A Population Pharmacokinetic Model for Aripiprazole & Dehydro-aripiprazole

Julia Korell[1], Bruce Green[1], An Vermeulen[2]

[1]Model Answers Pty Ltd, Brisbane, Australia; [2]Janssen R&D, a division of Janssen Pharmaceutica NV, Beerse, Belgium

Background

- Aripiprazole is an atypical antipsychotic with a mechanism of action that differs from other currently marketed antipsychotics as it acts as partial agonist on D_2 receptors.
- Elimination of aripiprazole occurs mainly through hepatic metabolism involving both CYP2D6 and CYP3A4.
- The major active metabolite, dehydro-aripiprazole has affinities for D_2 receptors similar to the parent, and represents approximately 40% of parent drug exposure in plasma.

Aim

- To develop a population pharmacokinetic (PK) model for aripiprazole and its active metabolite, dehydro-aripiprazole.

Methods

- 1366 steady-state plasma concentration-time observations for aripiprazole and dehydro-aripiprazole were available from an open-label PK study in 86 subjects (Table 1).

Table 1: Subject Demographics

	Age (years)	Weight (kg)	LBW (kg)	BMI (kg/m^2)	CRCL (mL/min)	Race	Sex	CYP2D6 Phenotype
N	86	86	86	86	86	49 White	45 Male	4 Poor
Mean	44	88	56.3	30.3	124	24 Black	41 Female	2 Intermediate
SD	11.3	17.2	11.5	5.47	30.3	1 Asian		68 Extensive
%CV	25.6	19.5	20.3	18	24.3	9 Hispanic		6 Ultra-rapid
Median	45.5	89.9	54.5	30.8	124	2 Other		6 Unknown
Min	19	50.9	34.8	19.2	51.8	1 Unknown		Metabolisers
Max	65	124	79.8	40	213			

BMI=body mass index, CRCL=creatinine clearance, %CV=coefficient of variation in percent, LBW=lean body weight, SD=standard deviation.

- Model development was performed in two steps:
  1. A population PK model for the parent drug was developed on the aripiprazole data;
  2. Sequential modelling using the PPP+D method[1] was applied to obtain a parent-metabolite PK model using the combined aripiprazole and dehydro-aripiprazole data.
- Covariates tested for the parent and parent-metabolite model included weight, lean body weight (LBW), age, sex, race, and CYP2D6 phenotype.
- Model development was performed in NONMEM 7.2, using FOCE with interaction.

Results

- A one-compartment model with first-order absorption and elimination together with a proportional error best described the aripiprazole data (Table 2, Figure 1).
- The PK of dehydro-aripiprazole was also best described by a one-compartment model with first-order elimination and an independent proportional error in the final parent-metabolite model (Table 2, Figure 1).
  - The fraction of aripiprazole metabolised to dehydro-aripiprazole was fixed at 1.
  - The volume of distribution of the metabolite was fixed to the estimate of the parent drug.
- LBW and CYP2D6 phenotype were significant covariates on aripiprazole plasma clearance, while LBW was also a significant covariate on dehydro-aripiprazole plasma clearance.
- Prediction corrected visual predictive checks (pcVPCs) for the final parent-metabolite model showed adequate predictive performance (Figure 2).

Table 2: Final Parameter Estimates

Parameter	Estimated Value (%SE)	BSV CV% (%SE)
Aripiprazole		
Apparent clearance EM (CL_{EM}/F, L/hr)	3.44 (3.9)	32.6 (7.8)
Apparent clearance PM & IM (CL_{PM}/F, L/hr)	1.61 (14.9)	32.6 (7.8)
Apparent clearance UM (CL_{UM}/F, L/hr)	5.14 (7.4)	32.6 (7.8)
Exponent for LBW on CL/F	0.688 (25.0)	
Apparent volume of distribution (V_c/F, L)	243 (4.9)	38.3 (23.2)
Absorption rate constant (KA, hr^{-1})	1.54 (12.8)	73.2 (25.3)
Proportional RUV (CV%)	10.9 (9.2)	
Dehydro-aripiprazole		
Apparent clearance (CL_m/f_m, L/hr)	10.9 (4.6)	42.6 (8.4)
Exponent for LBW on CL_m/f_m	0.567 (35.0)	
Apparent volume of distribution (V_m/f_m, L)	243 FIX	
Fraction metabolised (f_m)	1 FIX	
Proportional RUV (CV%)	9.1 (11.0)	

BSV=between-subject variability, RUV=residual unexplained variability, %SE=relative standard error.
EM=extensive, IM=intermediate, PM=poor, and UM=ultra-rapid CYP2D6 metabolisers.

