Characterization of Population Pharmacokinetics of Cariprazine and Its Major Metabolites

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Abstract

Objectives

To determine the characterization of pharmacokinetics of cariprazine and its major metabolites, desmethyl-cariprazine (DCAR) and didesmethyl-cariprazine (DDCAR), in a diverse population of patients.

Methods

Population pharmacokinetic analysis included 2016 patients (600 patients per cohort) recruited from 21 studies. Pharmacokinetic data were analyzed using NONMEM to characterize the pharmacokinetics of desmethyl-cariprazine (DCAR) and didesmethyl-cariprazine (DDCAR) using a one-compartment model with first-order absorption and elimination for CDAR and DDCAR and a two-compartment model for CAR. Covariates included age, weight, gender, race, creatinine clearance, and 32 demographic variables.

Results

A total of 2016 patients were included in the analysis, with 336 patients in each cohort. Median (IQR) age, weight, gender, and race were 41 (37, 46) years, 82.5 (70, 100) kg, 64% male, and 64% white. The central compartment volume of distribution of CAR was 247 (210, 293) liters and the total clearance was 42 (36, 47) liters per minute. DCAR and DDCAR were the predominant metabolites, representing 28.1% and 7.7% of Total CAR, respectively. Weight, gender, and race were statistically significant predictors of PK parameters. However, the resulting model could account for only 41% of the interindividual variability in the disposition of DDCAR. While weight, gender, and race were statistically significant predictors of PK parameters, only weight and race were statistically significant predictors of PK parameters. However, the resulting model could account for only 41% of the interindividual variability in the disposition of DDCAR.

Conclusion

Cariprazine is extensively metabolized. CYP3A4 and, to a lesser extent, CYP2D6, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5 enzymes convert cariprazine to several metabolites, two of which (desmethyl-cariprazine [DCAR] and didesmethyl-cariprazine [DDCAR]) possess similar pharmacological activity to the parent compound. Cariprazine is slowly absorbed, multiexponential disposition, and slow elimination. Cariprazine is extensively metabolized. CYP3A4 and, to a lesser extent, CYP2D6, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5 enzymes convert cariprazine to several metabolites, two of which (desmethyl-cariprazine [DCAR] and didesmethyl-cariprazine [DDCAR]) possess similar pharmacological activity to the parent compound.