

Population pharmacokinetics of tribendimidine metabolites in adults with *Opisthorchis viverrini* in Laos

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Background

In south-east Asia, an estimated 8-10 million people are infected with the liver fluke *Opisthorchis viverrini*.¹ Praziquantel is the only drug currently available, therefore there is a pressing need to identify alternatives.^{2,3} Oral tribendimidine is a promising candidate, but its population pharmacokinetic (PK) properties are unknown.^{4,5}

Methods

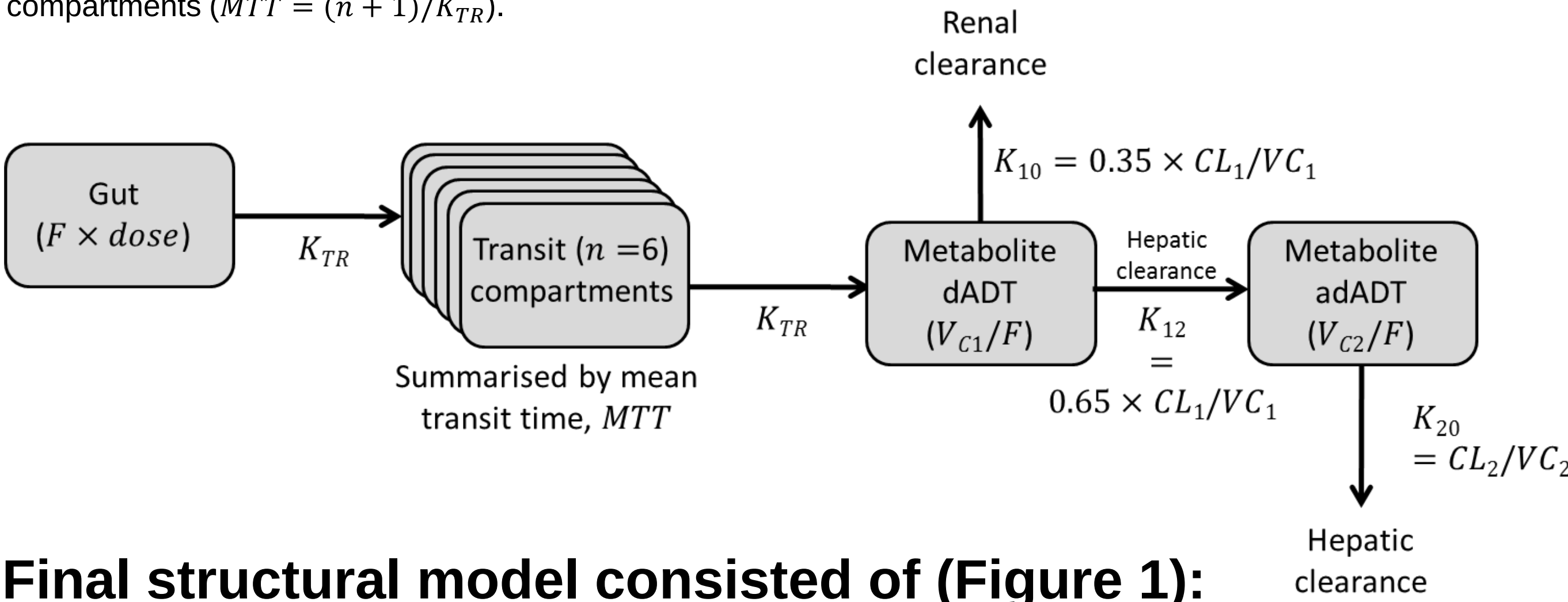
Within the framework of two phase IIa trials conducted in Laos, we enrolled *O. viverrini*-infected adults receiving single oral doses of 25-600 mg (study 1 used 200 mg tablets and study 2 used 50 mg tablets, with different absorption properties). Venous whole-blood, plasma and capillary dried blood spots (DBS) were sampled frequently. Concentrations of the tribendimidine metabolites dADT (deacetylated amidantal) and adADT (deacetylated dADT) were measured.⁶ Egg burden in stool was assessed at enrolment and at 21 days, with cure being no eggs. The two studies were pooled and population PK were assessed using nonlinear mixed-effects modelling with NONMEM, version 7. We assumed fixed renal dADT clearance of 35%, with the remainder metabolising into adADT.⁷ Values below the quantification limit were treated as missing data. We included body weight with allometric scaling and assessed other covariates by stepwise selection. We used bootstrapping to obtain confidence intervals and standard errors (200 reps). We used univariable logistic regression to assess the relationship between PK and cure.

Results

Table 1. Patient demographics. Results are n (%) or median (interquartile range).

