



UPPSALA
UNIVERSITET

Pharmacokinetics of high-dose methotrexate in adults and children

Åsa M. Johansson¹, Nicola Mayne², Stefanie Hennig¹, Martha Perisoglou², Jeremy Whelan²,
Mats O. Karlsson¹ and Joseph F. Standing¹

1. Dept of Pharmaceutical Biosciences, Uppsala University, Sweden

2. University College London Hospital, London, UK.

Background and Objective

Patients with osteosarcoma receive high dose (12 g/m²) methotrexate followed by daily TDM. Folinic acid rescue commences 24 hours after start of methotrexate infusion, and continues until methotrexate concentrations fall below 0.2 µmol/L.

The aims of the study were:

- To develop a population pharmacokinetic methotrexate model
- To investigate opportunities to improve TDM.

Methods

943 plasma concentrations from 46 patients (mean age 17 yr, range 4-51) on up to 12 occasions were included, and log-transformed concentrations were modeled in NONMEM VI (FOCE INTER).

- 1-, 2- and 3-compartment structural models were tested.
- Between occasion variability was tested on CL, V1 and F.
- CL was divided into two components: filtration and secretion [1,2].
- Assuming a fraction unbound (fu) of 0.4 [3], filtration was scaled to expected GFR [4] multiplied by fu, and secretion was estimated.
- Covariates tested were body weight, body mass index, creatinine clearance, serum creatinine (SeCr) and age.
- The final model was used to predict time to fall below 0.2 µmol/L using only the first 2 measurements, and prediction errors calculated (predicted – “observed”).

$$GFR = 6.72 \cdot \left(\frac{WT_i}{70}\right)^{0.632} \cdot e^{\eta_i} \quad CL_{sec} = \theta_{CL} \cdot \left(\frac{WT_i}{70}\right)^{\theta_{WT, CL_{sec}}} \cdot e^{(\eta_i + \kappa_{ij})}$$

$$CL_{filt} = fu \cdot GFR \quad CL_{tot} = (CL_{filt} + CL_{sec}) \cdot \left(\frac{SeCr_{Mean}}{SeCr_i}\right)^{\theta_{SeCr, CL}}$$

Box 1. Clearance model split into filtration (CL_{filt}) and secretion (CL_{sec}). Expected GFR calculated from Rhodin et al [4], mean age and sex adjusted SeCr (SeCr_{Mean}) calculated from Cerotti et al [5].

