

Population pharmacokinetic model of amisulpride for dosage individualization in psychiatric patients

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Introduction & Objectives

- Amisulpride is an antipsychotic used at a wide range of daily doses (100-800 mg)
- It is eliminated by hepatobiliary ways mainly (51%), by renal excretion through OCT1/2 transporters and P-glycoprotein (P-gp) (25%) and is weakly metabolized by CYP3A4 into two inactive metabolites.
- Therapeutic drug monitoring is strongly recommended based on an established strong concentration-response relationship. The reference range of trough concentrations is 100-320 ng/mL to avoid non-clinical response and extra-pyramidal side effects^{1,2}
- This work aimed to describe the pharmacokinetic profile of amisulpride in psychiatric patients and to detect genetic and non-genetic sources of variability in order to better individualize doses.

Methods

- 513 amisulpride concentrations from a cohort of 242 hospitalized patients at the Department of psychiatry of the Lausanne University hospital.
- One compartment model developed in NONMEM with a 1st order absorption and a fixed bioavailability of 48%³
- Covariates
 - Demographic: age, sex
 - Clinical: body weight (BW), lean body weight estimated by the Boer formula⁴, body mass index, creatinine clearance estimated by the Cockcroft-Gault formula (CLCRG)⁵, or the Salazar-Corcoran formula (CLCRSZ)⁶ or both (CLCR = CLCRG if BW<100 kg and CLCR = CLCRSZ if BW≥100 kg)
 - Genetic: 17 single nucleotide polymorphisms (SNPs) of the OCT1/2, P-gp and nuclear receptors genotyped using the Cardio-MetaboChip (Illumina)
 - Comedications: P-gp inhibitors
- Statistical significance was determined by a p-value ≤0.05 for one additional parameter in model building and a Bonferroni-corrected p≤0.0025 during backward deletion steps in covariate analysis to account for multiple testing.
- Model validation by bootstrapping (n=2000) and prediction-corrected visual predictive check (pc-VPC)
- Simulations of trough concentrations at steady-state (C_{min,ss}) based on the final model
 - in 500 individuals per strata of age (40 and 85 years) and CRCL (30, and 120 mL/min)
 - after administration of daily doses of 100, 200, 400 or 800 mg

Results

- Concentrations ranged from 5 to 1514 ng/mL (median=207 ng/mL) for a range of daily doses from 50 to 2000 mg (median= 600 mg) and were measured from 0.05 h to 58 h (median= 13.3 h) post drug intake
- Among the tested covariates, only age and CRCL influenced amisulpride elimination:
 - CL decreased by 38 % in a 75-year individual as compared to a 40-year patient
 - CL decreased by 40 % in an individual with a CLCR=30 mL/min as compared to a patient with a normal CLCR (120 mL/min).

Table 1: Demographic and clinic characteristics of the study populations

Characteristics	Value	% missing data
Sex (male), n (%)	110 (45%)	0
Age (years), median (range)	39 (18-91)	0
Body weight (kg), median (range)	73 (43-185)	8.7
Lean body weight (kg), median (range)	52 (32-107)	34.7
Body mass index (units), median (range)	25 (15-60)	34.7
CLCRG ^a	116.3 (23.6-268.7)	34.3
CLCRSZ ^b	115.4 (26.1-218.5)	48.8
CLCR ^c	115.8 (23.6-221.7)	35.1

a, b. CLCRG, CLCRSZ creatinine clearance estimated by the Cockcroft-Gault formula and by the Salazar-Corcoran formula
c. CLCR, creatinine clearance estimated by the Cockcroft-Gault formula if body weight < 100 kg and estimated by the Salazar-Corcoran if body weight ≥ 100 kg.

References

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Table 2: Final population pharmacokinetic parameter estimates and their bootstrap evaluations.

Parameter	Final population parameter		Bootstrap evaluation (n=2000 samples)	
	Estimate	RSE ^a (%)	Median	CI _{95%}
CL (L/h)	43.7	4	43.6	39.5; 48.1
V (L)	985	10	983	741; 1319
k _a (h ⁻¹)	1.8 fixed	-	1.8	-
θ _{AGE_CL}	-0.39	16	-0.38	-0.51; -0.19
θ _{CLCR_CL}	0.51	26	0.51	0.21; 0.79
IIV _{CL} (CV%)	32	11	32	22; 41
IIV _V (CV%)	52	35	52	27; 75
proportional residual error (%)	54	3	54	47; 61

CL, typical amisulpride clearance; V, typical volume of distribution; k_a, typical absorption rate constant.
^aRelative standard errors of the estimates; ^bInterpatient variability;

Figure 1: pcVPC of the final model. Open circles represent observed amisulpride plasma concentrations. The continuous line represents the population median prediction from the final model and the broken lines represent the 5th and the 95th percentiles of the prediction intervals. Areas represent the 95% confidence interval of the percentiles.