	Second study (50 mg tablets, N=37)				First study (200 mg tablets, N=31)			Total
Dose, mg	25	50	100	200	200	400	600	
N. participants	9	9	9	10	13	9	9	68
Sex, female	3 (33%)	6 (67%)	5 (56%)	5 (50%)	6 (46%)	5 (56%)	5 (56%)	35 (51%)
Age, years	45 (39, 56)	42 (26, 44)	44 (34, 51)	39 (23, 40)	44 (41, 56)	37 (29, 42)	43 (34, 45)	42 (31, 48)
Weight, kg	51 (49, 60)	48 (42, 54)	47 (44, 54)	55 (48, 58)	54 (49, 59)	49 (48, 51)	53 (46, 58)	52 (47, 57)
<i>O. viverrini</i> egg burden, eggs per gram	414 (384, 432)	2214 (1224, 3024)	612 (504, 774)	588 (438, 792)	1410 (648, 1914)	978 (204, 1476)	3294 (1848, 5256)	897 (435, 1827)

Figure 1. Final structural PK model. *F*, bioavailability; *K_{TR}*, transit absorption rate; *CL*, clearance; *V_C*, apparent central volume of distribution (subscript 1 for dADT and subscript 2 for adADT); *MTT*, mean transit time; *n*, total number of compartments (*MTT* = (*n* + 1)/*K_{TR}*).



Final structural model consisted of (Figure 1):

- One-compartment disposition model for each metabolite.
- Six transit absorption compartments.
- Proportional error model.
- Allometric scaling of dADT and adADT clearance and volume of distribution parameters.
- Formulation- and age-dependent pharmacokinetics (Table 2).

Figure 2. Model diagnostics (goodness of fit).

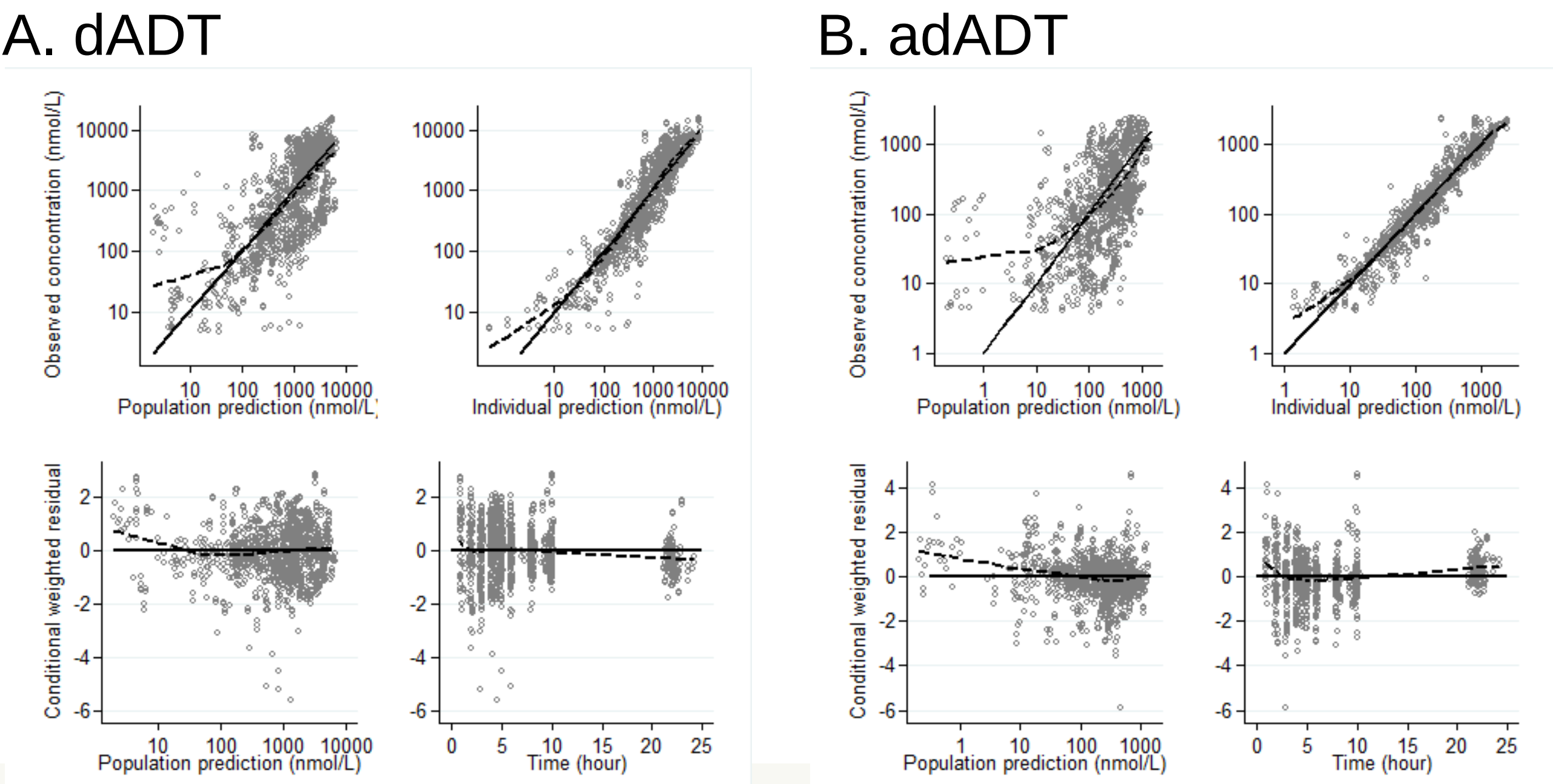
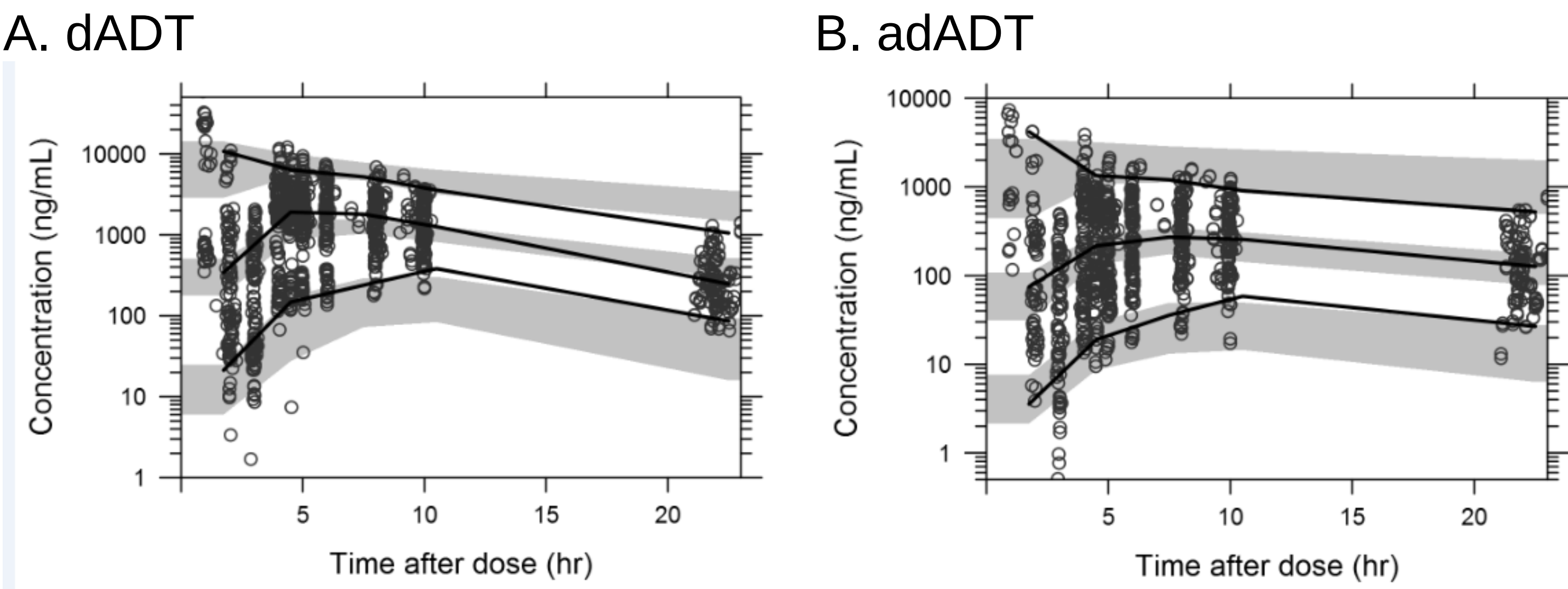


