A Population PK Model for Cariprazine and the Metabolites

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INTRODUCTION

Cariprazine (CAR) is a potent dopamine D_3/D_2 receptor partial agonist with preferential binding to D_3 receptors. Cariprazine was originally discovered by Gedeon Richter Plc. in Budapest, Hungary, and is under development by Forest Research Institute, Inc. (FRI) and Gedeon Richter Plc. for the treatment of schizophrenia, bipolar disorder, and major depressive disorder and also by Mitsubishi Tanabe Pharma Corporation for the treatment of schizophrenia in Japan.

CAR possesses two major pharmacologically active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR). Metabolism of cariprazine and its major active metabolites is mediated by two enzymes, CYP3A4 and, to a lesser extent, CYP2D6.

OBJECTIVES

The purpose of the analyses described herein was:

- To describe the pharmacokinetics of CAR, DCAR and DDCAR in patients with schizophrenia or bipolar mania following once daily oral dosing with CAR using a population PK (PPK) modeling approach;
- To evaluate the influence of demographic characteristics, renal function, CYP2D6 genotype and certain classes of concomitant medications on the PK of CAR, DCAR and DDCAR;
- To assess the time to steady state, and functional half-life of CAR, DCAR and DDCAR.

METHODS

Data were obtained from 12 clinical studies:

- **Three** clinical pharmacology studies up to 35 days in duration with rich PK sampling in patients with schizophrenia;
- **Four** clinical studies up to 6 weeks in duration in patients with schizophrenia and **two** studies up to 3 weeks in duration in patients with manic or mixed episodes associated with bipolar I disorder evaluating the safety, efficacy, and tolerability of cariprazine relative to placebo;
- **Two** clinical studies up to 48 weeks in duration in patients with schizophrenia and **one** clinical study up to 16 weeks in duration in patients with manic or mixed episodes associated with bipolar I disorder evaluating the long-term safety, tolerability, and pharmacokinetics of cariprazine.

The PK population across all the studies consisted of 2392 patients, with doses ranging from 1.5 to 18 mg/day. The average age of the patients was 39 years, average weight 79 kg and ideal body weight (IBW) 64 kg, 66% of the subjects were male, 47% white, 35% African American and 15% Asian. Patients with normal renal function made up 82% of the PK population, while patients with mild and moderate renal impairment accounted for 17% and 1%, respectively.

All patients signed an informed consent for participation in the study. All the studies included dose titration.

Covariates: Multiple covariates were evaluated to explore their potential in explaining PK variability: age, BMI, weight, IBW (calculated as shown below), race, sex, ALB, AST, TBIL, CrCL (calculated using Cockcroft and Gault equation), NCI liver dysfunction classification, CYP2D6 metabolizer status.

$$\text{IBW (adult male) [kg]} = 51.65\ [\text{kg}] + 1.85\ [\text{kg/inch}] \times (\text{height [inch]} - 60)$$
$$\text{IBW (adult female) [kg]} = 48.67\ [\text{kg}] + 1.65\ [\text{kg/inch}] \times (\text{height [inch]} - 60)^{1}$$

The concomitant administration of medications classified as CYP2D6 inhibitors, CYP3A4 inhibitors, and P450 inducers was also evaluated.[2]

Model Development followed the steps:

1. Base structural model development
   - Initial base structural model development performed using the studies with rich PK sampling. Final base structural model development using rich and sparsely sampled PK.
   - The 3 PPK models for CAR, DCAR and DDCAR were fitted sequentially, with individual PK parameters for CAR fixed and serving as input to the DCAR PPK model and with individual PK parameters for CAR and DCAR fixed and serving as input to the DDCAR PPK model.
2. Evaluation of covariate effects
   - The influence of demographics and indices of hepatic and renal function was explored on each PK parameter separately using a step-wise generalized additive model (GAM) procedure in SAS and S-Plus. The direction of each step-wise search was both forward and backward. The final model for each PK parameter obtained from GAM analysis was then fit to the data in NONMEM. Univariate step-wise backward elimination of covariates in NONMEM proceeded until all remaining covariates were significant ($p<0.001$).
   - Next, the effects of the concomitant medication classes (CYP2D6 inhibitors, CYP3A4 inhibitors, and general CYP inducers) on apparent clearances (CL/F) for each moiety were added simultaneously to the model. The backward elimination procedure ($p<0.001$) was then followed to determine which concomitant medication covariates were statistically significant.
   - As a last step of the covariate analysis, the effect of CYP2D6 genotype status on the CL/F of CAR, DCAR and DDCAR was evaluated for a subset of patients sampled for genotype
   - The post-hoc Bayesian individual parameter estimates for CL/F, dose-normalized $AUC_{0\text{-}24}$, C_{max}, and C_{min} at steady state were used in a Wilcoxon signed-rank test to evaluate the effect of CYP2D6 metabolizer status on the PK of CAR, DCAR and DDCAR
3. Model refinement and validation was performed using visual predictive check and bootstrapping methods

