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Population Pharmacokinetics of Perphenazine in Schizophrenia Patients from CATIE: Impact of Race and Smoking

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Abstract

The goal of the study was to characterize population pharmacokinetics (PPK) for perphenazine in patients with schizophrenia from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). Patients (n = 156) received 8–32 mg of perphenazine daily for 14 to 600 days for a total of 421 plasma concentrations measurements. Nonlinear mixed-effects modeling was used to determine PPK characteristics of perphenazine. One- and two-compartment models with various random effect implementations and mixture distributions were evaluated. Objective function values and goodness of fit plots were used as model selection criteria. Age, weight, sex, race, smoking, and concomitant medications were evaluated as covariates. A one-compartmental linear model with proportional error best described the data. The population mean clearance and volume of distribution for perphenazine were 483 L/h and 18,200 L, respectively. Race and smoking status had significant impacts on perphenazine clearance estimates. In addition, the estimated population mean clearance was 48% higher in nonsmoking African Americans than in nonsmoking other races (512 L/h versus 346 L/h). Active smokers eliminated perphenazine 159 L/h faster than nonsmokers in each race. Clearances for smoking African Americans versus smokers in other races were 671 L/h versus 505 L/h, respectively.

Keywords

Perphenazine; Population Pharmacokinetics; Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE); Race and Smoke; Schizophrenia

Introduction

Schizophrenia affects about 1.1 percent of the U.S. population age 18 and older each year (<http://www.nimh.nih.gov/health/publications/schizophrenia/complete-publication.shtml>). Current pharmacologic treatment for schizophrenia includes the first generation antipsychotics (FGA) and second generation antipsychotics (SGA). The NIMH funded Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) Schizophrenia Trial was the first systematically designed clinical trial that studied treatment selections for schizophrenia. The CATIE schizophrenia trial compared relative effectiveness of SGA to a typical representative of the FGA, perphenazine¹. Although SGAs are more commonly used clinically than FGAs, the results of the study showed that perphenazine, a conventional FGA, had similar efficacy to most of the SGAs including quetiapine, risperidone, and ziprasidone. Olanzapine appeared to have better efficacy than perphenazine, but it caused greater weight gain and glucose/lipid metabolism derangements^{2, 3}. In addition, the CATIE studies also found that perphenazine was more cost effective when compared with second-generation antipsychotics without significant differences in measured outcome⁴. Similar to other phenothiazine antipsychotics, perphenazine is thought to produce its antipsychotic effect by binding to dopamine receptors.⁵ After intravenous dosing, perphenazine is extensively metabolized by CYP2D6 in the liver⁶. The total body clearance of perphenazine is around 100 L/h with a volume of distribution from 10 to 34 L/kg⁷. The half-life of perphenazine is approximately 9.5 hrs with an oral bioavailability of 20%⁷.

So far, limited data on the population pharmacokinetics (PPK) of perphenazine is available in the literature⁸. PPK analysis is a robust tool for obtaining valuable pharmacokinetic (PK) information from large clinical trials under conditions of sparse concentration sampling^{9, 10}. The effect of potential covariates on drug exposure can also be evaluated in PPK analysis by incorporating patient specific information into the modeling process. Data from the CATIE schizophrenia trial provided the opportunity to determine PPK parameters for perphenazine in a typical schizophrenic patient population and evaluate the effect of potential covariates (eg. age, body weight, sex, smoking status, and concomitant medications etc.) on perphenazine drug exposure.

The goal of this study was to characterize PPK for perphenazine in patients with schizophrenia from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and to identify the potential contributors to variability in perphenazine exposure.

Subjects and Methods

Subjects and Samples

The details of the study design of CATIE schizophrenia trial have been published elsewhere^{2, 11, 12}. The study was conducted at multiple sites in the US. Patients diagnosed with schizophrenia were recruited into the study. Patients prescribed perphenazine (n = 156) received 8–32 mg of medication daily for 14 to 600 days. One blood sample per patient per visit was collected during patient clinical visits with up to six visits total. The last dose time before each blood sample was recorded as reported by the patient and the sample time noted exactly by the phlebotomist. This analysis excluded data that had undetectable perphenazine concentrations in a sample, unreported dose magnitude, or a missing time for the dose and/or blood sample. A total of 421 plasma concentration measurements meeting the aforementioned criteria were available for model development. The PK sampling for each patient was sparse with an average of 2.7 perphenazine concentration measurements per patient.

