

Background and Objectives

Rifamycins are antibiotics largely used in the treatment of TB and are potent inducers of a wide range of drug-metabolising enzymes, including the CYP450 family, which gives rise to a number of drug-drug interactions.

Midazolam (MDZ) is a substrate for CYP3A which hydroxylates it to **α-OH-MDZ**. This metabolite is then glucuronidated by UDP-glucuronosyltransferases.

The objective is to quantify of CYP3A induction caused by **rifapentine (RPT)** and **rifampicin (RIF)** by using MDZ as a probe drug.

Methods

29 healthy volunteers, plasma concentrations of MDZ and α-OH-MDZ on 2 occasions:

- Single oral dose **MDZ** (15 mg) alone
- Single oral dose **MDZ** (15 mg) after 14 days of daily dosing of either **RIF** (10 mg/kg) or **RPT** (5, 10, 15, or 20 mg/kg)

The data was modelled in NONMEM VII.

A **well-stirred liver model** similar to [2] was used to capture with a single parameter (CL_{int}) both hepatic CL (CL_H) and first-pass metabolism due to hepatic extraction (E_H)

$$E_H = \frac{CL_{int} \cdot f_u}{Q_H + CL_{int} \cdot f_u} \quad CL_H = E_H \cdot Q_H$$

In the typical individual, liver volume (V_H) was assumed 1 L and liver plasma flow (Q_H) 40 L/h, while and the plasma free fractions (f_u) of MDZ and OH-MDZ were fixed to 3% and 11%, respectively.

Allometric scaling [3] was applied to all CL and V parameters, including the liver. A transit compartment model catered for the variability in absorption and the M6 method [4] handled BLQ values.

The effect of rifamycins exposure on MDZ PK was investigated.

