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Predicting brain occupancy from plasma levels using PET: superiority of combining pharmacokinetics with pharmacodynamics while modeling the relationship

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Positron emission tomography (PET) studies of dopamine receptor occupancy can be used to assess dosing of antipsychotics. Typically, studies of antipsychotics have applied pharmacodynamic (PD) modeling alone to characterize the relationship between antipsychotic dose and its effect on the brain. However, a limitation of this approach is that it does not account for the discrepancy between the time courses of plasma concentration and receptor occupancy by antipsychotics. Combined pharmacokinetic–PD (PK–PD) modeling, by incorporating the time dependence of occupancy, is better suited for the reliable analysis of the concentration–occupancy relationship. To determine the effect of time on the concentration–occupancy relationship as a function of analysis approach, we measured dopamine receptor occupancy after the administration of aripiprazole using [^{11}C]raclopride PET and obtained serial measurements of the plasma aripiprazole concentration in 18 volunteers. We then developed a PK–PD model for the relationship, and compared it with conventional approach (PD modeling alone). The hysteresis characteristics were observed in the competitor concentration–occupancy relationship and the value of EC_{50} was different according to the analysis approach (EC_{50} derived from PD modeling alone = 11.1 ng/mL (95% confidence interval (CI) = 10.1 to 12.1); while that derived from combined PK–PD modeling = 8.63 ng/mL (95% CI = 7.75 to 9.51)). This finding suggests that PK–PD modeling is required to obtain reliable prediction of brain occupancy by antipsychotics.
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Introduction

Characterizing the relationship between drug dose and occupancy at its site of action in the brain is important for clinical practice and drug development. In the absence of this information, patients may be treated with too low or too high a dose of drug and consequently risk receiving less than optimal treatment or experiencing unnecessary side effects. Pharmacokinetic (PK) data describe drug absorption, distribution, metabolism, and elimination, while pharmacodynamic (PD) data describe the mechanism of drug action, for example its occupancy of specific receptors. Data on both are required to understand fully the dose–response relationship of a drug (Holford and Sheiner, 1981*b*).

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Molecular neuroimaging has been used to study the dose–occupancy relationships relevant to treatment with antipsychotic drugs (de Greef *et al*, 2011; Lim *et al*, 2007) (see review articles Fischman *et al*, 2002; Howes *et al*, 2009; McGuire *et al*, 2008; Pien *et al*, 2005; Willmann *et al*, 2008). In particular, [^{11}C]raclopride positron emission tomography (PET) is a useful method for measuring dopamine receptor occupancy by antipsychotic drugs. The affinity of antipsychotic drugs for dopamine D_2 receptors closely parallels their clinical potency (Seeman and Lee, 1975), and antipsychotic dopamine D_2 receptor occupancy *in vivo* predicts both the clinical response of patients and their risk of side effects during antipsychotic treatment (Kapur *et al*, 2000). Thus, dopamine receptor occupancy is a meaningful PD biomarker for understanding the drug–receptor interaction that underlies an antipsychotic's clinical effect and predicting the likely doses needed for a given antipsychotic medication. While ultimately the dose ranges should be determined in terms of clinical response, dopamine receptor occupancy will enable the likely dose range to be determined, reducing the risk of misdosing in clinical trials.

Compartmental models have been widely used in PK studies to model how the plasma concentration of an antipsychotic drug changes over time, with good agreement between their predictions and actual observations (Kim *et al*, 2008; Locatelli *et al*, 2010; Samtani *et al*, 2009). Pharmacodynamic studies typically apply the E_{max} model to relate drug concentrations to receptor occupancy (Schoemaker *et al*, 1998); $\text{Occupancy} = E_{max} \times \text{Concentration}/(EC_{50} + \text{Concentration})$, where E_{max} is the maximum occupancy (100% of receptors occupied by drug), and EC_{50} is the drug concentration associated with 50% occupancy of dopamine receptors. The E_{max} model is based on the basic pharmacology of drug interactions with receptors and reflects a saturable process of receptor occupancy by drugs (Alvan *et al*, 1999).

While it is necessary to characterize both the PK and PD behavior of a drug to fully predict its action *in vivo* and determine its dosing (Meibohm and Derendorf, 1997), most studies of antipsychotic drugs have just applied the E_{max} model to characterize the relationship between plasma drug concentration and dopamine receptor occupancy (Grunder *et al*, 2008; Mamo *et al*, 2004; Remington *et al*, 2006; Vernaleken *et al*, 2008). This approach makes two assumptions: first that the drug concentration at the site relevant to its action rapidly reaches equilibrium with the drug concentration in plasma, and second that the effect of the drug is immediate following its arrival at the site (Holford and Sheiner, 1981*a*; Sheiner *et al*, 1979). However, these assumptions are unlikely to be valid for central nervous system active drugs such as antipsychotics, since the partitioning of the drug in plasma across the blood–brain barrier is unlikely to be instantaneous, and may be hindered by plasma protein binding of the drug (Mensch *et al*, 2010) and active processes mediated by P-glycoprotein, as appears to be the case for aripiprazole (Chen *et al*, 2004; Kirschbaum *et al*, 2010), as illustrated in Figure 1A. The delayed approach to equilibrium can have clinically important effects: for example the usual clinical doses of some antipsychotic drugs, such as amisulpride and risperidone, are higher than would be predicted from their *in vitro* pharmacology and plasma PKs because they show poor blood–brain barrier penetration and dissociation between their brain and plasma PKs (Bressan *et al*, 2004; Kapur *et al*, 2002). Furthermore, *in vivo* evidence shows that there is a discrepancy between the time courses of drug plasma concentration and antipsychotic dopamine receptor occupancy (Tauscher *et al*, 2002).