Patient characteristics

Patient demographics are summarized in Table 1. Patients in the study included 115 males and 41 females between the ages of 18–65. The average age of the subjects was 40 years with an average body weight of 88.9 kg. The patient population was predominantly Caucasian (65% (n=102)), with 29% (n=46) black/African American, 4% (n=6) Asian, and 1% (n=2) two/more races. In addition, 67% (n=104) of the subjects were active smokers.

Determination of Perphenazine Concentrations

Perphenazine was measured by reverse phase high performance liquid chromatography (HPLC) using electrochemical detection with settings of detector 1: +0.20V, detector 2: +0.73V, and the guard cell: +0.75V. This method was developed by the Clinical Pharmacology Lab at the University of Pittsburgh¹³. Plasma was extracted using liquid-liquid extraction (ethyl acetate - n-hexane (4:2), v/v) and back extracted using 0.025M potassium phosphate; pH 2.4 separation was completed using a Nucleosil C18, 5 micron, 120 × 4.6mm I.D. with a flow rate of 1ml/min at room temperature. The assay was linear in the range from 0.5 – 25 ng/ml with inter-assay variability (C.V.) of 4.1–10.0% and reproducibility (C.V.) of 3.37–9.13%. The limit of quantitation for perphenazine was 0.5 ng/ml for this assay.¹³

Population Pharmacokinetic Analysis

PPK analysis of perphenazine was performed using NONMEM® (version 5.1.1, Icon, Hanover, MD). The initial modeling focused on developing a base model where a model structure was identified without incorporating any covariates. One and two-compartment linear mammillary PK models with first-order absorption and elimination were evaluated using ADVAN2 TRANS2 and ADVAN4 TRANS4 during model development, respectively. Inter-individual variability was included in the base model as a random effect and to be log-normally distributed. The individual estimates of PK parameters ($P_j = P_{TV} \times e^{\eta_P}$) was a function of the both the population estimates (P_{TV}) and random variables (η_P). The parameter P_j was the estimated PK parameter value for the j^{th} individual, P_{TV} was the estimated value for the population, and η_P described the difference between P_j and P_{TV} , which was assumed to be a normally distributed with a mean of zero and variance of ω_P^2 ^{14, 15}. The absorption rate constant (K_a) was fixed to 1.6 hr⁻¹ based on literature reported $t_{1/2}$ and t_{max} values^{6, 7} because of difficulty directly estimating this parameter within this dataset. The residual error was comprised of, but not limited to, intra-individual variability, experimental errors, process noise, and model misspecifications, if any. Additive ($y_{ij} = \hat{y}_{ij} + e_{ij}$), proportional ($y_{ij} = \hat{y}_{ij}(1 + e_{ij})$) and combined error structures ($y_{ij} = \hat{y}_{ij}(1 + e_{ij}) + e_{ij}'$) were tested, where y_{ij} is the j^{th} observed perphenazine concentration in the i^{th} individual, $\hat{y}_{ij}$ is the corresponding model prediction, and e_{ij} (or e_{ij}') is a random variable assumed normally distributed with a mean of zero and a variance of σ_1^2 (or σ_2^2).

Patient demographic information, such as patient age, weight, race etc., may explain some of the variability in the perphenazine PK parameter estimates. In the study, both continuous covariates (e.g., age, weight) and discrete covariates (e.g., sex, race, smoking status, and concomitant medications) were tested. The effect of continuous covariates on PK clearance estimates was evaluated using the following model structures:

$$\begin{aligned}
 TVCL &= \theta_{CL} * (Cov / Med_{Cov})^{\theta_{Cov}} \quad (\text{centered power model}) \\
 TVCL &= \theta_{CL} * \exp(\theta_{Cov} * (Cov / Med_{Cov})) \quad (\text{centered exponential model}) \\
 TVCL &= \theta_{CL} + \theta_{Cov} * (Cov - Med_{Cov}) \quad (\text{linear model}) \\
 TVCL &= \theta_{CL} + \theta_{Cov} * Cov \quad (\text{linear model}) \\
 CL &= TVCL * e^{\eta_l}
 \end{aligned}$$

where $TVCL$ is the population estimate for clearance; Cov represents the subject specific value of continuous covariate; Med_{Cov} is the median value of the Cov . θ_{CL} and θ_{Cov} are estimated fixed effect parameters; η_j is the random variable describing the difference of the estimated CL for j^{th} subject from the typical population value.

Categorical variables were assigned to each of race (Black/African American=1, other races=2). The coding example of incorporating the effect of race on CL estimate was shown as following:

$$\begin{aligned} IF (RACE.EQ.1) TVCL &= \theta_{CL1}; \\ IF (RACE.EQ.2) TVCL &= \theta_{CL2} \end{aligned}$$

where θ_{CL1} and θ_{CL2} are typical values of CL for Black/African American and other races, respectively. The effect of discrete covariates such as sex, smoking status, and concomitant medication were tested using the following structures:

$$TVCL = \theta_{CL} + Cov * \theta_{Cov}$$

For male and female patients, sex was assigned to be 0 and 1, respectively. For smoking status, nonsmoker and smoker were assigned to be 0 and 1, respectively. If patients had a concomitantly administered medication, the Cov was assigned to be 1 for that medication, otherwise Cov was 0. θ_{Cov} was the estimated fixed effect parameter for the covariate. Other parameters (eg, $TVCL$, η_j , and θ_{CL}) were the same as previously described.

A Bayesian approach conditioned on the population characteristics was used to estimate individual specific parameters. Both the base and final model were estimated using the first-order conditional estimation (FOCE) with interaction method. Continuous covariates (e.g., age, weight) and discrete covariates (e.g. sex, race, smoking status, and concomitant medications) were incorporated into each parameter by forward incorporation and backward elimination method. The covariate was retained in the model if the objective function value (OFV) decreased by 3.84 when adding one additional fixed effect parameter into model (χ^2 $p < 0.05$ $df = 1$). Goodness of fit plots were used as additional model selection criteria. These were generated using R[®] (version 2.6.2). Post-processing of NONMEM[®] outputs were performed using SPSS (version 14.0).

Bootstrapping and visual predictive check were used for model evaluation. Confidence intervals for the final parameter estimates were calculated from bootstrapping. A randomization test for significant covariates in the final model was performed using a method as implemented by Holford^{16, 17}. This was done by creating 1000 new data sets that were generated identically except for re-randomization of the association of the covariate so that the Null Hypothesis will be true under randomization. The delta OFVs from the original null OFVs were calculated by running the final model with these 1000 randomized new data sets. The delta OFVs were sorted and the quantiles for the delta OFVs corresponding to original data set as well as P values were identified (significance criteria of $P < 0.05$).

Results

Population pharmacokinetic modeling

A one-compartment model with linear elimination and proportional error best described the perphenazine PK in this patient population. Race and smoking status during the last week were significant covariates affecting clearance. The process of final model development is

summarized in Table 3. Diagnostic plots for the final model are listed in APPENDIX I. The final model was evaluated by bootstrapping as well as visual predictive check plots. Please refer APPENDIX II for predictive check plots. The randomization test showed that both race and smoking status were statistically significant factors that affected perphenazine. A histogram showing the delta OFVs for race and smoking status are presented in Figures 2a & Figure 2b, respectively.

The PK parameter estimates for the final model are listed in the Table 2. The population mean clearance and volume of distribution for perphenazine in the base model were 483 L/h and 18,200 L, respectively, without incorporating any covariates. Race and Smoking status were identified as two significant covariates for clearance of perphenazine. Patients who smoked in the past week eliminated the drug 159 L/h faster than nonsmokers, corresponding to a 33% increase in clearance compared to the whole population (483 L/h). Estimated population clearances for nonsmoking non-African Americans, smoking non-African Americans, nonsmoking African American, and smoking African Americans were 346 L/h, 505 L/h (346+159 L/h), 512 L/h, and 671 L/h (512+159 L/h), respectively. Estimated population mean clearance of perphenazine was 48% higher in nonsmoking African Americans than nonsmoker in other races. The combined effect of these two covariates is that smoking African Americans (671L/h) clear perphenazine 94% faster than non-smoking non-African Americans (346 L/h).