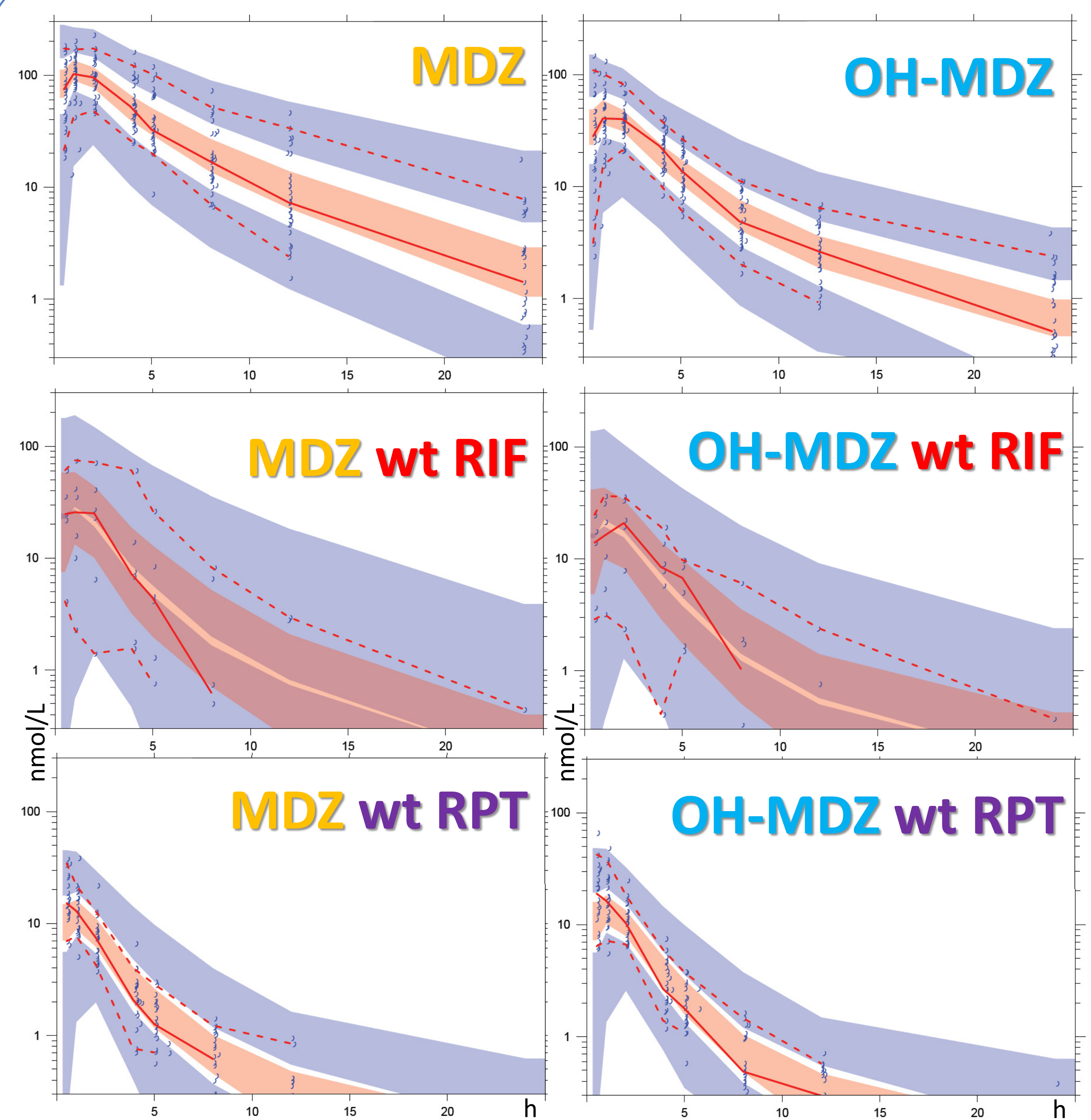


Figure 2 Visual predictive check for MDZ (left) and OH-MDZ (right) when administered alone (top), with RIF (middle) and RPT (lower panel).

The effect of rifamycins was best captured as an **increase in hepatic CL_{int}** , which regulates both CL_H and E_H .

The model estimated that RIF induced MDZ CL_{int} (due to CYP3A) about 6 fold, and RPT twice as much. Also CL_{int} of OH-MDZ (UDP glucuronidation) was found enhanced, 3 fold by RIF and 4.5 by RPT.

A **large variability in the level of induction** was detected in the **RIF** (smaller) cohort, and was captured in the model with a proportionality factor for the BOV (^a in Tab. 1).

Attempts to estimate induction of gut metabolism did not prove robust.

The effect of changes in CL_{int} on exposure depends on f_u . When CL_{int} is already large and f_u is not a limiting factor, the effect is more pronounced on first-pass metabolism than systemic CL. The values of CL_{int} for MDZ and OH-MDZ and their effect on CL_H and E_H are shown in Tab. 2.

Table 2 Hepatic CL parameters

	CL_{int} [L/h]	CL_H [L/h]	E_H []
MDZ	1250	19.4	0.484
MDZ wt RIF	7890	34.2	0.855
MDZ wt RPT	18300	37.3	0.932
OH-MDZ	1870	33.5	0.837
OH-MDZ wt RIF	5620	37.6	0.939
OH-MDZ wt RPT	8410	38.3	0.959

Results

Model structure is in Fig.1 and final parameters in Tab. 1.

