Population Pharmacokinetic-Pharmacodynamic Modeling of Haloperidol in Patients With Schizophrenia Using Positive and Negative Syndrome Rating Scale

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Abstract: The aim of this study was to develop a pharmacokinetic-pharmacodynamic (PKPD) model that quantifies the efficacy of haloperidol, accounting for the placebo effect, the variability in exposure-response, and the dropouts. Subsequently, the developed model was utilized to characterize an effective dosing strategy for using haloperidol as a comparator drug in future antipsychotic drug trials. The time course of plasma haloperidol concentrations from 122 subjects and the Positive and Negative Syndrome Scale (PANSS) scores from 473 subjects were used in this analysis. A nonlinear mixed-effects modeling approach was utilized to describe the time course of PK and PANSS scores. Bootstrapping and simulation-based methods were used for the model evaluation. A 2-compartment model adequately described the haloperidol PK profiles. The Weibull and E_{max} models were able to describe the time course of the placebo and the drug effects, respectively. An exponential model was used to account for dropouts. Joint modeling of the PKPD model with dropout model indicated that the probability of patients dropping out is associated with the observed high PANSS score. The model evaluation results confirmed that the precision and accuracy of parameter estimates are acceptable. Based on the PKPD analysis, the recommended oral dose of haloperidol to achieve a 30% reduction in PANSS score from baseline is 5.6 mg/d, and the corresponding steady-state effective plasma haloperidol exposure is 2.7 ng/mL. In conclusion, the developed model describes the time course of PANSS scores adequately, and a recommendation of haloperidol dose was derived for future antipsychotic drug trials.

Key Words: haloperidol, population pharmacokinetics-pharmacodynamics, PANSS total, schizophrenia, dropout model

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Haloperidol, a typical antipsychotic, was the most widely used drug for many years in the treatment of patients with schizophrenia and other psychotic disorders.[1] Haloperidol is still widely used as the prototypical comparator antipsychotic for randomized controlled trials. The effective dose of haloperidol is still not known, which is a problem when it is used as a comparator drug.[2] McEvoy et al[3] recommended about 3 mg/d, whereas Van Putten et al[4] found that the efficacy increased with doses up to 20 mg/d. The American Psychiatric Association guideline recommends a broad range of 5 to 20 mg/d[5] for the acute and the maintenance treatment of schizophrenia symptoms. In addition, in many clinical trials, higher doses of haloperidol are used as a comparator. This may be linked to higher incidence of adverse effects such as extrapyramidal side effects, and therefore comparison between drugs could be biased.[6] Recently, Giegling et al[7] discussed a statistical strategy for choosing an appropriate dose and the corresponding exposure of haloperidol for clinical studies based on the observed response. However, the observed interindividual variability (IIV) in the pharmacokinetics (PK) and pharmacodynamics (PD) of haloperidol was not fully characterized because of the small sample size of patients. To our knowledge, there is no literature available on population-based pharmacokinetic-pharmacodynamic (PKPD) modeling of haloperidol using the Positive and Negative Syndrome Scale (PANSS) total score that would help in determining the effective haloperidol dose. Hence, in the present study, we developed a PKPD model that describes the time course of the PANSS total scores accounting for the contributors to the variability in the haloperidol exposure-response. Subsequently, a methodology for estimating an effective dosing strategy (dose and corresponding effective exposure) when haloperidol is used as a comparator drug in clinical trials is described. To achieve these goals, we applied a nonlinear mixed-effects modeling (NONMEM) approach to describe the population PK (POP-PK) of haloperidol. Consequently, the developed POP-PK was used as an input model for building the PKPD model that describes the time course of PANSS total score accounting for the placebo effect, the variability in exposure-response, and the dropouts. Based on the developed PKPD model, we calculated the effective dose of haloperidol. Furthermore, the developed PKPD model was utilized to quantify the efficacy of haloperidol toward the PANSS subscales.

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MATERIALS AND METHODS

Participants and Study Design

In total, data from 515 patients were used to develop and to evaluate the PK and PKPD model. The overview of the data sets with their study design, patient demographics, summary statistics of the PANSS scores, and dropout rates across the studies used in the development of the PKPD model is shown in Table 1. In brief, the population PK model for haloperidol was developed from 7 studies, with data from 122 individuals (healthy volunteers [n = 20] and schizophrenic patients [n = 102]) and 538 plasma concentrations obtained from a wide dose range of 1 to 60 mg/d administered either as a single or multiple doses. The studies that provided PK data were well-controlled studies and were conducted either to measure the dopamine-2 receptor occupancy (D_2RO) of haloperidol or to evaluate the effects of haloperidol on the central nervous system. Studies with healthy volunteers provided a rich PK sampling. On the other hand, PANSS data from 4 studies in 473 schizophrenic patients with 2342 PANSS observations were utilized to describe the exposure-response relationship of haloperidol. The data for PKPD model were obtained from 3 phase III trials (via TI Pharma mechanism-based PK-PD modeling platform, the Netherlands; www.tipharma.com) and 1 open-label study data from Ludwig Maximilians University (LMU) study. All these studies were short-term (4-8 weeks) efficacy trials, with the main inclusion criteria being a diagnosis of schizophrenia under the *Diagnostic and Statistical Manual of Mental Disorders* version III and an observed PANSS score of at least 60. In the open-label study, patients were treated with haloperidol without any dose limitation during the acute phase of the illness. All studies were approved by their respective ethics review board and were performed according to ethical standards laid down in the 1964 Declaration of Helsinki.