Figure 1B illustrates that applying the E_{max} model without fully modeling the PK–PD relationship can lead to marked discrepancies in estimates where there is a difference between the plasma concentration and drug occupancy curves over time. In contrast, Figures 1C and 1D illustrate that modeling the full PK–PD relationship gives a consistent relationship regardless of the time points at which the data are acquired. The analysis of the dose–time–response relationship of antipsychotic drugs thus requires simultaneous PK–PD modeling to predict first the dose–plasma concentration relationship, and then the concentration–occupancy relationship (Holford and Sheiner, 1981*a*; Sheiner *et al*, 1979). To investigate this relationship, we will first describe the development and evaluation of a PK–PD model for the particular case of treatment of healthy volunteers with aripiprazole, in conjunction with [^{11}C]raclopride PET. Second, we carry out simulations to test the effect of time on the relationship between drug concentration and dopamine receptor occupancy.

Materials and methods

This study was approved by the Institutional Review Board of Seoul National University Hospital, Seoul, Korea.

Participants

In all, 18 right-handed, healthy, male volunteers participated in the study. After complete description of the study to the subjects, written informed consent was obtained. Screening tests comprised a complete blood count, blood electrolyte analysis, urine analysis, electrocardiography, and a psychiatric interview with the Structured Clinical Interview for DSM-IV-TR Axis I disorders, Research Version, Non-patient Edition (First *et al*, 2002). Subjects with any medically significant abnormality on investigations and/or psychiatric disease were excluded. Mean (± s.d.) age, height, and body weight of the healthy volunteer group was 22.9 ± 2.4 years, 174.6 ± 4.9 cm, and 69.6 ± 6.3 kg, respectively.

Study Design

The study was conducted according to a single-blind, single oral parallel dose group design. The dose of

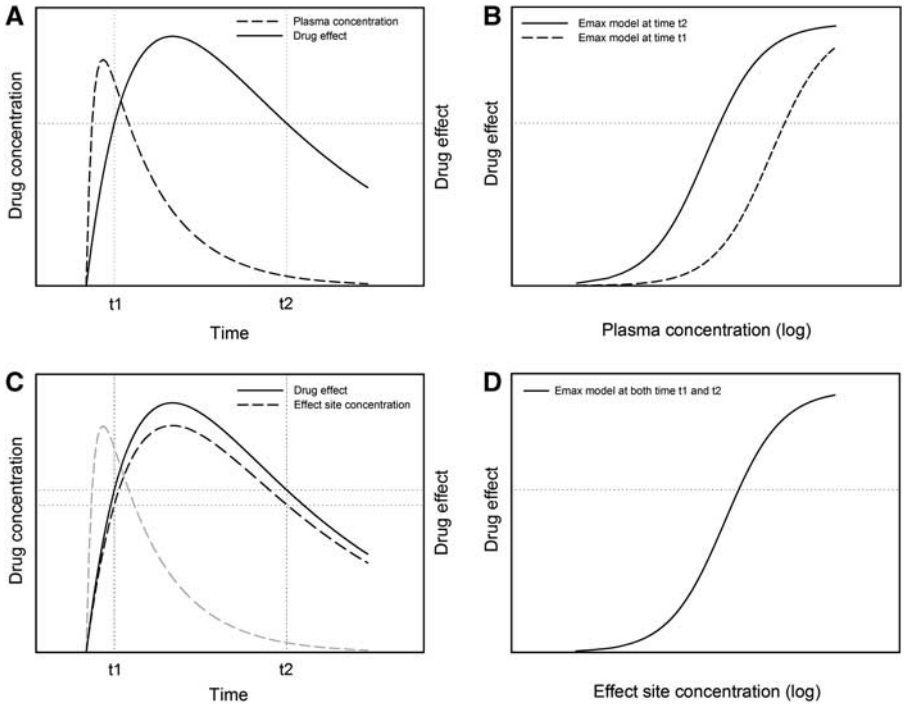

Figure 1 Schematic illustration for pharmacodynamic modeling (**A**, **B**) and pharmacokinetic–pharmacodynamic modeling (**C**, **D**). (**A**) Changes in plasma drug concentration and drug effect over time. (**B**) The difference in the concentration–effect relationship between the two time points (t1 and t2) when this relationship is modeled using pharmacodynamic model alone. (**C**) The estimation of effect compartment concentration in pharmacokinetic–pharmacodynamic modeling. (**D**) The concentration–effect relationship independent of the time point when the data are obtained.

aripiprazole was 2 mg for four subjects, 5 mg for four subjects, 10 mg for five subjects, and 30 mg for five subjects, respectively. We selected the doses that were expected to give a wide range of receptor occupancies based on published data on dopamine receptor occupancy by aripiprazole (Kegeles *et al*, 2008).

