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in Medical Sciences (Clinical Pharmacology)

Modelling the Steady-State Brain Receptor Occupancy by Aripiprazole in Patients with Schizophrenia from a Single-Dosing Study in Healthy Volunteers

정상인에서 아리피프라졸 단회투약 자료를 이용한
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Abstract

Background: While embarked from a serendipitous discovery, antipsychotic medications antagonising brain dopamine D2 receptor (D2R) have actively been developed. Recently, compounds possessing unique pharmacodynamic (PD) properties such as D2R partial agonist aripiprazole were developed as antipsychotics. Yet, despite unmet need for newer therapeutics in psychiatry, their development has been dampened by several difficulties in clinical trials. To facilitate drug development, strategies that employ healthy volunteers instead of patients has been suggested. Since few relevant studies have been conducted, we aimed to develop and validate a model predicting steady-state D2R occupancy by aripiprazole in patients with schizophrenia using data from a single-dosing study in healthy volunteers.

Methods: Data were collected from a single-dosing study with 18 healthy volunteers which conducted serial pharmacokinetic (PK) samplings and [11C]raclopride positron emission tomography (PET) scans to obtain brain D2R occupancy after administering 2-30 mg aripiprazole. Steady-state D2R occupancy in patients with schizophrenia taking 2-30 mg aripiprazole was simulated using PK and PD parameters estimated from healthy volunteers. The simulated D2R occupancy was compared to the actual occupancy measured in 8 patients taking aripiprazole for 2 years on average, and measures to correct the difference was employed to better predict the actual occupancy.

Results: Data from the single-dosing healthy volunteer study overestimated the steady-state D2R occupancy in the patients. The discrepancy in PD response was addressed with introduction of tolerance compartment in the PD modelling.

Conclusion: The finding suggests that certain compounds such as aripiprazole behave distinctively at steady-state in patient with schizophrenia than single-dosing state in healthy individuals. The difference may be attributed to receptor internalisation and up-regulation following interaction of D2R with aripiprazole. The finding implies that although single-dosing

studies could be used to inform steady-state in patients, considerations should be given to potential change of physiology due to characteristics of each drug and pathology of each illness to predict drug response more reliably.

Keyword: Aripiprazole; Dopamine Receptors; Drug Development; Pharmacodynamics; Pharmacokinetics.

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Table of Contents

Chapter 1. Introduction

Schizophrenia and antipsychotic medications

Schizophrenia is one of the most common and debilitating psychiatric disorder with approximate lifetime prevalence of 1% (Perala et al., 2007). The disorder is characterised by distinct syndromes consisting of 'positive' symptoms, which is defined as productive symptoms including hallucinations, delusions, and disorganised speech and behaviour; and 'negative' symptoms, which represent deficits in cognitive, social, and affective functions (Kay, Opler, & Fiszbein, 1986). Also, schizophrenia often shows enduing disease course with high suicide rate and frequent recurrence accompanying self-neglect and social objectionability that leads to considerable impact on quality of life and socioeconomic burden (Robinson et al., 1999; Siris, 2001). According to the Global Burden of Disease Study 2016, schizophrenia contributed 13.4 million years of life lived with disability to burden of disease worldwide (Charlson et al., 2018). Moreover, the most recent estimate of the economic burden of schizophrenia in the United States was as much as $155.7 billion in 2013 (Cloutier et al., 2016).

Before the coming of 20th century, few clinically effective treatments for schizophrenia were available; accordingly, individuals with schizophrenia were mostly hopelessly managed with confinement in asylums, until the synthesis of the first antipsychotic medication, chlorpromazine, in 1950 (Lopez-Munoz et al., 2005). Discovered by the French pharmaceutical company Laboratoires Rhône-Poulenc, chlorpromazine was intended as a new sedative substance to be used during surgeries (Lopez-Munoz et al., 2005). However, incidental findings of calming and relaxing effect on the patients after surgery during which used chlorpromazine as a booster

anaesthetic was reported (Swazey, 1974). In 1952, a report of 38 psychotic patients treated with chlorpromazine injections described drastic improvement of aggressiveness and psychotic symptoms beyond the sedative effect (Delay & Deniker, 1955). The next few years have seen the arrival of several pharmaceuticals other than chlorpromazine, whose widespread use led to release of numerous inmates from psychiatric asylums, opening a new era of biological psychiatry (Turner, 2007).

New pharmaceutical development for schizophrenia and aripiprazole

Although first antipsychotics were discovered serendipitously, they have long proved their efficacy in treatment of schizophrenia (Leucht et al., 2013), and are already traversing the seventh decade to pursue pathophysiology of schizophrenia. The fact that the first generation antipsychotics (FGAs) act as dopamine antagonist in common led to the hypothesis that the antipsychotic efficacy may come from anti-dopaminergic properties (Carlsson & Lindqvist, 1963). Later, it was also noted that clinical potency of FGAs highly correlates with their affinity to the dopamine D2 receptor (D2R), further reinforcing the dopaminergic hypothesis postulating that schizophrenia may result from excessive dopaminergic activity in the brain (Creese, Burt, & Snyder, 1976). Thus, almost all approved antipsychotics so far have been D2R antagonists, and pharmaceutical industries have made extensive efforts to antagonise D2R (Li, Snyder, & Vanover, 2016). However, whilst the FGAs were efficacious in alleviating positive symptoms as well as in preventing recurrence (Kane, 1989), the second generation antipsychotics (SGAs) were developed to address frequent adverse effects of FGAs and their lack of efficacy for negative symptoms, mood symptoms, and cognitive impairments in schizophrenia. The SGAs were characterised by several “off-site”

targets such as serotonergic, adrenergic, cholinergic, and histaminergic receptors (Huttunen, 1995; Lieberman, 1993).

Still, SGAs as a class had debilitating adverse effects such as excessive weight gain, sedation, and increased risk for metabolic syndrome (Li et al., 2016). Advancement in basic neuroscience thereupon suggested the concept of presynaptic dopamine auto-receptors that decrease dopaminergic activity when activated (Ford, 2014). It led to the idea of deploying an agonist or partial agonist to achieve selective presynaptic activation to evoke antipsychotic effects. Hence, the newest, "dopamine stabilizer" third generation antipsychotics (TGAs) with a D2 partial agonistic property were developed, with their prototype being aripiprazole (Mailman & Murthy, 2010). Interestingly, beyond its distinctive action on D2R, aripiprazole has been shown to evoke a range of differential effects on dopaminergic signalling, gene induction, transcriptional effectors, and cellular pathways than full D2R antagonists (de Bartolomeis, Tomasetti, & Iasevoli, 2015). Following aripiprazole, D2R partial agonists such as cariprazine and brexipiprazole have been approved so far as the TGAs, changing the concept of antipsychotic action on D2R (Stahl, 2016).

Drug development and pharmacokinetic-pharmacodynamic modelling

For psychiatric disorders such as schizophrenia, advancement of clinical practice has heavily relied on the development of new pharmaceuticals (Lehman et al., 2004). However, the productiveness of new drug development is poor and the cost for development is growing especially for central nervous system (CNS) disorders over the past several years, which led to exits of large pharmaceutical companies from CNS drug development despite serious unmet clinical need (Lindsley, 2014). For example,

compared to the 13.3% approval success rate for non-CNS compounds entering clinical trial, that for CNS compounds was only 6.2%.

Given the difficulties in the new compound development, attempts have been made to facilitate the development using pharmacokinetic (PK) and pharmacodynamic (PD) techniques (Sheiner & Steimer, 2000). However, for CNS pharmaceuticals, data beyond blood concentrations of drugs are required because of the presence of blood-brain barrier (BBB) that limit and regulate passage of compounds from circulation into the CNS (Pardridge, 2005; Pien, Fischman, Thrall, & Sorensen, 2005). These days, the advent of advanced molecular imaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) allow measurement of drug action at the target site in CNS (Catafau et al., 2011). In case of medications targeting schizophrenia, candidate compounds mainly target brain D2R, whose receptor availability can be directly measured using specific radioligands including [11C]raclopride (Shin et al., 2018). Calculation of D2R occupancy by drugs has been reported to be a useful biomarker which predicts not only clinical response but also emergence of adverse effects from medications (Kapur, Zipursky, Jones, Remington, & Houle, 2000).

However, U.S. Food and Drug Administration (FDA) recently reported 22 case studies where drugs failed in phase 3 due to their divergent results from phase 2 (Administration, 2017). Surprisingly, in some cases, short-term results found in phase 2 trials would not translate into long-term benefits in phase 3 trials, or unexpected toxicity from phase 2 trial would be uncovered in phase 3 trials: The report suggests the complexity of interactions between a medication and the patient (Administration, 2017). Moreover, for psychiatric disorders such as schizophrenia, recruiting patients to

clinical trials is particularly challenging due to ethical issues of vulnerable population and their psychiatric symptoms, making the drug development even more demanding and costly. Yet, few studies address this issue with psychotropic medications and additional work therefore is guaranteed in this area.

Since recruiting patients with mental illnesses is particularly challenging and because measuring target site occupancy in CNS may be useful in informing appropriate dose and dosing schedule (Arakawa et al., 2008; Vernaleken et al., 2008), conducting some early phases of clinical trials with healthy volunteers instead of patients has been suggested (Kim, Howes, Kim, et al., 2011). This would have benefits in that healthy volunteers are relatively easier to recruit than the patients and that they are free from factors complicating pharmacometrics analyses such as existing medications which should be washed out before the study and change in physiology due to illnesses. However, while healthy volunteer studies are usually conducted with single-dosing design, patients would take the medication chronically, which may result in change of bodily physiology such as receptor down-regulation or tolerance development in response to medications (Poulos & Cappell, 1991; Schrader et al., 2019). Also, despite limited evidence suggesting that healthy individuals and patients with schizophrenia may have similar PD profiles (Arakawa et al., 2010; Kim, Howes, Kim, et al., 2011), little is known about differences of drug behaviour between patients and healthy individuals, between single versus chronic dosing schedule, or among various drugs.

Objectives

Therefore, this study sought to determine if pharmacometric estimates of an atypical antipsychotic, aripiprazole, derived from a single-dosing healthy volunteer study could

predict the steady-state brain D2R occupancy in patients with schizophrenia. This study hypothesised that PK/PD model derived from a single-dosing study with healthy volunteers may not adequately predict brain D2R occupancy at steady-state in patients with schizophrenia.

Hence, plasma aripiprazole concentration and brain D2R occupancy at steady-state were simulated using PK/PD parameter estimates from a single-dosing study: The simulated D2R occupancy was then compared to the actual D2R occupancy calculated with [11C]raclopride PET scans in patients with schizophrenia who have been continuously taking aripiprazole. If the simulated D2R occupancy was different from the actual data, this study aimed to implement additional steps to predict the steady-state occupancy in patients with schizophrenia.

Chapter 2. Methods

Participants

Data of 18 healthy volunteers were retrospectively collected from a previous study which measured plasma drug level by serial pharmacokinetic samplings just before and 0.5, 1, 2, 3, 5, 8, 11, 20, 24, 29, 45, 49 and 120 hours after a single oral administration of aripiprazole (Kim et al., 2012). Doses of aripiprazole were either 2, 5, 10, or 30 mg; and striatal D2R binding potential (BP) was measured serially at predose, 3, 45, and 120 hours after aripiprazole administration using [11C]raclopride PET.

Additionally, the data for validation were also collected retrospectively from another study with 8 patients with schizophrenia from where the patients had been given long-term prescription with aripiprazole at various dosage: Striatal D2R BP were determined with [11C]raclopride PET at 2, 26, and 74 hours after the last aripiprazole administration and plasma aripiprazole concentration was measured within 5 minutes before each PET scan (Shin et al., 2018). The patients were on treatment with aripiprazole for at least 10 weeks and thus were expected to be in steady-state.