Model Development

A nonlinear mixed-effects modeling approach to describe the time course of PK and PANSS scores was implemented using the NONMEM VII software[8] (ICON Development Solutions, Hanover, MD). Perl-speaks-NONMEM[9] (PsN, version 3.2.4) was used to operate NONMEM. R (version 2.11; www.r-project.org) was used for graphical inspection of the results. Log-transformed plasma haloperidol concentrations were used to estimate the PK parameters, whereas absolute PANSS scores were used for the PD model. The first-order conditional estimation method with or without interaction option in NONMEM was used to estimate PK and PKPD model parameters. First-order conditional estimation along with the Laplace approximation method in NONMEM was utilized for estimating the dropout model parameters.[10]

Interindividual variability for the structural model parameters was evaluated using a log-normally or a normally distributed model:

$$P_j = PTV \times exp^{(\eta j)} or\ P_j = PTV + \eta_j$$

where PTV represents the population typical value of the parameter, and P_j is the value of the parameter for subject j; η_j denotes an individual-specific random effect that distinguishes the value of the jth subject from the PTV. The values of η_j are assumed to be normally distributed with mean zero and variance ω^2. Interindividual variability is expressed as percent coefficient of variation (%CV).

The intraindividual or residual variability (RUV) describes the error terms, which remain unexplained, and refers to, for example, dosing inaccuracies, analytical assay error, or error in recording sampling times, and structural model misspecifications.

An additive residual error model, which is proportional when log-transformed plasma concentrations are back transformed, was used to describe RUV in the plasma concentration, whereas an additive term was used to account for the unexplained variability in PANSS score as shown in the following equations:

$$ln(y_{ij}) = ln(\hat{y}ij) + \varepsilon_{ij} : \text{ for PK model}$$

$$y_{ij} = \hat{y}_{ij} + \varepsilon_{ij} : \text{ for PD model}$$

where y_{ij} is the jth observation in the ith individual, $\hat{y}_{ij}$ is the corresponding model prediction, and ϵ_{ij} is a normally distributed random error with a mean of zero and a variance of σ^2. Different sigma values were estimated for PK and PD models.

Model selection was based on comparison of the objective function values (ΔOFV: 3.84, corresponding to a P value of 0.05) and the goodness-of-fit plots. Goodness-of-fit was assessed graphically by evaluation of the agreement between observed and predicted plasma concentrations or PANSS scores, the range of conditional weighted residuals, and uniformity of the distribution of conditional weighted residuals about zero across the range of the predicted concentrations or PANSS scores. The percentage relative SEs (%RSEs) of the parameter estimates and reductions in both IIV and RUV were also used to discriminate between competing models. The ΔOFV and Kaplan-Meier–based visual predictive check (VPC) plots were used to choose the best dropout model.

Influences of patient- and study-specific covariates such as age, sex, body weight, dosage regimen (once daily vs twice daily), subject type (healthy vs patients), and disease status (acute vs chronic) were evaluated as possible explanatory variables for the variability in the PK or PKPD model parameters. Covariate analysis was performed in NONMEM using PsN with a stepwise forward additive approach followed by a stepwise backward elimination approach with P values of 0.05 and 0.01, respectively.[9] Uncorrelated covariates were included in the model using different functional forms such as linear, piece-wise linear, power, and exponential functions.

Population PK Analysis

One- and two-compartment models with first-order absorption and with or without absorption lag time were evaluated. Prespecified subroutines (ADVAN2 or 4) in the NONMEM software were used to model the time course of haloperidol exposure. The available covariates were tested for their influence on clearance (CL/F) and central volume of distribution (Vc/F). If no significant effect of any of the tested covariates (eg, age, sex, body weight, population type etc) was found, a fixed allometric relationship with individual body weight and CL/F was assumed: CL/F = TVCL * [weight / 70]$^{0.75}$. This was done because the relationship between body weight and clearance is well documented[11] and allows for taking into account IIV even in the studies where no individual PK was known. Using post hoc empirical Bayesian step in NONMEM, the individual parameter estimates were obtained.

PKPD Model

As a first step in building the exposure-response relationship, a placebo model that was developed and validated previously[12,13] was incorporated into the drug effect model such that the pharmacological effectiveness of the drug was estimated on top of the placebo effect. The time course of the placebo response could be described using the Weibull model as described by Friberg et al.[12] Previously reported predictors of variable placebo effect were also

TABLE 1. Summary of Data Sets Used for the Population-Based PK and PKPD Analysis

Data set: PK model

Reference	Population	Dose, Dosage Regimen	PK Sampling
Kapur et al[28]	7 schizophrenic patients (aged 20–32 y)	Fixed dose of 2 mg/d, multiple dosing	12–14 h post dose
Kapur et al[29]	5 schizophrenic patients (aged 21–43 y)	Fixed dose of 1–5 mg/d, multiple dosing	12–14 h postdose
Xiberas et al[30]	4 schizophrenic patients (aged 22–42 y)	Flexible dose of 3–60 mg/d, multiple dosing	18–20 h postdose
Farde et al[31]	6 schizophrenic patients (aged 18–29 y)	Flexible dose of 4–12 mg/d, multiple dosing	6 h postdose
Liem-Moolenaar et al[32]	16 healthy male volunteers (aged 18–38 y)	Fixed dose of 3 mg/d, single dose	Rich sampling up to 24 h
Nordstrom et al[33]	4 healthy male volunteers (aged 26–39 y)	Fixed dose of 2–7.5 mg/d, single dose	Rich sampling up to 27 h
Giegling et al[7]	80 schizophrenic patients (aged 18–64 y)	Flexible dose of 2.5–40 mg/d, multiple dosing	~1–2 h postdosing

Data Set: PKPD Model

Study	Trial Phase	Study Duration	ROA	Disease Type	Age, y	Sex (Female to Male), n	Race (White: Black: Hispanic: Asian/Other), n	Dose, mg	Subjects,* n	Median Baseline PANSS	PANSS Change From Baseline	Dropout, %
INT-2†	III	8 wk	Oral/BID	Chronic	37 (19–68)	76:150	184: 15: 16: 11	5	226	87	−14.8	28
INT-3†	III	8 wk	Oral/BID	Chronic	37.5 (18–64)	13:69	61: 15: 3: 3	7.5	82	93	−5.0	60
128-115*	III	6 wk	Oral/BID	Acute	37 (18–69)	25:60	57: 24: 0 : 4	7.5	85	94	−15.0	44
LMU	Open	4 wk	Oral/QD	Acute	34 (18–64)	35:45	80: 0: 0: 0	2.5–40	80	106	−41.8	42

Haloperidol was used as an active comparator in *ziprasidone and †risperidone clinical trials from Pfizer and Janssen Pharmaceuticals, respectively.