After fasting for at least 4 hours, the subjects received the randomly assigned single oral dose of aripiprazole, with 240 mL water, at 12:30 p.m. Serial blood samples for the measurement of aripiprazole plasma concentration were obtained just before and 0.5, 1, 2, 3, 5, 8, 11, 20, 24, 29, 45, 49, and 120 hours after administration of aripiprazole. Each subject had four [^{11}C]raclopride PET scans in total, performed predose and at 3, 45, and 120 hours after administration of aripiprazole. Subjects were admitted to the Clinical Trial Center, Seoul National University Hospital for the first 49 hours of the study. They returned to the Center for the final measurements. All subjects were required to abstain from caffeine or caffeine-containing products (e.g., coffee, cola, black tea, green tea, chocolate), grapefruit-containing products, alcohol, and smoking for the duration of study.

Positron Emission Tomography Scanning Procedure and Image Analysis

All PET scans were performed on an ECAT EXACT 47 scanner (Siemens-CTI, Knoxville, TN, USA). Before administration of [^{11}C]raclopride, transmission scanning was performed using three Ge-68 rod sources for attenuation correction. Dynamic 3D emission scans over 60 minutes (15 seconds $\times$ 8 frames, 30 seconds $\times$ 16, 60 seconds $\times$ 10, 240 seconds $\times$ 10) were conducted after a bolus intravenous injection of 370 to 740 mBq [^{11}C]raclopride. The acquired data were reconstructed in a $128 \times 128 \times 47$ matrix with a pixel size of $2.1 \times 2.1 \times 3.4$ mm by means of a filtered back-projection algorithm employing a Shepp–Logan filter, with a cutoff frequency of 0.3 cycles/pixel.

Magnetic resonance (MR) images were acquired on a GE Signal 1.5 T scanner. Static PET images, obtained by combining all the frames of dynamic images, were coregistered with the MR images of the same individual. The MR images were used to define the ROI (regions of interest), which comprised the striatum (putamen and caudate nucleus) and the reference region (the cerebellum). The ROIs were drawn on the subject's T1 MR images by a single rater on 10 axial slices for the striatum and cerebellum. The ROIs for the striatum were drawn covering the level of Monro's foramen (Ito *et al*, 1998). The ROI was transferred onto the dynamic PET images to obtain the time–activity curves for the whole volume of interest using the transformation parameters obtained by the coregistration of the static PET and MR images with the statistical parametric mapping software version 2 (SPM2).

The dopamine $D_{2/3}$ receptor-binding potential (BP_{ND}) in the striatum was calculated using a simplified reference tissue model (Lammertsma and Hume, 1996; Olsson and Farde, 2001).

The dopamine $D_{2/3}$ receptor occupancy by aripiprazole was calculated as the percentage reduction of BP_{ND} with drug treatment, compared with the baseline:

$$\text{Occupancy}\,(\%) = \frac{BP_{\text{ND}_{\text{baseline}}} - BP_{\text{ND}_{\text{drug}}}}{BP_{\text{ND}_{\text{baseline}}}} \times 100$$

Concentration–Occupancy Analysis

To determine the effect of time on the concentration–occupancy relationship according to the analysis approach, we analyzed the data using both PD modeling alone and PK–PD modeling.

Population Model Building : The models were built using population nonlinear mixed effects modeling with NONMEM VII, level 1.0 software (GloboMax, Ellicott City, MD, USA). Nonlinear mixed effects modeling simultaneously estimated fixed effects and random effects in the models. The fixed effects are parameters in the models such as clearance, volume of distribution, E_{max}, and EC_{50}. The random effects consist of interindividual variability and residual variability. The interindividual variability is the variability of parameters, which explains the difference between individual and population values.

The interindividual variability of the parameters was modeled using an exponential error model as follows:

$$P_i = \theta \exp(\eta_i)$$

where P_i represents the hypothetical true parameter for the i-th individual, θ is the typical population value of the parameter, and η_i is the normally distributed random interindividual variability with zero mean and variance ω^2.

The residual variability is within-subject variability or measurement error, which results in the difference between individual values from observation and prediction. Additive, proportional, and combined error models were compared to determine a model of best fit;

$$\text{Additive error model}: \; V_{ij}^{obj} = V_{ij}^{pred} + \varepsilon_{ij}^{add}$$

$$\text{Proportional error model}: \; V_{ij}^{obj} = V_{ij}^{pred} \times (1 + \varepsilon_{ij}^{pro})$$

$$\text{Combined error model}: \; V_{ij}^{obj} = V_{ij}^{pred} \times (1 + \varepsilon_{ij}^{pro}) + \varepsilon_{ij}^{add}$$

V_{ij}^{obj} is the j-th observed concentration or occupancy for the i-th individual and V_{ij}^{pred} is the j-th predicted concentration or occupancy for the i-th individual. The ε is the normally distributed residual error with mean 0 and variance σ^2. The superscripts add and pro on the ε values represent the proportional and additive errors, respectively.

The first-order conditional estimation with interaction method was used to obtain model fits. The model was developed based on hypothesis tests and goodness-of-fit. The hypothesis tests were performed based on the likelihood ratio test, in which the change in object function value (−2log likelihood) approximates the χ^2 distribution and the decrease in objective function value >3.84 (the critical value for the χ^2 distribution at $P=0.05$ with 1 degree of freedom) was required for newly added parameters to be statistically significant at $P<0.05$. Goodness-of-fit was determined by the visual inspection of the scattered plots including population and individual predictions versus observed values and the distribution of the weighted residuals over time.