Post-processing of empirical Bayesian estimates for individual parameters are listed in Table 4. An independent-samples *t*-test showed a significant difference in the empirical Bayes estimated CL/F of perphenazine between African Americans (n=46) and other races (n=110) ($P<0.05$) (Figure 1a), active smokers (n=104) and non-smokers (n=52) ($p<0.01$) (Figure 1b), and smoking African Americans (n=38) and non-smoking non-African Americans (n=44) ($p<0.001$) (Figure 1c).

The analysis of the study showed that sex, age, weight were not significant covariates affecting the PK of perphenazine. The number of subjects on concomitant medications was less or equal to six for any medication and none of concomitant medications were identified as significant covariates for perphenazine clearance. (See APPENDIX III for detail)

Discussion

In this study, we successfully captured the exposure characteristics for perphenazine in schizophrenic patients using a PPK approach. Before incorporating any significant covariates, the population mean clearance and volume of distribution for perphenazine were 483 L/h and 18,200 L, respectively. Estimated sub-population clearances for non-African American non-smokers, non-African American smokers, African American nonsmoker, and African American smokers were 346 L/h, 505 L/h, 512 L/h, and 671 L/h, respectively. Hansen and his colleague reported the clearance of perphenazine at approximately 100 L/h with the volume of distribution of 10 to 34 L/kg after intravenous administration. The bioavailability of perphenazine is around 20% ⁷, hence the oral clearance should be around 500 L/h with a oral volume of distribution of 3,500–11,900 L based on their study. The population kinetics study conducted by Jerling ⁸ showed that population mean value for oral clearance and volume of distribution was 520 L/h and 16,140 L. Hence, the population estimated PK parameters in this study using highly sparse sampling data are consistent with other literature reported values.

Smoking status in the most recent week was also identified as a statistically significant contributor to the variability in estimated perphenazine clearance in schizophrenia patients. Patients who smoked in the past week had a mean clearance of 748 L/h compared to 453 L/h

for nonsmokers. An in-vitro metabolism study conducted by Olessen and his colleague¹⁸ showed that besides CYP2D6, other enzymes such as CYP1A2, 3A4, and 2C19 are involved in the N-dealkylation of perphenazine. In addition, smoking has been identified as a potent inducer of hepatic CYP1A1, 1A2, and 2E1¹⁹. Hence, metabolism of CYP1A2 substrate can be induced in smokers¹⁹. It is possible that perphenazine is metabolized by CYP1A2 clinically, which induced clearance of perphenazine at active smoker. The number of patients with schizophrenia who smoke is very high.^{20, 21} One study reported the prevalence to be 88%²², nearly three times the rate in the general population. Bigos and colleagues¹⁴ has reported that 66% of patients with schizophrenia who attended CATIE olanzapine study were active smokers. In our study, 67% of schizophrenia patients were active smokers. Due to the fact that many patients with schizophrenia smoke, it is important to pay more attention to the effect of smoking on perphenazine pharmacokinetics.

Racial differences in clearance have been identified in a few antipsychotic agents which are CYP2D6 substrate, such as olanzapine¹⁴, risperidone²³, and paroxetine¹⁵. In these studies, African Americans cleared these drugs faster than Caucasians. In this study, the population mean clearance of perphenazine was 48% higher in African Americans than that in other races in patients with schizophrenia. Feng et al. found that race was a significant covariate for both paroxetine and risperidone clearance, but the race effect on clearance was no longer significant when CYP2D6 genotype was incorporated for paroxetine or when a 3-component mixture model for clearance was used for risperidone. Perphenazine is primarily metabolized by CYP2D6 located in the liver⁶. Jerling and his colleague⁸ also reported that CYP2D6 genotype was a significant covariate on estimated oral clearance of perphenazine. So it is possible that CYP2D6 genotype is confounding factor for the racial difference in perphenazine clearance. There is evidence supporting racial differences in CYP2D6 polymorphism expression frequencies between African Americans and Caucasians. Specifically, Caucasians showed approximately 3-fold higher frequencies for the non-functional allele CYP2D6*4²⁴ compared to African Americans. These results suggest that observed race differences in clearance of perphenazine might due to racial differences in CYP2D6 polymorphism frequencies between African Americans and others.