BID indicates twice daily; QD, once daily; ROA, route of administration.

included in the placebo model.[13] The treatment effect was modeled as a relative change from the baseline PANSS score as shown in the following equation:

$$\text{PANSS Score} = \text{Baseline PANSS} \times \left[\left(1 - P_{max} \times \left(1 - e^{-\left(\frac{\text{time}}{TD}\right)^{POW}} \right) \right) \times \left(1 - \left(\frac{E_{max} \times C_{ss}}{EC_{50} + C_{ss}} \right) \times \left(1 - e^{-KT \times \text{time}} \right) \right) \right]$$

where P_{max} is the maximum placebo effect, TD is the time to reach 63.2% of maximum change in PANSS from baseline; POW is the shape parameter; E_{max} is the maximum drug effect; C_{ss} is the patient-specific average steady-state plasma concentration, which was estimated using the dose, dosing interval and the individual estimate of CL/F values obtained from the final POP-PK model: [C_{ss} = dose / CL/F / dosing interval]. For patients in whom PK was not assessed or available, the population-based PK parameter estimates from POP-PK model (adjusted for body weight) were used for the predictions of PK profile. We assumed that C_{ss} is constant over the dosing interval, as little fluctuation in the exposure can be anticipated once a patient reaches steady-state levels (ie, after 5–6 half-lives), and most PANSS observations were done at steady-state conditions. EC_{50} is the steady-state concentration required to achieve 50% of E_{max}, and KT is a rate constant associated with the time required to obtain the maximum drug effect. Interindividual variability for baseline PANSS and EC_{50} was assumed to be log-normally distributed. Normally distributed IIV was used for P_{max} and E_{max} parameters, which allows the placebo and drug effect to be positive (improvement, ie, decrease of PANSS score) or negative (worsening, ie, increase in PANSS score). All the parameters that were described in the above equation were estimated except 2 placebo model parameters, namely, POW and TD, which were fixed, based on our earlier results. During the model development and simulations, the PANSS score data were not constrained to fall within the rating scale range of 30 to 210 because attempts to constrain the model to predict/simulate only scores between 30 and 210 resulted in numerical difficulties during the estimation of the model parameters. Moreover, there were no simulated data points greater than 210, and only 0.2% of the simulated data points were less than 30. The covariates of the placebo effect were fixed during the subsequent PKPD modeling. The influences of clinically relevant covariates such as disease condition, age, sex, and dosage regimen were tested on drug effect parameters (E_{max} and EC_{50}). We extended the use of the developed PKPD model to the PANSS subscales (ie, positive and negative subscales) accounting for their respective placebo effects.

To predict the mean changes in the PANSS adequately via simulations, it was necessary to account for the dropouts.[13] The exponential time-to-event dropout model was used jointly with the PD model. The probability of a patient dropping out from a trial can be predicted by describing the hazard for the dropout event. Hazard is the instantaneous rate of the dropout event: $h(t)$.

$$h(t) = \text{BHAZ} \times \exp(-\text{predictor} \times \text{BETA})$$

The model assumes that baseline hazard (BHAZ) is independent of time and estimates the BHAZ and BETA as dropout model parameters; BHAZ is baseline hazard without influence of predictors, whereas BETA is a parameter that describes the probability of a patient dropping out based on the predictors such as observed PANSS score, unobserved (predicted), unobserved (predicted) + observed PANSS, change in the PANSS score from baseline, or drug exposure. Several predictors can be included within the time-to-event model structure with parameterizing different BETAs for each of the predictors. Cumulative hazard (CHZ) predicts the risk of a patient dropping out from the study over the time interval, which is obtained by integrating the hazard over time. The probability of survival (not dropping out) can be predicted from the cumulative hazard: $S(t) = \exp(-\text{CHZ})$. Finally, the probability of dropping out at time t is given by $D(t) = S(t) \times h(t)$. The best predictor(s) of dropout was selected based on the ΔOFV. A sequential approach[14,15] was used to estimate the dropout model parameters conditioning on the estimates of the PKPD model.

Model Evaluation

The developed PK and PKPD models were evaluated by bootstrap analysis and simulation-based methods within the NONMEM software using PsN.[9] One thousand bootstrap data sets were obtained by resampling with replacement from the original haloperidol data set with stratification based on study, and then the final model was fitted to each of the bootstrapped data sets. The bootstrap median and 2.5th and 97.5th percentiles were obtained for each parameter from the distribution of parameter estimates from successful NONMEM estimation runs. These were compared with the estimates obtained from the original data set.[16,17] The other model evaluation method used was the stochastic simulation and estimation (SSE), which is a simulation-based tool for evaluating model appropriateness and adequacy. The final model was used to generate a number of simulated data sets, which were subsequently fit to this input model. The median parameter estimates of the simulations were compared with the final parameter estimates from the input model. The accuracy of parameter estimates was measured by computing the % bias [bias = 100% × mean (estimated parameter − true parameter) / true parameter].

Monte Carlo simulations were performed for the final PK and PKPD model to construct the VPC plots. In brief, 1000 data sets identical in structure to the original PK and PKPD data set were simulated, using the parameter estimates and interindividual and intraindividual variability from the respective final models. Separate VPC plots were plotted for both the PK and PKPD models after calculating the 2.5th, 50th, and 97.5th percentiles of plasma concentrations or PANSS scores for the simulated data sets.

With respect to VPCs of the PK model, a VPC plot was constructed only for the LMU study where the steady-state plasma haloperidol concentrations were available.

For the PKPD model, initially, simulations were performed for the base PKPD model (without dropout model and predictors of placebo effect). Subsequently, simulations for the final PKPD model were performed along with the dropout model + predictors of placebo effect and dropout model, in which the observed PANSS scores were replaced with the simulated PANSS scores from the final PKPD model. Then, VPC plots were plotted separately for different studies after calculating the 2.5th, 50th, and 97.5th percentiles of PANSS scores for the simulated data sets.