Data preparation and presentation was performed using SAS® Version 9.2 and KIWI Version 1.1.[3] PPK modeling was performed in NONMEM Version 7.1.2. NONMEM analyses were performed on an Intel cluster with the Linux operating system

RESULTS

A total of 14613 CAR measurable plasma concentrations from 2392 patients, 14380 measurable DCAR plasma concentrations from 2387 patients and 13531 measurable DDCAR plasma concentrations from 2344 patients were used in the development of the PPK models.

The PPK analyses were conducted across doses ranging from 1.5 to 18 mg/day. The PK of CAR, DCAR and DDCAR in that dose range were linear.

The most parsimonious structural model describing CAR was a two-compartment disposition model with first-order elimination and sigmoid absorption, characterized by a zero-order input of the dose in a depot compartment followed by a first-order transfer into the central compartment. The diagram of the structural model is shown in Figure 1 and estimates of the final model parameters are shown in Table 1.

The most parsimonious structural model for DCAR was a one-compartment model with first-order elimination. Estimates of the final model parameters have been omitted for the purpose of this poster.

The most parsimonious structural model for DDCAR was also a one-compartment model with first-order elimination. Estimates of the final model parameters are shown in Table 2.

The dose-normalized observed plasma concentrations for all three moieties overlaid with model predictions are displayed in Figure 2

All three PPK models described the data adequately. Selected goodness of fit plots are shown in Figure 3. While a small number of observations at higher concentrations were underestimated by the PPK models, the overwhelming majority of the data were explained by the models well. A total of 500 bootstrap datasets were also generated by re-sampling with replacement (results not shown). Each parameter estimate of the final models was within the bootstrap 90% CI. VPC was performed with 100 replicates and described the predictive ability of the model adequately (the results are not shown).

The CL/F and V_c/F of each moiety were statistically dependent upon a function of body weight. Race, gender, and age were also statistically significant predictors of the CL/F or V_c/F of some moieties. However, none of these covariates were found to be clinically relevant (their effect ranged between 2-32%). Other variables describing hepatic and renal function were not found to be statistically significant.

The influence of all the covariates that were identified to be statistically significant in CAR, DCAR and DDCAR analyses were further examined for their influence on the total cariprazine (CAR+DCAR+DDCAR) steady-state exposure measures ($AUC_{0\text{-}24}$, C_{max} and C_{min}). While all of the identified covariates were of statistical significance, none were deemed to be clinically meaningful.

- Patients with IBW of 36-57 kg had, on average, 25% greater steady-state $AUC_{0\text{-}24}$ than those with IBW of 63-67 kg, whereas patients with IBW of 72-89 kg had, on average, 20% smaller steady-state $AUC_{0\text{-}24}$ than those with IBW of 63-67 kg

A total of 861 patients had both PK samples collected in the study and CYP2D6 genotype was determined by giving a blood sample. Of these, 39 patients were poor metabolizers. There were no statistical differences ($p>0.05$) in CAR and DCAR exposures and no clinically relevant differences in DDCAR exposures for poor metabolizers as compared to others (16% statistically higher in poor metabolizers, $p \le 0.05$).

Final CAR, DCAR, and DDCAR PPK models were used to determine time to steady state. It takes CAR, DCAR, DDCAR and total cariprazine approximately 4, 4, 31, and 27 days, respectively to achieve 90% of the absolute steady state; this corresponds to functional half-lives of 1.1, 1.1, 8.9 and 7.7 days, respectively.

Based on the final PPK models, at steady state CAR, DCAR and DDCAR plasma concentrations were estimated to be 25%, 7%, and 68%, respectively, of the total cariprazine.

