between the steady-state plasma concentration of HAL and the daily dose of HAL in the three ethnic groups, respectively (Koreans: $n = 120$, $r = 0.77$; Japanese: $n = 75$, $r = 0.92$; Swedes: $n = 50$, $r = 0.82$, $p<0.0001$; linear regression analysis) (Figure 1). The steady-state plasma concentrations of HAL were corrected by using equation 1 for the Japanese patients, and those corrected values were used for further analysis. The descriptive statistics of the patients are shown in Table 1. Korean subjects had steady-state concentrations of HAL that were more than 5 times those of the Swedish subjects, and almost twice those of the Japanese subjects. The

Japanese subjects had steady-state concentrations of HAL that were approximately 3 times higher than those of the Swedish subjects.

A significant difference was observed in the mean daily dose of HAL among the three ethnic groups ($p<0.001$, one-way ANOVA). The mean daily dose in Korean patients (21 mg/day) was significantly higher than that in the Japanese (15 mg/day) or Swedish patients (9 mg/day) ($p<0.001$, Bonferroni's post test). Moreover, a significant difference in terms of the daily dose of HAL was observed between the Japanese and Swedish patients ($p<0.01$).

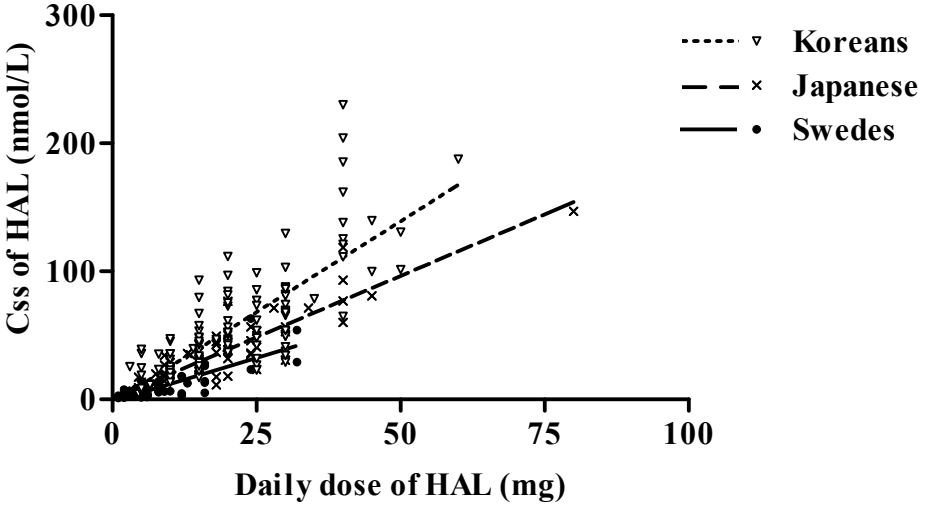

Figure 1A. The relationships between the steady-state plasma concentrations (Css) and daily doses of HAL in the three ethnic groups. Equations for linear regression: Koreans: Css = 2.838 × daily dose of HAL - 2.703 (n = 120, r = 0.77); Japanese: Css = 1.916 × (daily dose of HAL) + 0.742 (n = 75, r = 0.92); Swedes: Css = 1.359 × (daily dose of HAL) - 1.531 (n = 50, r = 0.82).

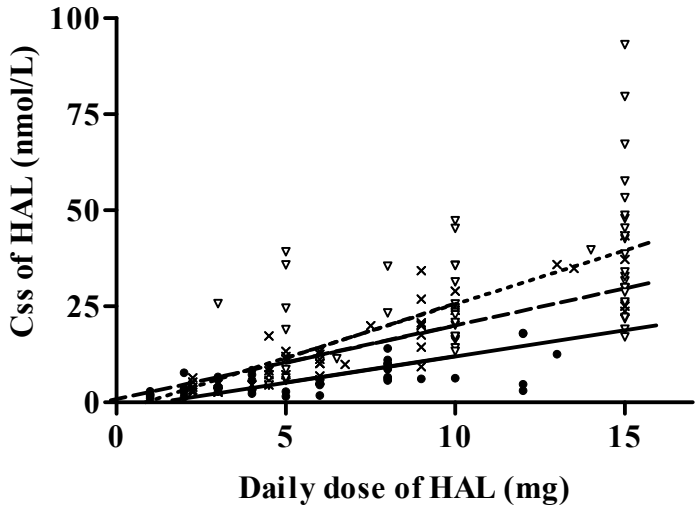

Figure 1B. A magnified view of part of Figure 1A.

