

Cystic fibrosis does not alter the pharmacokinetics of tobramycin

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Background and Objective

There are conflicting data (1-3) on whether the pharmacokinetics (PK) of tobramycin differ in individuals with cystic fibrosis (CF). One theory is that PK differences might reflect body composition changes, resulting from reduced adipose tissue due to malnutrition in CF patients compared to the non-CF population.

The aim of this study is to perform a meta-analysis of data collected from several clinical centres to determine whether having CF influences the PK of tobramycin.

Methods

A population PK meta-analysis was performed using NONMEM 7 on tobramycin concentration-time data obtained from adults and children with and without CF, who received tobramycin by bolus dosing or short intravenous infusion.

Data were available from 4 published studies (4-7) and collected at 3 additional sites (Royal Children's Hospital, Brisbane Australia, Cincinnati Children's Hospital, Cincinnati, USA and Gartnavel General Hospital, Glasgow, UK).

Results and Discussion

Data from 732 patients were included providing 5605 tobramycin concentration-time points from 0.17 to 15 hours post-administration (Figure I & II). Table 1 summarises the demographic data of the patient group.

Tobramycin disposition was well described by a two-compartment model with first-order elimination. Typical parameter estimates are shown in Table II.

Lean body weight (LBW) was superior to total body weight as a descriptor of CL and Q and of V_c and V_p . Patient age and serum creatinine were also included as covariates in the final model. SCR_{mean} was derived according to Ceriotti et al (8).

CF, as an independent disease process, had no significant influence on CL, V_c , Q or V_p at any stage during model building.

The final model showed excellent predictive properties in a prediction corrected visual predictive check (pcVPC) (Figure III) and no major flaws in goodness of fit plots (GOF) (Figure IV). Bootstrap results are shown in Table II. Final model equations are given below:

$$CL_{female} = \theta_{CL,f} * \left(\frac{LBW}{70}\right)^{\theta_{LBW}} * [1 + \theta_{AGE} * (AGE - 18)] * \left(\frac{SCR_{mean}}{SCR}\right)^{\theta_{SCR}}$$

$$V_{c,female} = \theta_{vc,f} * (LBW/70)^1$$

$$CL_{male} = \theta_{CL,m} * \left(\frac{LBW}{70}\right)^{\theta_{LBW}} * [1 + \theta_{AGE} * (AGE - 18)] * \left(\frac{SCR_{mean}}{SCR}\right)^{\theta_{SCR}}$$

$$V_{c,male} = \theta_{vc,m} * (LBW/70)^1$$

$$Q = \theta_Q * (LBW/70)^{\theta_{size}}$$

$$V_p = \theta_{VP} * (LBW/70)^1$$

Conclusions

The PKs of tobramycin in patients with and without CF were characterised in a population meta-analysis. Significant covariates were subject age, LBW, gender and renal function.

No independent influence of CF as a disease process on the PKs of tobramycin was identified therefore any differences in tobramycin dosing between CF and non-CF patients should be based on differences in expected pathogen sensitivity.

References

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Number	Infants and Children (<18 years)	Adults
Patients	524	208
CF	351	114
non-CF	173	94
Occasions	4.08 (1 – 25)	5.9 (1 – 25)
CF	4.45 (1-25)	7.31 (1-25)
non-CF	2.31 (1-12)	1.54 (1-4)
Demographic data		Median (range) or Number
Age (years)	7.68 (0.01 – 17.9)	31.7 (18.0 – 85.0)
CF	11.1 (0.01 – 17.9)	24.3 (18 – 66.4)
non-CF	5.0 (1.0 – 17.0)	52.0 (20 – 85)
Gender (F/M/unknown)	207 / 183 / 134	99 / 109 / –
CF	182 / 169 / –	56 / 58 / –
non-CF	25 / 14 / 134	43 / 51 / –
LBW (kg)	19.8 (3.0 – 53.6)	43.5 (28.7 – 65.1)
CF	25.4 (3.0 – 53.6)	40.7 (28.7 – 60.9)
non-CF	13.7 (5.0 – 51.5)	45.9 (31.4 – 65.1)
CL _{Cr} (mL/min)	84.1 (33.8 – 129.9)	71.5 (22.8 – 144.6)
CF	83.5 (33.8 – 127.2)	68.4 (22.8 – 134.3)
non-CF	84.3 (47.7 – 129.9)	76.2 (41.0 – 144.6)

