Population pharmacokinetic modelling of aripiprazole and its active metabolite, dehydroaripiprazole, in psychiatric patients

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Almost all reported studies have investigated the pharmacokinetics of aripiprazole in healthy volunteers.
- The pharmacokinetics of dehydroaripiprazole have not been identified in a combined model with aripiprazole.

WHAT THIS STUDY ADDS

- The data on aripiprazole and dehydroaripiprazole in psychiatric patients were modelled jointly using a population approach.
- The apparent clearance of aripiprazole in cytochrome P450 (CYP) 2D6 intermediate metabolizers (IM) was approximately 60% of that in CYP2D6 extensive metabolizers (EM) having two functional alleles, but the exposure to dehydroaripiprazole in CYP2D6 IM was similar to that in EM.

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AIMS

The aims of this study were to develop a combined population pharmacokinetic model for both aripiprazole and its active metabolite, dehydroaripiprazole, in psychiatric patients and to identify to what extent the genetic polymorphisms of cytochrome P450 (CYP) enzymes contribute to the variability in pharmacokinetics (PK).

METHODS

A population pharmacokinetic analysis was performed using NONMEM software based on 141 plasma concentrations at steady state from 80 patients receiving multiple oral doses of aripiprazole (10–30 mg day⁻¹).

RESULTS

A one-compartment model with first-order kinetics for aripiprazole and dehydroaripiprazole each was developed to describe simultaneously the concentration data. The absorption rate constant was fixed to 1.06 h⁻¹. The typical value of apparent distribution volume of aripiprazole was estimated to be 192 l. Covariate analysis showed that CYP2D6 genetic polymorphisms significantly influenced the apparent clearance of aripiprazole (CL/F), reducing the interindividual variability on CL/F from 37.8% CV (coefficient of variation) to 30.5%. The CL/F in the CYP2D6 IMs was approximately 60% of that in CYP2D6 EMs having two functional alleles. Based on the CYP2D6 genotype, the metabolic ratios were calculated at 0.20–0.34. However, the plasma concentration : dose ratios of dehydroaripiprazole were not different across the CYP2D6 genotype.

CONCLUSIONS

This population pharmacokinetic model provided an adequate fit to the data for both aripiprazole and dehydroaripiprazole in psychiatric patients. The usefulness of CYP genotyping as an aid to select the starting dose should be further investigated.

Introduction

Aripiprazole (Figure 1) is an atypical antipsychotic agent that functions as a partial agonist at the dopamine 2 and the serotonin 1A receptors, and as an antagonist at the serotonin 2A receptor [1]. The elimination of aripiprazole is mainly mediated through the hepatic metabolism by the human cytochrome P450 (CYP) isozymes 3A4 and 2D6, and dehydroaripiprazole, one of metabolites, has been shown to have affinities for the dopamine 2 receptor similar to aripiprazole and represents approximately 40% of aripiprazole exposure in plasma [2].

The determination of the optimal dosage for atypical antipsychotic agents often requires individual titration to minimize adverse events [3, 4]. For aripiprazole, due to its long half-life, it takes 2 weeks to achieve new steady state in terms of plasma concentration after the dosage regimen of aripiprazole is changed [2]. Although the dosage of aripiprazole should be adjusted on the basis of clinical course and adverse events are reported to be usually mild, it is highly desirable to select an adequate starting dose and to predict target dose before treatment, especially for elderly patients who are more likely to be vulnerable to adverse events [5].

A recent study has shown high interindividual variability in the range of a 37-fold concentration : dose ratio for aripiprazole [6]. Such variability could be explained by individual differences partly in the CYP2D6 metabolic activity associated with genetic polymorphisms [7, 8] and partly in the hepatic expression level of CYP3A4, which can vary up to more than 100-fold [9]. In addition, it has been reported that some drugs metabolized by CYP3A4 are also metabolized by CYP3A5 [10], and their plasma concentrations could be altered by CYP3A5 genetic polymorphisms [11].