Figure 4 shows average CAR, DCAR, and DDCAR exposures for a typical patient following 21 days of dosing titrated to 12 mg/day dose by Day 10.

Figure 1. Final PPK Model Diagram with Typical Value Parameter Estimate Equations

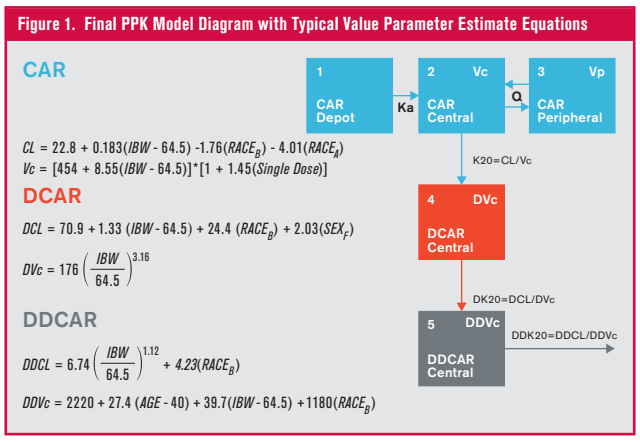


Figure 2. Model-Predicted Cariprazine, DCAR and DDCAR Values for a Typical 40-Year Old White Male Patient Versus Dose-Normalized Observed Plasma Concentrations

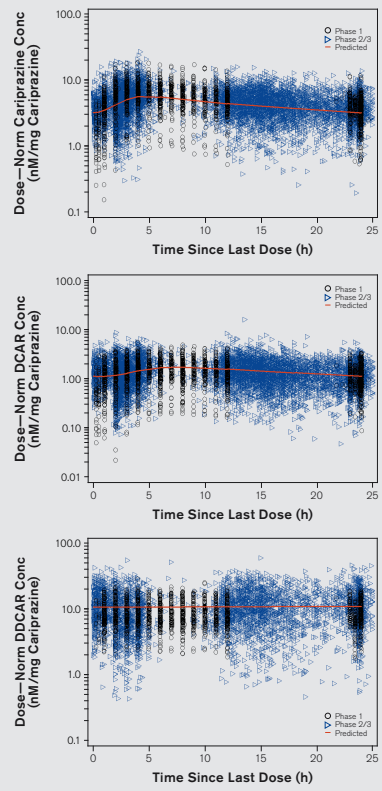


Table 1. Parameter Estimates and Standard Errors for the Final CAR PPK Model

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability	
	Typical Value	%SEM	Magnitude	%SEM
DUR: duration of zero-order process (h)	3.14	4.67	NE	NE
K_a: first-order absorption rate constant (1/h)	0.578	8.28	96.5 %CV	12.0
CL: apparent central clearance in white patients with IBW of 64.5 kg	22.8	1.25	34.2 %CV	5.47
CL: linear effect of IBW (L/h/kg)	0.183	12.8		
CL: additional shift in black patient (L/h)	-1.76	24.3		
CL: additional shift in Asian patient (L/h)	-4.01	11.8		
V_c: central volume of distribution (L)	454	5.05	44.0 %CV	16.8
V_c: proportional shift in V_c for single dose	1.47	FIXED		
V_c: linear effect of IBW (L/kg)	8.55	14.5		
Q: intercompartmental clearance (L/h)	92.3	12.1	NE	NE
V_p: peripheral volume of distribution (L)	415	7.02	NE	NE
RV for Study RGH-MD-01 (log units)	0.0733	15.5	0.271 SD	NA
RV for other studies (log units)	0.118	4.84	0.343 SD	NA

Abbreviations: %CV, coefficient of variation expressed as a percentage; IBW, ideal body weight; NA, not available; NE, not estimated; RV, residual variability; SD, standard deviation; %SEM, standard error of the mean expressed as a percentage.