Table 2. Population PK parameter estimates. For a typical patient aged 52 years, weighing 51.5 kg and receiving 50 mg tablets (study 2). [1] 200 mg tablets (study 1) vs. 50 mg tablets (study 2).

	Population estimate	95% CI	RSE
Transit compartments	6	Fixed	Fixed
Mean transit time, h	3.23	1.81, 3.48	13.6%
Metabolite dADT			
CL/F, L/h	16.7	14.7, 18.7	6.0%
V _C /F, L	112	105, 141	7.2%
σ	90.2%	78.7, 103	10.6%
Metabolite adADT			
CL/F, L/h	52.6	38.9, 65.0	12.7%
V _C /F, L	5.40	3.45, 20.0	92.5%
σ (%)	49.6%	39.1, 60.1	19.0%
Covariate effects (%)			
Formulation on mean transit time [1]	45.3%	24.3, 155	78.4%
Formulation on dADT CL/F [1]	-18.1%	-28.0, -3.77	34.3%
Formulation on dADT V _C /F [1]	55.2%	-2.25, 160	72.0%
Formulation on adADT V _C /F [1]	416%	-4.67, 499	35.5%
Age on dADT CL/F, per 10 yr higher	-12.4%	-19.9, -5.52	30.4%
Inter-individual variability (%CV)			
Mean transit time	65.3%	48.4, 82.6	22.0%
dADT CL/F	16.6%	0.15, 21.3	41.8%
dADT V _C /F	90.4%	54.1, 130	30.3%
adADT CL/F	131%	94.8, 214	24.2%
adADT V _C /F	263%	88.5, 680	38.9%

Figure 3. Visual predictive checks.



High cure rates (≥55% of participants) were observed with doses ≥100 mg. Higher dADT, but not adADT, C_{max} and AUC were associated with cure (both p=0.003).

Conclusions

We have for the first time described the population PK of tribendimidine. Known differences in the 200 mg versus 50 mg formulations were captured by covariate modelling. Further studies are needed to validate the structural model and confirm covariate relationships.