Figure 1: Model Schematic

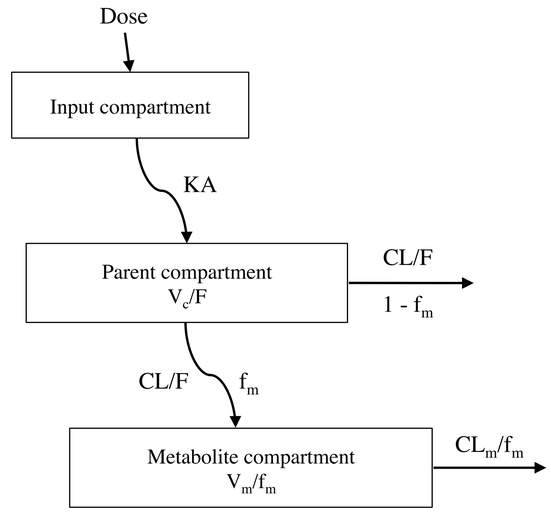
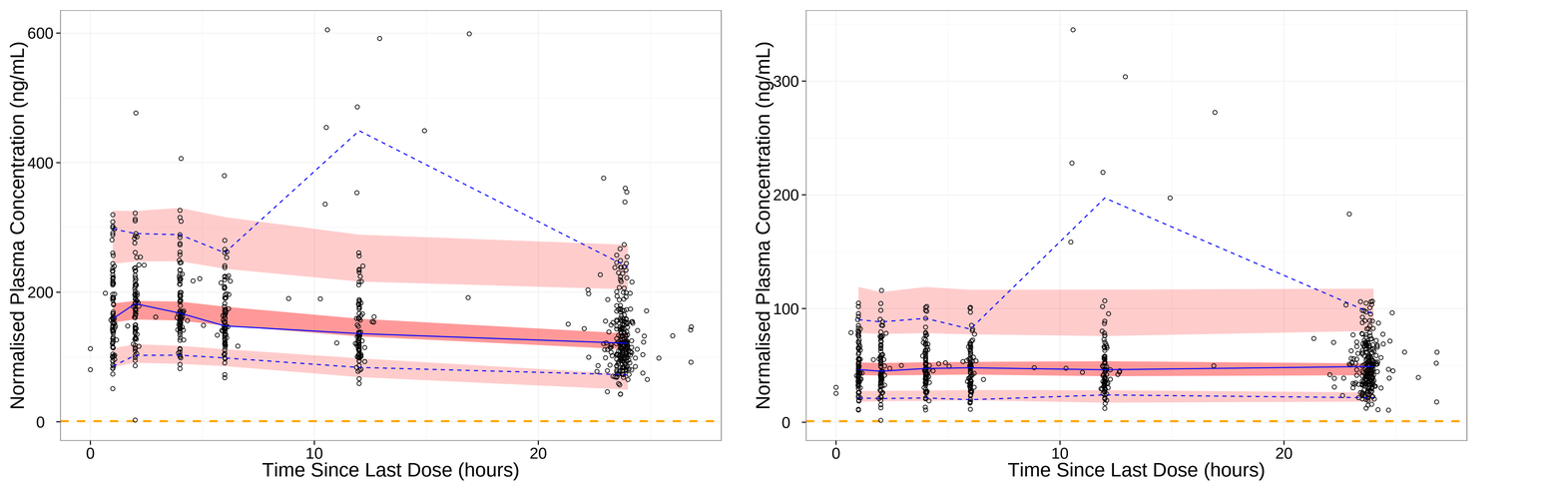


Figure 2: pcVPCs for Aripiprazole (left panel) & Dehydro-aripiprazole (right panel)



Blue dashed lines=observed 5th & 95th percentiles, blue solid line=observed median, black circles= observed data, light shaded red areas=95% confidence interval (CI) for the simulated 5th & 95th percentiles, dark shaded red area=95% CI for the simulated median, orange dashed line=lower limit of quantification (1 ng/mL).

Conclusions

- A sequential parent-metabolite PK model for aripiprazole and dehydro-aripiprazole with adequate predictive performance was developed.

References

1. Zhang L, Beal S, Sheiner L. Simultaneous vs. Sequential Analysis for Population PK/PD Data I: Best-Case Performance. Journal of Pharmacokinetics and Pharmacodynamics 2003;30(6):387-404.

Contact

email: julia@model-a.com.au
web: www.model-a.com.au

ModelAnswers

janssen | Pharmaceutical Companies of Johnson & Johnson