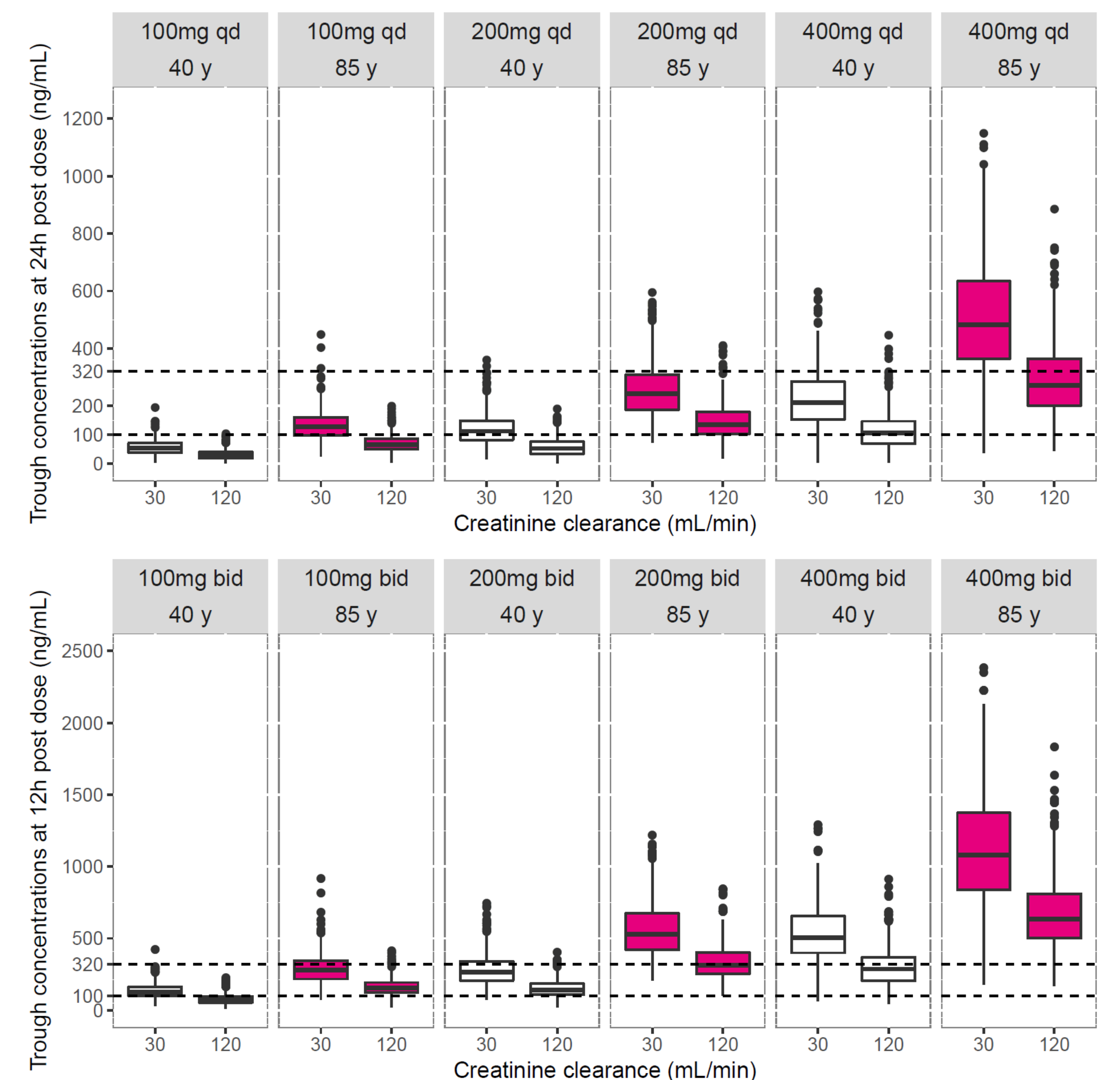
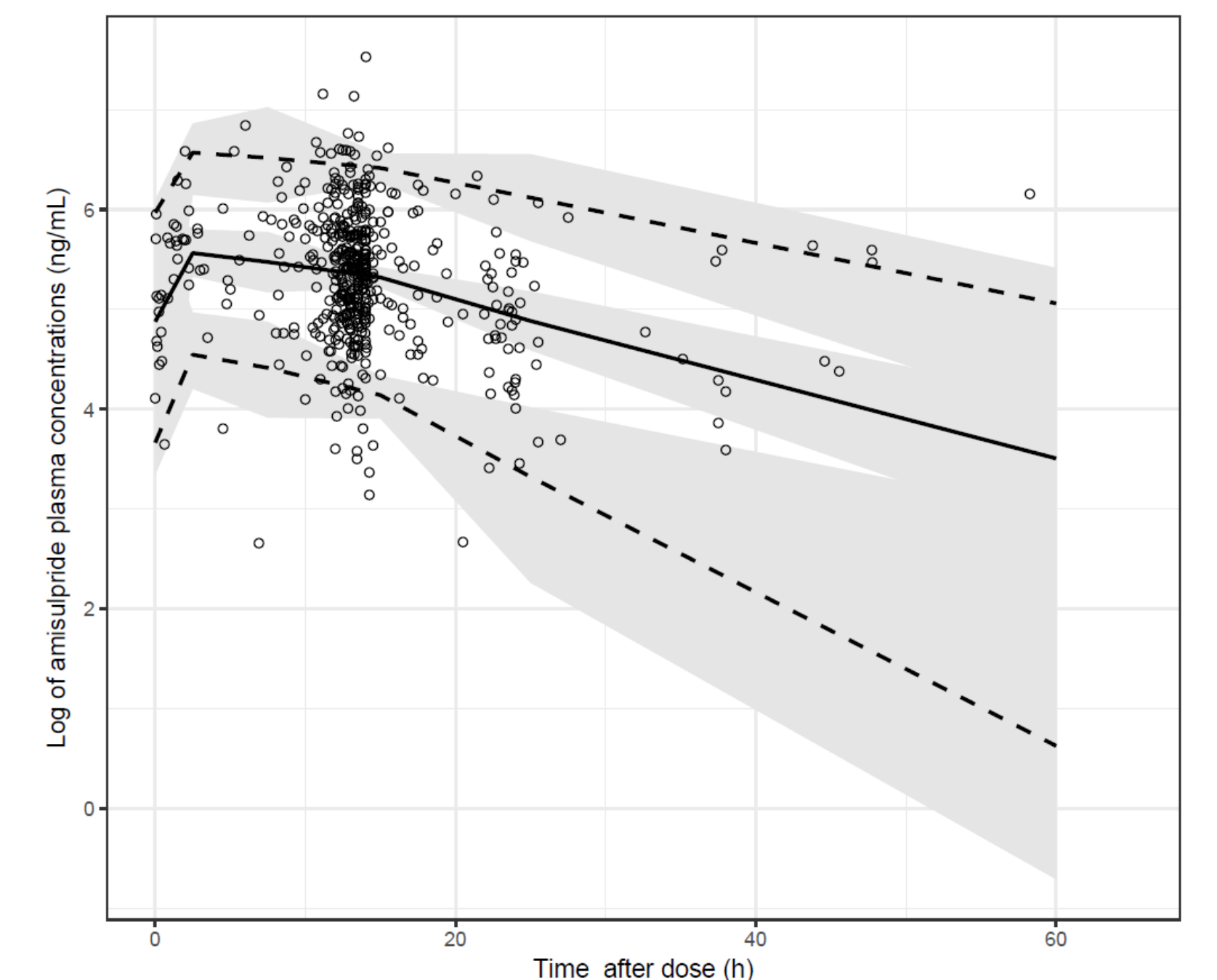


Figure 2: Distribution of the simulated amisulpride C_{min,ss} after administration of amisulpride qd (a.) and bid (b.). Dashed lines represent the reference range of trough concentrations

Conclusions

- Age and creatinine clearance significantly contribute to amisulpride plasma concentrations variability. The additional influence of age could reflect the decreased hepatobiliary elimination in older patients.
- In adults (40y) with normal CLCR, dosage regimens over 200mg bid increase the risk of side effects. Elderly patients (85y), and in particular those with decreased renal function, are at higher risk of side effects and dosage regimens not exceeding 200mg qd should be preferred.