Effects of Escitalopram on Plasma Concentrations of Aripiprazole and its Active Metabolite, Dehydroaripiprazole, in Japanese Patients

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Abstract

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Introduction: The effects of escitalopram (10 mg/d) coadministration on plasma concentrations of aripiprazole and its active metabolite, dehydroaripiprazole, were studied in 13 Japanese psychiatric patients and compared with those of paroxetine (10 mg/d) coadministration.

Methods: The patients had received 6–24 mg/d of aripiprazole for at least 2 weeks. Patients were randomly allocated to one of 2 treatment sequences: paroxetine-escitalopram (n=6) or escitalopram-paroxetine (n=7). Each sequence consisted of two 2-week phases. Plasma concentrations of aripiprazole and dehydroaripiprazole were measured using liquid chromatography with mass spectrometric detection.

Results: Plasma concentrations of aripiprazole and the sum of aripiprazole and dehydroaripiprazole during paroxetine coadministration were 1.7-fold (95% confidence intervals [CI], 1.3–2.1, p < 0.001) and 1.5-fold (95% CI 1.2–1.9, p < 0.01) higher than those values before the coadministration. These values were not influenced by escitalopram coadministration (1.3-fold, 95% CI 1.1–1.5 and 1.3-fold, 95% CI 1.0–1.5). Plasma dehydroaripiprazole concentrations remained constant during the study.

Conclusion: The present study suggests that low doses of escitalopram can be safely coadministered with aripiprazole, at least from a pharmacokinetic point of view.

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Introduction

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Aripiprazole is a novel second-generation antipsychotic drug with a pharmacological profile of dopamine and 5-HT$_{1A}$ partial agonisms, and 5-HT$_{2A}$ antagonism [1]. The efficacy of aripiprazole has been established for the treatment of schizophrenia [2]. It is also reported that aripiprazole is efficacious for a range of symptoms associated with pervasive developmental disorders [3]. Aripiprazole undergoes N-dealkylation, hydroxylation and dehydrogenation, yielding its active metabolite [4], dehydroaripiprazole. Dehydroaripiprazole is further hydroxylated and N-dealkylated [4]. Kubo et al. [5] have suggested that the cytochrome (CYP) 2D6 enzyme is involved in the metabolism of aripiprazole after a single oral dose of aripiprazole. This finding has been confirmed by the authors' previous study [6] on the steady-state plasma concentration of the drug in subjects with different *CYP2D6* genotypes. Because dehydroaripiprazole has similar pharmacological properties as the parent compound [2], and the plasma concentration of the metabolite amounts to 40% of that of aripiprazole at steady state [7], the sum of the 2 compounds is considered to contribute to the overall antipsychotic efficacy.

Selective serotonin reuptake inhibitors (SSRI) are widely used for treatment of several psychiatric disorders. SSRI augmentation of antipsychotics is considered to be one of the options for ameliorating negative symptoms of schizophrenia [8]. In clinical settings, SSRI can be coadministered to patients with schizophrenia or pervasive developmental disorders being treated with antipsychotic drugs for the alleviation of depressive and/or obsessive-compulsive symptoms. The authors have already studied the effect of paroxetine, which is a potent inhibitor of CYP2D6, on plasma concentrations of aripiprazole and dehydroaripiprazole in Japanese patients with schizophrenia [9], showing that even low doses of paroxetine coadministration increase plasma concentrations of aripiprazole and the sum of aripiprazole and dehydroaripiprazole.

Escitalopram is a weak inhibitor of CYP2D6 [10]. Previous studies [11, 12] suggested that escitalopram increases serum concentrations of aripiprazole. However, these reports [11, 12] were based on group comparisons between patients who were and were not taking escitalopram, utilizing therapeutic drug monitoring data. In addition, one of the reports [11] did not deal with serum dehydroaripiprazole concentrations. Therefore, the authors aimed to intraindividually examine the effects of escitalopram coadministration on plasma concentrations of aripiprazole and dehydroaripiprazole, in comparison with paroxetine coadministration.

Materials and Methods
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Patients

The study included 13 Japanese inpatients (8 males and 5 females) who all fulfilled the DSM-IV-TR criteria for schizophrenia (n=9) or pervasive developmental disorders (n=4). They were physically healthy without any history of substance abuse, neurological disorder, delirium or dementia and without any clinically significant abnormalities, including clinical laboratory examinations, electrocardiography and electroencephalography. The mean±SD age and body weight were 34.5±9.7 years and 62.3±13.4 kg, respectively. There were no smokers or heavy drinkers among the patients. The study was approved by the Ethics Committee of the University of the Ryukyus, and all the patients had given written informed consent to participate in this study.