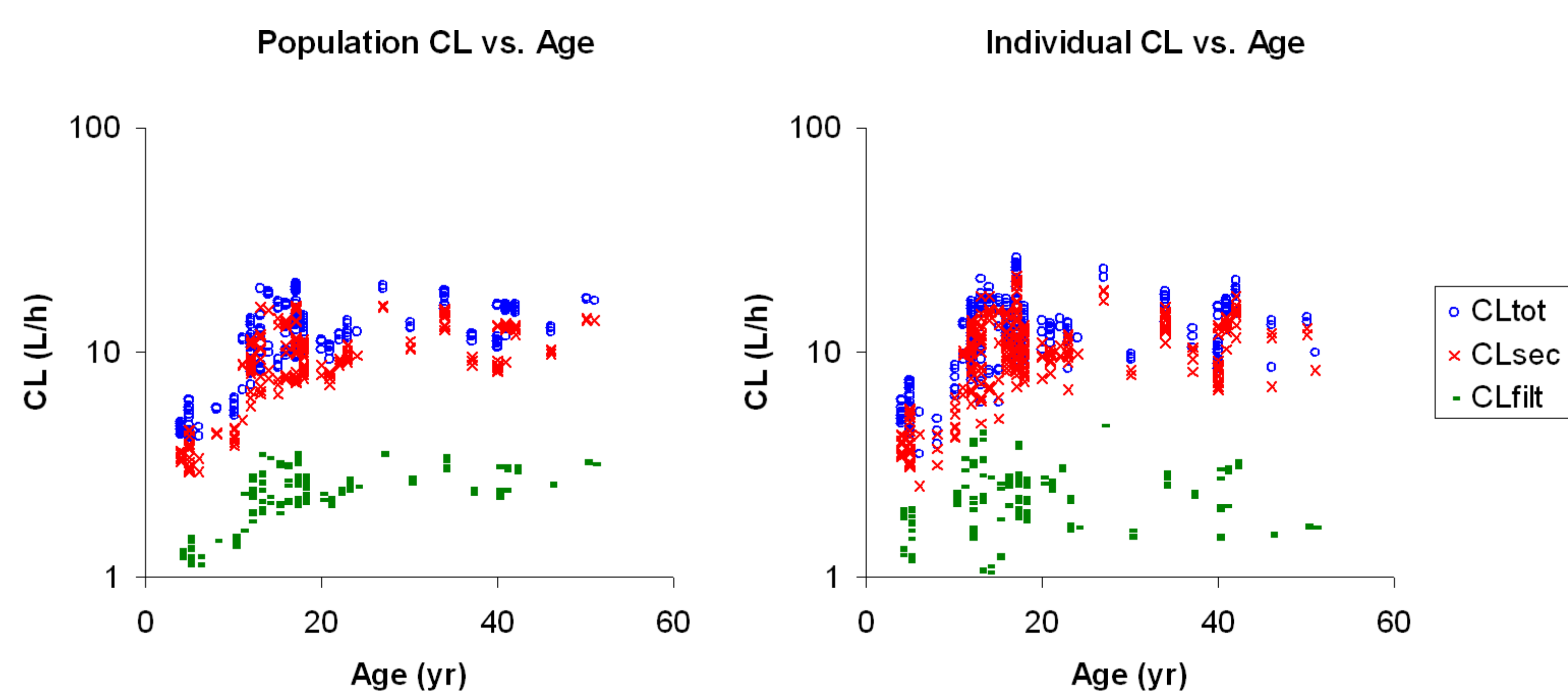


Figure 1. Total CL and the two components: secretion and filtration. The left plot shows the population predictions of CL and the right plot shows the individual predictions of CL.

Table 1. Parameter estimates and bootstrap estimates (455 out of 500) of the final model with RSE %.

Parameter	Model Estimate			Bootstrap Estimate		
	Fixed effects (RSE %)	IIV % (RSE %)	BOV % (RSE %)	Mean (RSE %)	IIV % (RSE %)	BOV % (RSE %)
CL _{sec} (L/h/70kg)	10.9 (19.6)	12.9 (62.3)	12.0 (20.6)	10.9 (12.5)	11.9 (54.0)	12.1 (18.7)
V ₁ (L/70kg)	74.3 (20.1)	8.02 (133)		74.7 (12.3)	8.69 (91.9)	
Q (L/h/70kg)	0.110 (19.0)	29.2 (59.1)		0.11 (15.7)	27.3 (60.2)	
V ₂ (L/70kg)	4.1 (30.2)	36.5 (46.2)		4.23 (20.9)	33.9 (36.5)	
θ _{WT, CL_{sec}}	0.944 (10.9)			0.935 (9.5)		
θ _{WT, Q}	0.693 (18.9)			0.698 (17.9)		
θ _{SeCr, CL}	0.0831 (25.5)			0.0874 (55.8)		
RUV (%)	29.3 (5.5)			29.3 (5.7)		

Results

• A 2-compartment model described the data well, although a 3-compartment model gave a significantly lower OFV, possibly due to the effect of data being censored by the cessation of TDM after concentrations were less than 0.2 µmol/L.

• All parameters were scaled with body weight, and CL additionally scaled with age and sex adjusted SeCr [5].

• CL was described by the equations in Box 1 and predictions of CL components vs. age are shown in Figure 1.

• Using only the first 2 concentrations, the mean (SD) prediction error of time to reach 0.2 µmol/L was 0.34 (8.2) hours. Excluding the occasions with preceding concentrations above 0.8 µmol/L (20.6 %) the variability was reduced (1.88 (3.3) hours).