Racial differences in adherence to prescribed perphenazine regimen between African Americans and other races may be another possible contributor to differences in perphenazine clearance. Lower adherence to antipsychotic treatment has been reported by other studies.²⁵ Some examples have demonstrated that African Americans are less likely to be adherent to antihypertensive medications^{26, 27} and inhaled corticosteroids²⁸ than Caucasians. Hence, both differences in the frequency of CYP2D6 polymorphism expression and adherence patterns to prescribed perphenazine regimen might contribute to racial differences in perphenazine clearance observed in this study. Further studies are required to identify the mechanisms contributing to the observed differences in perphenazine clearance across race. Racial information alone is not currently recommended for adjusting perphenazine dosage regimens in patients with schizophrenia.

To further explore the clinical significance of the difference in estimated clearance of perphenazine among these subpopulations, a response or tolerability analysis between these subpopulations should be performed. Due to lack of response data, we compared the administered dose across each of the subpopulations (Table 5). This evaluation was based on the assumption that physicians titrated the dose upward to achieve desired effects or titrated downward to avoid side effects and that these effects were concentration related. The average dose administered to active smokers was significantly higher than in patients who were not active smokers. In addition, the dose administered to African American was slightly higher than that to Caucasian patients, but this difference was not statistically significant. Therefore, until the mechanisms associated with the observed racial difference in

perphenazine clearance are better understood, smoking status seems to be a more clinically significant factor for dose adjustment.

Similar to olanzapine¹⁴ and risperidone^{23, 29} in the CATIE trial, there were very large variabilities in perphenazine exposure. Jerling *et al.*⁸ also reported wide variability for the PK of perphenazine. This wide variability in drug exposure, which may result from sociologic (e.g. adherence etc.) or biological factors (CYP 2D6 polymorphism expression rates), poses a clinical challenge in schizophrenia treatment and may be one of the reasons for the high discontinuation rate observed in CATIE study. Another potential contributor to the large degree of exposure variability observed for perphenazine in this study relates to the nature of the dosage input information and assumptions. The PPK models were developed based on patient reported last dosing time along with the assumption of steady state and full adherence. In a study of escitalopram³⁰, it was shown that inaccurate dosing history and patient adherence information affected estimation of absorption rate, volume of distribution, but not the clearance parameters for escitalopram.

In conclusion, race and smoking status in the past week were identified as two significant covariates affecting clearance. The dosage regimen of perphenazine in these populations may need to be adjusted clinically based on patients smoking status.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1a

Figure 1b

Figure 1c

Figure 1. Perphenazine clearance by subpopulation

Figure 1a: Perphenazine clearance by smoking status Figure 1b: Perphenazine clearance by race

Figure 1c: Combined effect of smoking and race on perphenazine clearance

Figure 2a: Randomization Test for Race (Histogram of Delta Objective Function Values)

Original Objective Function Value decreases was -5.189, $P=0.031$.

Figure 2b: Randomization Test for Smoking (Histogram of Delta Objective Function Values)

Original Objective Function Value decreases was -12.771, $P=0.000$

Figure 2. Randomization Test

Figure 2a: Randomization Test for Race (Histogram of Delta Objective Function Values)

Figure 2b: Randomization Test for Smoking (Histogram of Delta Objective Function Values)