Positron emission tomography scanning and image analysis

All PET images were scanned on an ECAT EXACT 47 scanner (Siemens-CTI, Knoxville, TN, USA). Before injection of [11C]raclopride, transmission scanning was done using three Ge-68 rod sources for attenuation correction. Dynamic 3D emission scans over 60 minutes (15 seconds × 8 frames, 30 seconds × 16, 60 seconds × 10, 240 seconds × 10) were performed after a bolus intravenous administration of 370 to 740

mBq of [11C]raclopride. The scanned data were reconstructed in 128 × 128 × 47 matrix with a pixel size of 2.1 × 2.1 × 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 scanned on a GE Signal 1.5T scanner. Static PET images, obtained by combining all the frames of dynamic images, were co-registered with the MR images of the same individual to define regions of interest (ROI). The ROIs included striatum and the reference region, cerebellum, which were manually drawn by a single rater on 10 axial slices for both striatum and cerebellum. The ROIs were transferred onto the dynamic PET images to obtain the time-activity curves for the whole volume of interest using the parameters obtained by the co-registration of static PET and MR images with the Statistical Parametric Mapping software version 2 (SPM2).

The D2R binding potential (BP_{ND}) in the striatum was calculated using the simplified reference tissue model (SRTM) (Lammertsma & Hume, 1996). Then, the D2R occupancy by aripiprazole was calculated as the percentage reduction of BP_{ND} with drug treatment, compared with baseline binding potential (BP_0) at drug-free condition.

$$Occupancy\ (\%) = \frac{BP_0 - BP_{ND}}{BP_0} \times 100$$

For calculation of D2R occupancy by aripiprazole in patients with schizophrenia whose BP_0 was unknown since the patients were on aripiprazole treatment for months or years before the PET scans, BP_0 was estimated using the inhibitory E_{max} (I_{max}) model as previously described (Kim, Howes, Yu, et al., 2011; Lee et al., 2018). The measured BP after administration of aripiprazole was assumed to follow the I_{max} model below:

$$BP = BP_0 - \frac{I_{max} \times C^{\gamma}}{IC_{50}^{\gamma} + C^{\gamma}}$$

where I_{max} being the maximum inhibitory effect of aripiprazole on BP, C being plasma aripiprazole concentration, γ being the Hill coefficient, and IC_{50} being the aripiprazole concentration at which 50% of the maximum inhibitory effect is produced.

Pharmacokinetic-pharmacodynamic modelling and simulation

The models were built using population nonlinear mixed effects modelling with NONMEM 7.4.4 software (ICON plc, Dublin, Ireland). Nonlinear mixed effects modelling estimates both fixed effects and random effects in the models. The fixed effects are the parameters in models such as clearance (CL), volume of distribution (V), the maximum effect (E_{max}), and the drug concentration associated with half the maximum effect (EC_{50}); and the random effects include interindividual variability and residual variability. The first-order conditional estimation with interaction method was used to obtain model fits. A likelihood ratio test, graphical evaluation, and visual predictive checks (VPCs) were used to evaluate the goodness of fit of the models.

A sequential modelling approach was used to estimate PK and PD parameters from the healthy volunteer data: Population PK modelling was first done and then derived individual PK parameter estimates were applied in following population PD analysis. An effect compartment (link) model was used to build the PD model. The effect compartment is a compartment at a hypothetical effect site reflecting different time-concentration relationship than plasma, which is the case for many antipsychotics that cross BBB (Pardridge, 2005). Assumptions for the effect compartment postulate that

the volume of effect compartment (V_e) is small enough to not have a significant impact on drug distribution.

In the PK analysis, the semilogarithmic plasma concentration-time curve was visually inspected to determine the best PK model structure. The 2-compartment model consisting of central and peripheral compartments was selected (Figure 1). Then, to combine PK and PD modelling, the effect compartment was added to calculate the drug concentration in effect compartment. Plasma concentration of aripiprazole in effect compartment (C_e) was then applied to the E_{max} model to estimate PD parameters as below:

$$Occupancy = \frac{E_{max} \times C_e^{\gamma}}{EC_{50}^{\gamma} + C_e^{\gamma}}$$

where E_{max} being the maximum D2R occupancy by aripiprazole, C_e being aripiprazole concentration at effect compartment, γ being the Hill coefficient, and EC_{50} being the aripiprazole concentration at effect compartment at which 50% of the maximum occupancy is produced.

Simulation of striatal D2R occupancy was conducted using Trial Simulator 2.3 (Certara, Princeton, NJ, USA). A simulation scenario using the PK and PD parameters derived from the above analyses was designed (Figure 2). Then, simulated 95 percent confidence interval of D2R occupancy was compared to the actual D2R occupancy calculated in the patients with schizophrenia.

Chapter 3. Results

Demographic data

Eighteen healthy volunteers were all males, and their mean (± SD) age was 22.9 (± 2.4) years. They took a single dose of either 2, 5, 10, or 30 mg of aripiprazole (n = 4, 4, 5, and 5, respectively).

Among 8 patients with schizophrenia, 2 of them were males, and their mean age was 32.4 (± 8.6) years. The mean aripiprazole dose was 12.4 (± 10.7) mg and ranged from 2 to 30 mg with the dosage fixed for at least 10 weeks. The duration during which the patients have taken aripiprazole ranged from 10 weeks to 6 years. The summary of demographic data for both groups is given in Table 1.

PK analysis results from healthy volunteers

The plasma aripiprazole concentrations in healthy volunteers were best described by a two-compartment model with first order elimination kinetics. The interindividual variability (IIV) was modelled exponentially to the CL, K_a, and V_c. The proportional error model best fitted the residual variability. Goodness-of-fit plots and VPC results are shown in Figure 3 and Figure 4, respectively.

Table 2 shows PK parameters derived from healthy volunteers. The typical value of CL, K_a, V_c, V_p, and Q were 5.75 L/hr, 0.358 /hr, 158 L, 256 L, and 36.9 L/hr, respectively. The IIV (coefficient of variation, %) of CL, K_a, and V_c were 34.1, 40.7, and 27.0, respectively.

PD analysis results from healthy volunteers

The D2R occupancy by aripiprazole was fitted with an effect compartment model where concentration of aripiprazole at effect site was incorporated into the E_{max} model. The volume of effect compartment was set as 0.000001 L. The IIV was modelled exponentially to the EC_{50}. The additive error model best described the residual variability. Goodness-of-fit plots and VPC results are shown in Figure 5 and Figure 6, respectively.

Table 2 shows PD parameter estimates from the healthy volunteer data. The typical value of E_{max}, EC_{50}, γ, and equilibrium rate constant of effect compartment (K_e) were 90%, 7.42 ng/mL, 1.11, and 0.889 L/hr, respectively. The IIV (coefficient of variation, %) of EC_{50} was 20.0.

Simulation of steady-state D2R occupancy in patients

The PK-PD parameter estimates from healthy volunteer data were used for the simulation to predict D2R occupancy by aripiprazole at steady-state. The simulation scenario included administration of aripiprazole once daily at 8 a.m. for 30 days, measurement of plasma aripiprazole concentration and D2R occupancy at predose and 1, 2, 3, 5, 8, 11, and 24 hours after the first administration: and then 0, 1, 2, 3, 5, 8, 11, 24, 36, 48, 60, and 72 hours after the last administration at day 30. The subjects were allocated 1:1:1:1:1:1 to aripiprazole 2, 2.5, 5, 10, 25, and 30 mg. Replication in 100 subjects per study and 10 studies resulted in the total number of subjects of 1,000.

The simulated results relatively well reflected the healthy volunteer data on which the simulation was based. Comparisons of actual data in healthy volunteers and predicted plasma aripiprazole concentrations and D2R occupancy by simulation are shown in Figure 7 and Figure 8, respectively.

However, the simulated results did not adequately predict the steady-state plasma concentration or D2R occupancy in patients with schizophrenia. Figure 9 and Figure 10 compare actual steady-state plasma aripiprazole concentrations in patients with schizophrenia and predicted steady-state plasma aripiprazole concentrations simulated with healthy volunteer data. Plasma aripiprazole concentration was shown to be largely underestimated by the simulation. Figure 11 and Figure 12 show contrast of actual steady-state striatal D2R occupancy following chronic administration of aripiprazole in patients with schizophrenia and predicted steady-state striatal D2R occupancy simulated with healthy volunteer data. Overestimation of striatal D2R occupancy was noted especially in subjects taking higher doses of aripiprazole.

Development of the model fitting steady-state D2R occupancy in patients

Since the calculated striatal D2R occupancy in patients in schizophrenia were overestimated and the steady-state occupancy in some patients turned out to be contradictorily lower than that of healthy individuals who took aripiprazole of the same dosage only once, PD models reflecting build-up of delayed tolerance were developed. To develop a PD model fitting both D2R occupancy right after the initial dosing and that at the steady-state, the data from healthy volunteers and those from patients were pooled. PD models implementing hypothetical non-competitive antagonist (Porchet, Benowitz, & Sheiner, 1988) or turnover models to account for development of tolerance

failed to fit the data mainly because of the immediate manifestation of tolerance in those models. Hence, a model implementing a hypothetical tolerance compartment connected to an effect compartment was built to resolve the delayed occurrence of tolerance (Figure 13). The distribution volume of effect and tolerance compartments were both set as 0.000001 L. Also, to avoid over-parametrization, Emax and γ were fixed at 100% and 1, respectively. The IIV was modelled exponentially to the I_{max} and EC_{50}. The proportional error model best fitted the residual variability. Goodness-of-fit plots and VPC results are shown in Figure 14 and Figure 15, respectively.

Table 3 shows PD parameter estimates from the pooled data using the tolerance PD model. The typical value of I_{max}, EC_{50}, IC_{50}, K_e, and equilibrium rate constant of tolerance compartment (K_{tol}) were 28.5%, 5.48 ng/mL, 5.07 ng/mL, 0.306 L/hr, and 0.0187 L/hr, respectively. The IIV (coefficient of variation, %) of Imax and IC_{50} was 26.9 and 45.5.

Chapter 4. Discussion

Summary

The findings show that PK parameters derived from a single-dosing study with 18 volunteers underestimated plasma aripiprazole concentration at steady-state in patients with schizophrenia, while PD parameters from a single-dosing study with the healthy volunteers largely overestimated striatal D2R occupancy at steady-state in patients with schizophrenia. The discrepancy of striatal D2R occupancy between observed values and predicted values were addressed by implementation of tolerance compartment in the PD model.

Prediction of plasma aripiprazole concentration

Aripiprazole is known to have high PK variability: In terms of concentration/dose (C/D) ratios, individual C/D ratios are reported to be as divergent as 37-fold for aripiprazole and 78-fold for its active metabolite, i.e., dehydroaripiprazole (Molden, Lunde, Lunder, & Refsum, 2006). The PK variability is not reported to be dependent on dosage or sex, but on the metabolism of aripiprazole involving enzymes CYP2D6 or CYP3A4 (Jukic, Smith, Haslemo, Molden, & Ingelman-Sundberg, 2019; Molden et al., 2006). Aripiprazole is mainly metabolized by CYP3A4 and CYP2D6 into dehydroaripiprazole and several other metabolites (Kubo et al., 2005). Then, dehydroaripiprazole is metabolized only by CYP3A4 and CYP2D6, and its metabolites are excreted into urine or faeces (Kubo, Koue, Maune, Fukuda, & Azuma, 2007). While the activity of CYP3A4 is not so affected by genotypes, reports describe up to 60%

higher exposure in individuals with specific CYP2D6 genotypes (Otsuka Pharmaceutical Co., 2014), or as large as 50% reduction of clearance by CYP2D6 inhibitors (Kubo et al., 2005). In addition, aripiprazole is not reported to have time-dependent PK (Otsuka Pharmaceutical Co., 2014). While some previous studies estimated that simulated steady-state aripiprazole concentration at 30 mg dose would range around 300-400 ng/mL (Salzman, Raoufinia, Legacy, Such, & Eramo, 2017), there were studies reporting steady-state aripiprazole concentration exceeding 1,000 ng/mL (Grunder et al., 2008).