Study design

All the subjects had received aripiprazole for at least 2 weeks, because it has been shown that plasma concentrations of both aripiprazole and dehydroaripiprazole reach steady-state by 2 weeks of repeated oral administrations [13]. The daily dose was fixed at 24 mg in 7 cases, 12 mg in 3 cases, and 6 mg in 3 cases during the study period and was given once a day at 12:30 pm. Except for 2–4 mg/d flunitrazepam (n=4) and 4 mg/d biperiden (n=2) the patients received no drugs. Female patients did not receive oral contraceptives. The doses of these coadministered drugs were also fixed throughout the study period. The subjects were randomly allocated to one of 2 treatment sequences, either escitalopram-paroxetine at 7 pm (n=6) or paroxetine-escitalopram at 7 pm (n=7). Each sequence consisted of two 2-week phases, with no washout period between the 2 phases. The daily dose of escitalopram or paroxetine was 10 mg. The patients' adherence was confirmed by the nursing staff. Blood samples were taken before the coadministration, 2 weeks after the first SSRI, and 2 weeks after the second SSRI. All the samples were taken at 8 am. On the same days, the severity of illness and extrapyramidal adverse effects were evaluated using the Clinical Global Impressions (CGI) [14] and Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) [15], respectively.

Laboratory methods

Plasma concentrations of aripiprazole and dehydroaripiprazole were measured using the liquid chromatography method with mass spectrometric detection described by Kubo et al. [16]. The lower limit of quantification for both compounds was 0.1 ng/mL using 0.4 mL of plasma, and the interassay coefficient of variation was less than 8 % at 0.2 ng/mL for both aripiprazole and dehydroaripiprazole. 1 ng/mL of aripiprazole and dehydroaripiprazole are corresponding to 2.23 nM and 2.24 nM, respectively. The plasma drugs concentrations were normalized to a dose of 24 mg/d, and the values were used in statistical analyses.

DNA was isolated from peripheral leukocytes using QIA-amp DNA Blood Maxi (QIAGEN, Tokyo, Japan). Long polymerase chain reaction analysis was used to detect the *CYP2D6*5(*5)* allele [17]. The *CYP2D6(*4), CYP2D6*10(*10)* and *CYP2D6*14(*14)* alleles were identified by polymerase chain reaction analyses as described by Heim and Meyer [18], Johansson et al. [19] and Kubota et al. [20], respectively. Alleles other than *4, *5, *10 and *14 were defined as wild type (*wt*). The *CYP2C19*2* and *CYP2C19*3* alleles were detected as described by Kimura et al. [21]. These mutated alleles and the *wt* allele, which are regarded as predominant over other *CYP2D6* and *CYP2C19* alleles, were selected based on the frequency of *CYP2D6* [22] and *CYP2C19* [21] alleles in a Japanese population.

Statistics

The Friedman test followed by the Wilcoxon signed-rank test with Bonferroni correction were used for the comparison of the plasma concentrations of aripiprazole and dehydroaripiprazole and the scores of clinical assessments. A 2-tailed *P* value of less than 0.05 was regarded as statistically significant. SSPS 19.0 for Windows (SPSS, Japan Inc, Tokyo, Japan) was used for these statistical analyses.

Results
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⊖ **Table 1** shows the changes in the plasma concentrations of aripiprazole, dehydroaripiprazole, the sum of aripiprazole and dehydroaripiprazole, and the CGI and DIEPSS scores before and after the 2 treatment sequences. The mean plasma concentrations of aripiprazole and the sum of the 2 compounds during the coadministration of paroxetine were 1.7-fold (95 % confidence intervals [CI], 1.3–2.1, p<0.001) and 1.5-fold (95 % CI 1.2–1.9, p<0.01, ⊖ **Fig. 1**) higher than those values before the coadministration. Those values were not influenced by escitalopram coadministration (1.3-fold, 95 % CI 1.1–1.5 and 1.3-fold, 95 % CI 1.0–1.5). The mean plasma concentrations of dehydroaripiprazole were constant throughout the study period.

The patients had the following genotypes for *CYP2D6* and *CYP2C19*: *10/wt (n=11), wt/wt (n=1), and *10/*10 (n=1); *2/*2 (n=5), wt/wt (n=4), *2/wt (n=3), and *3/wt (n=1) The genotypes were not associated with the increases of the plasma concentrations (data not shown). The mean CGI and DIEPPS scores remained unchanged during the study.