Calculations of the Haloperidol Therapeutic Dose and Concentrations

Calculations of the haloperidol therapeutic dose and plasma concentrations based on the final PKPD model using PANSS total scores are discussed below. The PANSS scores corresponding to the targeted % change were calculated based on the following

equation correcting for minimum possible PANSS total score of 30.

$$\%\ \text{chage in PANSS Total} = \frac{\text{PANSS} - \text{Baseline PANSS}}{\text{Baseline PANSS} - 30} \times 100.$$

Rearranging the above equation,

$$\text{PANSS} = \text{change in PANSS total}/100 \times (\text{Baseline PANSS} - 30) + \text{Baseline PANSS}$$

The corresponding PANSS value is obtained using the estimate of baseline PANSS from the final PKPD model and knowing the desired % change in PANSS score from baseline.

For example, with a targeted 30% reduction from baseline with a baseline PANSS score of 90:

$$\text{PANSS} = (-30/100) \times (90 - 30) + 90$$

will yield a PANSS score of 72. Above calculated PANSS was then integrated into the equation describing the change in score from baseline in our PKPD model: PANSS = baseline PANSS × (1 − placebo effect) × (1 − drug effect). Assuming maximum (at the end of the trial) placebo and drug effect, the equation becomes

$$\text{PANSS} = \text{Baseline PANSS} \times (1 - \text{P}_{\max}) \times \left(1 - \text{E}_{\max} \times \text{C}_{\text{eff}}/(\text{C}_{\text{eff}} + \text{EC}_{50})\right).$$

After rearrangement of the above equation we obtain the steady-state effective concentration (C_{eff}) necessary to reach the targeted PANSS score:

$$\text{C}_{\text{eff}} = \text{EC}_{50}/\left(\text{E}_{\max}/\left(1 - \text{PANSS}/\left(\text{Baseline PANSS} \times (1 - \text{P}_{\max})\right)\right) - 1\right).$$

The corresponding therapeutic dose is calculated using the following relationship Effective dose (mg/d) = C_{eff}* CL/F. The above calculations were also extended to PANSS subscales.

RESULTS

Haloperidol PK Analysis

Haloperidol PK following oral administration was best described by a 2-compartmental model with first-order absorption. The appropriateness of the 2-compartment over the 1-compartment PK model was based on the visual comparison of goodness-of-fit plots (Fig. 1; top panel) and the lower objective function value. The ADVAN4 TRANS4 subroutines and the first-order conditional estimation method with interaction option in NONMEM were used to estimate the 2-compartment PK model parameters. The final population PK parameters for haloperidol are shown in Table 2. Interindividual variability could only be estimable for CL/F and Vc/F. The unexplained variability (RUV) in the PK model was 44%. This high variability may be partly caused by lack of individual PK information for a number of patients. None of the patient-related covariates in our data set influenced the population typical PK parameters at the *P* level of 0.05. The median parameter estimates obtained from the 985 successful bootstrap replicates of the PK data were within 5% of those obtained with the final PK model and the original data set. Median values of the parameter estimates from the SSE analysis are in most cases in good agreement with the model-estimated

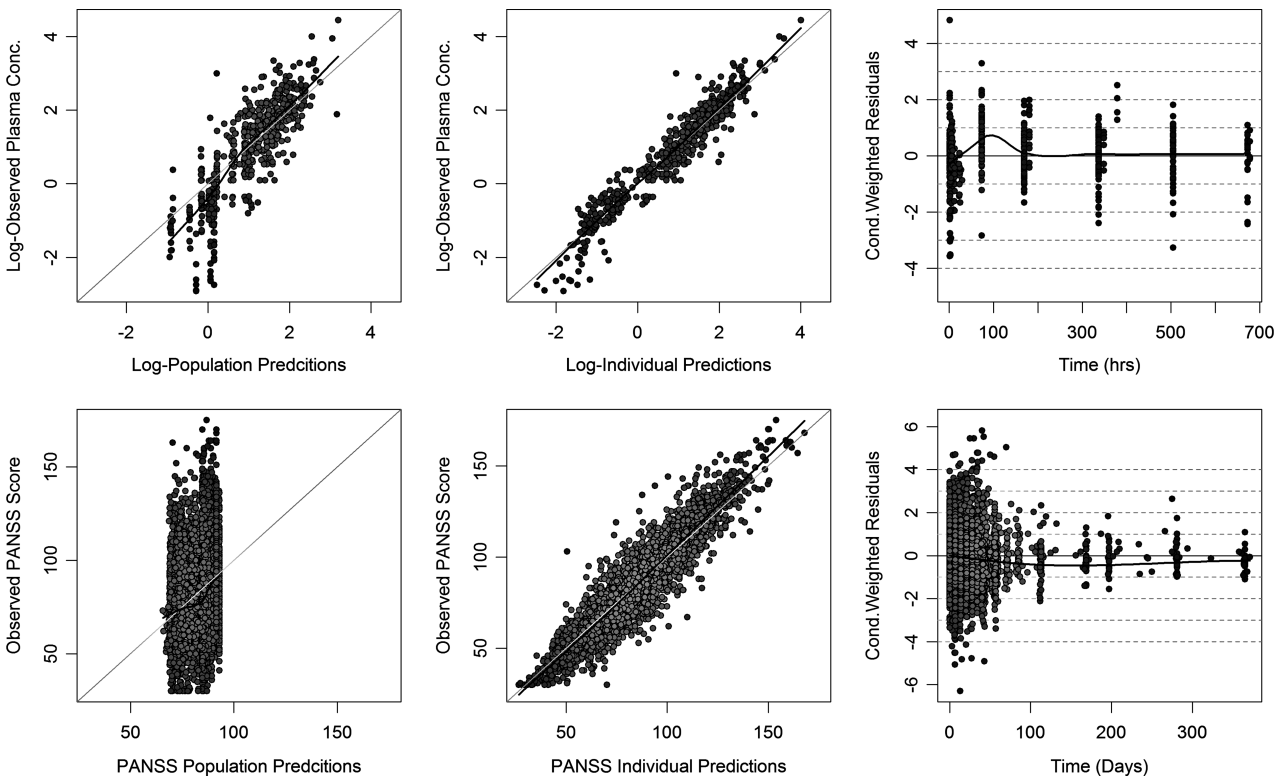

FIGURE 1. Goodness-of-fit-plots of the haloperidol final PK (top panel) and PKPD model (bottom panel). Gray line represents identity line, and black line represents a LOESS fit. Dots are observed data.