The data of present study also shows no definite correlation between plasma aripiprazole concentration and demographic variables such as sex or gender. Given that genotypes of the enzymes responsible for metabolism of aripiprazole was not available in this study and that the current study was not able to adequately predict the steady-state plasma aripiprazole concentration, it would be suggested that predicting steady-state plasma concentration of a specific patient may not be possible from a single-dosing study if there is not enough relevant information regarding PK of the drug, especially CYP2D6 genotypes for aripiprazole.

Prediction of striatal D2R occupancy

Generally, aripiprazole has been known to completely saturate (~100%) D2Rs at plasma concentrations higher than 100-200 ng/mL in both healthy individuals and patients with schizophrenia (de Bartolomeis et al., 2015), without causing apparent extrapyramidal side effects (EPS) despite exceptionally high D2R occupancy when compared to other antipsychotics (Yokoi et al., 2002). However, mainly because of the hurdles related to performing PET or SPECT scans, there are limited studies reporting

or comparing brain D2R occupancy after a single dose and/or at steady-state. Some studies reported steady-state striatal D2R occupancy in patients with schizophrenia calculated by using BP_0, the baseline BP without medication, measured from unmedicated healthy controls: two study reported very high striatal D2R occupancy ranging 81-99% following sub-chronic 2-week administration of 10-30 mg aripiprazole (Mamo et al., 2007; Mizrahi et al., 2009). Another study reported steady-state striatal D2R occupancy in healthy individuals following 2 weeks of administration of 30mg aripiprazole resulting in 92.3% measured with [11C]raclopride PET (Yokoi et al., 2002). Some other reports were available which used a different radioligand, [18F]fallypride, reporting 50-94% striatal D2R occupancy after 4-week treatment with 5-30 mg aripiprazole calculated using BP_0 measured in other drug-free patients with schizophrenia (Grunder et al., 2008), and reporting 71-96% D2R occupancy in patients taking 2-40 mg aripiprazole for at least 10 days (Kegeles et al., 2008).

Whilst the studies above reported D2R occupancy following sub-chronic administration of aripiprazole or calculated the occupancy using the BP_0 from healthy controls, the current data presents notably lower striatal D2R occupancy below 80% following chronic administration of aripiprazole of 2 years on average, which falls between the therapeutic window of 60-80% D2R occupancy for antipsychotics (Grunder, Carlsson, & Wong, 2003). When predicted using the data from healthy volunteers, D2R occupancies in steady-state were much higher than the threshold at which would provoke EPS, even regarding relatively lower plasma concentrations in healthy volunteers.

Development of a model using the concept of tolerance

In the current study, to predict observed steady-state D2R occupancy in patients, a PD model reflecting delayed development of tolerance to occupancy by aripiprazole was implemented. However, the development of "tolerance" following chronic administration of aripiprazole should be translated with caution: it would not be precise to interpret as that a patient develops tolerance to aripiprazole in a psychological sense. This concept of pharmacodynamical "tolerance" would encompass mechanisms possibly lowering steady-state D2R occupancy compared to the acute phase. Rather, it would be more appropriate to assume this concept of pharmacodynamical "tolerance" would encompass mechanisms possibly lowering the pharmacological effect, D2R occupancy, following chronic administration of aripiprazole due to certain reasons.

These reasons for the divergence between observed and predicted D2R occupancy following chronic administration of aripiprazole could be attributed to several aspects: First, BP_0 or D2R availability would be different in healthy individuals and patients with schizophrenia. At the "baseline" state without medications, the receptors are not vacant but are occupied by endogenous ligands. Occupancy of D2R by endogenous dopamine in schizophrenia was reported to be around 19% whilst that in healthy individuals is approximately 9% (Abi-Dargham et al., 2000). Also, a meta-analysis revealed that patients with schizophrenia have a small (12%) elevation of striatal D2R (Frankle, 2007) and the findings were replicated in unmedicated first-episode psychosis patients as well (Corripio et al., 2011). However, in this study, estimation of unmedicated BP_0 in the patients using the I_{max} model may have largely addressed this facet (Kim, Howes, Yu, et al., 2011). Second, it is possible that long-term administration of antipsychotics may evoke D2R up-regulation at the steady-state, resulting in the elevation of apparent BP_0 following chronic administration. There is an evidence from an animal study that chronic treatment with antipsychotics evokes

dopamine D2/3 receptor up-regulation in animal studies (Burt, Creese, & Snyder, 1977), as well as in human studies (Silvestri et al., 2000). Third, there is a chance that acute administration of aripiprazole brings about overestimation of D2R occupancy. There is a report of human study showing stimulation of dopaminergic transmission in striatum after acute haloperidol challenge, which leads to elevation of endogenous dopamine level and overestimation of receptor occupancy due to reduction of apparent BP_0 after acute administration (Vernaleken et al., 2006). Lastly, there could be down-regulation mechanism such as D2R remodelling or internalisation following acute administration of aripiprazole which would lead to overestimation of D2R occupancy owing to reduced D2R availability in the acute phase. G-protein coupled receptors including dopamine D2 receptor is subject to bountiful of regulatory processes, particularly following activation by an agonist to down-regulate the receptor activity after repeated or prolonged exposure to stimuli (Bohm, Grady, & Bunnett, 1997). Those regulatory mechanisms for desensitisation include decoupling from G-proteins, receptor phosphorylation, and receptor internalisation by endocytosis (Ferguson, 2001). Among these, D2 receptor internalisation by agonists is reported to happen on about 58% of the receptors following agonist treatment in about 5 minutes (Guo et al., 2010). These processes such as receptor internalisation can significantly influence cellular responses to medications and aripiprazole, a dopamine D2 partial agonist, is shown to potently induce receptor internalisation, specifically D2S receptor isoform, up to 52% under certain circumstances among antipsychotic medications (Heusler, Newman-Tancredi, Loock, & Cussac, 2008). It is also notable that there is a study reporting aripiprazole not significantly internalising the other isoform of D2 receptor, D2L receptor (Urban, Vargas, von Zastrow, & Mailman, 2007), whereas another study reports that aripiprazole potentiates internalisation process of D2L in 24 hours (Schrader et al.,

2019). There are reports showing that the radioligand raclopride can bind to the internalised D2R, but to the 2.1-fold less degree than to D2R on cell surface (Guo et al., 2010; Sun, Ginovart, Ko, Seeman, & Kapur, 2003). So, there has been speculations that, if aripiprazole induced D2R internalisation, BP would be underestimated due to lower apparent receptor availability, hence D2R occupancy would be overestimated than the "true" occupancy by the drug (Yokoi et al., 2002).

When addressing the difference of D2R occupancy between acute and chronic phase, an alternate model than one using the concept of tolerance, such as a model fitting "dynamic BP_0", could be developed where the BP_0 changes along time and is set as a dependent variable. This approach could be more physiologically plausible since the delayed development of observed tolerance would likely arise from the alteration of D2R availability, or BP_0. Still, the approach was inapplicable because if BP_0 is assumed to change over time, an assumption that D2R occupancy is known at certain time points should be made to estimate "dynamic BP_0". However, D2R occupancy is not directly measurable from PET scans. Also, assuming that D2R occupancy calculated from either the healthy volunteer data or the patient data reflects true occupancy may pose a significant risk of bias. Hence, a model incorporating the concept of tolerance as described above might best interpret the data in this study. For instance, from the tolerance model, it could be implied from much lower estimate of K_{tol} compared to K_e that the process of tolerance development would require considerable time following chronic administration.

Interestingly, similar phenomena were also reported for other antipsychotic, ziprasidone. Subchronic administration of ziprasidone 40-160 mg/day in patients with schizophrenia for 3 weeks resulted in D2R occupancy of 10-73% (mean 56%) using

BP_0 from healthy controls (Mamo et al., 2004), whereas in the other study 85% of D2R occupancy after a single 60 mg dose of ziprasidone had been shown, revealing unexpectedly higher occupancy (Bench et al., 1993). The other study compared patients with schizophrenia taking 80-200 mg/day of ziprasidone for at least 1 week and healthy controls who took a single 40 mg dose of ziprasidone. Whilst healthy volunteers after a single dose of ziprasidone 40 mg showed 59-75% dopamine D2 receptor occupancy, the patients taking 80-200 mg/day at steady-state ziprasidone showed unexpectedly lower 22-84% D2R occupancy (Vernaleken et al., 2008). It was noted that ziprasidone, shows low hydrophilicity as of aripiprazole, and has active uptake mechanism (Summerfield et al., 2007). Also, although not directly comparable, a review of D2R occupancy in patients receiving long-acting injectable forms of various antipsychotics, who would have taken the medication chronically, revealed rather low mean D2R occupancy of 65%, implying possibility of similar phenomenon on other antipsychotics as well (Uchida & Suzuki, 2014). Vernaleken et al. suggested that in case of medications with peculiar pharmacological characteristics, a single-dose study may be not sufficient to predict steady-state pharmacodynamics (Vernaleken et al., 2008). Taken together, the findings of this study provide insight for prediction of efficacy of investigational drugs in patients: Building a prediction model for novel medications may benefit from integration of data from healthy volunteer studies as well as those from in vitro studies.

Limitations and strengths

This study has several limitations. First, this study only investigated a single compound, which is an antipsychotic aripiprazole. Although aripiprazole would be of

interest since it possesses unique mechanisms of action, more studies with diverse compounds acting on CNS is guaranteed to generalise the finding from this study and to bolster other classes of medication than antipsychotics. Second, this study did not include analysis nor provided prediction of concentration of the active metabolite of aripiprazole, dehydroaripiprazole. Third, given a relative lack of diversity in the sample, such as the healthy volunteers who were mostly consisted of young male individuals, there is a possibility that the sample may not represent population having diverse covariate status including CYP2D6 genotypes, which is unknown in the present sample. Future studies with larger samples would further enrich the findings. Lastly, while this study could implement a tolerance PD model to account for lower D2R occupancy at steady-state, the present study does not clarify the mechanism by which the occupancy differs according to time nor is able to determine whether when and how D2R availability is altered. Future in vitro and in vivo studies examining the behaviour of D2R at various timeframe (i.e., acute, subchronic, and chronic phase) are therefore recommended.

These limitations notwithstanding, this study comes with several strengths. This thesis is the first comprehensive investigation of in vivo D2R occupancy in both acute phase and steady-state and both healthy individuals and patients with schizophrenia. Also, the present data were obtained at the same institution with the same instruments, minimising the probability of bias in data. Furthermore, compared to other studies using the substitution method to calculate steady-state occupancy that assumes the BP_0 is similar between healthy individuals and patients, this study employed modelling approach which would be more robust in estimating unmedicated BP_0 in patients, more robustly reflecting distinct BP_0 in patients with schizophrenia.

Chapter 5. Conclusion

The finding suggests that certain compounds such as aripiprazole behave distinctively at steady-state in patient with schizophrenia than single-dosing state in healthy individuals. The difference may be attributed to receptor internalisation and up-regulation following interaction of D2R with aripiprazole. The finding implies that although single-dosing studies could be used to inform steady-state in patients, considerations should be given to potential change of physiology due to characteristics of each drug and pathology of each illness to predict drug response more reliably.

