

POPULATION PHARMACOKINETICS OF OLANZAPINE AND QUETIAPINE IN CRITICALLY ILL ADULTS WITH DELIRIUM

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INTRODUCTION. The optimal drug and dosage for treating acute delirium lack consensus, particularly among critically ill patients whose altered pharmacokinetics (PK) pose challenges. Additionally, data on antipsychotic drug use in this patient population remains scarce. **We sought to characterise the population PK parameters of olanzapine and quetiapine in critically ill patients with delirium.**

METHODS. Critically ill adults (≥18 years) receiving immediate-release enteral olanzapine or quetiapine for acute delirium were enrolled. Blood samples were collected at 6 and 24 h post-dose or immediately before the next dose for olanzapine, and at 1.5, 5, and 12 h post-dose or immediately before the next dose for quetiapine. For patients continuing the medication, additional trough samples were drawn at 24, 48, and 72 h after the initial trough event. Plasma concentrations were measured using UPLC–MS/MS.

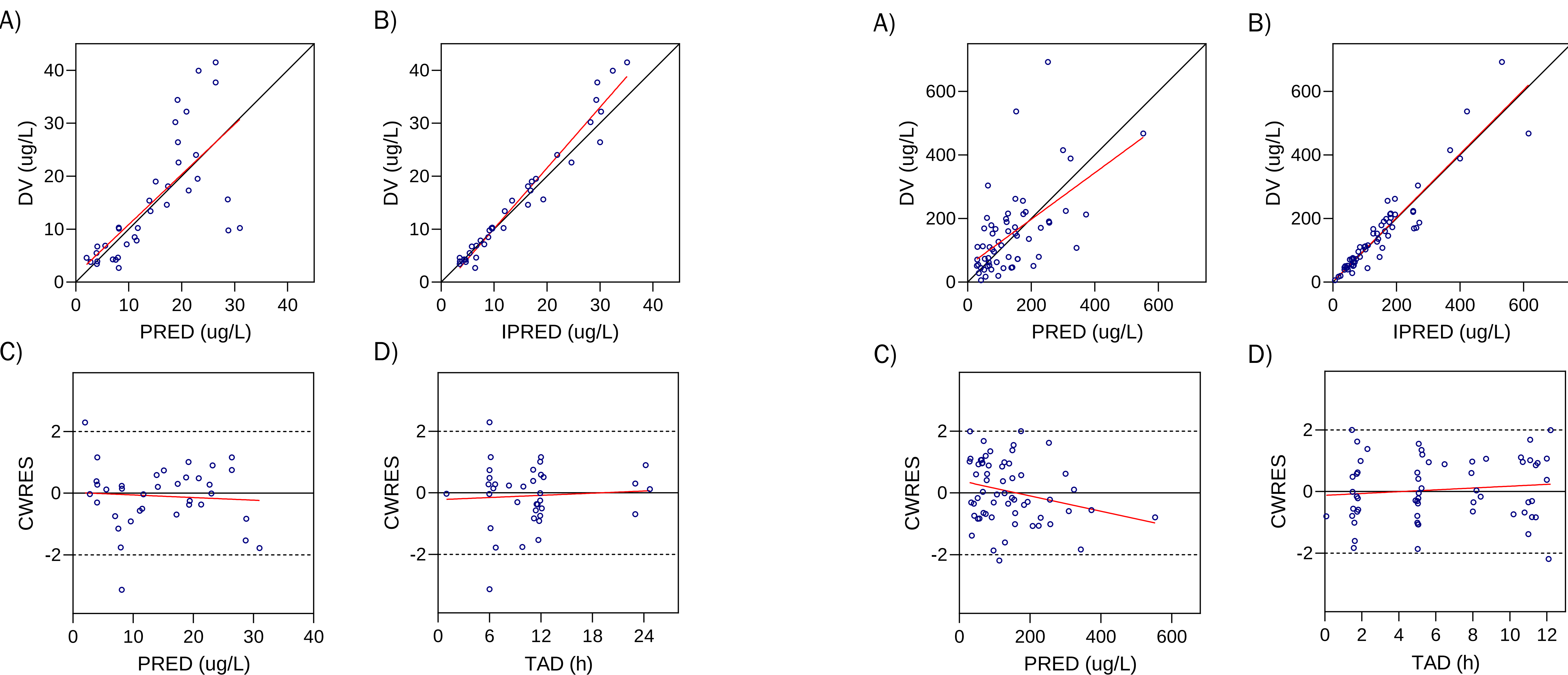
Population PK analysis was conducted using NONMEM® 7.5.1 with the first-order conditional estimation with interaction (FOCE+I) method. Covariates screened included age, weight, albumin, bilirubin, international normalised ratio, and sex. For olanzapine, smoking status and concurrent use of fluvoxamine, sertraline, or valproate were evaluated. For quetiapine, concurrent use of erythromycin was assessed. Model evaluation was based on goodness-of-fit (GOF) plots and prediction corrected visual predictive check. Final models were validated through bootstrap analysis (n=1000).

RESULTS. Twenty-seven patients provided a total of 96 samples. Both models incorporated first-order absorption and linear elimination, with exponential interindividual variability (IIV) and proportional residual variability. No covariates were retained in either final model.

OLANZAPINE			QUETIAPINE		
One-compartment model (n= 11 patients, 36 samples)			Two-compartment model (n= 16 patients, 60 samples)		
Parameter	Estimates (RSE) [Shr.]	Bootstrap median (95% CI)	Parameter	Estimates (RSE) [Shr.]	Bootstrap median (95% CI)
CL/F (L/h)	19.7 (28%)	20.2 (8.9–31.7)	CL/F (L/h)	24.8 (16%)	24.3 (18.4–34.0)
Vc/F (L)	1080 (18%)	1073 (760–1522)	Vc/F (L)	34.7 (25%)	33.8 (18.3–58.1)
KA (h ⁻¹)	0.49 FIX	0.49	Q/F (L/h)	18.4 (22%)	16.9 (6.1–27.4)
Interindividual variability			Interindividual variability		
IIV_CL (CV%)	70.8 (27%) [18%]	61.5 (22.9–112.8)	IIV_CL (CV%)	67.4 (14%) [2%]	61.5 (43.8–85.3)
IIV_V (CV%)	39.6 (21%) [20%]	36.6 (17.3–69.6)	Residual variability		
Residual variability			Proportional (CV%)	25.4 (0%) [12%]	24.2 (17.7–30.1)
Proportional (CV%)	21 (0%) [20%]	20.5 (10.5–30.4)			

RSE, relative standard error; Shr, shrinkage; CI, confidence interval; CL/F, apparent oral clearance; Vc/F, apparent central volume of distribution; Q/F, apparent intercompartmental clearance; Vp/F, apparent peripheral volume of distribution; KA, first-order absorption rate constant; CV% of variability calculated as $\sqrt{\omega} \times 100$.

The mean estimated parameters closely aligned with the median of the corresponding bootstrapped parameters and fell within their respective 95% CI, demonstrating the stability of both models.



GOF plots (left: olanzapine; right: quetiapine); A) observed (DV) vs predicted (PRED) concentrations; B) DV vs individual predicted (IPRED) concentrations; C) conditional weighted residuals (CWRES) vs PRED; D) CWRES vs time after dose (TAD).

CONCLUSION. High variability in drug clearance was observed. Ongoing data collection will further improve model performance and be used to support proposal of optimised dosing regimens.