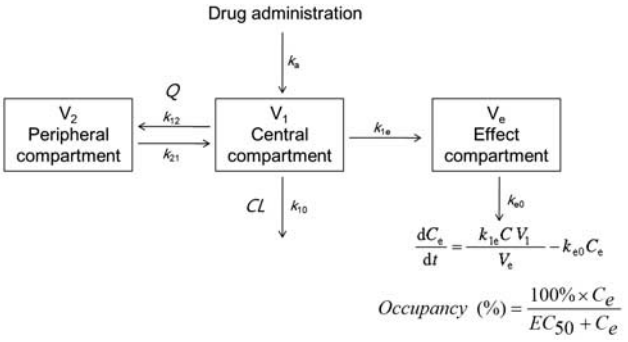

Figure 2 Pharmacokinetic–pharmacodynamic model of aripiprazole. C, drug concentration in the central compartment; C_e, drug concentration in the effect compartment; CL, apparent clearance from central compartment; EC_{50}, drug concentration needed to obtain half of E_{max}; E_{max}, maximum occupancy; k_a, absorption rate constant; k_{e0}, equilibrium rate constant; Q, intercompartmental clearance; V_1, central volume of distribution; V_2, peripheral volume of distribution; V_e, effect compartment volume of distribution.

Pharmacodynamic Modeling: The concentration–occupancy relationship was characterized using the E_{max} model as follows;

$$\text{Occupancy}\,\% = \frac{E_{\text{max}} \times C_{\text{p}}}{EC_{50} + C_{\text{p}}}$$

where E_{max} is the maximum occupancy (100% of receptors occupied by drug), EC_{50} is the drug concentration associated with 50% occupancy of dopamine receptors and C_p is the plasma drug concentration. The ADVAN6 subroutine in NONMEM and the additive error model were employed for the analysis.

Pharmacokinetic–Pharmacodynamic Modeling: To combine PKs with PDs, we used an indirect link model that included an effect compartment (Figure 2) (Sheiner *et al*, 1979). In general, the compartmental model is a conceptual framework for the interpretation of pharmacological observations. The effect compartment for a PK–PD model is a compartment for linking plasma drug concentration to the drug effect compartment when they show different time courses as appears to be the case for antipsychotic drugs. The bound compartment for conventional compartmental analysis of PET data, which should not be confused with the effect compartment in the PK–PD model, is a compartment for the analysis of ligand kinetics in the brain (Schmidt and Turkheimer, 2002). The effect compartment and the bound compartment thus derive from different conceptual framework for different observations.

The assumptions for the indirect link model were as follows: (1) the effect compartment is small enough to not have a significant impact on drug disposition so that PK

parameters are independent of PD process; (2) the effect compartment has a one-way connection with the central compartment and the input and output from the effect compartment follow the first-order kinetics; (3) the relationship between drug concentration and receptor occupancy follows the E_{max} model: $Occupancy\,\% = E_{max} \times C_e/(EC_{50} + C_e)$, where E_{max} is 100% of receptors occupied by drug, EC_{50} is drug concentration needed to obtain half of E_{max} and C_e is drug concentration in the effect compartment.

Based on the assumption, a sequential modeling approach was used for the PK–PD modeling. Population PK analysis was performed, and the individual PK parameter estimates were used in the population PD analysis.

For the population PK analysis, exploratory analyses of the time–concentration relationship were initially conducted by visually evaluating the semilogarithmic plot of plasma concentration versus time to determine the best model structure. In the compartmental approach for PK analysis, the body is viewed as being composed of so-called equilibrium compartments. Each compartment is defined as representing nonspecific body regions where the rates of drug disappearance are of a similar order of magnitude. The semilogarithmic plot showed a biphasic line, suggesting the two-compartment model with first-order absorption and elimination were the basic structural model (Figures 2 and 3). The two-compartment model consists of central compartment where the drug is rapidly distributed and peripheral compartment where slow distribution of drug is observed. The PK structural model was parameterized in terms of the first-order absorption rate constant (k_a), apparent clearance from central compartment (CL), central volume of distribution (V_1), intercompartmental clearance (Q), and peripheral volume of distribution (V_2). The differential equations to describe the rate of mass transport are as follows:

$$dA_d/dt = -k_a \times A_d$$

$$dA_1/dt = k_a \times A_d - CL/V_1 \times A_1 - Q/V_1 \times A_1$$

$$dA_2/dt = Q/V_1 \times A_1 - Q/V_2 \times A_2$$

where A_d is the amount of drug remaining to be absorbed in the gut, whereas A_1 and A_2 represent the amount of drug in central compartment and peripheral compartment, respectively. The ADVAN4 subroutine in NONMEM and the proportional error model were employed for the analysis.

To combine PK model with PDs, effect compartment was added (Figure 2). Under the assumption above, the differential equation for the amount of drug in the effect compartment can be described as follows:

$$dA_e/dt = k_{1e} \times A_1 - k_{e0} \times A_e$$

$$k_{1e} \times V_1 = k_{e0} \times V_e$$

where A_e is the amount of drug in the effect compartment, k_{1e} is the rate constant for drug transit from the central compartment to the effect compartment, k_{e0} is the equilibrium rate constant, and V_e is the volume of distribution in the effect compartment. In the model development step, incorporation of k_{e0} into PK–PD model lowered the minimum value of the objective function significantly.