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Tables

Table 1. Demographic characteristics of the participants

	Healthy volunteers (n = 18)	Patients with SZ (n = 8)	*P* value
Age (yr)	22.9 (2.4)	32.4 (8.6)	< .001
Sex (male %)	100	25	< .001
Weight (kg)	69.6 (6.3)	63.9 (14.6)	.089
Aripiprazole dose (mg)	12.7 (11.4)	12.5 (10.6)	.984
Duration on aripiprazole (months)	-	25.2 (27.1)	-

Abbreviations: SZ, schizophrenia.
Displayed in mean (SD).
Mann-Whitney U test for age, weight, aripiprazole dose; Fisher's exact test for sex.

Table 2. Pharmacokinetic and pharmacodynamic parameters derived from healthy volunteers

Parameters	Estimates	RSE (%)	IIV	RSE (%)
Pharmacokinetic parameters				
CL (L/hr)	5.75	9	34.1	26
K_a (/hr)	0.358	20	40.7	33
V_c (L)	158	19	27.0	121
V_p (L)	256	10	-	-
Q (L/hr)	36.9	12	-	-
Proportional residual error	0.285	5	-	-
Pharmacodynamic parameters				
E_{max} (%)	90.0	5	-	-
EC_{50} (ng/mL)	7.42	11	20	29
γ	1.11	16	-	-
K_e (L/hr)	0.889	24	-	-
Additive residual error	5.46	17	-	-

Abbreviations: RSE, relative standard error; IIV, interindividual variability (coefficient of variation, %); CL, clearance; K_a, absorption rate constant; V_c, volume of distribution of central compartment; V_p, volume of distribution of peripheral compartment; Q, intercompartmental clearance; E_{max}, the maximum occupancy; EC_{50}, drug concentration at which drug shows efficacy of half of E_{max}; γ, the Hill coefficient; K_e, equilibrium rate constant of effect compartment.

Table 3. Pharmacodynamic parameters derived from pooled data using the tolerance model

Parameters	Estimates	RSE (%)	IIV	RSE (%)
E_{max} (%)	100	-	-	-
I_{max} (%)	28.5	14	26.9	104
EC_{50} (ng/mL)	5.48	25	45.5	49
IC_{50} (ng/mL)	5.07	45	-	-
K_e	0.306	24	-	-
K_{tol}	0.0187	111	-	-
Proportional residual error	0.011	61	-	-

Abbreviations: RSE, relative standard error; IIV, interindividual variability (coefficient of variation, %); E_{max}, the maximum occupancy; I_{max}, the maximum inhibitory effect on occupancy; EC_{50}, drug concentration at which drug shows efficacy of half of E_{max}; IC_{50}, drug concentration at which drug shows inhibitory efficacy of half of I_{max}; K_e, equilibrium rate constant of effect compartment; K_{tol}, equilibrium rate constant of tolerance compartment.

Figures

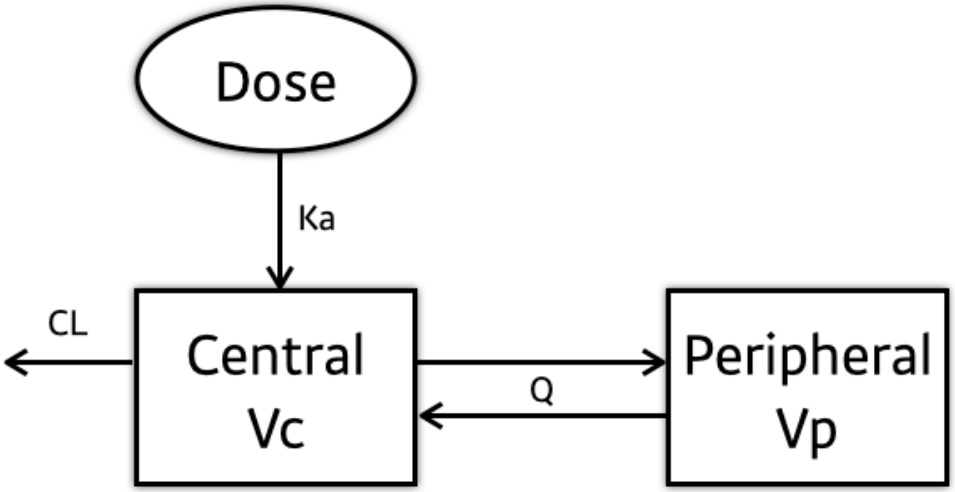

Figure 1. Diagram of two-compartment pharmacokinetic model for aripiprazole. CL, clearance; Ka, absorption rate constant; Q, intercompartmental clearance; Vc/Vp, volume of distribution of central/peripheral compartment.

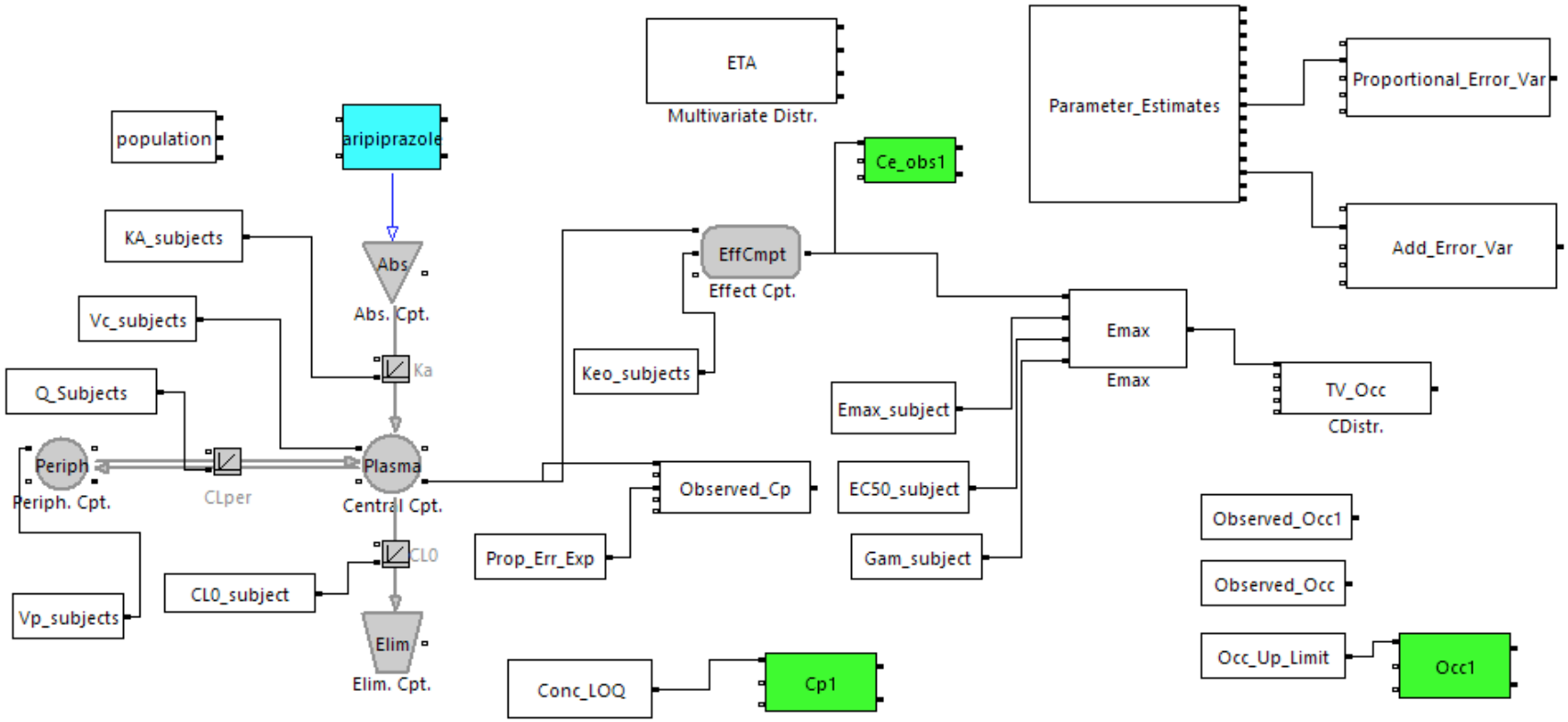

Figure 2. Simulation model designed to predict steady-state dopamine D2 receptor occupancy by aripiprazole in patients with schizophrenia using data from a healthy volunteer study. Abs, absorption; Add/Prop Err, additive/proportional error; CL0, clearance; CLper, intercompartmental clearance; Ce/Cp, effect compartment/plasma drug concentration; Conc LOQ, limit of quantitation of concentration; Cpt, compartment; EC50, drug concentration at which shows efficacy of half of Emax; Elim, elimination; Emax/Imax, the maximum excitatory effect; Gam, the Hill coefficient; Ka, absorption rate constant; Ke, equilibrium rate constant for effect compartment; Occ, occupancy; Q, intercompartmental clearance; TV, typical value; Vc/Vp, volume of distribution of central/peripheral compartment.

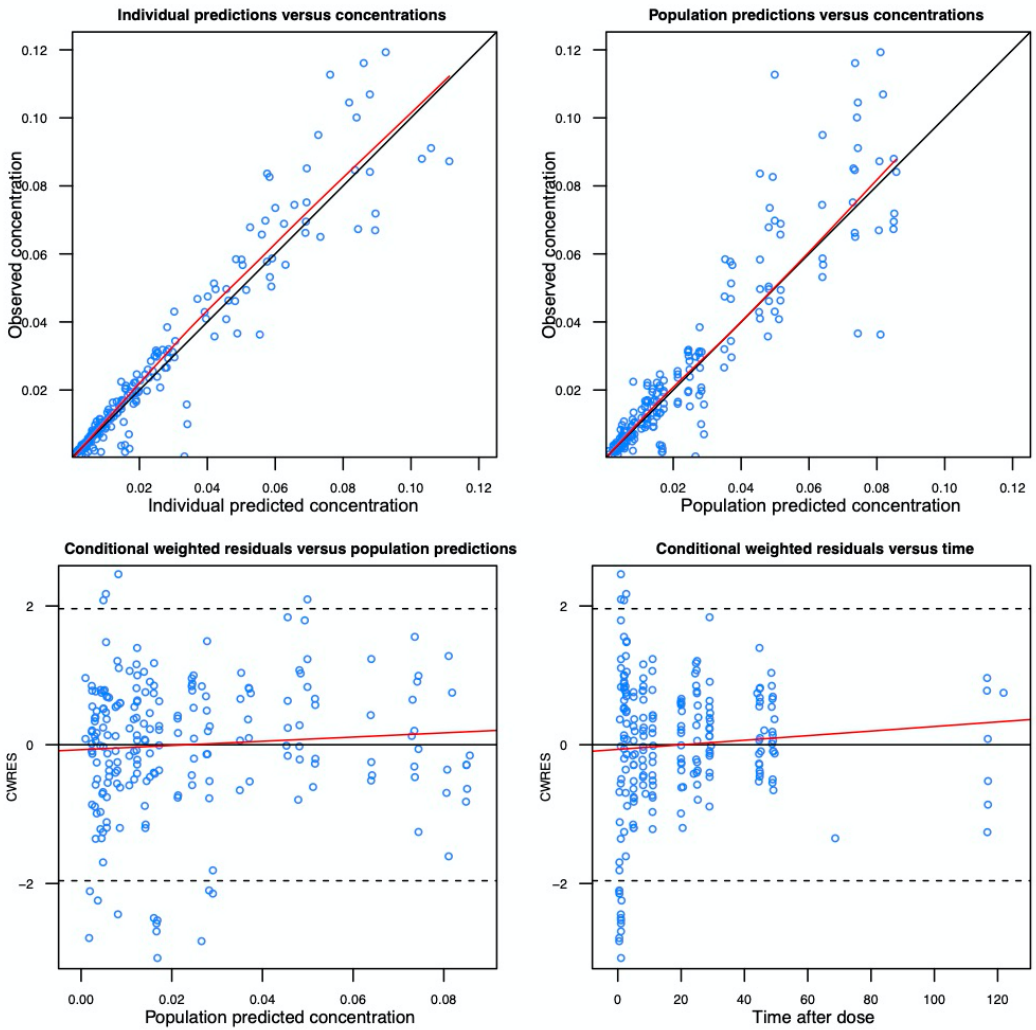

Figure 3. Goodness-of-fit plots for the final pharmacokinetic model for healthy volunteer data