Discussion
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In the present study, escitalopram coadministration did not significantly change the mean plasma concentrations of aripiprazole. The finding suggests that escitalopram does not affect the metabolism of aripiprazole. There were 2 plausible explanations for this negative finding. The first is due to the less inhibitory effect of escitalopram on the CYP2D6 activity [10] compared with paroxetine [9]. The second is that aripiprazole may have a higher affinity for this isoenzyme than escitalopram. The present result is not consistent with previous reports [11, 12] based on group comparisons suggesting that escitalopram increased serum aripiprazole concentrations. However, this study may be
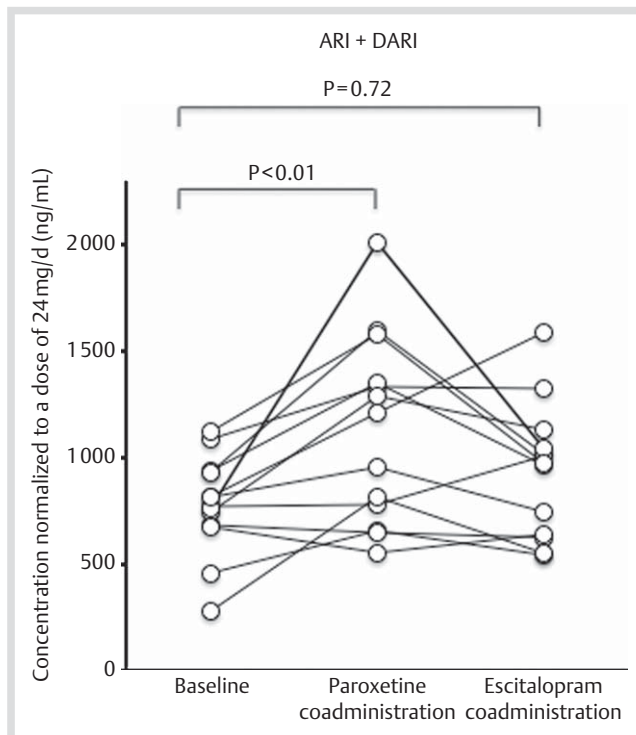
Table 1 Plasma concentrations normalized to a dose of 24 mg/d of ARI, DARI, and the sum of ARI and DARI, and CGI and DIEPSS scores before and after paroxetine or escitalopram coadministration in Japanese psychiatric inpatients.

	Before coadministration	Paroxetine coadministration	Escitalopram coadministration
ARI (ng/mL)	514±156	862±336*	661±238
ratio to baseline		1.7 (1.3–2.1)	1.3 (1.1–1.5)
DARI (ng/mL)	260±96	273±117	274±86
ratio to baseline		1.2 (0.7–1.8)	1.2 (0.9–1.5)
ARI+DARI (ng/mL)	774±231	1135±443†	934±312
ratio to baseline		1.5 (1.2–1.9)	1.3 (1.0–1.5)
CGI	3.5±0.8	3.1±1.2	3.0±1.0
DIEPSS	2.8±2.0	3.0±3.5	2.7±2.9

ARI=aripiprazole; DARI=dehydroaripiprazole; CGI=Clinical Global Impressions; DIEPSS=drug-induced extrapyramidal symptoms scale. The values of concentrations and scores are mean±SD. The ratios to baseline are mean (95% confident intervals)

*p<0.001 compared with before coadministration

†p<0.01 compared with before coadministration

Fig. 1 Intraindividual changes in plasma concentrations normalized to a dose of 24 mg/d for the sum of aripiprazole and dehydroaripiprazole before and after paroxetine or escitalopram coadministration. ARI=aripiprazole; DARI=dehydroaripiprazole.

more reliable than the previous ones [11, 12] because the present study prospectively examined the effect of escitalopram on aripiprazole metabolism intraindividually. Although type II error cannot be entirely ruled out due to small number of subjects in this study, the impact of escitalopram coadministration on the metabolism of aripiprazole would still remain marginal at best. Thus, escitalopram can be safely coadministered to aripiprazole in Japanese patients, at least from a pharmacokinetic point of view.

A 2-week coadministration of paroxetine 10 mg/d significantly increased the mean plasma concentrations of aripiprazole. The result replicates the authors' previous study [9] showing that 1-week coadministration of paroxetine 10 mg/d significantly increased those values. It is confirmed that even a low dose of paroxetine inhibits aripiprazole metabolism via CYP2D6 inhibition. However, the degree of increase in plasma aripiprazole concentrations is 1.7-fold, which is similar to the 1.5-fold found in the previous study [9]. Therefore, the degree of increase in aripiprazole concentration by paroxetine 10 mg/d may be limited to 2-fold at best.

The mean plasma concentrations of dehydroaripiprazole remained constant during the study period, which shows that neither paroxetine nor escitalopram affect the metabolism of dehydroaripiprazole. This is in line with the authors' previous studies which showed no involvement of *10 in the steady-state plasma concentrations of dehydroaripiprazole [6], and that the addition of paroxetine does not influence the metabolism of dehydroaripiprazole [9]. Therefore, it is confirmed that CYP2D6 activity is not related to plasma concentration of dehydroaripiprazole.

Paroxetine significantly increased the sum of aripiprazole and dehydroaripiprazole, while escitalopram did not. However, no significant changes in CGI and DIEPSS scores were observed during the study. There are 4 possible reasons for the result, which are associated with limitations in this study. First, the subjects were heterogeneous in age, gender, and diagnoses. Second, the duration of SSRI coadministration might not have been long enough to detect pharmacodynamic changes. Third, the doses of aripiprazole were not unified. Fourth, the sample size was small. Thus, the present study should be replicated with a larger number of homozygous subjects whose clinical symptoms are more precisely evaluated after longer periods of SSRI coadministration.

In conclusion, escitalopram can be safely coadministered to aripiprazole in Japanese patients, at least from a pharmacokinetic point of view.

Conflict of Interest
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Dr. Mihara has received honoraria from GlaxoSmithKline and Otsuka. Dr. Nakamura has received honoraria from Dainippon Sumitomo Pharma and Otsuka. Dr. Kondo has received honoraria from GlaxoSmithKline and Otsuka.

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