TABLE 2. Summary of Haloperidol Final PK Model and Model Evaluation Results

Parameters	Original Data Set (%RSE)	Bootstrap Results Median (95% Confidence Interval)	SSE Results Median	SSE Results % Bias
PK model				
CL/F (L/h)	88 (6)	89 (77–101)	86	−2
Q/F (L/h)	233 (28)	225 (56–391)	250	12
Vc/F (L)	669 (29)	637 (91–1143)	700	9
Vp/F (L)	2500 (39)	2487 (573–3565)	2715	12
Ka (h^{-1})	0.236 (18)	0.227 (0.056–0.387)	0.235	6
IIV-CL (%CV)	44.5 (13)	44 (31–55)	44	−0.5
IIV-Vc (%CV)	116 (14)	119 (95–180)	122	−5
RUV proportional	0.44 (3)	0.44 (0.38–0.50)	0.44	−6
PKPD model				
Baseline PANSS	91.6 (1)	91.6 (90.8–92.3)	91.7	0.5
P_{max}	0.081 (9)	0.075 (0.064–0.096)	0.083	4
E_{max}	0.31 (20)	0.34 (0.19–0.66)	0.29	−2
EC_{50} (ng/mL)	3.58 (39)	4.03(1.89–10.78)	2.71	−15
KT (1/d)	0.116 (4)	0.113 (0.062–0.167)	0.12	6
$t_{½}$ (delay in drug effect in days)*	6	—	—	—
BHAZ: placebo (1/d)	0.00139 (9)	0.00144 (0.0009–0.0015)	0.00139	0.1
BHAZ: haloperidol (1/d)	0.0009 (9)	0.00087 (0.00066–0.00111)	0.0009	0.1
BETA	−0.0295 (2)	−0.0292 (−0.0317 to 0.0271)	−0.0292	−0.2
IIV P_{max} (SD)	0.20 (4)	0.20 (0.19–0.22)	0.21	−0.2
IIV baseline PANSS (%CV)	16 (4)	16 (15–17)	16	−1
IIV E_{max} (SD)	0.29 (35)	0.28 (0.17–0.48)	0.27	−7
IIV EC_{50} (%CV)	152 (48)	151 (76–287)	138	16
RUV as SD (additive)	8.7 (1)	8.7 (8.3–9.1)	8.6	0.1

*Calculated using equation $t_{½} = 0.693 / KT$. The IIV shrinkage values were less than 20% except for EC_{50} (>50%). The RUV shrinkage was 16.2%. The accuracy (bias %) in parameter estimation by the SSE method is computed as = 100 × mean (estimated parameter − true parameter) / true parameter. $\%CV = \sqrt{\omega^2} * 100$.

BETA indicates parameter relating hazard to PANSS score; BHAZ, baseline hazard; CL/F, apparent clearance; EC_{50}, concentration to achieve 50% of E_{max}; E_{max}, maximum drug effect; ka, absorption rate constant; KT, rate constant to account for delay in drug effect; P_{max}, maximum placebo effect; Q/F, inter-compartmental clearance; RUV, residual unexplained variability; Vc, central volume of distribution; Vp, peripheral volume of distribution.

original value. The bias in the parameters estimates were not more than 12% for all the PK parameters. A representative VPC plot following 1000 simulations based on the final PK model is shown in Figure 2.

Haloperidol PKPD Analysis

An E_{max} model was used to quantify the drug effect. To quantify the exposure-response relationship of haloperidol, a patient-specific steady-state plasma concentration was used. The maximum placebo effect (P_{max}) for a typical schizophrenic patient was estimated to be 0.081 (ie, the maximum relative decrease in PANSS from the baseline PANSS score was 8.1%). The estimate of P_{max} and the placebo model fits were similar to our previously reported work.[13] The maximum drug effect (E_{max}) of haloperidol was found to be 0.31 (ie, the maximum relative decrease in PANSS score from baseline following haloperidol treatment on top of the placebo effect was 31%). We explored different model structures such as additive drug effect and combination of additive placebo effect and proportional drug effect to the baseline PANSS score to describe the time course of PANSS. Proportional relative placebo/drug effect to baseline PANSS was found to be a better and more stable model when compared with the other models. The typical EC_{50} value for PANSS total was found to be 3.58 ng/mL. The IIV of EC_{50} parameter (152% CV) was found to be relatively large in our analysis. This high variability may be partly caused by lack of individual PK information for a number of patients. To investigate the effect of IIV-EC_{50} on the precision of the PD parameter estimates, we compared the models with estimating IIV-EC_{50} and fixing IIV-EC_{50} at 50% CV. The PD parameter estimates (E_{max} and EC_{50}) were found to be comparable with similar precision. Hence, based on ΔOFV value, we choose the PKPD model with estimating the IIV-EC_{50} for further model evaluation steps.

The bootstrap results from the 957 successful runs are shown in Table 2. The difference between the median parameter estimates obtained from the successful bootstrap replicates of the PKPD data and those obtained with the final PKPD model with the original data set were less than 2.5%. Moreover, the final parameter estimates from the developed model were well within the bootstrap 95% confidence interval. Simulation-based (SSE) results indicated that PKPD model parameters were estimated precisely (Table 2). Case-by-case deletion diagnostics of the PKPD model showed that the model parameters were robust and precise toward the deletion of any one study (data not shown).