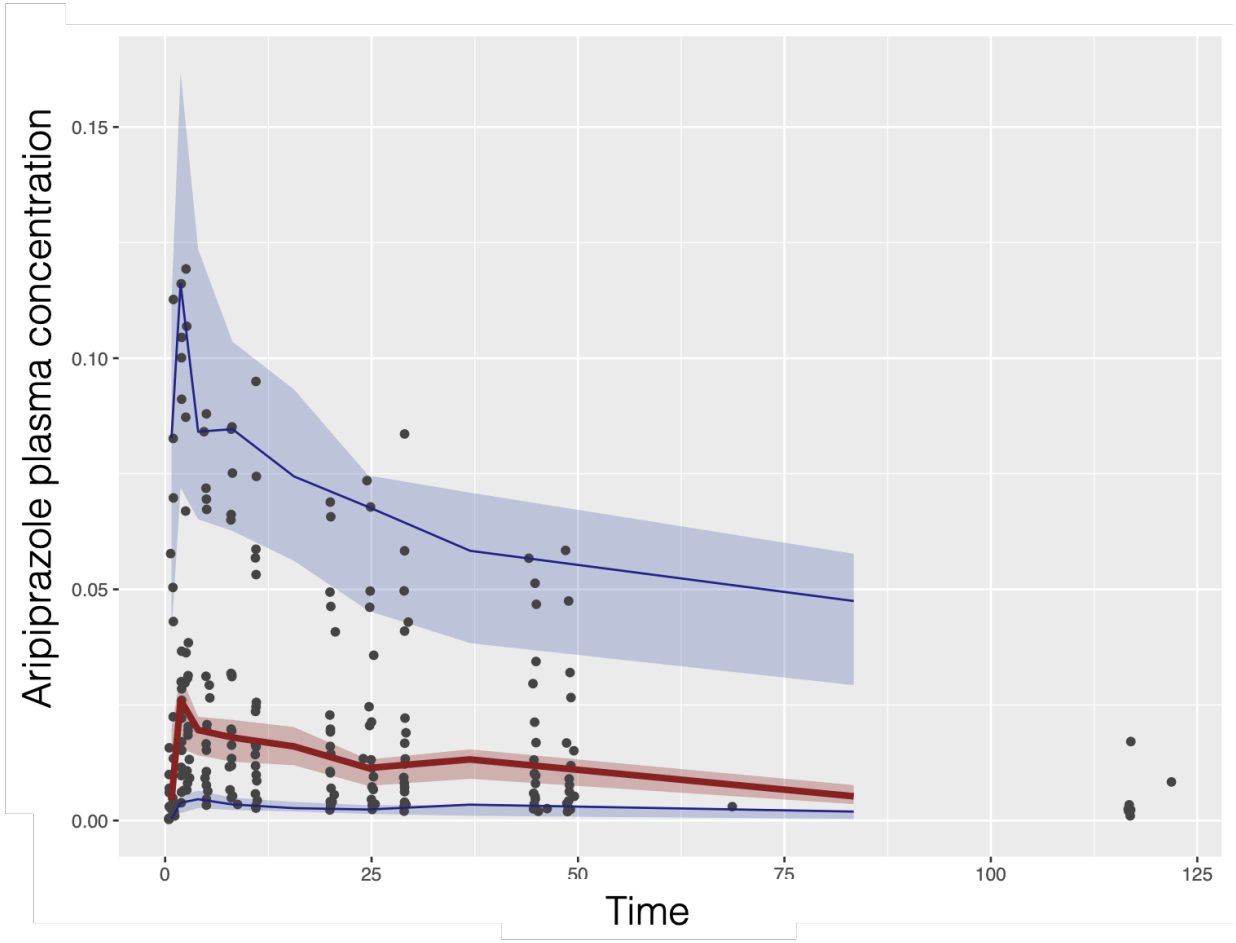

Figure 4. Visual predictive check plot for the final pharmacokinetic model for healthy volunteer data. The lines represent the median (red) and the 5th and 95th percentiles (blue) of the actual plasma aripiprazole concentration. The shaded areas represent the 95% confidence intervals for the median (red) and the 5th and 95th percentiles (blue) of the predicted plasma aripiprazole concentration by the model.

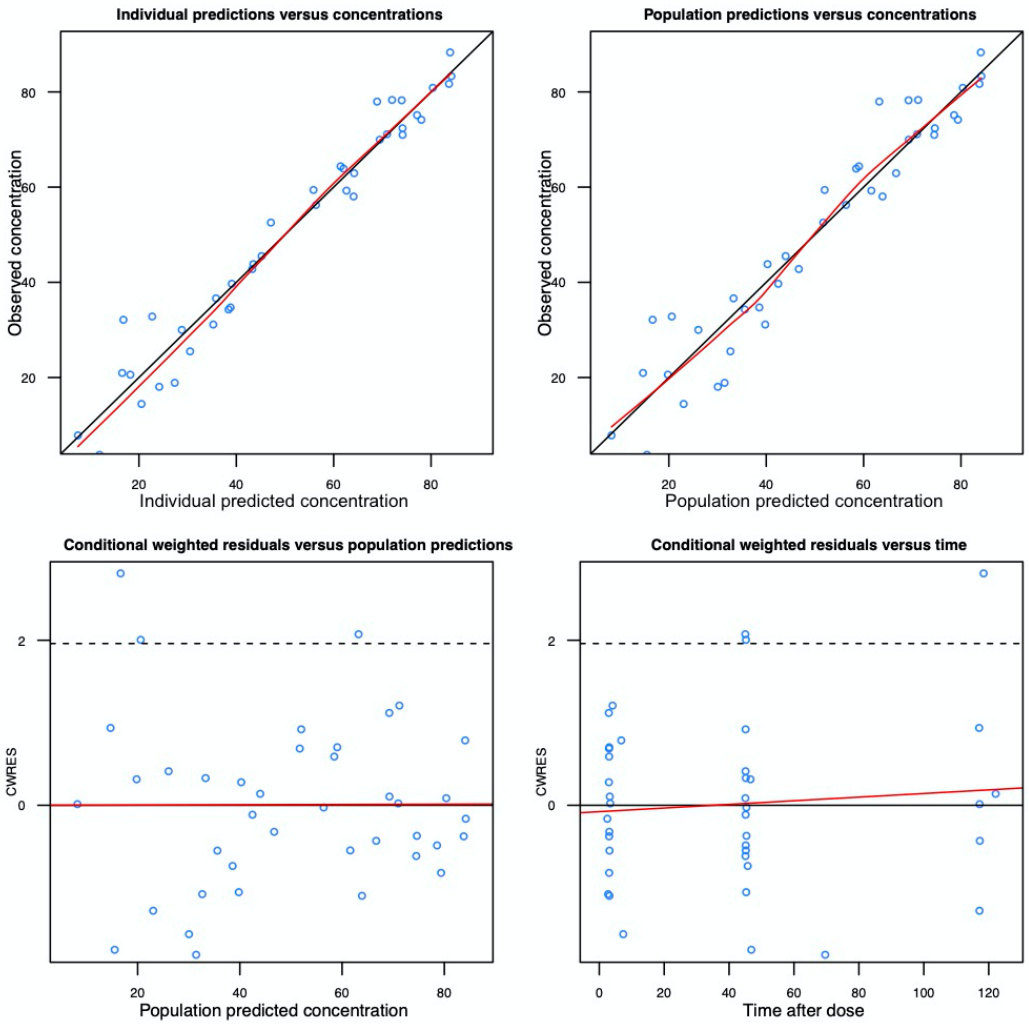

Figure 5. Goodness-of-fit plots for the final pharmacodynamic model for healthy volunteer data

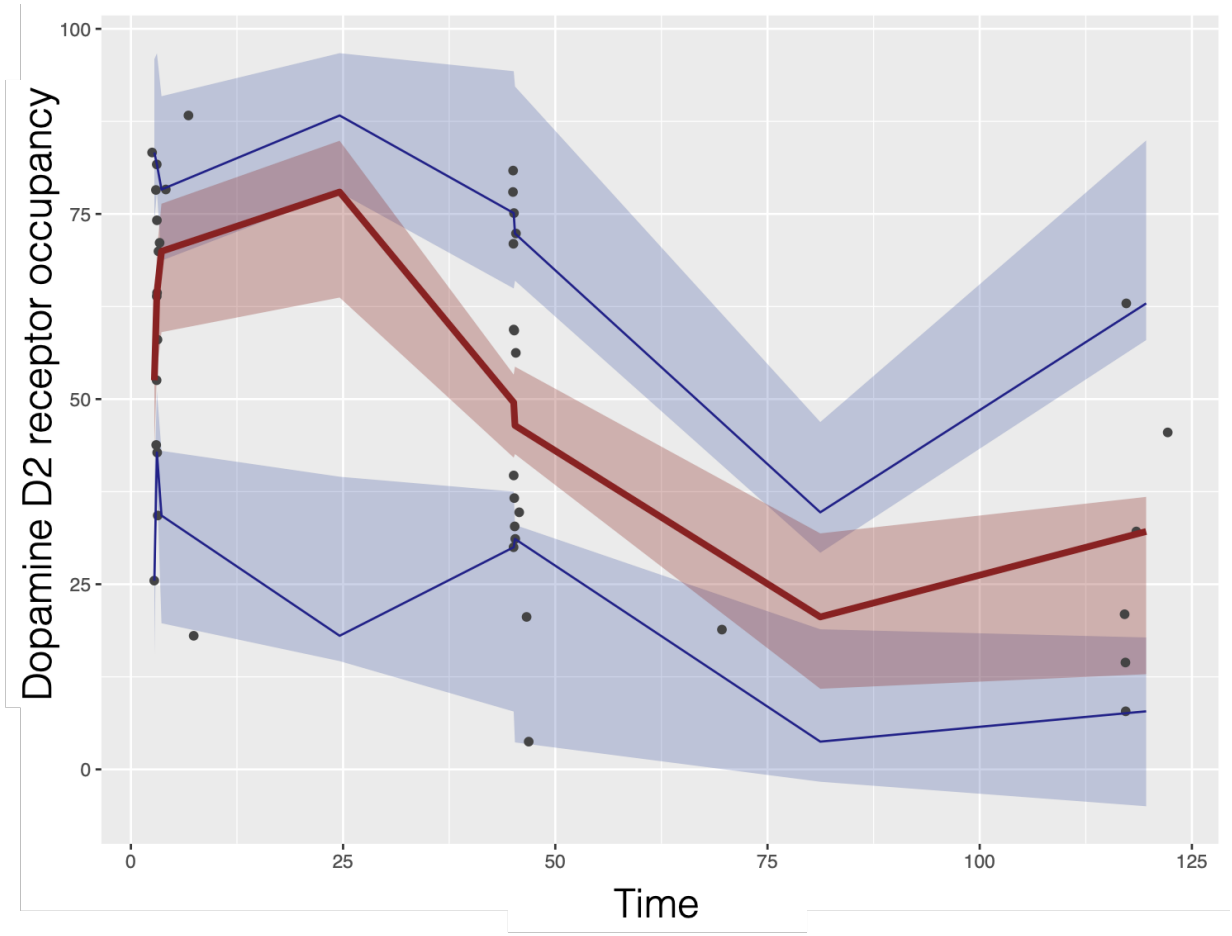

Figure 6. Visual predictive check plot for the final pharmacodynamic model for healthy volunteer data. The lines represent the median (red) and the 5th and 95th percentiles (blue) of the actual dopamine D2 receptor occupancy. The shaded areas represent the 95% confidence intervals for the median (red) and the 5th and 95th percentiles (blue) of the predicted dopamine D2 receptor occupancy by the model.