The C_e at time 't' was estimated from the A_e at time 't' with a constant V_e, which is small enough to not have

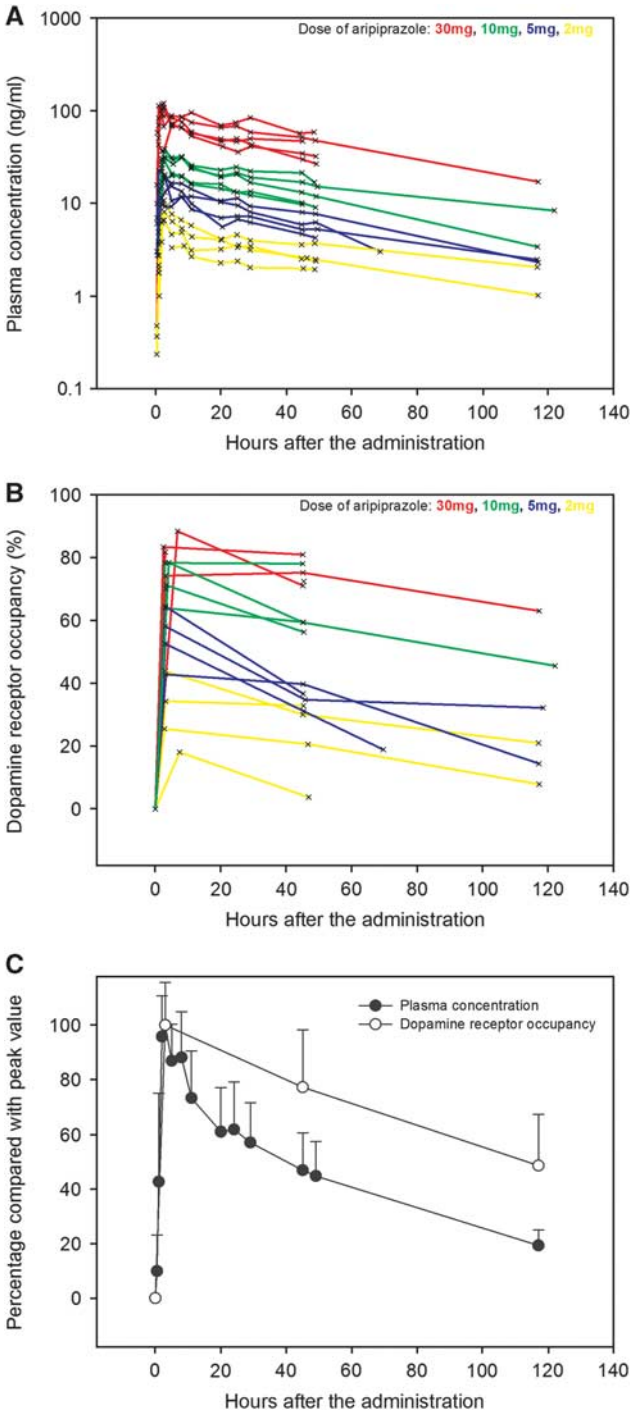

Figure 3 Plasma concentration (**A**), dopamine receptor occupancy (**B**), and normalized values of plasma concentration and dopamine receptor occupancy (**C**) versus time profiles of aripiprazole after single oral administration. Normalized value means concentration or dopamine receptor occupancy normalized to 100% of their peak value. The error bar indicates standard deviation.

significant impact on drug disposition. The calculated C_e was then incorporated into the E_{max} model. The PK–PD parameters were determined by fitting the model above to the observed plasma concentration–occupancy–time data, and the ADVAN6 subroutine in NONMEM and the additive error model for residual variability were employed for the analysis.

Simulation: To observe time effect on the concentration–occupancy relationship, we simulated individual plasma concentration of aripiprazole and dopamine receptor occupancy at the time points when plasma concentrations of aripiprazole were measured using parameter estimates from the PK–PD model as follows;

$$\text{Concentration}_i, \text{Occupancy}_i(t) = \text{PK}-\text{PD model}(P_i, t)$$

where Concentration_i and Occupancy_i are the estimated plasma concentration and receptor occupancy for the i-th individual at time 't' after the administration of aripiprazole and P_i is the hypothetical true parameter for the i-th individual.

Results

The mean value (±s.d.) of maximum observed plasma concentration (C_{max}) corrected by dose was 3.4 ± 0.9 ng/mL per mg and the mean time (±s.d.) to reach the maximum observed plasma concentration (T_{max}) was 4.0 ± 2.9 hours. The postpeak occupancies for the three different doses decline in parallel. The average elimination half-life ($t_{1/2}$) (±s.d.) calculated by noncompartmental analysis was 44.9 ± 16.8 hours (Figure 3A). The mean baseline BP_{ND} (±s.d.) was 2.0 ± 0.2 and the mean maximum dopamine receptor occupancies (±s.d.) were 30.4 ± 11.1% in the 2-mg group, 54.4 ± 9.1% in the 5-mg group, 72.3 ± 6.1% in the 10-mg group, and 81.9 ± 5.9% in the 30-mg group (Figure 3B). The different time courses of drug plasma concentration and drug dopamine receptor occupancy are shown in Figure 3C.