Table 1

Patient demographics

Demographics	CATIE-Perphenazine
Sample size	156
Number of observations	421
Number of observations per subject	2.70
Age, mean years $\pm$ SD (range)	40.3 $\pm$ 10.6 (18–65)
Weight, mean kg $\pm$ SD (range)	88.9 $\pm$ 23.0 (49.4–195.0)
Gender, n (%)	
Male	115 (74%)
Female	41 (26%)
Race, n (%)	
Caucasian	102 (65%)
African American	46 (29%)
Asian	6 (4%)
Two or more races	2 (1%)
Smoking status, n (%)	
Active smoker	104 (67%)
Nonsmoker	52 (33%)

Table 2

Pharmacokinetic parameter estimates for perphenazine

Parameters	Parameter Estimates	95% CI
CL _{AA_nonsmoker} (l/h)	512	385~646.4
CL _{nonAA_nonsmoker} (l/h)	346	270~434.7
Smoke on CL (l/h)	159	63.5~267.4
V (l)	19300	13865~65795
K _a (h ⁻¹) (fixed)	1.6	N/A
ω_{cl} %	79.30%	68.1%~87.4%
ω_v %	78.50%	20%~122%
ω_{ka} %	336.10%	0.35%~518%
ω_{cl-v} %	100.00%	29% ~ 170%
σ_1 %	37.40%	33.3%~41.0%

CL, clearance; CL_{AA_nonsmoker}, clearance for nonsmoking African American; CL_{nonAA_nonsmoker}, clearance for nonsmoking non-African American; Smoke on CL, effect of smoking status on clearance, which was assumed to be independent on race; V, volume of distribution; ω , coefficient of variation of inter-individual variability; σ_1 , coefficient of variation of residual error (proportional); N/A, not available; 95% confidence interval (95%CI) was calculated from boots trapping step (re-sampling times=1000).

Table 3

Population Pharmacokinetic model development steps for perphenazine

Covariate	Model	-2LL	D-2LL	P value
	One compartment model	559.11		
base model	Two compartment model	557.861	-1.249	> 0.05
1-1 (CL)				
Age (centered power model)	M1	558.589	-0.521	> 0.05
Weight (centered power model)	M2	557.037	-2.073	> 0.05
Sex	M3	558.349	-0.761	> 0.05
Race	M4	553.352	-5.758	< 0.05
Smoking status	M5	545.87	-13.24	< 0.001
1-2 (V)				
Age (centered power model)	M6	555.758	-3.352	> 0.05
Weight (centered power model)	M7	558.973	-0.137	> 0.05
Sex	M8	556.941	-2.169	> 0.05
2				
Smoking status(CL)+Race(CL)	M9	540.681	-5.189	< 0.05

* Abbreviations: -2LL, objective function value; Δ-2LL, difference in objective function values between two models, -2LL values in CL (Smoking status) and CL (Race) were compared with base model; -2LL values in CL (Smoking status, Race) was compared with model CL (Smoking Status). Δ-2LL of 3.84 units was considered significant (χ^2 df=1 p<0.05). The function structure of incorporating covariate was described in the methods section. Race: African American vs. other races; Smoke: subjects who smoked in the past week vs. subjects who did not smoke in the past week.

Table 4

Post processed perphenazine clearance by population

Population	Mean Clearance (L/hr)	Standard Deviation	P value
Race			<0.05
African American (n=46)	775.90	513.52	
Other Races (n=110)	597.05	477.98	
Smoking Status			<0.01
Active Smoker (n=104)	748.24	513.76	
Non-Smoker (n=52)	452.87	385.93	
Race & Smoking Status			<0.001
Smoking African American (n=38)	833.90	536.95	
Non-Smoking Non African American (n=44)	444.23	406.64	

Table 5

Prescribed daily dose by population

Population	Mean of Prescribed Daily Dose (mg)	P value
Race		>0.05
African American (n=46)	25.04 ($\pm$ 7.47)	
Other Races (n=110)	23.63 ($\pm$ 7.77)	
Smoking Status		<0.05
Active Smoker (n=104)	25.33 ($\pm$ 7.39)	
Non-Smoker (n=52)	21.62 ($\pm$ 7.71)	
Race & Smoking Status		<0.05
Smoking African American (n=38)	25.55 ($\pm$ 7.36)	
Non-Smoking Non African American (n=44)	21.27 ($\pm$ 7.70)	