CONCLUSIONS

- The linear population PK models adequately described the PK profiles of CAR and its two major active metabolites in patients with schizophrenia or patients with manic or mixed episodes associated with bipolar I disorder after exposure to doses ranging from 1.5 to 18 mg/day
- No statistically significant effect on the PK of any of the moieties was noted for hepatic function, renal function, concomitant administration of CYP2D6 inhibitors, mild/moderate CYP3A4 inhibitors, or general CYP inducers
- Although race, gender, and age were found to be of statistical significance on either CL/F or V_c/F of some of the moieties, their effect size ranged between 2% and 32% and none of these covariates were found to be clinically relevant
- Patients classified as CYP2D6 poor metabolizers had no clinically relevant difference in exposure compared to non-poor metabolizers
- The typical functional half lives of CAR, DCAR and DDCAR were about 1 day, 1 day, and 9 days, respectively, which support once daily dosing for cariprazine in the patient population described above

Table 2. Parameter Estimates and Standard Errors for the Final DDCAR PPK Model

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability	
	Typical Value	%SEM	Magnitude	%SEM
CAR and DCAR model parameters were fixed at their individual Bayesian values				
DDCL: apparent DDCAR clearance (L/h)	6.74	2.54	68.9 %CV	6.63
DDCL: power effect of IBW (-)	1.12	15.7		
DDCL: additional shift in black patient (L/h)	4.23	10.9		
DDV_c: apparent DDCAR central volume of distribution (L)	2220	2.49	70.3 %CV	6.66
DDV_c: linear effect of AGE (L/y)	27.4	14.2		
DDV_c: linear effect of IBW (L/kg)	39.7	11.3		
DDV_c: additional shift in black patient (L)	1180	10.5		
DDCAR Study RGH-MD-01 RV (log units)	0.0131	22.4	0.114 SD	NA
DDCAR other studies RV (log units)	0.0930	5.57	0.305 SD	NA

Abbreviations: %CV, coefficient of variation expressed as a percentage; DCAR, desmethyl-cariprazine; DDCAR, didesmethyl-cariprazine; IBW, ideal body weight; NA, not available; RV, residual variability; SD, standard deviation; %SEM, standard error of the mean expressed as a percentage.

Figure 3. Goodness-of-Fit Plots for the Final CAR (top row) and DDCAR (bottom row) PPK Models

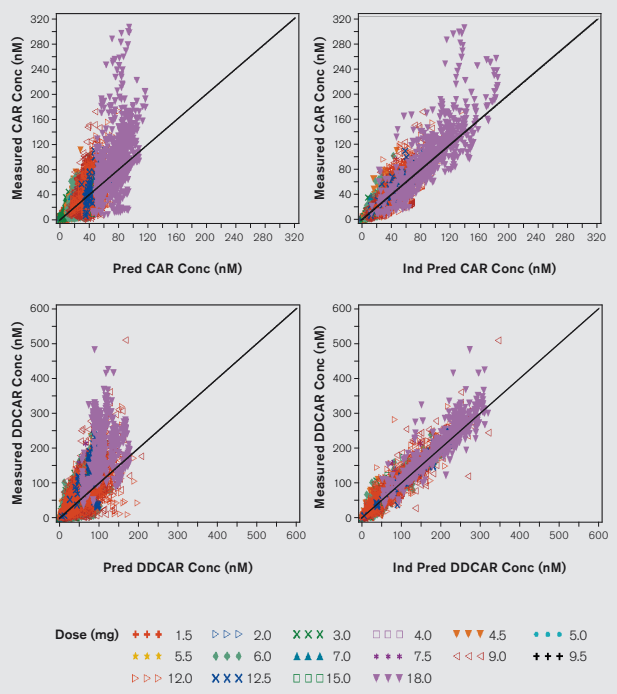
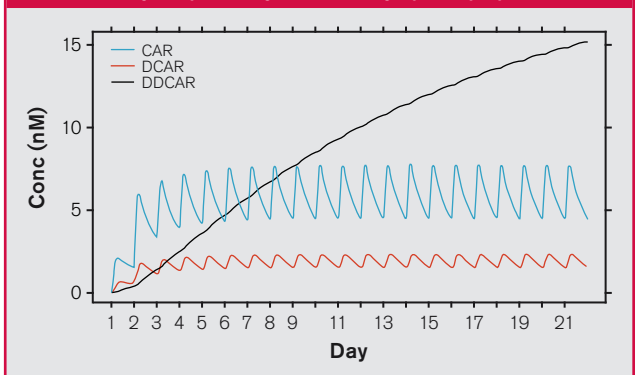


Figure 4. Predicted CAR, DCAR, and DDCAR Concentrations for a Typical Patient Following 21 Days of Dosing Titrated to 12 mg/day Dose by Day 10



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