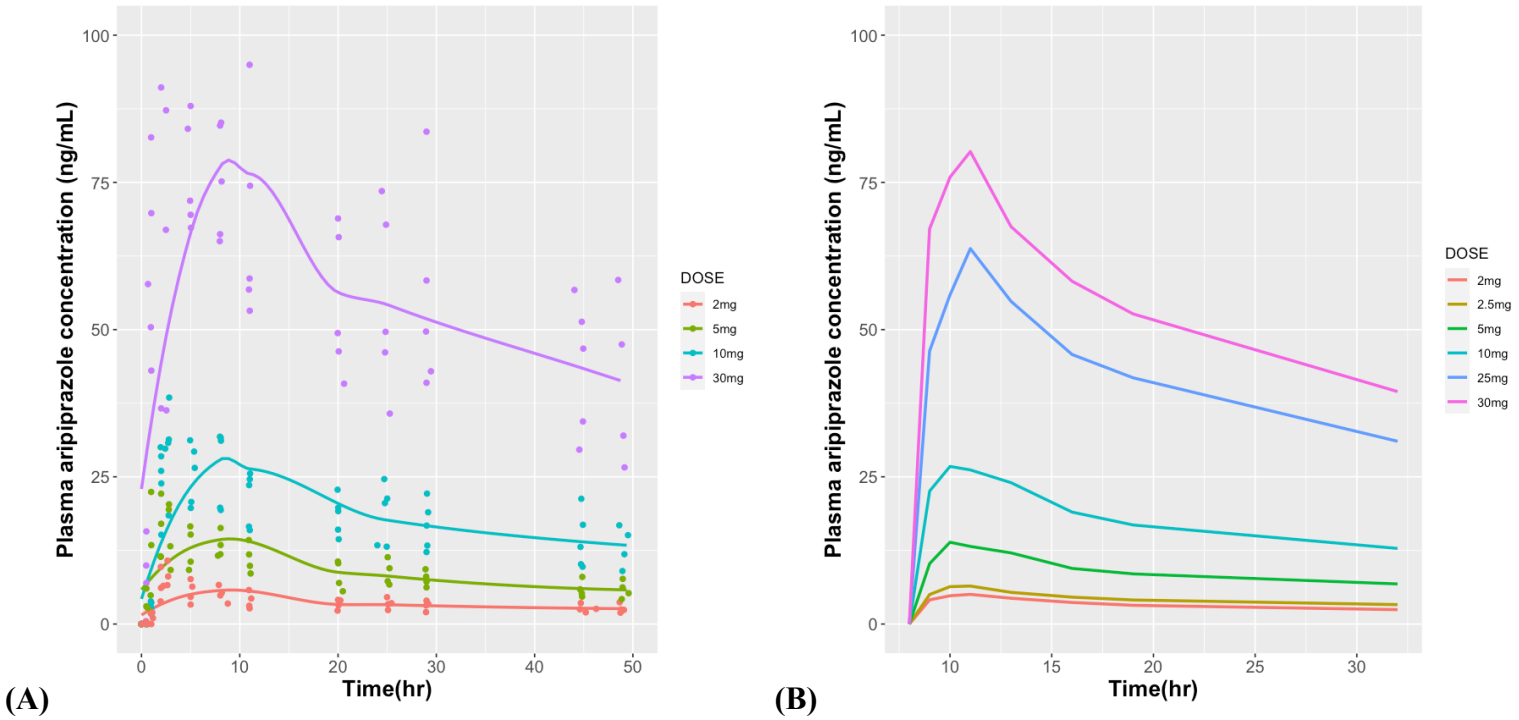

Figure 7. Comparison of (A) observed plasma aripiprazole concentration in healthy volunteers and (B) predicted plasma aripiprazole concentration by the simulation.

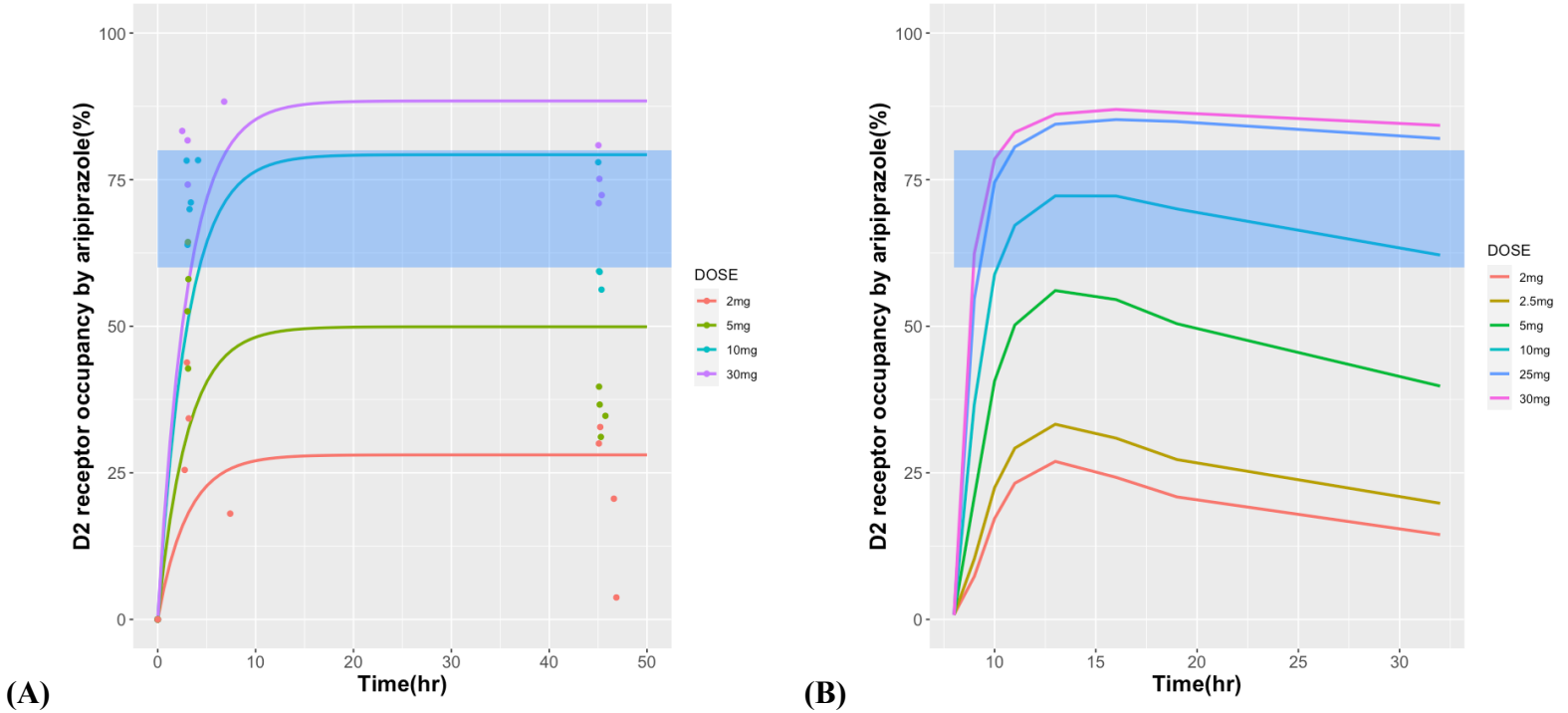

Figure 8. Comparison of (A) observed striatal dopamine D2 receptor occupancy in healthy volunteers and (B) predicted striatal dopamine D2 receptor occupancy by the simulation. Regression lines in (A) are drawn with the formula 100*(1-exp(-x)) for reference, and the shaded areas in blue represent therapeutic window considered for antipsychotics, i.e., D2 receptor occupancy of 60-80%.

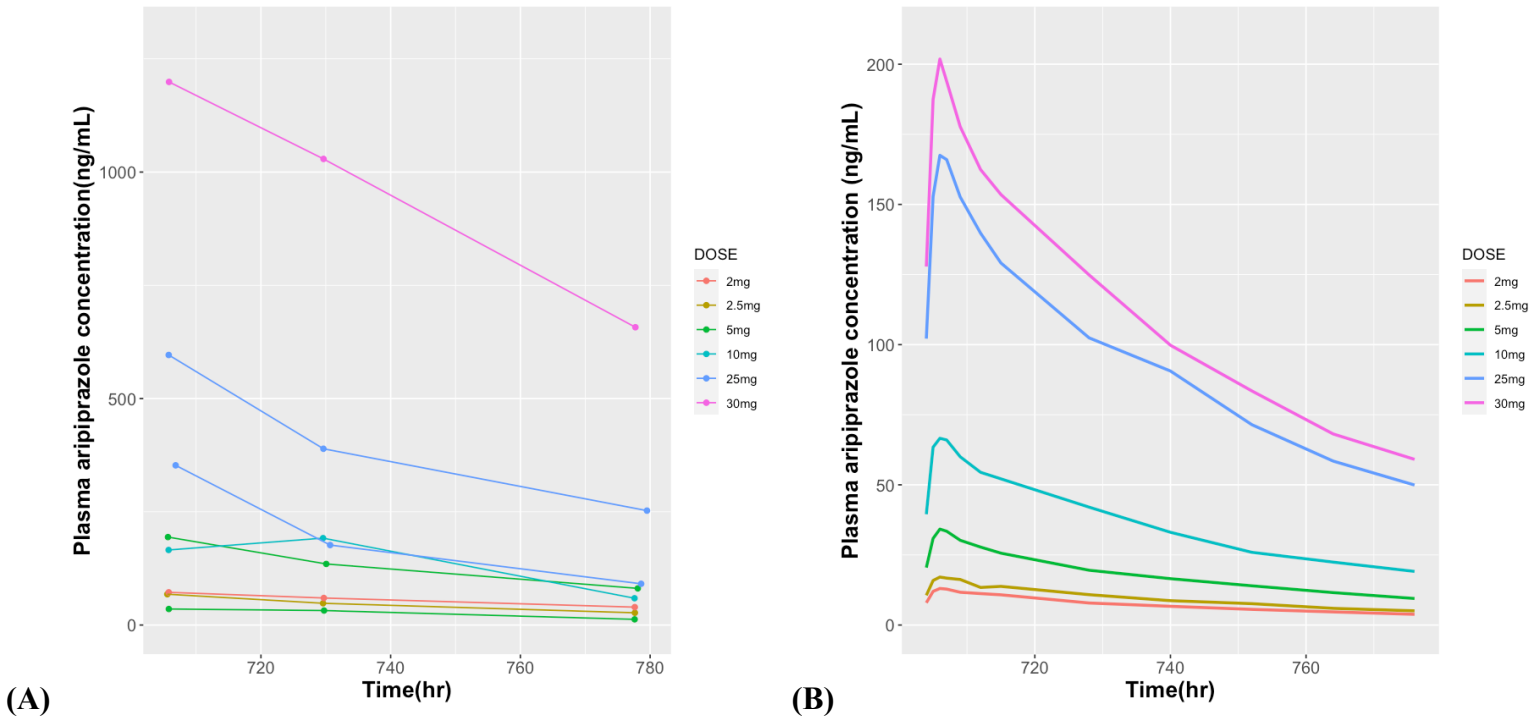

Figure 9. Comparison of (A) observed steady-state plasma aripiprazole concentration in patients with schizophrenia and (B) predicted plasma aripiprazole concentration by the simulation with healthy volunteer data. Note the difference of scale of vertical axes.