Table I: Summary of demographic data on all patients in the analysis

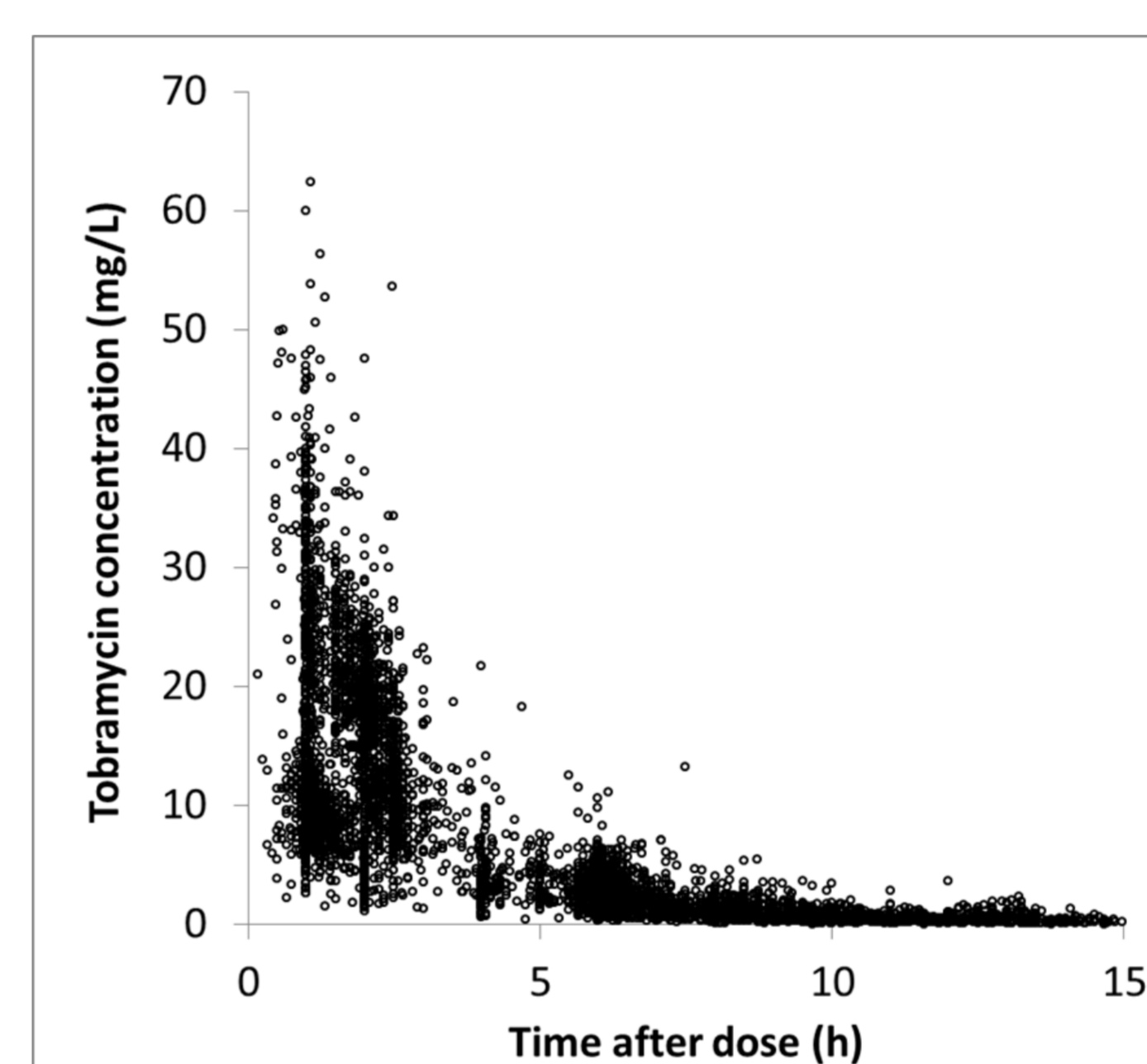


Figure I: Concentration-time plot of all data