We extended the use of the developed PKPD model to the PANSS subscales. The model was able to describe the time course of positive and negative symptoms adequately without any further

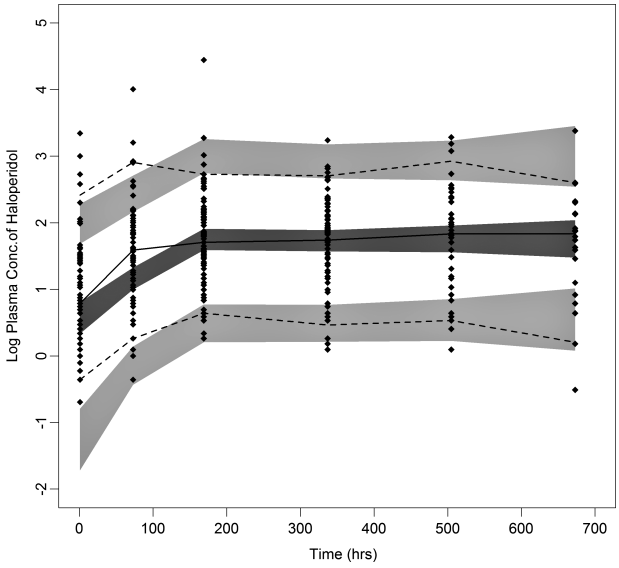

FIGURE 2. A representative VPC plot for the final PK model (shown only for LMU data). The gray shaded areas represent the 95% confidence intervals of the corresponding 2.5th, 50th, and 97.5th percentiles of the simulated data; the black dashed area represents the 2.5th and 97.5th percentiles of the observed data, and the black solid line represents the median of the observed data.

modification. The predictors of the placebo effect (unpublished data) for both symptoms were also accounted for in the model. The efficacy of haloperidol (E_{max}) for positive symptoms was approximately twice that of negative symptoms (0.48 vs 0.21), respectively, and the corresponding EC_{50} values were 1.28 and 6.39 ng/mL (Table 3). The parameter estimates of both subscales were estimated precisely with %RSE of less than 35%. Haloperidol exposure to produce a 30% change in PANSS total score from baseline PANSS was found to be 2.7 ng/mL, and the corresponding dose was 5.6 mg/d.

A dropout model based on the observed PANSS score was selected for further evaluation. The BHAZ parameter describing the hazard of a patient dropping out at baseline levels of covariates or predictors may be different for different treatments; hence, we estimated separate BHAZ for the placebo and the haloperidol treatment.

The estimates of BHAZ for placebo and haloperidol were found to be 0.0014 and 0.0009, respectively. The BETA parameter, which describes the hazard of a patient dropping out from a trial based on the observed PANSS irrespective of treatment, was estimated to be −0.0295. The value −0.0295 indicates that probability of a patient dropping out from a trial increased exponentially with increasing PANSS score. Monte Carlo simulations were performed along with the combined PANSS + dropout model + covariates, in which the observed PANSS scores were replaced with the simulated PANSS scores from the final PKPD model after accounting for dropouts and its predictors (see Supplementary Figure, Supplemental Digital Content 1, http://links.lww.com/JCP/A210; bottom panel). When dropout was ignored, the simulations showed wide prediction intervals at the end of the study, whereas the actual observed percentile intervals were much narrower (see Supplementary Figure, Supplemental Digital Content 1; top panel http://links.lww.com/JCP/A210). When the dropout model was included in the simulations, the simulated prediction intervals were in close agreement with those of the observed percentile intervals, indicating that patients, who had higher PANSS, or worsening of disease condition, had dropped out before the end of the trial. The LMU study was an open-label study with a flexible-dosage regimen in which the haloperidol dose was adjusted based on psychotic symptoms and tolerability; therefore, it may have some consequences on drug effect parameters.[12] Omitting an LMU study did not result in any marked changes in parameter estimates, but resulted in less precise parameter estimate of EC_{50}.

DISCUSSION

In clinical practice and drug development, an understanding of the exposure-response relationship is crucial for the efficient determination of a suitable therapeutic range for the majority of patients. Population PK modeling has been used in analyzing data from clinical trials, as well as data derived from routine clinical practice.[18] This approach has the advantage of incorporating all patient-related covariates into the PKPD model, whereas the conventional noncompartmental approach of PK analysis considers these factors as a burden for data analysis and hence to be controlled.[17] The nonlinear mixed-effects modeling approach allows analyzing the data of all individuals at once and considers interindividual and intraindividual random effects. This ensures that confounding correlations and disparity that may occur in observational data are properly accounted for.[19]

Dose-response analyses ignore drug-target interaction (eg, binding, activation, transduction mechanisms) and do not take individual differences in exposure into account. Thus, they are a poor descriptor for understanding the system pharmacology. On the other hand, exposure-response analysis linking dose, plasma concentration, and clinical effects can support dosage adjustments in patients where PK differences are expected to arise from factors such as race or demography, disease, genetic polymorphism, smoking, and drug interactions. In this regard, PKPD modeling

TABLE 3. Calculated Effective Haloperidol Dose and Concentrations for PANSS Total, PANSS Positive, and PANSS Negative Subscales at 30% Reduction in Score From Baseline

	PKPD Model Estimated Parameters				Effective Concentration (C_{eff}), ng/mL	Corresponding Dose: Effective Dose = Css × CL/F, mg/d
	Baseline Score	P_{max}	E_{max}	EC_{50}		
PANSS total	91.6	0.081	0.31	3.6	2.7	5.6
PANSS positive subscale	23.4	0.099	0.41	1.2	0.54	1.2
PANSS negative subscale	24.1	0.047	0.21	6.4	31	65

$C_{eff} = EC_{50} / (E_{max} / (1 - \text{PANSS} / (\text{baseline PANSS} \times (1 - P_{max}))) - 1)$; % change in score is given by (PANSS − baseline PANSS) / (baseline PANSS − number of PANSS items) × 100.