Previous clinical studies to evaluate the pharmacokinetics (PK) of aripiprazole and/or dehydroaripiprazole have certain limitations. First, many studies investigated the PK only in healthy volunteers [7, 12, 13] since it is not always easy to perform intensive blood sampling on psychiatric patients. Next, the concentration data for dehydroaripiprazole, even in patients, were analyzed using a conventional two-stage method separately from those for aripiprazole [14, 15]. No reported attempt has been made at combined population modelling for pharmacokinetic analysis. Finally, the reported studies on the PK in CYP2D6 IMs, a phenotype known to be quite common in Asians, are not adequate.

Figure 1

Chemical structure of aripiprazole

The aim of this study was to develop a combined population pharmacokinetic model for aripiprazole and dehydroaripiprazole in psychiatric patients and to identify the extent of the contribution of the genetic polymorphisms related to the CYP enzymes to the variability in the PK of aripiprazole and dehydroaripiprazole.

Methods

Study population

A multicentre, single treatment, clinical phase IV study was conducted in patients with schizophrenia, schizophreniform disorder, and schizoaffective disorder at 30 sites in Korea. The study protocol was approved by the Institutional Review Board of each site, and all patients gave written informed consent before the study began. The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization guideline for Good Clinical Practice.

Both men and women who were either of non-childbearing potential or using contraception were included in this study (Table 1). The main exclusion criteria were as follows: concomitant use of drugs that could induce or inhibit CYP enzymes, other medical conditions that could interfere with oral absorption or evaluation of the response, ongoing psychiatric diseases other than schizophrenia, schizophreniform disorder, and schizoaffective disorder.

Drug administration and blood sampling

Patients were administered 15 mg aripiprazole once a day for the first several days, followed by titration from 5 to 45 mg day⁻¹ according to clinical judgment, and then maintained at steady state. Venous blood (10 ml) for the determination of plasma concentrations was drawn by direct venepuncture and collected into heparinized tubes

Table 1

Patient characteristics

	<i>n</i> (%)	Mean (SD)	Median (range)
Gender			
Male	34 (42.5)		
Female	46 (57.5)		
Race			
Korean	80 (100)		
Age (years)		35.2 (9.8)*	34 (17–61)*
Body weight (kg)		60.8 (10.9)	61.9 (38.0–95.0)
Aripiprazole dose administered (mg)		24.3 (6.7)	27.5 (10–30)
Aripiprazole concentration (ng ml ⁻¹)		445.6 (220.9)	413 (55.5–1442)
Dehydroaripiprazole concentration (ng ml ⁻¹)		129.3 (60.4)	120 (31.7–428)

*Excluding one patient whose age was unknown; SD, standard deviation.

at just before and/or around 6 h after drug administration. However, some patients changed their normal dosing time or visited the hospital irregularly, which meant that the samples taken on a visit from those patients were not trough samples. Plasma was separated by centrifugation for 10 min at 1000 *g* and stored at -70°C until analysis. For CYP genotyping, additional venous blood (5 ml) was also collected from each patient using an ethylene-diamine-tetra-acetate (EDTA) tube.

CYP genotyping

For 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 this study, the CYP2D6 alleles including CYP2D6*2, CYP2D6*4, CYP2D6*5, CYP2D6*10, CYP2D6*14, CYP2D6*36, and CYP2D6*41 were investigated, and all alleles other than these were regarded as CYP2D6*1. 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) [16, 17]. The presence of the CYP2D6*10 (100 C > T) allele was determined using amplification by PCR-restriction fragment length polymorphism (RFLP). The presence of the CYP2D6*2 (285 C > T), *4 (1846 G > A), *14 (1758 G > A), 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). For the CYP3A5 allele, we investigated CYP3A5*3 (CYP3A5 gene alternative splicing) allele using PCR-PFLP [11].

CYP2D6 alleles were classified into the following categories according to the metabolic enzyme activity investigated in previous studies [17, 18]. That is, CYP2D6*1 and *2 were classified into functional alleles, *10, *41 were partially deficient alleles, *4, *5, *14, *36 were null alleles and *2N was a multiplied allele. In addition, CYP3A5*3 were classified into null allele. Based on this classification, patients were stratified to evaluate the effect of CYP genetic polymorphisms as shown in Table 2. The CYP2D6 EM was defined as a patient carrying at least one functional allele without the multiplied allele, which then fell into Group I, Group II, and Group III. The CYP2D6 IM was defined as a patient carrying at least one partially deficient allele without the functional allele, and belonged to Group IV. With regard to CYP3A4, patients with two CYP3A5*3 alleles were regarded as CYP3A5 non-expressers and the others as CYP3A5 expressers.