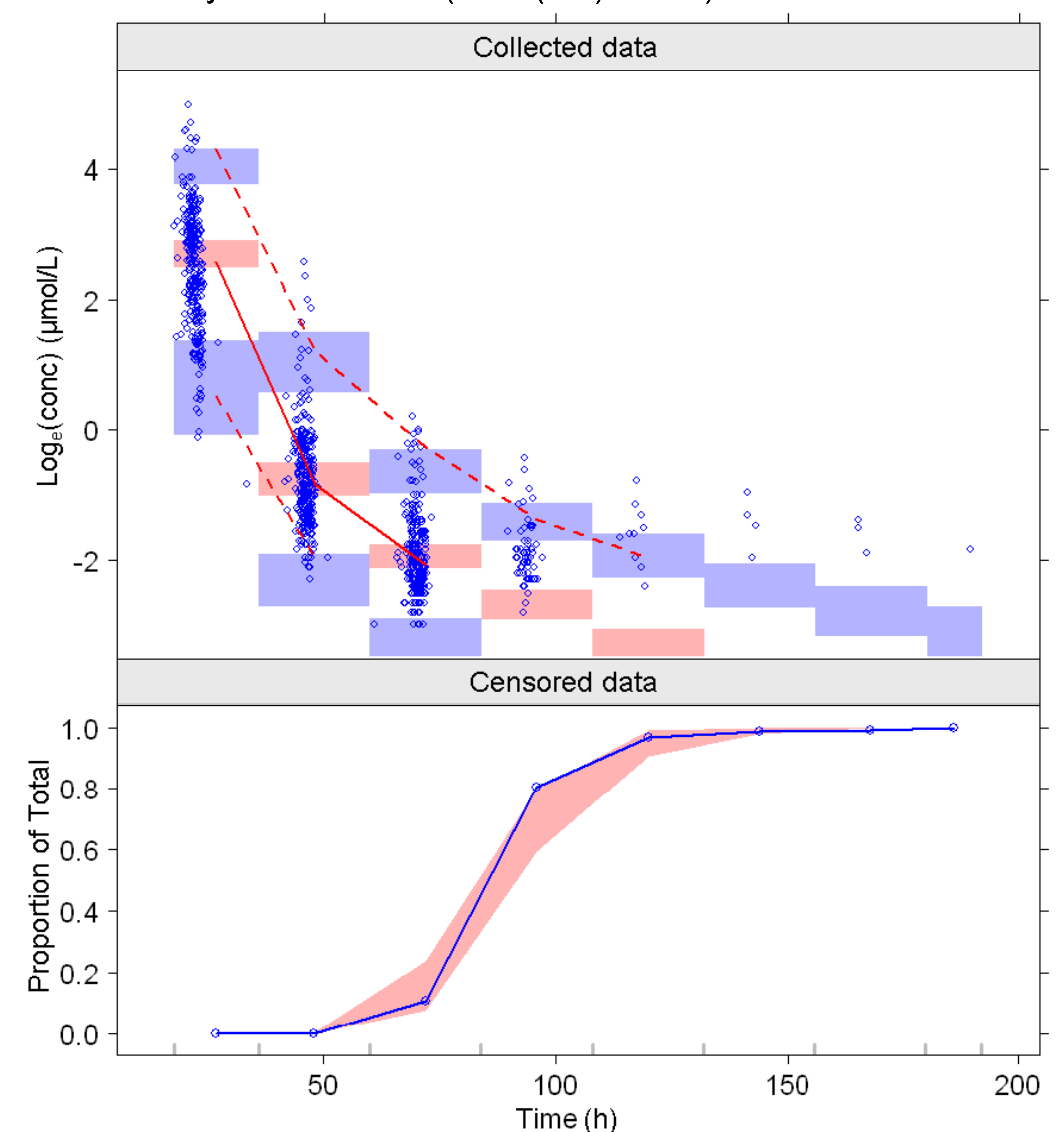


Figure 2. The upper plot shows the VPC for all data and the lower plot shows the proportion of observations below 0.2 µmol/L [6]. Observations (○), observed median (—), observed 97.5 and 2.5 percentiles (---), 95% CI for the simulated 97.5 and 2.5 percentiles (■) and 95% CI for the simulated median (the fraction of censored observations) (■).

Conclusions

A 2-compartment model with body weight and SeCr scaling adequately described the data, and predicted the time for concentration to fall below 0.2 µmol/L. This model will now be used for Bayesian forecasting in TDM. Censoring of the data by patients being discharged after levels were below 0.2 µmol/L may affect structural model selection. Methods for handling this type of censoring in pharmacometric data warrant further investigation.

References

1. Christophidis N et al. Cancer Chemotherapy and Pharmacology, 1981; 6: p. 59-64.
2. Winograd B et al. European Journal of Clinical Pharmacology, 1986; 30: p. 231-238.
3. Maia MB et al. International Journal of Clinical Pharmacology and Therapeutics, 1996. 34: p. 335-341
4. Rhodin MM et al. Pediatric Nephrology, 2009. 24: p. 67-76.
5. Ceriotti F et al. Clinical Chemistry, 2008. 54: p. 559-566.
6. Bergstrand M et al. PAGE 18 (2009) Abstr 1604 [www.page-meeting.org/?abstract=1604].

Collected Data

Table 2. Demographics of patients included in the analyze.