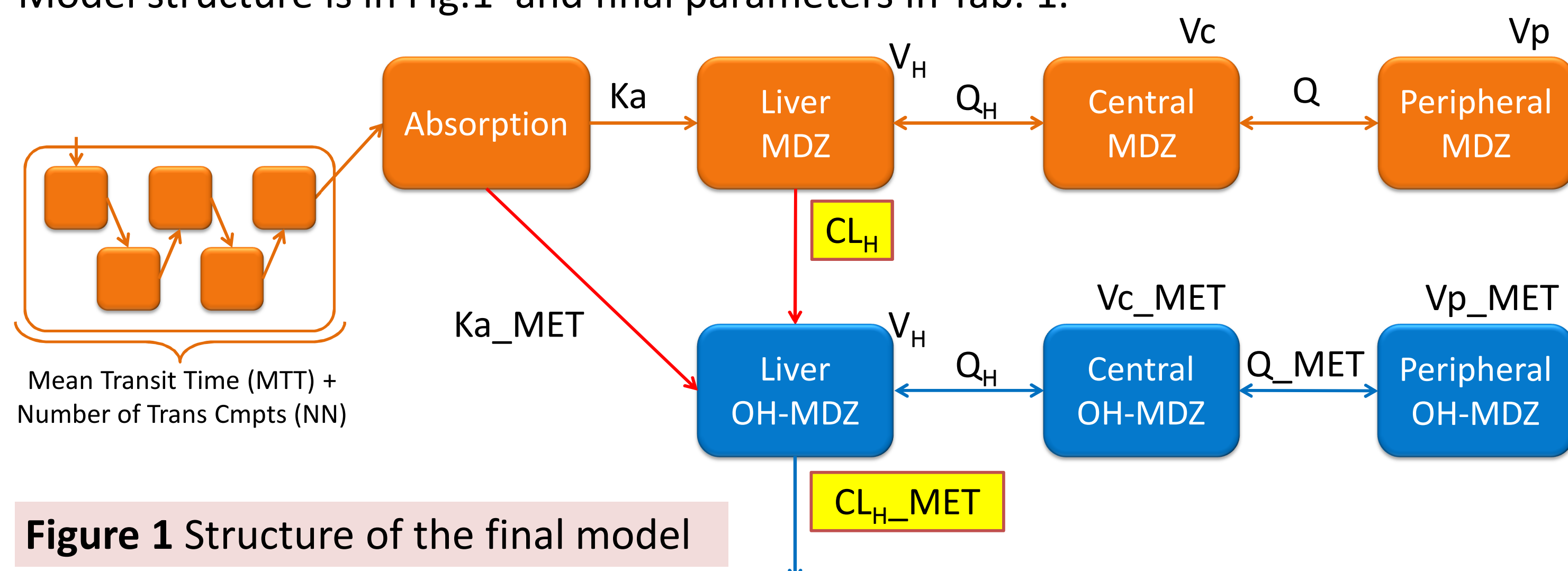


Figure 1 Structure of the final model

MDZ appears in the absorption compartment after going through a transit model. The dose was taken after a meal, so absorption was mostly very fast, but very erratic.

Some drug gets absorbed as **MDZ**, some already as **OH-MDZ** due to metabolism in the gut wall. Both compounds pass through the liver and then reach systemic circulation. Kinetics outside the liver is 2 compartments.

Strong correlations among parameters for MDZ and OH-MDZ were detected and included in the model (lower section of Tab. 1)

Table 1 Final parameter estimates:

Parameter	MDZ		OH-MDZ	
	TV	BSV or *BOV	TV	BSV or *BOV
CL_{int} [L/h]	1250	35.1% 32.7%*	1870	26.9% 30.7%*
V [L]	56.7	24.8%	67.2	20.7%
Q [L/h]	7.37	19.5%	4.87	30.3%
V3 [L]	30.4	25%	47.8	47.9%
Ka [1/h]	1.03	61.8%*	1.09	81.5%*
MTT [h]	0.0492	170%*	-	-
NN []	2.49	-	-	-
ADD [nmol/L]	0.242	-	0.209	-
PROP [%]	19.3%	-	26%	-
CL_{int} wt RIF [L/h]	7890	35.1% 64.4% ^a *	5620	26.9% 61.4% ^a *
CL_{int} wt RPT [L/h]	18300	35.1% 32.7%*	8410	26.9% 30.7%*
Correl BSV CL_{int}	Correl BSV V	Correl BOV CL_{int}	Correl BOV Ka	
42.0%	98%	85.8%	98.4%	

Conclusions

The well-stirred liver model was used to describe the PK of MDZ capturing hepatic CL and first-pass metabolism, and their induction due to rifamycins.

Quantification of both hepatic and pre-hepatic metabolism was attempted in the model, but more robust information, possibly including IV data, should be included to confirm the findings.

No dose effect was detected for **RPT** induction, and only one dose of **RIF** was used, but the incorporation of rifamycin exposure in the model may help further refining the model.

References

- [1] K. E. Dooley, E. E. Bliven-Sizemore, M. Weiner, Y. Lu, E. L. Nuermberger, W. C. Hubbard, E. J. Fuchs, M. T. Melia, W. J. Burman, and S. E. Dorman, "Safety and pharmacokinetics of escalating daily doses of the antituberculosis drug rifapentine in healthy volunteers," *Clinical pharmacology and therapeutics*, vol. 91, no. 5, pp. 881–8, May 2012.
- [2] T. Gordi, R. Xie, N. V. Huong, D. X. Huong, M. O. Karlsson, and M. Ashton, "A semi-physiological pharmacokinetic model for artemisinin in healthy subjects incorporating autoinduction of metabolism and saturable first-pass hepatic extraction," *British journal of clinical pharmacology*, vol. 59, no. 2, pp. 189–98, Feb. 2005.
- [3] B. J. Anderson and N. H. G. Holford, "Mechanism-based concepts of size and maturity in pharmacokinetics," *Annual review of pharmacology and toxicology*, vol. 48, pp. 303–32, Jan. 2008.
- [4] S. L. Beal, "Ways to fit a PK model with some data below the quantification limit," *Journal of pharmacokinetics and pharmacodynamics*, vol. 28, no. 5, pp. 481–504, Oct. 2001.