*Number of PANSS items: PANSS total: 30; PANSS positive: 7; PANSS negative: 7.

could be an excellent tool not only to characterize the time course of drug effects but also to separate drug-specific and system-specific factors contributing to the PD of a drug. Furthermore, simulations can be performed using a developed PKPD model parameters to answer "what if" scenarios, for example, for different doses, dosing frequency, sample size selection, and trial duration for future clinical trials. In this article, we have focused on exposure-response analysis rather than optimizing the clinical trials.

So far, no population-based PKPD model is available for haloperidol. The aim of this study was to develop a PKPD model that quantifies the efficacy of haloperidol, accounting for the placebo effect and dropouts. Subsequently, the developed PKPD model was utilized to characterize an improved dosing strategy (what dose and related exposure) for using haloperidol as a comparator drug in future antipsychotic drug trials or observational clinical studies.

The current data analysis utilized pooled data from 3 randomized controlled trials and 1 open-label clinical study, which consists of heterogeneous populations including whites, black, Asian, and Hispanic people. The parameter estimates from the PK model were comparable to those reported in Japanese patients by Yukawa et al.[20] None of the tested demographic covariates had a significant effect on haloperidol disposition. However, we used a fixed allometric relationship with individual body weight as the adjustment of clearance to body size as it reduced OFV and uncertainty in the parameter estimates to a certain extent. The paucity of PK information in the data set could have masked the influence of covariates on haloperidol disposition. Nevertheless, Yukawa et al[20] reported that haloperidol oral clearance in Japanese patients was affected by 4 covariates, namely, body weight, age, dose, and antiepileptic drug comedication. Therefore, the effect of covariates in patients from another race/ethnicity (eg, whites) cannot be ruled out completely. We did not have plasma measurements from the chronic patients, and C_{ss} for these patients was calculated based on the population PK model adjusted to the patient's body weight, dose, and dosage regimen. Hence, we did not succeed in quantifying precisely the influence of covariates on the drug effect parameters such as EC_{50}. However, based on a population approach, the EC_{50} value for chronic patients was found to be 8.5 ng/mL (data not shown). Santos et al[21] reported that a different therapeutic window for a subchronic and chronic patient exists for haloperidol. This finding was further supported with our covariate results, suggesting that chronic patients need higher plasma levels than do the acute patients, which could be due to development of resistance (eg, D_2 receptor levels) by chronic patients to haloperidol exposure. Using PK-PD modeling, it is possible to adjust the dose for a specific set of patients.

Because of the lack of information about reduced haloperidol, that is, the main metabolite of haloperidol, metabolite kinetics was not included in our PK model. However, evidence suggests that the antipsychotic effect in patients with acute schizophrenia is mainly due to parent drug, and there is no additional contribution of reduced haloperidol.[22] Hence, absence of metabolite kinetics in our PK model may be of less concern while estimating the PD parameters.

Haloperidol has a high affinity (K_i) to dopamine D_2 receptors (0.7 nM) and a slow rate of dissociation (0.017 min^{-1}),[23] whereas it has a low affinity to other receptors such as 5-HT_{2A}, D_1, and D_3.[24] Because of these pharmacological properties, it is hypothesized that haloperidol may exhibit a lower potency toward the negative symptoms.[23] We used the final PKPD model to characterize the efficacy of haloperidol toward the PANSS positive and negative symptoms. Haloperidol exhibited a lower E_{max} for negative symptoms over positive symptoms; this finding is in line with the hypotheses that the negative symptoms do not only depend on dopaminergic hyperactivity, and the involvement of other receptors plays an important role in exhibiting a better efficacy toward the negative symptoms.

At present, the PANSS total score is more commonly used than the Brief Psychiatric Rating Scale. Thus, an investigation was performed using the PANSS score as a clinical end point to estimate the precise therapeutic dose or exposure range of haloperidol required in the clinic. Haloperidol exposure to produce a 30% change in PANSS total score from baseline PANSS was found to be 2.7 ng/mL (Table 3), which is in agreement with the effective mean concentration of haloperidol of 3.82 ng/mL as reported by Giegling et al.[7] The corresponding dose for a 30% change in PANSS score from baseline PANSS was found to be 5.6 mg/d. The baseline PANSS was opted as reference in this analysis, as in routine clinical practice, the % change in PANSS score from baseline is the most commonly used end point. Moreover, in our case, not all studies were placebo-controlled trials, not allowing the calculation of real drug effect from placebo.

To characterize the relationship between the clinical efficacy and D_2RO levels, we used the following relationship: $D_2RO = RO_{max} * C_{eff} / (K_d + C_{eff})$, where RO_{max} is the maximum receptor occupancy, and K_d is the plasma level of haloperidol associated with 50% of D_2RO. The values of K_d (0.32 ng/mL) and RO_{max} (84%) were directly obtained from a recent article by Uchida et al,[25] whereas the C_{eff} is calculated value (2.7 ng/mL) from our final PKPD model and was used in the above equation to calculate mean D_2RO. The PKPD model–derived haloperidol C_{eff} value relates to 75% D_2RO, which is in close agreement with the presumed D_2RO therapeutic window of 65% to 80%.[26,27]

In the standard statistical analysis, the estimation of drug effect may be influenced by the high placebo effect and the high dropout rate. We used a model-based normalized placebo effect after accounting for the predictors of placebo response to quantify the drug effect. In addition, we demonstrated that joint modeling of drug effect and dropout should be considered,[13] while predicting the drug effect in clinical trials (see Supplementary Figure, Supplemental Digital Content 1; bottom panel http://links.lww.com/JCP/A210). The limitation of this work is that we mainly focused on linking the exposure to the efficacy parameters; however, an additional support for this choice of dose by linking the exposure to safety parameters (eg, modeling of extrapyramidal side effects) to further optimize the therapeutic dose range of haloperidol is in progress. In conclusion, based on our data analysis, the haloperidol recommended dose if used as a comparator in clinical trials with diverse schizophrenic patients to achieve a good clinical effect is 5.6 mg/d, and the corresponding plasma haloperidol exposure is found to be 2.7 ng/mL.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no relevant conflicts of interest.