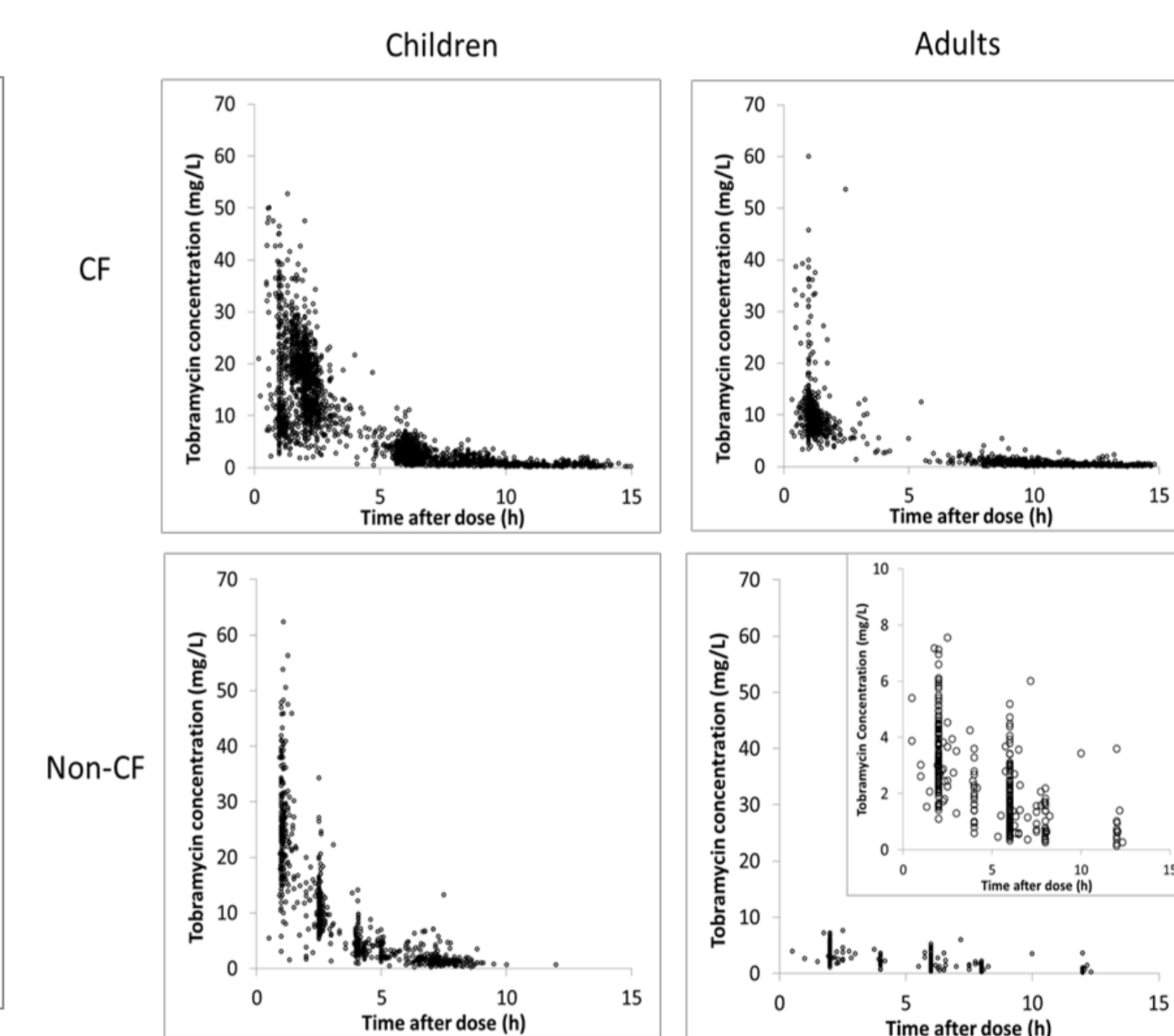


Figure II: Concentration-time data from CF children (n = 2748), CF adults (n = 1766), non-CF children (n = 803) and non-CF adults (n = 292)