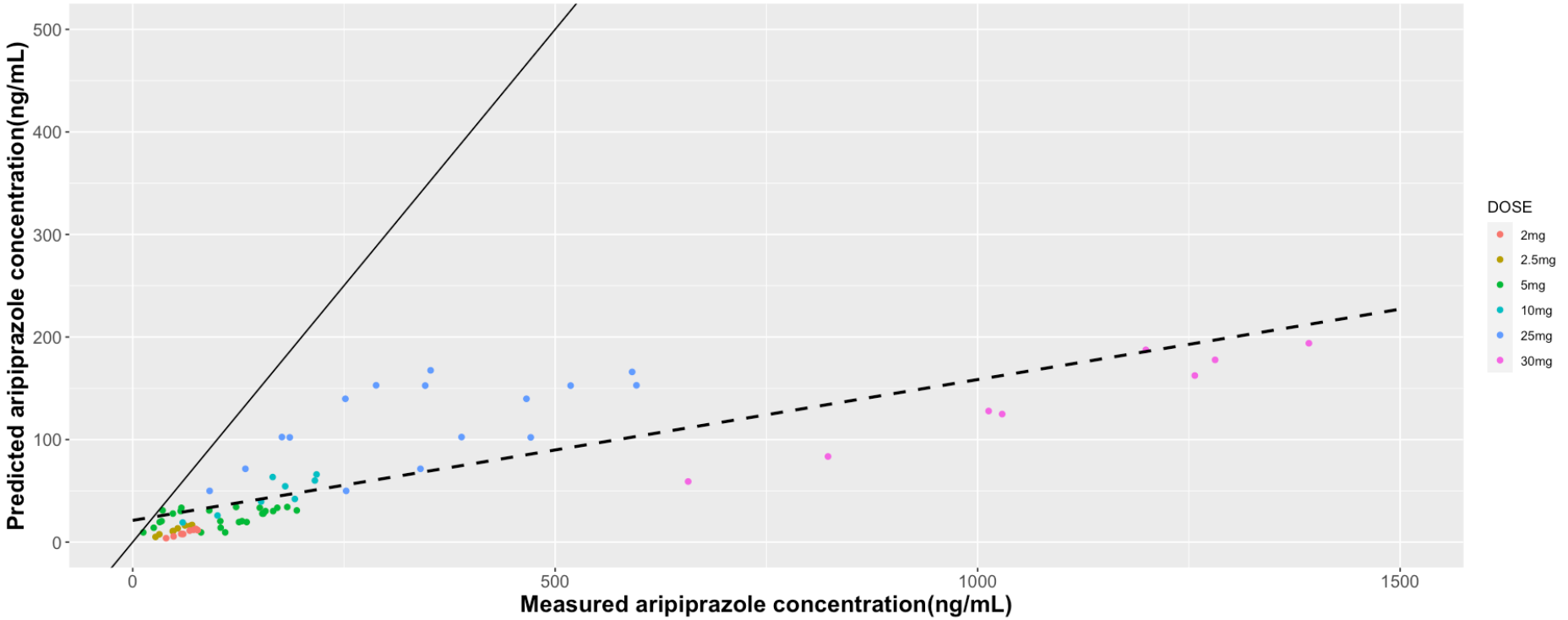

Figure 10. Measured steady-state plasma aripiprazole concentration in patients with schizophrenia plotted versus predicted steady-state plasma aripiprazole concentration by the simulation with healthy volunteer data. The solid line represents the identity line, and the dashed line represents predictions from a linear model.

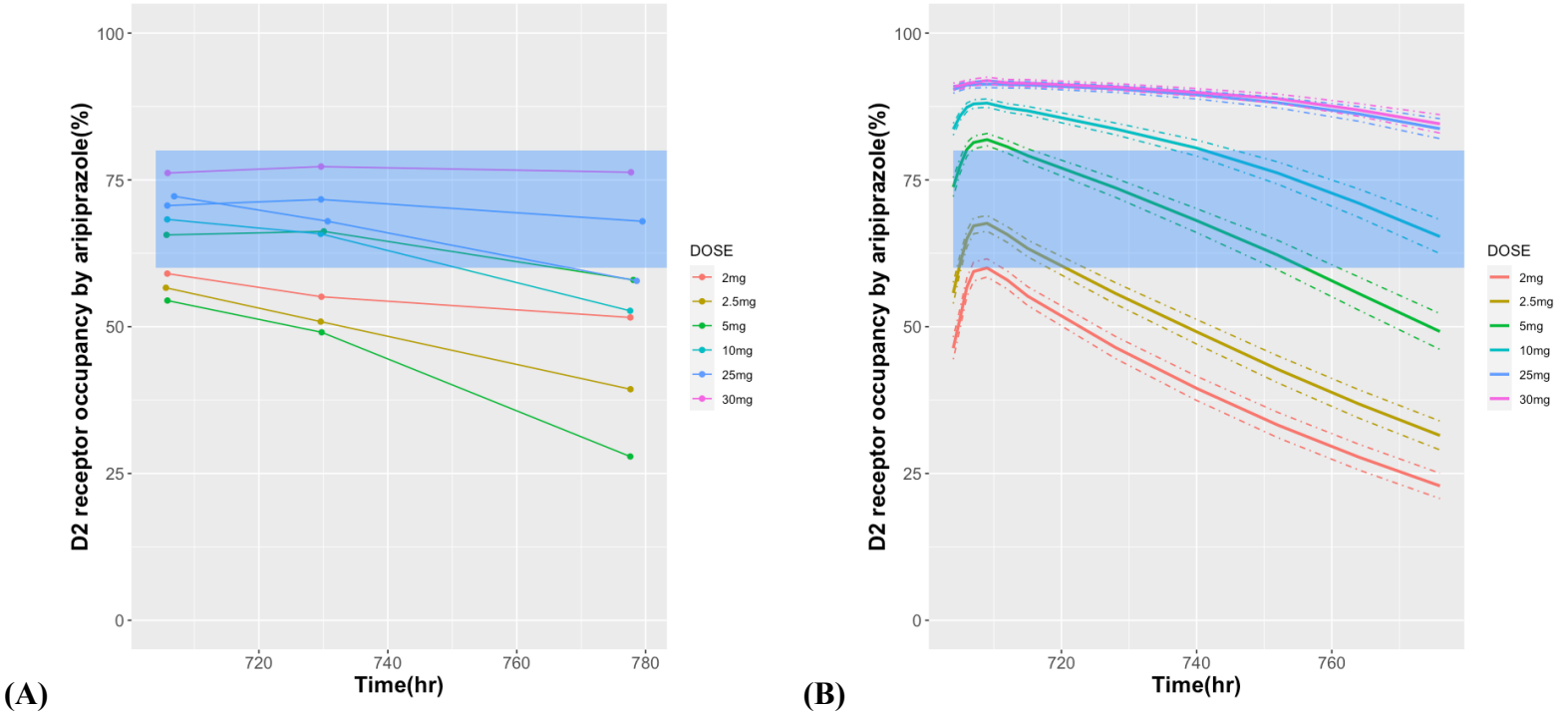

Figure 11. Comparison of (A) observed steady-state striatal dopamine D2 receptor occupancy in patients with schizophrenia and (B) predicted striatal dopamine D2 receptor occupancy by the simulation with healthy volunteer data. The dashed lines indicate 95 percent confidence interval for each dose of aripiprazole, and the shaded areas in blue represent therapeutic window considered for antipsychotics, i.e., D2 receptor occupancy of 60-80%.

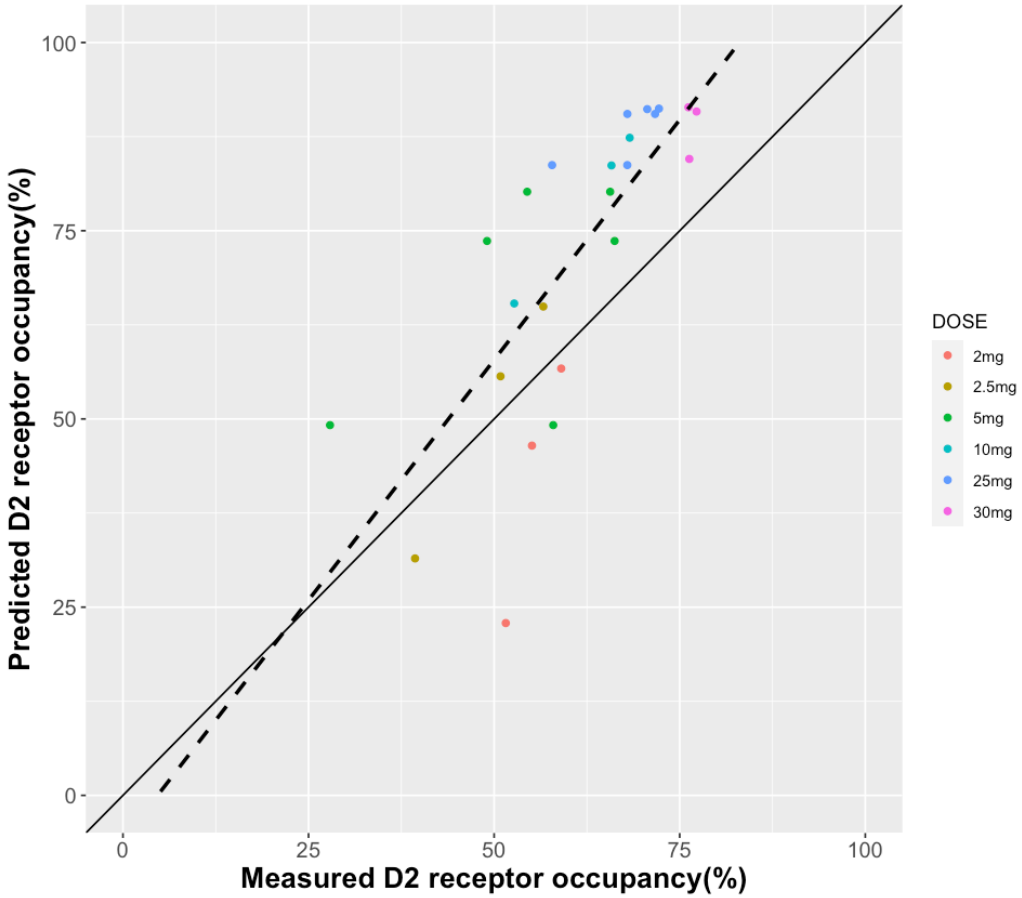

Figure 12. Measured steady-state striatal dopamine D2 receptor occupancy following chronic administration of aripiprazole in patients with schizophrenia plotted versus predicted steady-state striatal dopamine D2 receptor occupancy by the simulation with healthy volunteer data. The solid line represents the identity line, and the dashed line represents predictions from a linear model.