The estimated parameters for the PK–PD model are presented in Table 1. The fit of the relationship between drug plasma or effect site concentration and drug dopamine receptor occupancy to the E_{max} model is shown in Figure 4. The EC_{50} values in the different compartments were plasma EC_{50} = 11.1 ng/mL (95% confidence interval (CI) = 10.1 to 12.1); effect site (receptor) EC_{50} = 8.63 ng/mL (95% CI = 7.75 to 9.51). The equilibrium half-life for the effect site calculated from the equilibrium rate constant (k_{e0}) was 0.96 hours.

Figure 5 shows the simulated relationship between drug concentration and dopamine receptor occupancy. Figure 5A shows the relationship between drug plasma concentration and receptor occupancy after the single oral administration of 2 mg aripiprazole simulated using the PK–PD model. At a given drug concentration, the receptor occupancy differs according the time point when the measurements are obtained. This indicates the drug plasma concentration–receptor occupancy relationship shows hysteresis characteristics. Hysteresis is defined as 'the retardation or lagging of an effect behind the cause of the effect.' Thus, a system with hysteresis depends not only on its current environment but also on its past state. To predict the future state of the system, either its internal state or its history needs to be known. In pharmacology, rate-dependent hysteresis has been defined as 'a time delay between the observed pharmacological effect (occupancy) and the plasma drug concentration' (Pleuvry, 2008). Figure 5B shows the relationship between drug plasma concentration and dopamine receptor occupancy while Figure 5C shows the relationship between effect site concentration and dopamine receptor occupancy. As can be seen in Figures 5B and 5C, the data in plasma concentration–receptor occupancy plot appear more scattered than those in effect site concentration–receptor occupancy plot.

Discussion

This study aimed to develop a PK–PD modeling approach to determine the relationship between plasma concentration and dopamine receptor occupancy by antipsychotic drugs, and compare it with the conventional approach (PD modeling alone). Our main finding is that hysteresis characteristics were observed in the relationship between plasma concentration and dopamine receptor occupancy and, consequently, the value of EC_{50} was different depending on whether PK–PD modeling or PD modeling alone was used. This finding indicates that some of the assumptions underlying the use of PD modeling alone are not upheld and suggests that PK–PD modeling is required to obtain reliable prediction of brain dopamine receptor occupancy by antipsychotic drugs.

The EC_{50} estimated by applying the E_{max} model directly to the relationship between plasma concentration and dopamine receptor occupancy was similar to the result by Grunder *et al* (2008). However, the EC_{50} from the PD model was higher than that from PK–PD model. This may be due to the hysteresis in the relationship between plasma concentration and dopamine receptor occupancy. The high receptor occupancy can be observed shortly after the administration of aripiprazole and the low receptor occupancy can be seen long after the administration (Figure 3). This finding means the data point with high receptor occupancy by aripiprazole can be laid on the lower arm of hysteresis loop and that with low receptor occupancy can be observed in the upper arm of hysteresis loop (Figure 5A). This may cause less steep slope of E_{max} model and higher EC_{50} in the PD model.

Aripiprazole, a dopamine partial agonist, may preferentially bind to high affinity site of dopamine D_2 receptors. Thus, the receptor occupancy by

Table 1 Final model estimates of pharmacokinetic and pharmacodynamic parameters

Parameter	*Final estimate*	*RSE (%)*[a]	*95% Confidential interval*		*IIV (%)*[b]
			Lower bound	*Upper bound*	
Pharmacokinetic parameters					
CL[c] (l/h)	5.8	8.86	4.79	6.81	37.3
V_1[d] (l)	130	20.9	76.7	183	
k_a[e] (/h)	0.293	26.5	0.141	0.445	42.9
Q[f] (l/h)	37.1	8.68	30.8	43.4	
V_2[g] (l)	274	13.1	204	344	
Pharmacokinetic–pharmacodynamic parameters					
E_{max}[h]	100				
EC_{50}[i] (ng/mL)	8.63	5.2	7.75	9.51	
k_{e0}[j]	0.725	12.9	0.542	0.908	

[a]Relative standard error (RSE) of the parameter estimates from the NONMEM covariance step.
[b]Interindividual variability.
[c]Apparent clearance from central compartment.
[d]Central volume of distribution.
[e]Absorption rate constant.
[f]Intercompartmental clearance.
[g]Peripheral volume of distribution.
[h]Maximum occupancy.
[i]Drug concentration needed to obtain half of E_{max}.
[j]Equilibrium rate constant.

aripiprazole might have been different depending on the radioligand used, that is, agonist or antagonist. However, there have been reports that the receptor occupancy measured by agonist ligands like MNPA and PHNO was not different from the occupancy determined by antagonist ligands like raclopride (Peng *et al*, 2010). Both PK–PD model and PD model do not differentiate the binding of antipsychotic drugs to the high or low affinity state of the D_2 receptors. Thus, given that the value of the occupancy does not differ according to the radioligand used, our observations would not be changed by the ligand characteristics.