REFERENCES

1. Kudo S, Ishizaki T. Pharmacokinetics of haloperidol—an update. *Clin Pharmacokinet*. 1999;37(6):435–456.

2. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009;373(9657):31–41.
3. McEvoy JP, Schooler NR, Wilson WH. Predictors of therapeutic response to haloperidol in acute schizophrenia. *Psychopharmacol Bull*. 1991;27(2):97–101.
4. Van Putten T, Marder SR, Mintz J. A controlled dose comparison of haloperidol in newly admitted schizophrenic-patients. *Arch Gen Psychiatry.* 1990;47(8):754–758.
5. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry* 2004;161(2):1–56.
6. Pilla Reddy V, Petersson K, Suleiman AA, et al. Pharmacokinetic-pharmacodynamic modeling of severity levels of extrapyramidal side effects with Markov elements. Cpt: Pharmacometrics & Systems Pharmacology. 2012;1(9):e1.
7. Giegling I, Drago A, Schafer M, et al. Interaction of haloperidol plasma level and antipsychotic effect in early phases of acute psychosis treatment. *J Psychiatr Res*. 2010;44(8):487–492.
8. Beal S, Sheiner LB, Boeckmann A, et al. *NONMEM User's Guides (1989–2009)*. Ellicott City, MD: Icon Development Solutions; 2009.
9. Lindbom L, Pihlgren P, Jonsson N. Psn-Toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. *Comput Methods Programs Biomed*. 2005;79(3):241–257.
10. Beal SL, Sheiner LB, Boeckmann AJ. *NONMEM User's Guides*. Ellicott City, MD: Icon Development Solutions; 2010.
11. Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu Rev Pharmacol Toxicol*. 2008;48:303–332.
12. Friberg LE, De Greef R, Kerbusch T, et al. Modeling and simulation of the time course of asenapine exposure response and dropout patterns in acute schizophrenia. *Clin Pharmacol Ther.* 2009;86(1):84–91.
13. Pilla Reddy V, Kozielska M, Johnson M, et al. Modelling and simulation of the Positive and Negative Syndrome Scale (PANSS) time course and dropout hazard in placebo arms of schizophrenia clinical trials. *Clin Pharmacokinet*. 2012;51(4):261–275.
14. Zhang LP, Beal SL, Sheiner LB. Simultaneous vs. sequential analysis for population PK/PD data I: best-case performance. *J Pharmacokinet Pharmacodyn*. 2003;30(6):387–404.
15. Zhang LP, Beal SL, Sheiner LB. Simultaneous vs. sequential analysis for population PK/PD data II: robustness of methods. *J Pharmacokinet Pharmacodyn*. 2003;30(6):405–416.
16. Efron B. Bootstrap confidence-intervals for a class of parametric problems. *Biometrika*. 1985;72(1):45–58.
17. Efron B. Better bootstrap confidence-intervals. *J Am Stat Assoc*. 1987;82(397):171–185.
18. Wade JR, Sambol NC. Felodipine population dose-response and concentration-response relationships in patients with essential-hypertension. *Clin Pharmacol Ther.* 1995;57(5):569–581.
19. Ette EI, Williams PJ. Population Pharmacokinetics II: estimation methods. *Ann Pharmacother.* 2004;38(11):1907–1915.
20. Yukawa E, Hokazono T, Yukawa M, et al. Population pharmacokinetics of haloperidol using routine clinical pharmacokinetic data in Japanese patients. *Clin Pharmacokinet*. 2002;41(2):153–159.
21. Santos JL, Cabranes JA, Vazquez C, et al. Clinical-response and plasma haloperidol levels in chronic and subchronic schizophrenia. *Biol Psychiatry.* 1989;26(4):381–388.
22. Ulrich S, Neuhof S, Braun V, et al. Reduced haloperidol does not interfere with the antipsychotic activity of haloperidol in the treatment of acute schizophrenia. *Int Clin Psychopharmacol*. 1999;14(4):219–228.
23. Kapur S, Seeman P. Does fast dissociation from the dopamine D-2 receptor explain the action of atypical antipsychotics?: A new hypothesis. *Am J Psychiatry.* 2001;158(3):360–369.
24. Gardner DM, Baldessarini RJ, Waraich P. Modern antipsychotic drugs: a critical overview. *CMAJ.* 2005;172(13):1703–1711.
25. Uchida H, Takeuchi H, Graff-Guerrero A, et al. Predicting dopamine D(2) receptor occupancy from plasma levels of antipsychotic drugs a systematic review and pooled analysis. *J Clin Psychopharmacol*. 2011;31(3):318–325.
26. Kapur S, Zipursky R, Jones C, et al. Relationship between dopamine D-2 occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry.* 2000;157(4):514–520.
27. Nordstrom AL, Farde L, Wiesel FA, et al. Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects—a double-blind PET study of schizophrenic-patients. *Biol Psychiatry.* 1993;33(4):227–235.
28. Kapur S, Remington G, Jones C, et al. High levels of dopamine D-2 receptor occupancy with low-dose haloperidol treatment: a PET study. *Am J Psychiatry.* 1996;153(7):948–950.
29. Kapur S, Zipursky R, Roy P, et al. The relationship between D-2 receptor occupancy and plasma levels on low dose oral haloperidol: a PET study. *Psychopharmacology.* 1997;131(2):148–152.
30. Xiberas X, Martinot JL, Mallet L, et al. Extrastriatal and striatal D-2 dopamine receptor blockade with haloperidol or new antipsychotic drugs in patients with schizophrenia. *Br J Psychiatry.* 2001;179:503–508.
31. Farde L, Nordstrom AL, Wiesel FA, et al. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. *Arch Gen Psychiatry.* 1992;49(7):538–544.
32. Liem-Moolenaar M, Te Beek ET, De Kam ML, et al. Central nervous system effects of haloperidol on THC in healthy male volunteers. *J Psychopharmacol*. 2010;24(11):1697–1708.
33. Nordstrom AL, Farde L, Halldin C. Time course of D2-dopamine receptor occupancy examined by PET after single oral doses of haloperidol. *Psychopharmacology (Berl)*. 1992;106(4):433–438.