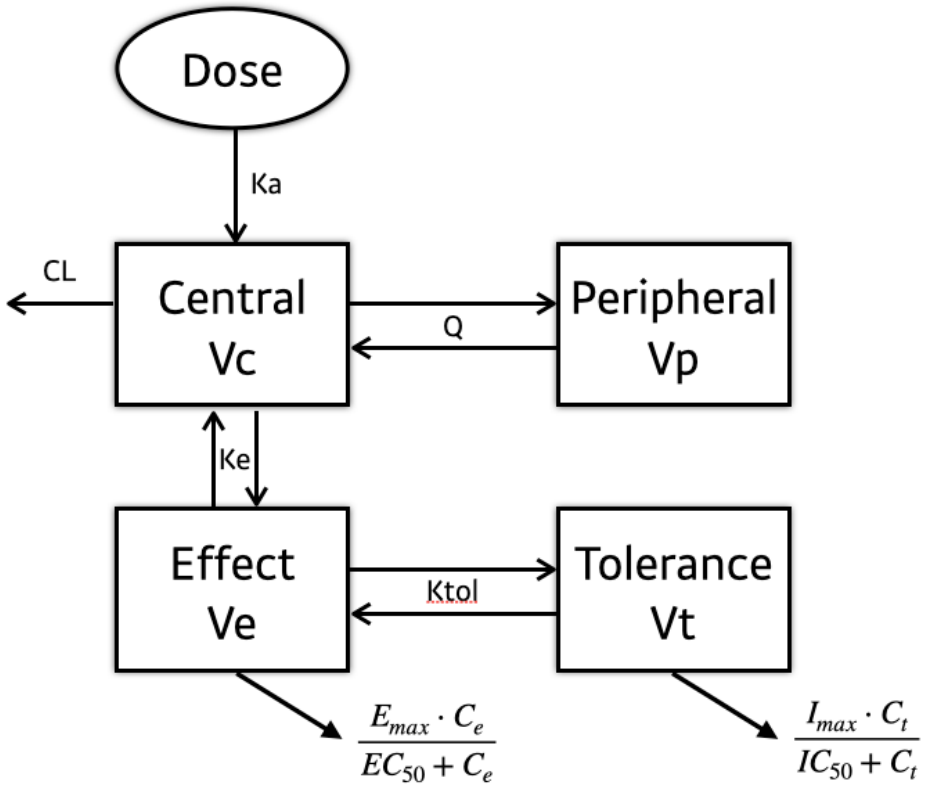

Figure 13. Diagram of pharmacokinetic-pharmacodynamic model incorporating an effect compartment and a tolerance compartment. Ka, absorption rate constant; Vc/Vp/Ve/Vt, volume of distribution of central/pheripheral/effect/tolerance compartment; Q, intercompartmental clearance; Ke/Ktol, equilibrium rate constant for effect/tolerance compartment; CL, clearance; Ce/Ct, drug concentration at effect/tolerance compartment; Emax/Imax, the maximum excitatory/inhibitory effect; EC50/IC50, drug concentration at which shows efficacy of half of Emax/Imax.

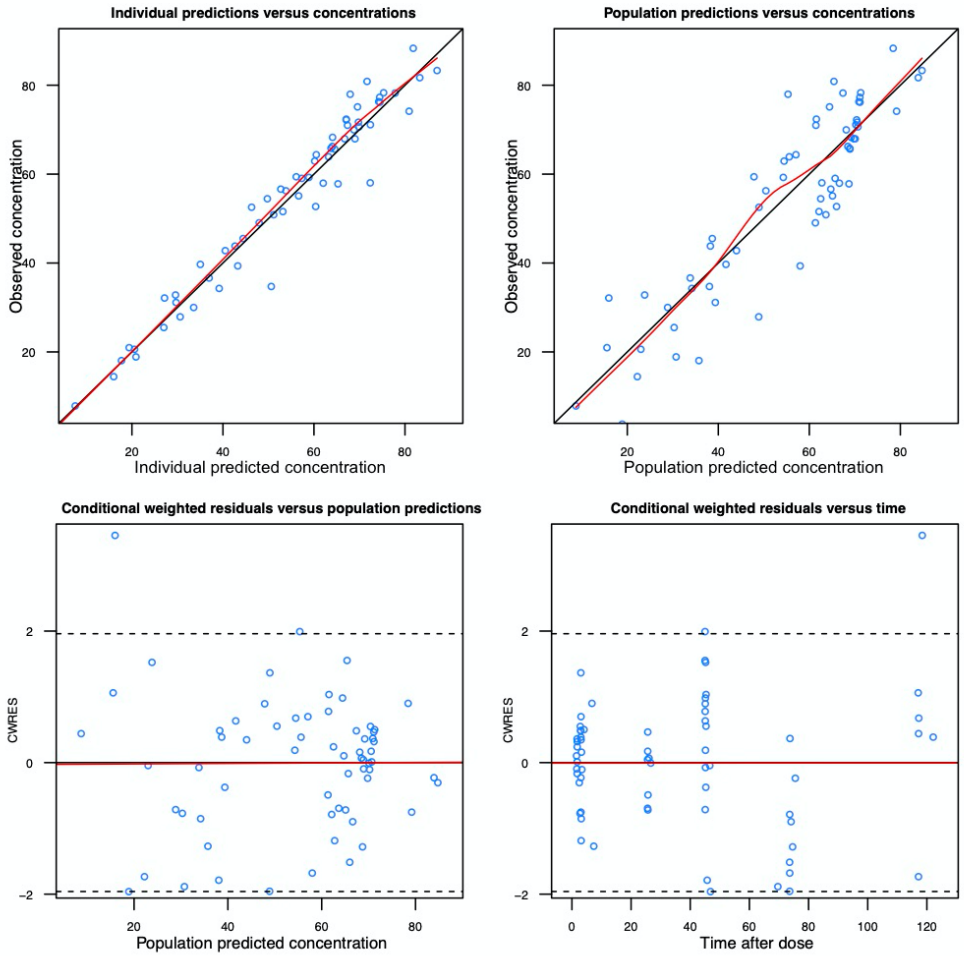

Figure 14. Goodness-of-fit plots for the pharmacodynamic model with tolerance compartment for the pooled data of healthy volunteers and patients with schizophrenia

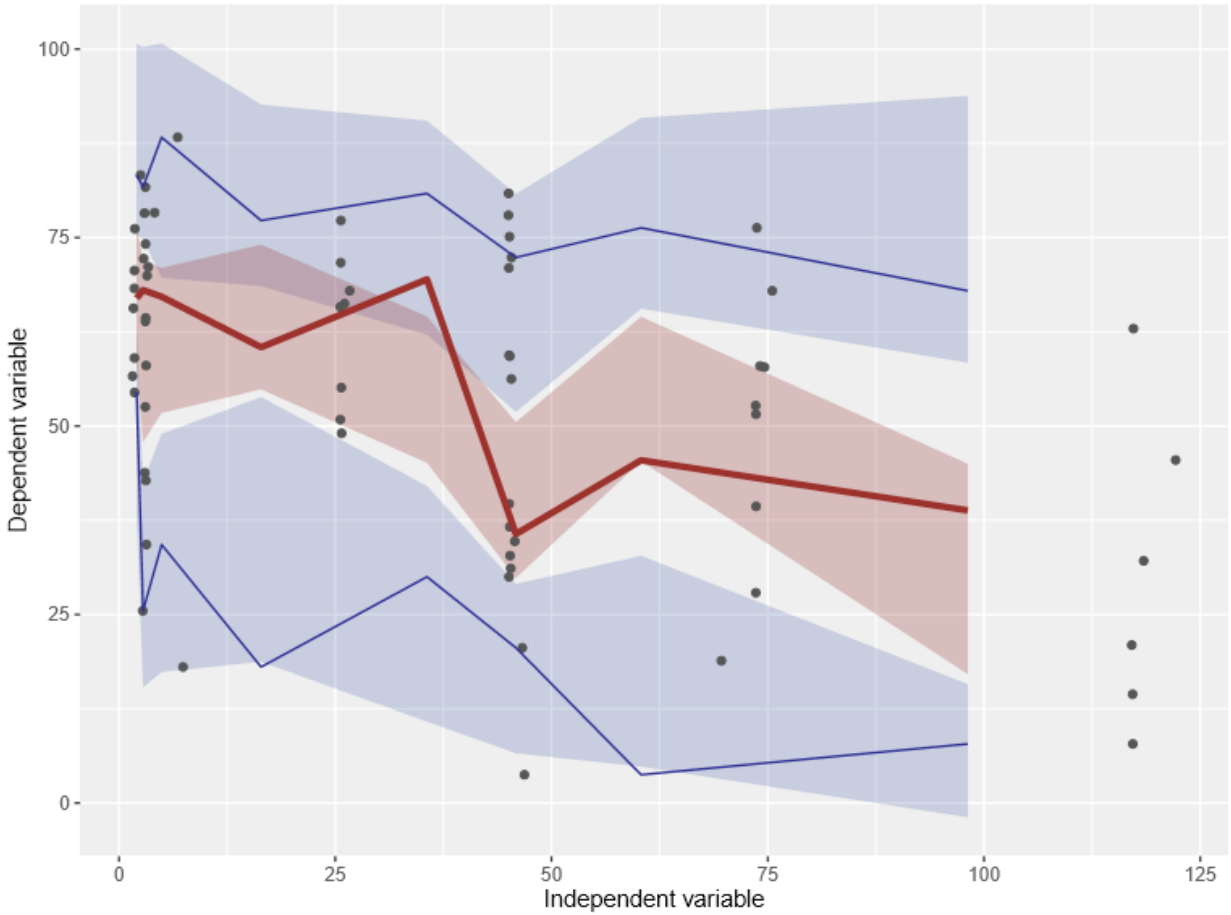

Figure 15. Visual predictive check plot for the pharmacodynamic model with tolerance compartment for the pooled data of healthy volunteers and patients with schizophrenia. The lines represent the median (red) and the 5th and 95th percentiles (blue) of the actual dopamine D2 receptor occupancy. The shaded areas represent the 95% confidence intervals for the median (red) and the 5th and 95th percentiles (blue) of the predicted dopamine D2 receptor occupancy by the model.

Abstract in Korean

연구배경: 조현병 등 정신질환 치료에 주로 사용되는 항정신병약물을 대개 도파민 D2 수용체 길항제이나, 최근 들어 D2 수용체 부분적 효현제인 아리피프라졸 등 독특한 약력학적 특성을 가지는 항정신병약물들이 개발되고 있다. 그러나 정신과학 분야의 임상적 특성으로 인해 정신질환 신약 개발에 어려움이 가중되어, 이를 해결하기 위해 일부 임상시험을 정신질환 환자 대신 건강자원자에서 수행할 수 있는지에 대한 논의가 있어왔다. 본 연구에서는 이를 확인하기 위해 아리피프라졸을 단회투약한 건강자원자 자료를 바탕으로 조현병 환자에서 항정상태 아리피프라졸 D2 수용체 점유율을 예측하는 모델을 만들고 검증하고자 한다.

방법: 2-30 mg 아리피프라졸을 단회 투약한 건강자원자 18 명을 대상으로 약동학적 채혈과 [11C]raclopride 양전자방출단층촬영을 통해 각각 아리피프라졸 혈중농도 및 D2 수용체 점유율의 예측모델 수립을 위한 자료를 수집했고, 2-30mg 아리피프라졸을 평균 2 년의 장기간 투약한 조현병 환자 8 명을 대상으로 같은 방법을 통해 모델 검증을 위한 자료를 수집했다. 예측모델을 이용해 시뮬레이션한 D2 수용체 점유율을 실제 조현병 환자에서 D2 수용체 점유율 값과 비교하고, 차이가 있는 경우 차이를 보정하여 실제 수용체 점유율을 더 잘 예측하는 모델을 수립했다.

결과: 건강자원자에서 단회 투약한 자료를 이용해 수립한 예측모델은 조현병 환자에서 항정상태 D2 수용체 점유율을 실제 값보다 높게 예측했다. 이 약력학적 반응의 차이를 약력학 모델에 내성 구획을 도입하여 보정했다.

결론: 본 연구의 결과에 따르면 아리피프라졸 등 특정 약물은 건강자원자에서 단회투약 했을 때와, 조현병 환자에서 항정상태에 도달했을 때 서로 다른 효과를 나타냄을 시사한다. 이러한 효과의 차이는 약물로 인한 D2 수용체 내재화 또는 상향조절의 결과로 추측할 수 있다. 따라서 건강자원자의 단회투약 자료로 환자의 항정상태를 예측할 수 있지만, 정확한 약물 반응 예측을 위해 각각 약물의 작용기전 및 질병 여부에 따른 인체의 생리적 변화를 고려하는 것이 권장된다.

주요어: 아리피프라졸, 도파민 수용체, 신약개발, 약동학, 약력학

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