Assay of drug and metabolite concentrations in plasma

Plasma concentrations of aripiprazole and dehydroaripiprazole were determined by high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS, Sciex Division of MDS Inc., Toronto, Canada). Plasma samples (0.2 ml) were spiked with 1 μg of an internal

Table 2

Genotype distribution in the study population

CYP	Group	Genotype	n (%)
CYP2D6	I	*1/*1	12 (15.0)
		*1/*2	3 (3.75)
	II	*1/*10	22 (27.5)
		*1/*41	1 (1.25)
	III	*2/*10	3 (3.75)
		*1/*5	6 (7.50)
		*1/*14	2 (2.50)
		*1/*36	1 (1.25)
		*2/*5	2 (2.50)
		*2/*36	1 (1.25)
	IV	*10/*10	21 (26.25)
		*10/*41	1 (1.25)
		*5/*10	2 (2.50)
		*10/*14	1 (1.25)
		*4/*41	1 (1.25)
		*5/*41	1 (1.25)
CYP3A5	A	*1/*1	3 (3.75)
		*1/*3	33 (41.25)
	B	*3/*3	44 (55.0)

standard (OPC-14714, a derivative of aripiprazole) and extracted with 4 ml of diethylether. After centrifugation, the organic phase was evaporated and the residue was then reconstituted in 0.2 ml of 70% acetonitrile, and 20 μl of this was analyzed in an API 3000 LC-MS/MS system equipped with an Agilent 1100 series HPLC system (Agilent, Wilmington, DE). Chromatographic separation was achieved using isocratic conditions on a Luna CN column (100 $\times$ 2.0 mm, 3 μm ; Phenomenex, Torrance, CA) with a Luna CN guard column (4 $\times$ 2.0 mm, 3 μm ; Phenomenex). The mobile phase consisted of deionized distilled water and acetonitrile (3 : 7, v : v) containing 0.1% formic acid at a flow rate of 0.3 ml min $^{-1}$. The MS/MS system was operated using an electrospray in positive ionization mode. For aripiprazole and dehydroaripiprazole, the precursor-to-product ion reactions monitored were m/z 448.1 $\rightarrow$ 285.2 and 446.0 $\rightarrow$ 285.2, respectively. The lower limit of quantification was 0.1 ng ml $^{-1}$ for both analytes. For the concentrations ranging from 0.1 to 100 ng ml $^{-1}$, intra- and inter-assay precisions were less than 7.3% for both analytes. Accuracy was between 96.7 and 112.5 for aripiprazole and between 90.2 and 108.8 for dehydroaripiprazole.

Pharmacokinetic model and data analysis

Considering the limited sampling time points, plasma concentration data were described using a one-compartment open model for both aripiprazole and dehydroaripiprazole with first-order absorption and elimination from the corresponding central compartment. The combined modelling for aripiprazole and dehydroaripiprazole was performed in a simultaneous manner on the basis of the following assumptions: the oral absorption

process occurred instantly without a lag time, aripiprazole was converted to dehydroaripiprazole only in the central compartment for aripiprazole through a first-order formation mechanism since aripiprazole is known to be almost completely absorbed from the gastrointestinal tract with an oral bioavailability of 0.87, dehydroaripiprazole was eliminated unidirectionally from its central compartment, and the orally administered drug contained no dehydroaripiprazole.

The pharmacokinetic structural model was parameterized in terms of the first-order absorption rate constant (k_a), apparent clearance and apparent distribution volume of aripiprazole (CL/F and V/F) where F is the unknown oral bioavailability of aripiprazole, the clearance and distribution volume of dehydroaripiprazole ($CL(m)$ and $V(m)$), and the fraction of the absorbed dose of aripiprazole converted to dehydroaripiprazole (fm). The differential equations to describe the rate of mass transport are as follows:

$$dA(\text{dose})/dt = -k_a \times A(\text{dose})$$

$$dA(p)/dt = k_a \times A(\text{dose}) - CL/V \times A(p)$$

$$dA(m)/dt = fm \times CL/V \times A(p) - CL(m)/V(m) \times A(m)$$

where $A(\text{dose})$ represents the amount of aripiprazole remaining to be absorbed in the gut, whereas $A(p)$ and $A(m)$ represent the amount of aripiprazole and dehydroaripiprazole in the corresponding central compartment, respectively. Since the molecular weight of dehydroaripiprazole is very close to that of aripiprazole, we used the mass unit rather than the molar unit just for convenience. Since the amount of dehydroaripiprazole converted from aripiprazole was unknown, pharmacokinetic parameters for dehydroaripiprazole such as fm , $CL(m)$, and $V(m)$ could not be estimated independently. Thus, we calculated $CL(m)$ and $V(m)$ setting fm to 1, and then the parameter estimates for $CL(m)$ and $V(m)$ were interpreted as the ratios of fm , in other words, $CL(m)/fm$ and $V(m)/fm$, respectively.

Interindividual variability on the pharmacokinetic parameter was modelled using an exponential random effect model. For instance, the clearance of aripiprazole was modelled as $CL_i = CL \times \exp(\eta_i)$, where CL_i is the clearance for individual i , CL is the typical value of clearance in the population, and η_i is a normally distributed random variable for individual i , with mean zero and variance ω^2_{CL} . Possible covariance between the variability parameters was also evaluated. A proportional error model might be sufficient to describe the residual variability for both aripiprazole and dehydroaripiprazole, since all of the concentration data were more than several times lower limit of quantification. The proportional error model is characterized by $C_{ij} = \hat{C}_{ij} \times (1 + \varepsilon_{ij})$ where $\hat{C}_{ij}$ is the j^{th} observed concentration in individual i , $\hat{C}_{ij}$ is the j^{th} predicted concentration in individual i , and ε_{ij} is a normally distributed random variable for individual i and measurement j , with mean zero and variance σ^2 .

Data were analyzed using the nonlinear mixed effect modelling software program NONMEM (version VI, level 1.0, double precision) [19]. The ADVAN6 subroutine and the first-order conditional estimation method with interaction were used. In the case of nested models, hypothesis tests were performed based on the likelihood ratio test, in which the change in objective function value (OFV) approximates the χ^2 distribution and a more complicated model was preferred when the decrease in OFV was more than 3.84 (the critical value for the χ^2 distribution at $P=0.05$ with 1 degree of freedom). The magnitude of interindividual and residual variability was expressed as a coefficient of variation (CV%), approximated by the square root of the variance estimate. Goodness-of-fit was determined by the OFV and visual inspection of the scatter plots of data against the population and individual predictions as well as against the weighted residuals.

From the pharmacokinetic estimates, we calculated the following pharmacokinetic parameters using a maximum *a posteriori* probability Bayesian method.

Metabolic ratio (MR)

$$= \frac{AUCm}{AUC} = \frac{\frac{fm \times F \times AMT}{CL(m)}}{\frac{F \times AMT}{CL}} = \frac{\frac{F}{CL(m)/fm}}{\frac{1}{CL/F}}$$

Elimination half-life for aripiprazole

$$= \frac{\ln 2 \times V}{CL} = \frac{\ln 2 \times V/F}{CL/F}$$

Elimination half-life for dehydroaripiprazole

$$= \frac{\ln 2 \times V(m)}{CL(m)} = \frac{\ln 2 \times V(m)/fm}{CL(m)/fm}$$

where AUC and AUCm are the area under the time-concentration curve of aripiprazole and dehydroaripiprazole, respectively, AMT represents aripiprazole dosage administered orally at steady state, and $\ln 2$ means the natural logarithm of 2.

Covariates

We evaluated the effects of the covariates such as age, body weight, gender, and genetic polymorphisms related to CYP2D6 and CYP3A5 for the final model. Continuous covariates were centred at the median values and were included in the model using linear relationships. For instance, the clearance of aripiprazole was modelled using $CL = \theta_1 + \theta_2 \times (\text{covariate} - \text{median})$, where θ_1 is the clearance for an individual with the median value for the covariate and θ_2 is a coefficient representing the relationship between the covariate and CL. Categorical covariates were incorporated using indicator variables. For the final model, stepwise forward addition and then backward elimination process was used. A covariate was considered significant

when the addition of this covariate resulted in a decrease in the OFV of >3.84 ($P < 0.05$) and elimination of this covariate resulted in an increase in the OFV of >6.63 ($P < 0.01$). The covariate analysis procedure was continued until only significant covariates remained in the model.