Parameter	Final Model		Bootstrap (n=300)		
	BSV CV%	BOV CV%	Parameter	BSV CV%	BOV CV%
OFV	7790.38		7651.39 (6843.10 – 8527.81)		
CL (female) (L/h/70kg)	8.1		8.2 (7.8 – 8.5)		
CL (male) (L/h/70kg)	9.4	25.9	9.5 (9.07 – 10.1)	25.7 (23.1 – 28.2)	12.7 (11.9 – 13.6)
V_c (female) (L/70kg)	20.1		20.2 (19.5 – 21.0)		
V_c (male) (L/70kg)	25.1	15.2	25.2 (24.3 – 26.1)	15.4 (12.7 – 18.1)	
Q (L/h/70kg)	1.5	41.8	1.5 (1.4 – 1.8)	45.1 (34.8 – 56.7)	
V_p (L/70kg)	10.0	58.5	9.8 (7.9 – 11.6)	62.6 (32.2 – 72.4)	
Infusion duration (D1) (min)	15.0	59.7	15.6 (13.2 – 22.2)	66.4 (44.8 – 89.3)	
Covariate model					
θ_{LBW}	0.95		0.98 (0.93 – 1.04)		
$\theta_{AGE (<18 \text{ years})}$	-0.021		-0.024 (-0.03 – -0.02)		
$\theta_{AGE (>18 \text{ years})}$	-0.010		-0.010 (-0.01 – -0.01)		
θ_{SCR}	0.222		0.230 (0.18 – 0.29)		
Correlation %					
CL, V_c	65.8		64.6 (56.2 – 71.9)		
CL, D1	84.1		71.4 (63.6 – 81.5)		
CL, Q	71.1		70.1 (38.4 – 80.9)		
V_c , D1	40.3		35.9 (-49.5 – 53.2)		
V_c , Q	47.5		40.6 (28.4 – 47.3)		
D1, Q	45.7		46.8 (-5.8 – 59.3)		
Residual error model %					
Proportional	20.4		20.2 (19.3 – 21.0)		