Parameter	Mean	Median	Min	Max	RSE %
Age (yr)	19.5	17.0	4.0	51.0	58.6
Bodyweight (kg)	60.9	59.0	17.4	107.0	38.4
Height (cm)	161	168	105	195	13.5
BSA (m ²)	1.64	1.69	0.72	2.39	24.6
BMI (kg/m ²)	22.5	21.5	12.8	35.7	25.7
MTX dose (g/m ²)	11.9	12.0	7.9	13.4	5.59
SeCr (μmol/L)	59.4	60.5	18.0	104.0	31.8
Occasions (#)	4.9	4	1	12	64.4

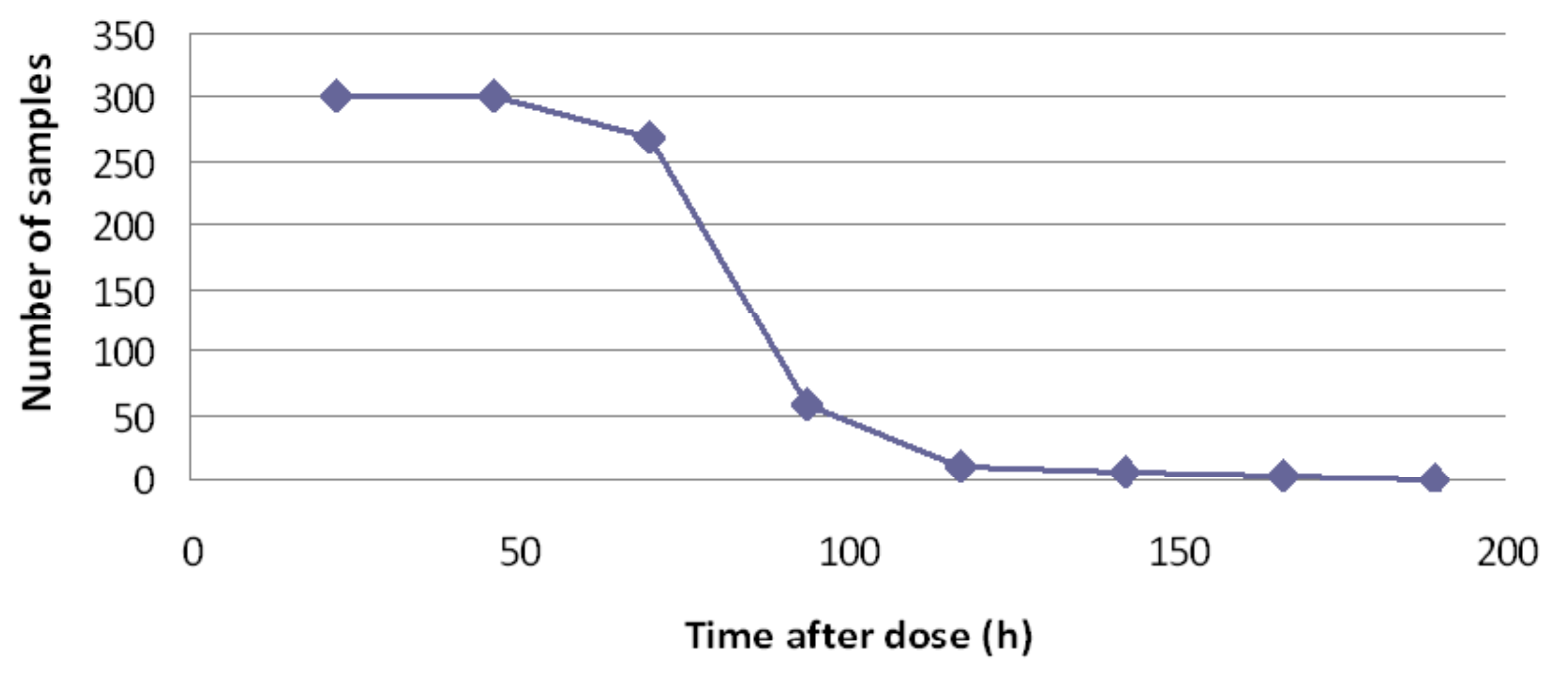


Figure 3. Number of collected samples at a certain time after dose

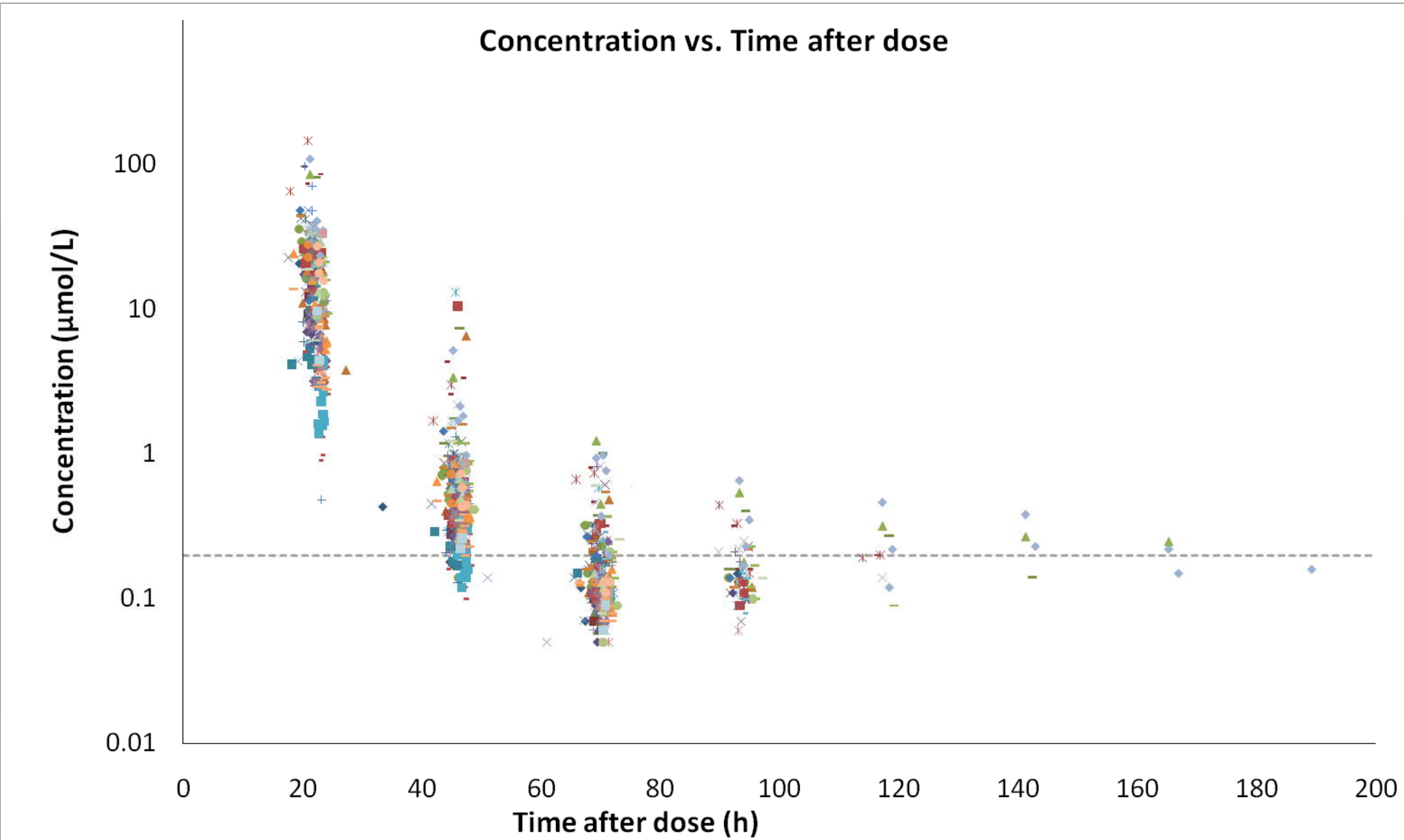


Figure 4. Concentration - time profile of the collected samples. The grey dotted line shows the concentration of 0.2 μmol/L.

Results

The mean, sex and age adjusted SeCr (μmol/L) was calculated according Cerotti et al [5]. To link the mean values for a 15 year old with the adult mean values two linear interpolations were used. The equation for calculation of $SeCr_{Mean}$ are shown in Box 2.

Age ≤ 15

$$SeCr_{Mean} = -2.37330 - 12.91367 \cdot \ln(age) + 23.93581 \cdot \sqrt{age}$$

15 < *Age* ≤ 17

Males

$$SeCr_{Mean} = 9.5471 \cdot age - 87.847$$

Females

$$SeCr_{Mean} = 4.7137 \cdot age - 15.347$$

Age ≥ 18

Males

$$SeCr_{Mean} = 84$$

Females

$$SeCr_{Mean} = 69.5$$

Box 2. Equations for calculation of $SeCr_{Mean}$ according to Cerotti et al and equations for the linear interpolations of $SeCr_{Mean}$ for the age group 15<Age≤17 years.