Results

Study subjects and samples

A total of 141 samples (one or two samples per patient) from 80 patients at 15 sites were collected: five and 14 samples were obtained only before and after drug administration, respectively. Fifteen patients carried two functional CYP2D6 alleles (Group I), 26 patients carried one functional allele and one partially deficient allele (Group II), 12 patients carried one functional allele and one null allele (Group III), and 27 patients were defined as IMs (Group IV). There were no patients who carried a multiplicated CYP2D6 allele or only null alleles. With regard to CYP3A5, 36 patients were CYP3A5 expressers (Group A) and 44 patients were CYP3A5 non-expressers (Group B). Statistical analysis showed that both mean age and mean body weight were not significantly different and the gender distribution did not deviate from expectations across the genotype groups (data not shown).

Pharmacokinetics

A one-compartment open model for both aripiprazole and dehydroaripiprazole adequately described the concentration data. Since the available data contained little information on the oral absorption of aripiprazole, k_a could not be estimated properly and was fixed to 1.06 h^{-1} in accordance

with previous population analysis [20]. Sparse sampling design led to the incorporation of interindividual variability (IIV) only for CL/F, V/F, and CL(m)/fm. Moreover, the addition of IIV for V(m)/fm had no influence on OFV and resulted in an unstable fit. Although correlations between IIV of CL/F, V/F, and CL(m)/fm were anticipated, the full variance-covariance model did not converge, probably due to over-parameterization. The model converged successfully when the covariance between CL/F and CL(m)/fm was assumed.

In the base model, the population typical values of CL/F and V/F were 2.37 l h^{-1} and 192 l , respectively. All population pharmacokinetic estimates are summarized in Table 3. The interindividual CV% was less than 40% for all pharmacokinetic parameters. The calculated elimination half-lives were 56.2 h for aripiprazole and 83.4 h for dehydroaripiprazole, and the MR was 0.26, given that the oral bioavailability of aripiprazole was 0.87 according to the prescribing information [2].

Covariates

The covariate analysis process is summarized in detail in Table 4. The results of stepwise forward addition showed that the age, body weight, and gender of the patient as well as CYP3A5 genetic polymorphisms did not have any influence on CL/F and/or V/F to a statistically significant extent in this population, while CYP2D6 genetic polymorphisms had a significant effect on CL/F ($P < 0.001$). The addition of this covariate decreased the OFV by 63.4 points and also reduced the interindividual CV% on CL/F from 37.8% to 30.5% (Tables 3 and 4).

The CL/F in Group I, Group II, Group III, and Group IV, classified according to CYP2D6 genetic polymorphisms,

Table 3

Population pharmacokinetic parameter estimates of aripiprazole and dehydroaripiprazole

Parameter	Base model Estimate (SE)	CV%	Final model Estimate (SE)	CV%
Aripiprazole				
CL/F (l h ⁻¹)	2.37 (0.0990)		—*	
CL/F _I (l h ⁻¹)†	—*		3.15 (0.223)	
CL/F _{II} (l h ⁻¹)†	—*		2.66 (0.119)	
CL/F _{III} (l h ⁻¹)†	—*		2.27 (0.123)	
CL/F _{IV} (l h ⁻¹)†	—*		1.83 (0.0715)	
V/F (l)	192 (11.2)		193 (11.7)	
k _a (h ⁻¹)	1.06‡		1.06‡	
ω ² _{CL/F}	0.143 (0.0281)	37.8	0.0930 (0.0174)	30.5
ω ² _{V/F}	0.0982 (0.0393)	31.3	0.100 (0.0475)	31.6
σ ²	0.00251 (0.0112)	5.0	0.00264 (0.00139)	5.1
Dehydroaripiprazole				
CL(m)/fm (l h ⁻¹)	7.90 (0.327)		8.02 (0.317)	
V(m)/fm (l)	950 (177)		587 (217)	
ω ² _{CL(m)/fm}	0.116 (0.0225)	34.1	0.113 (0.0220)	33.6
σ ² _m	0.00490 (0.000665)	7.0	0.00507 (0.000715)	7.1

*—, not applicable; †CL/F_I, CL/F_{II}, CL/F_{III}, and CL/F_{IV}, apparent clearance of aripiprazole in CYP2D6 Group I, Group II, Group III, and Group IV, respectively; ‡k_a fixed to 1.06; ω²_{CL/F}, ω²_{V/F}, and ω²_{CL(m)/fm}, IIV variance for the corresponding parameter; σ² and σ²_m, residual error variance for aripiprazole and dehydroaripiprazole, respectively.