Table II: Final parameter estimate and bootstrap results

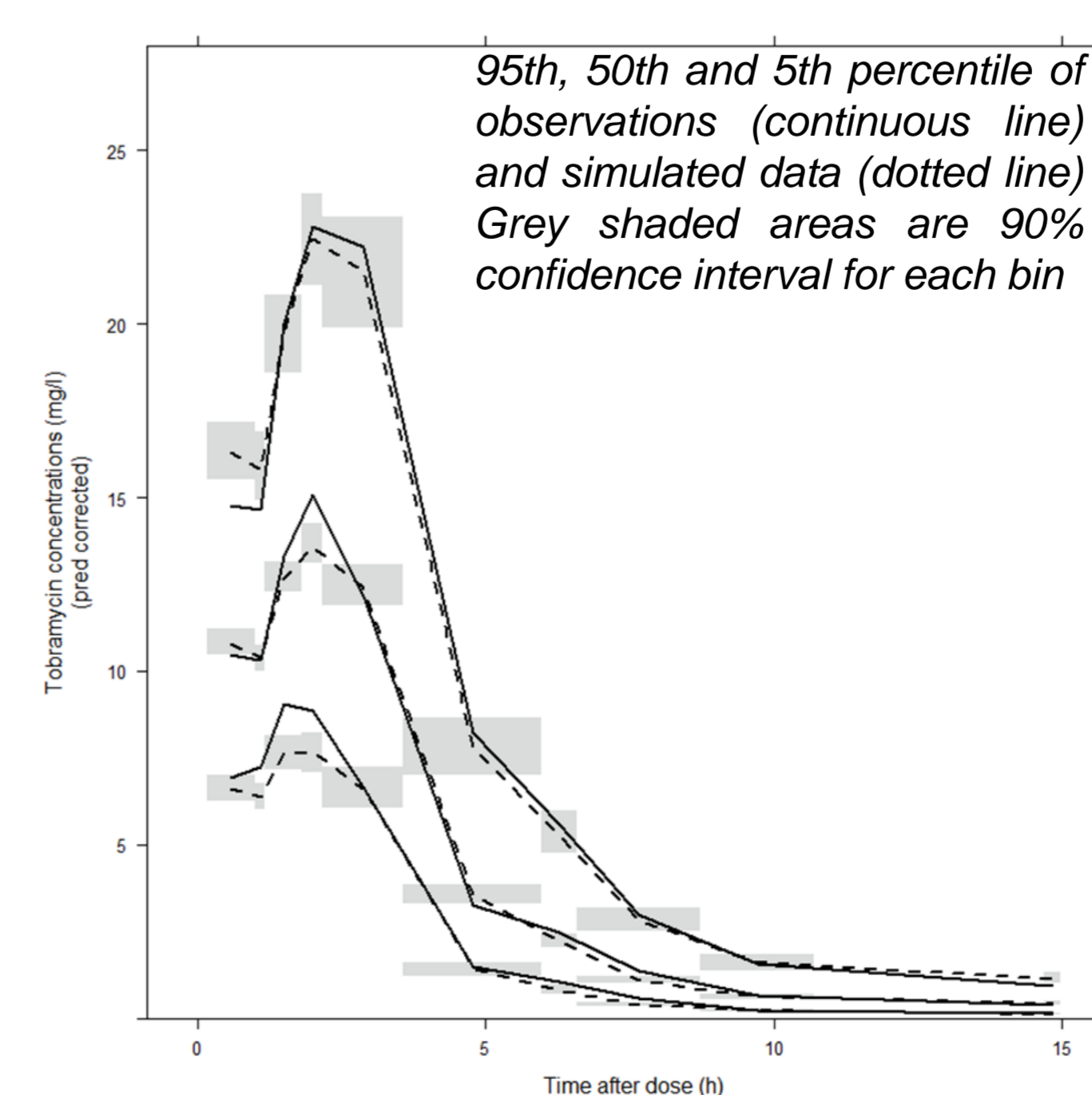


Figure III: pcVPC of final model

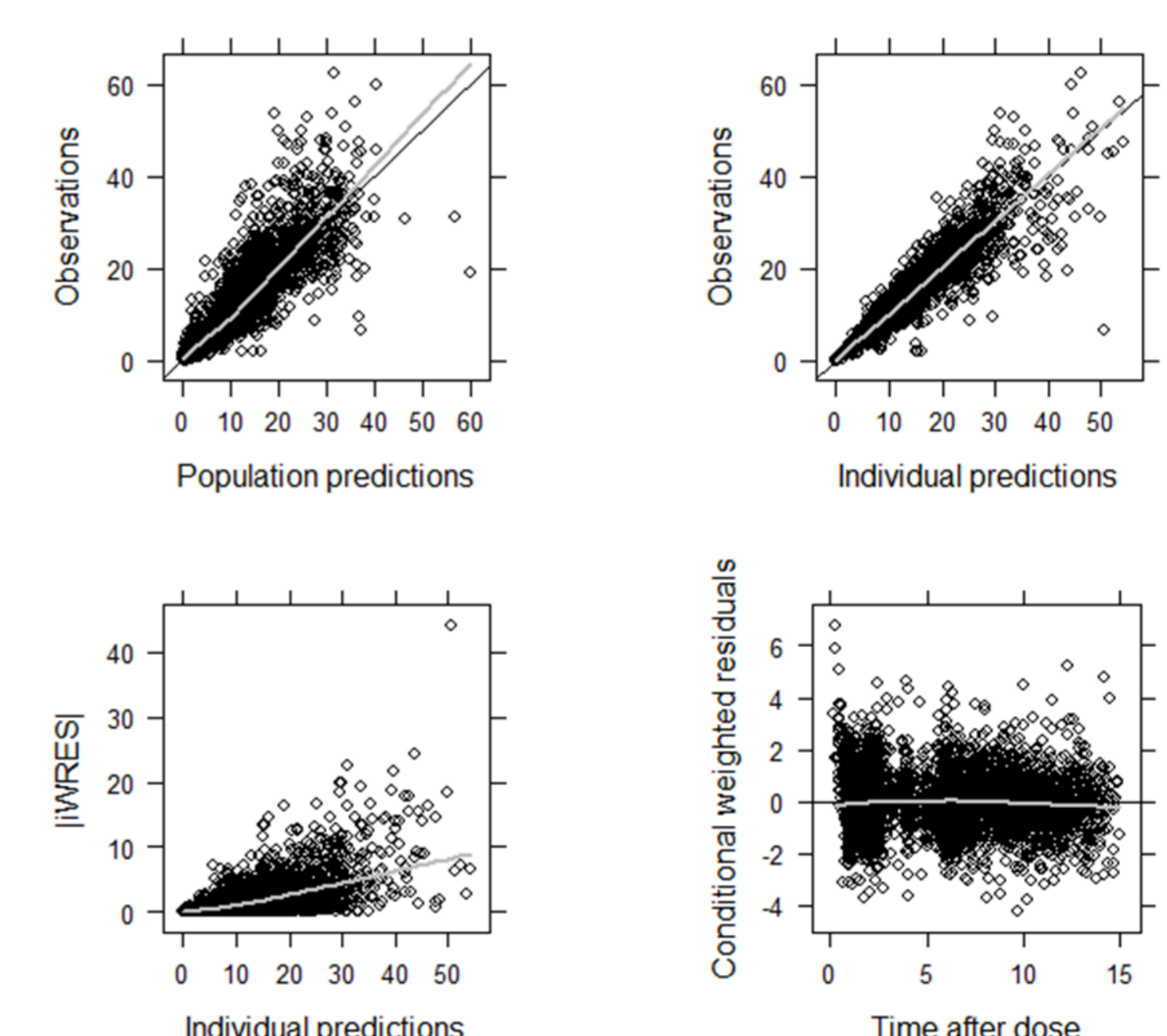


Figure IV: GOF of final model