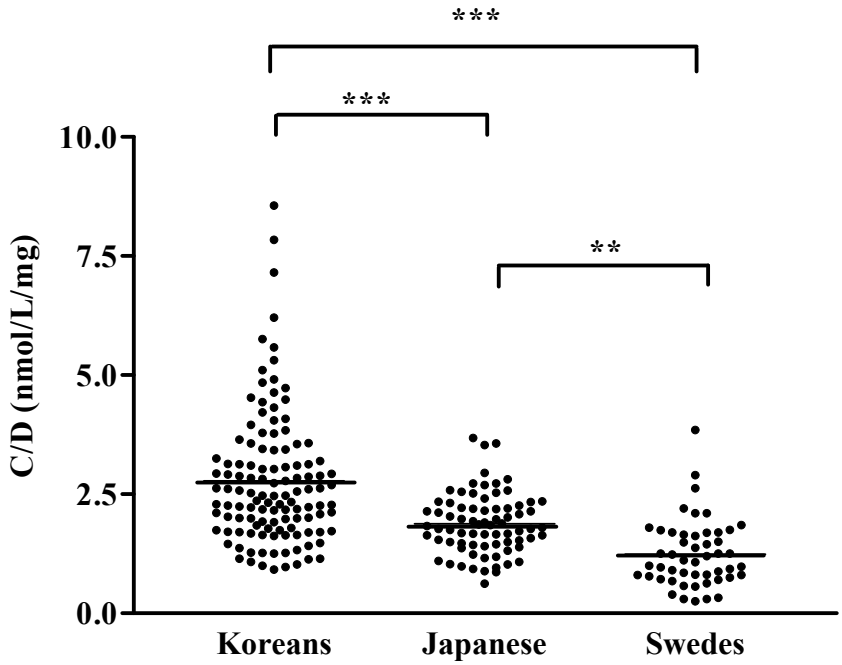

Figure 2. Steady state plasma concentration/daily dose of HAL in the three ethnic groups. Significant differences were observed among the three ethnic groups ($p<0.0001$) by one-way ANOVA. Direct pairwise comparison by Bonferroni's multiple comparison test revealed significant differences (** $p<0.01$, ***$p<0.001$). Horizontal lines show mean values.

Figure 2 shows the ratio of the steady-state plasma concentration of HAL to the daily dose of HAL (the C/D ratio) for the three ethnic groups. The mean C/D ratio in the Korean patients (2.78 nmol/L/mg) was approximately 2.2 times higher than that in the Swedish patients (1.24 nmol/L/mg) (Table 1). The mean C/D ratio in the Japanese patients (1.88 nmol/L/mg) was approximately 1.5 times higher than that in the Swedes. Significant differences in the mean C/D ratio were observed among the three ethnic groups ($p<0.0001$, one-way ANOVA).

To analyze the relationship between the plasma concentration of HAL and other factors, a linear multiple regression analysis with a stepwise method was performed. We used the daily dose of HAL, age, gender, and ethnicity as independent variables, in which the values for gender were 1 for male and 0 for female, the values for ethnicity were 0 for Swedish, 1 for Japanese, and 2 for Koreans, as dummy variables. The Log_{10} (HAL C/D ratio) was used as a dependent variable. The final model is illustrated by the following equation:

$Log_{10}(C/D) = 0.601 \times \text{ethnicity} - 0.177 \times \text{gender} + 0.076$ (ethnicity; $t = 11.541$, $p<0.001$, gender: $t = -3.401$, $p<0.001$, $r = 0.60$). Ethnicity and gender were each significant factors; neither the daily dose of HAL nor age were statistically significant.

DISCUSSION

The assay methods differed between the Swedish and Japanese laboratories in the present study. When we analyzed identical samples, the plasma levels of HAL determined in Japan were approximately 10% higher than those in Sweden. Even after taking the relative overestimation of HAL in the Japanese laboratory into consideration, significant differences were still observed among the three ethnic groups.

In Swedish patients, the mean age was significantly higher than in the other two groups. Morita and colleagues reported that age does not significantly affect the C/D ratio in patients between 20 and 70 years of age; however, patients over 70 years of age had C/D ratios that were 46% to 98% higher than those in patients less than 69 years of age [11]. In this study, only 2 Swedish patients over 70 years of age were included, and the findings of the present study cannot be attributed to the effect of age.

In the present study, gender was one of the significant factors affecting the C/D ratio; specifically, male patients had lower C/D ratios than female

patients. One possible explanation is the body weight difference between males and females. In Korean and Japanese patients for whom body weight data were available, the male patients were heavier than the female patients, and after correcting the C/D ratio by body weight, there was no significant difference in this parameter between male and female subjects. Among the Swedish patients, body weight was only available for 14 patients, so such a comparison could not be performed for the Swedish patients.

The pronounced interethnic difference in the C/D ratio among Koreans, Japanese and Swedes in the present study might be too large to be explained only by ethnic differences in CYP2D6 polymorphism. One possible explanation for these differences might be the differences among the three ethnic groups in terms of the daily dose. One report has suggested that, especially at lower doses of HAL (<20 mg daily), patients with *CYP2D6*10/CYP2D6*10* have significantly higher C/D [7-9], although this finding was not confirmed in another report [12]. The influence of *CYP2D6* genotype on the plasma levels of HAL might be limited to the lower range of the daily dose -- that is, another isozyme(s) may be responsible for the metabolism of HAL in individuals treated with higher daily doses of HAL. *In vitro* studies have suggested that the back oxidation of reduced haloperidol (RHAL) to HAL is mainly catalyzed by CYP3A4 [13-15]. The results of this study might be due to the involvement of enzymes other than CYP2D6, such as CYP3A4, in the metabolism of HAL, especially at higher doses. Hsieh and colleagues [16] reported that novel mutations of CYP3A4 may decrease CYP3A4 activity.

From a pharmacogenetic point of view, Koreans and Japanese are closely related [17,18], and we expected that the plasma levels of HAL in Japanese and Korean patients would be very similar. However, contrary to our expectations, the C/D ratios in the Korean patients were significantly higher than those in the Japanese patients. This might be partly due to the higher incidence of *CYP2D6*10* in the Korean population (53.8% [7] in Koreans compared with 25-43% in Japanese [8, 19-23]). Interethnic differences in the metabolic capacity of xenobiotics (e.g., nicotine [24]) have been reported between the two ethnic groups. One possible explanation is that the unknown pathway(s) responsible for HAL metabolism has a metabolic capacity that is different between the two ethnic groups.

Of course, the present study has some limitations. First, different HPLC methodologies were used to determine the plasma levels of HAL in Japan (Department of Psychiatry, Shiga University of Medical Science) and Sweden (Karolinska University Hospital, Karolinska Institutet). Additionally, *CYP2D6* genotyping was not performed to explain the interethnic differences in the HAL concentrations. However, the results of the present study reflect the "real world" clinical usage of HAL in the three countries studied.

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