Table 4

The model development process for population pharmacokinetics by forward addition to the base model and backward elimination from the covariate model

Hypothesis	OFV	ΔOFV	P value*
Base model	2371.84	–	–
Covariate model			
Age on CL/F	2371.61	–0.23	0.632
Age on CL(m)/fm	2371.67	–0.17	0.680
Body weight on CL/F	2370.09	–1.75	0.186
Body weight on CL(m)/fm	2369.00	–2.84	0.092
Body weight on V/F	2370.51	–1.33	0.249
Gender on CL/F	2371.77	–0.07	0.791
Gender on CL(m)/fm	2371.55	–0.29	0.590
CYP2D6 genetic polymorphisms on CL/F	2308.44	–63.40	<0.001
CYP3A5 genetic polymorphisms on CL/F	2370.15	–1.69	0.194
CYP3A5 genetic polymorphisms on CL(m)/fm	2371.29	–0.55	0.458
Final model	2308.44		

*P value calculated from the likelihood ratio test indicating the difference between the relevant model and the base model. OFV, objective function value; ΔOFV, difference of objective function value; CL/F, apparent clearance of aripiprazole; V/F, apparent distribution volume of aripiprazole; CL(m), clearance of dehydroaripiprazole; fm, the fraction of the absorbed dose of aripiprazole converted to dehydroaripiprazole.

were 3.15, 2.66, 2.27, and 1.83 l h^{–1}, respectively. Uniting Group I, Group II, and Group III to characterize the overall effect of the CYP2D6 EM did not improve the fit, with an increase of OFV by 15.8 points. The CL/F in Group IV, representing CYP2D6 IMs, was approximately 60% of that in the CYP2D6 EMs with two functional alleles. The MR was calculated at 0.34, 0.29, 0.25, and 0.20 in Group I, Group II, Group III, and Group IV, respectively.

The goodness-of-fit plots in the final model are shown in Figure 2. Weighted residuals were evenly distributed around zero with no trend, and the population prediction, especially for aripiprazole, was improved compared with the base model.

Discussion

To the best of our knowledge, this is the first combined population pharmacokinetic model for aripiprazole and dehydroaripiprazole in psychiatric patients. Although aripiprazole PK have been analyzed using a compartmental method [12, 20], dehydroaripiprazole concentrations were not included in the model building process. The proposed model in this study provided an adequate fit to the data for dehydroaripiprazole as well as for aripiprazole.

The result of covariate analysis showed that age, body weight, and gender did not have an influence on the PK

of aripiprazole and/or dehydroaripiprazole. In addition, CYP3A5 genetic polymorphism was not a significant covariate, indicating aripiprazole is a drug metabolized selectively by CYP3A4. However, it has been reported that aripiprazole PK are affected by body weight [20, 21]. The relationship between body weight and the apparent clearance and/or apparent distribution volume of aripiprazole should be cautiously interpreted since the range of body weights with a CV of 18% in this study was relatively narrow. As expected [7, 8, 13], aripiprazole PK were altered by CYP2D6 genetic polymorphisms.

The population typical value of CL/F in the base model (2.37 l h^{–1}) was lower than the mean CL/F in previous studies which ranged from 3.3 to 4.0 l h^{–1} [12, 13, 15]. This difference might be derived from ethnic differences in the distribution of CYP2D6 polymorphisms. It is well known that the CYP2D6 EM is more common in Western than Asian populations, of which the considerable proportion was made up by CYP2D6 IM [22]. Therefore, patients with the CYP2D6 EM phenotype are more likely to participate in studies conducted in Western populations. This inference was supported by the finding that the CL/F in Group I in the final model (3.15 l h^{–1}) was comparable with reported values.