Hysteresis in drug plasma concentration–response relationships originates from two main reasons: limited access to the site of action or slow receptor kinetics (Pleuvry, 2008). In the case of antipsychotic drugs, some hurdles such as the brain–blood barrier and transporter molecules on the barrier can explain the limited access of drugs to the brain. The receptor kinetics of antipsychotic drugs with D_2 receptors are described by k_{on} (the rate at which drug binds to receptors) and k_{off} (the rate at which it dissociates from receptors). While the k_{on} values show relatively little variation between different antipsychotic drugs, the k_{off} values are known to vary a 1,000-fold between antipsychotic drugs (Kapur and Seeman, 2000). Thus, the area of the hysteresis loop will be different with different antipsychotic drugs- smaller for fast-off drugs and greater for slow-off or irreversible drugs. The value of k_{e0} in the PK–PD model is an explanatory parameter for the relationship between the effect compartment and PK compartment, which summarizes the effect of the factors above related with the hysteresis.

The influence of hysteresis characteristics on EC_{50} also suggests that if PD modeling is used alone, the concentration–occupancy relationship described by the model will vary according to the time points when the data are measured. For example, another study, which measured plasma concentration and receptor occupancy by aripiprazole at the times similar to ours, reported similar EC_{50} (10 ± 4(s.d.) ng/mL in putamen) (Grunder *et al*, 2008). In contrast, another study by the same group reported that a single ziprasidone dose resulted in occupancies exceeding the 95% prediction limits of the occupancy versus plasma concentrations for chronic doses, suggesting different concentration–occupancy relationship between single and chronic doses (Vernaleken *et al*, 2008). Based on this observation, they argued that single-dose studies may not be reliable for final dose selection. However, the conclusion was drawn with data obtained at different time points applying only PD modeling for the analysis of the relationship between plasma concentration and dopamine receptor occupancy. Though it is required to confirm our result in ziprasidone, our data suggest if the time effect on the relationship between plasma concentration and receptor occupancy is not taken into consideration, the data will be more scattered (as seen in Figure 5B), and thus less reliable.

The data points in Figure 4A are not as scattered as might have been expected on the basis of our argument in the introduction and as illustrated in

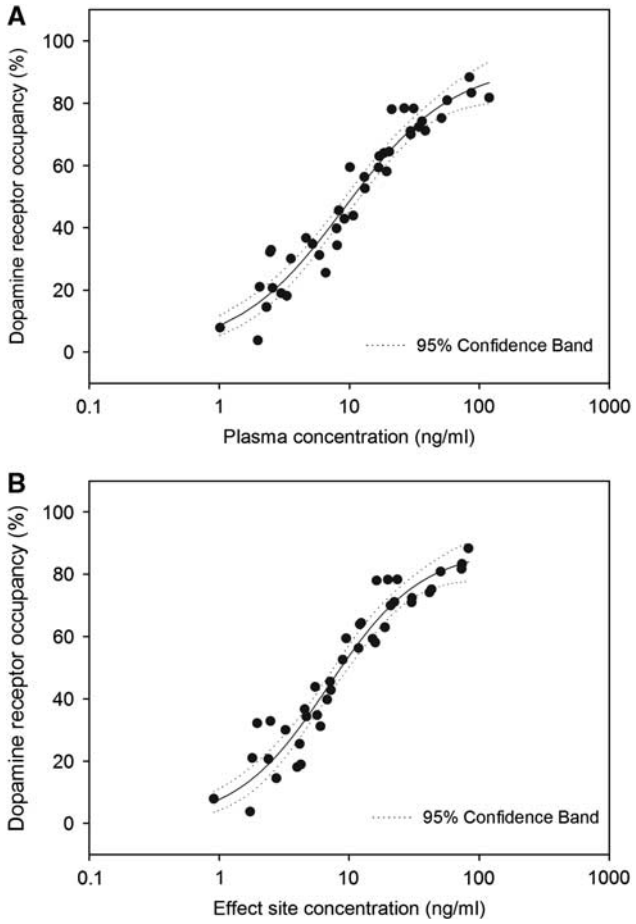

Figure 4 Aripiprazole concentration–dopamine receptor occupancy profiles in plasma (**A**) and effect site (**B**). Effect site concentrations were predicted by nonlinear mixed effects modeling.

Figure 1. In addition, the fitness of the model does not look different between PD modeling alone and PK–PD modeling (Figure 4). This unexpected lack of difference by the analysis approaches probably arises from the impossibility of obtaining PET measurements at as many time points as would be necessary to observe the hysteresis in the concentration–occupancy plot. This may be the reason why the time effect on the antipsychotic concentration–occupancy relationship has failed to draw attention of researchers. However, we can observe the time effect by plotting both concentration and occupancy data with time dimension as seen in Figure 3C or checking the varying values of EC_{50} according to the time points at which PET and plasma concentration data are acquired.

The EC_{50} value of a drug describes the relationship between drug concentration and receptor occupancy and is used to predict occupancy. Our finding that EC_{50} measured using PD modeling alone is different from that measured using full PK–PD modeling suggests that PD modeling alone is likely to be unreliable for the accurate prediction of receptor