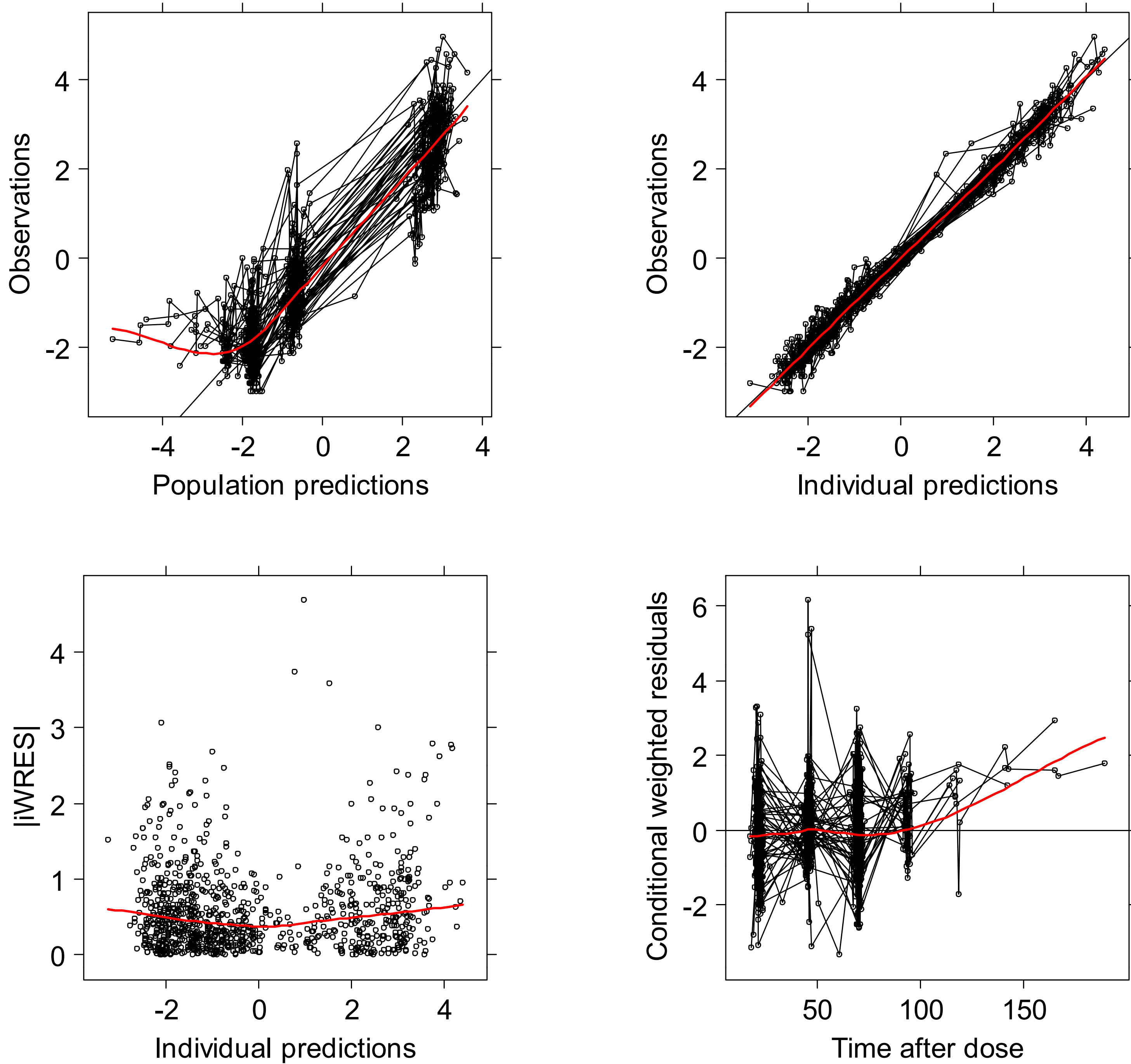


Figure 5. Basic goodness of fit plots for the final model.

Åsa Johansson
PhD student, MSc Chemical Engineering
Dep of Pharmaceutical Biosciences
Div of Pharmacokinetics and Drug therapy
Uppsala University

Box 591
SE-751 24 Uppsala, Sweden
Phone: +46-18-4714000
Fax: +46-18-4714003
Email: asa.johansson@farmbio.uu.se