The CL/F in IMs (Group IV) was lower than those in EMs (Group I, Group II, and Group III), but the plasma concentration : dose ratios of dehydroaripiprazole did not exhibit any distinctive trend in this study (Figure 3). Although several attempts have been made to study the PK of dehydroaripiprazole based on the CYP2D6 genotype, there is still room for further investigation into the exposure to dehydroaripiprazole. It is reported that the exposure to dehydroaripiprazole was lower by 30% in IMs than in EMs [7] as well as 30% lower in PMs than in EMs [2], whereas the median concentration : dose ratios of dehydroaripiprazole were similar in PMs and EMs [8]. However, only three healthy volunteers with the IM phenotype completed the single-dosing study [7], and the AUC of dehydroaripiprazole was higher in IM than in EM in the multiple-dosing study conducted by the same research group described above [13]. A possible reason for the similar AUC of dehydroaripiprazole regardless of CYP2D6 genotype is that CYP2D6 is less responsible than CYP3A4 for dehydrogenation among three metabolic pathways of aripiprazole. This inference can be supported by the finding that the concentration : dose ratio of dehydroaripiprazole in patients who were taking paroxetine or fluoxetine, the potent CYP2D6 inhibitor, was not different compared with other populations [6]. In addition, the CYP3A family is the most abundant in relative amounts found in the liver [23], and therefore considerable amounts of dehydroaripiprazole might be converted from aripiprazole by CYP3A4 in the CYP2D6 PM.

We obtained an intermediate V/F which was smaller than the reported values for the patient with a body weight of 60 kg [2, 20] and was larger than the estimate in

Figure 2

Goodness-of-fit plots of the final model for aripiprazole (left panels) and for dehydroaripiprazole (right panels). Upper, the population predicted concentration vs. observed concentration; Middle, the individual predicted concentration vs. observed concentration; Lower, the population weighted residuals vs. observed concentration. The solid line in the upper and middle panels represents the line of identity

a two-compartment model for aripiprazole [12]. As for the distribution volume of dehydroaripiprazole, the $V(m)/f_m$ in the final model was much smaller and less precise than that in the base model, implying that the typical value of $V(m)/f_m$ might be too variable to represent the entire population. A bootstrapping method might help to estimate the parameter more precisely.

The MR was in the range of 0.20 to 0.34 across CYP2D6 genetic polymorphisms, and it was in agreement with that calculated as AUC_m divided by AUC in the

healthy volunteer study [7, 13]. Assuming that the exposure to dehydroaripiprazole was not different between EMs and IMs, it is reasonable to suppose that the higher MR in EMs than in IMs resulted not from more aripiprazole being converted to dehydroaripiprazole, but from the reduced exposure to aripiprazole in EMs than IMs. The elimination half-life for aripiprazole was 25% shorter than the value in the prescribing information, but was quite similar to that estimated in the population analysis [20].

Figure 3

The plasma concentration : dose ratio for aripiprazole (left panel) and for dehydroaripiprazole (right panel). The thick horizontal mark in each group indicates the median concentration : dose ratio

A tendency was observed that the concentrations early after oral administration were underpredicted compared with the trough concentrations. This may be explained partly by model misspecification; multi-compartment models were not applied, k_a was predefined to a constant without IIV in spite of the imprecise variability reported [20], and the probability that the formation of dehydroaripiprazole occurred during oral absorption was ignored.

It has been reported that the dopamine 2 and 3 receptors were completely saturated when the concentration of aripiprazole exceeded 100–150 ng ml⁻¹ in patients [24] and 100–200 ng ml⁻¹ in healthy subjects [25], and that improvement was best in patients with a serum concentration between 150 to 300 ng ml⁻¹ [26]. However, the median concentration of aripiprazole was 413 ng ml⁻¹ in this study, and was as much as 594 ng ml⁻¹ in the CYP2D6 IMs. From the point of view of dopamine receptor occupancy, one might think that aripiprazole concentrations much higher than 300 ng ml⁻¹ do not provide additional benefit.

In conclusion, a combined population model developed here for the PK of aripiprazole and dehydroaripiprazole well described the sparse concentration data in psychiatric patients. A covariate analysis indicated that CYP2D6 genetic polymorphisms importantly contributed to the variability in the apparent clearance of aripiprazole. However, the usefulness of CYP genotyping as an aid to select starting dose should be further investigated in a larger scale study.

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