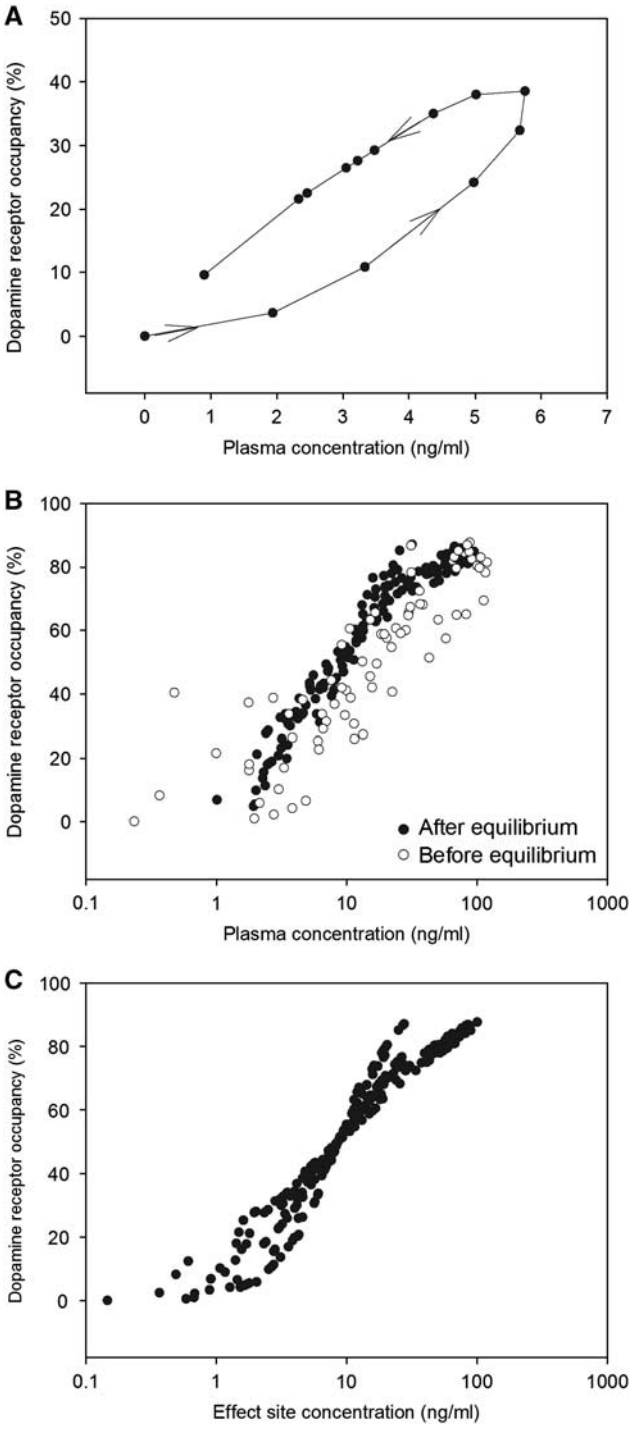

Figure 5 The relationship between aripiprazole concentration and dopamine receptor occupancy simulated based on pharmacokinetic–pharmacodynamic model. (**A**) Mean plasma aripiprazole concentration versus dopamine receptor occupancy hysteresis plot after single oral administration of 2 mg aripiprazole. The arrow indicates the direction of time course. The time points for data are 0, 0.5, 1, 2, 3, 5, 8, 11, 20, 24, 29, 45, 49, and 120 hours after the administration. (**B**) Aripiprazole concentration–dopamine receptor occupancy profile in plasma. (**C**) Aripiprazole concentration–dopamine receptor occupancy profile in effect site. The equilibrium in panel **B** indicates times required for the effect site equilibrium with plasma (equilibrium half-life $\times$ 5).

occupancy in the course of chronic treatment with antipsychotic medications. In contrast, full PK–PD modeling is likely to provide a more reliable estimate of EC_{50} that is not affected by the time points when the observations are measured. It demonstrates that the PK–PD modeling can bring more reliability and accuracy to the prediction of occupancy. Our finding is in agreement with the findings with duloxetine, where PK–PD modeling showed significantly better prediction of chronic dose occupancy from a single dose of duloxetine data than PD modeling alone (Abanades *et al*, 2011).

Figure 5B shows that greater spread of data points in the concentration–occupancy plot may be due to the data being measured before the effect site reaches equilibrium with the central compartment. After the attainment of equilibrium, the concentration–occupancy relationship appears to become stronger. However, this phenomenon cannot be generalized to all kinds of antipsychotic drugs, because it may depend on the ratio of the equilibrium half-life in the effect compartment to the elimination half-life in the central compartment. In the case of aripiprazole, the central compartment elimination half-life is 15.5 hours ($0.693 \times V_1/CL$), and the ratio is 0.06. In the case of another dopamine D_2 antagonist, YKP1358, whose concentration–occupancy relationship was previously reported using PK–PD modeling (Lim *et al*, 2007), the ratio is 0.73. The smaller ratio in the case of aripiprazole indicates that the effect compartment of aripiprazole responds more quickly to the change in the central compartment concentration. Some antipsychotic drugs with a larger ratio, such as YKP1358, do not show such a strong concentration–occupancy relationship as aripiprazole even after five times equilibrium half-life.

One potential limitation of our study is that the number of subjects at each dose is relatively small, although an advantage of this approach is that we were able to obtain serial data in the same subjects. We based the PK–PD model on data obtained after a single administration of aripiprazole. Theoretically, this model could be used to predict concentration–occupancy relationship after repeated dosing of aripiprazole, but confirmation is required that it can be applied to data acquired after multiple administration of aripiprazole.

Conclusion

Hysteresis characteristics in the relationship between plasma concentration and dopamine receptor occupancy by antipsychotic drugs can cause low reliability of the results, and PK–PD modeling approach can be more useful for exploring the relationship than PD modeling alone.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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