Development of a Physiologically Based Pharmacokinetic Model for Children with Severe Malnutrition

Wanchana Ungphakorn[1] , Alison H Thomson[1,2]

[1]*Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK*
[2]*Pharmacy Department, Western Infirmary, NHS Greater Glasgow and Clyde, Glasgow, UK*

Corresponding author: Wanchana.Ungphakorn@farmbio.uu.se

University of Strathclyde Glasgow

Introduction

Malnutrition in children remains a global health problem, particularly in developing and less developed countries. In this patient group, pharmacokinetics (PK) of drugs are affected by physiological changes, such as gastrointestinal structure and function and hypoproteinaemia. Physiologically based PK (PBPK) models can relate PK parameters to such physiological changes, and can be used to predict PK in patients.

AIMS

1) To develop a PBPK model for predicting drug disposition in children with severe malnutrition by using ciprofloxacin as a model drug.
2) To investigate the impact of different methods on Tissue:plasma partition coefficient (Kp) predictions.

Methods

[1] Model development

- The structural model comprises 13 physiologically realistic compartments (Figure I).
- Variability in tissue volumes was assumed to follow a truncated Dirichlet distribution.
- Blood flow rates were calculated as a fraction of tissue volumes.
- Dynamic processes of drug in each organ/tissue were described using linear ordinary differential equations (LODE).
- The model was implemented in MATLAB v.7.13.
- The PBPK model was initially developed for healthy adults then scaled to healthy children then to malnourished children.

[2] Input parameters

- Organ volumes and blood flows for healthy adults and children were obtained from the literature.
- For malnourished children, body weights were predicted using equations developed from data in the WHO database.

Age <2 years:

$$BW = -8.555 + (0.243 \cdot HT) + (0.883 \cdot SD) - (0.104 \cdot SEX)$$

Age 2-5 years:

$$BW = exp(0.773 + (0.0197 \cdot HT) + (0.0880 \cdot SD) - (0.0123 \cdot SEX)$$

Age >5 years:

$$BW = exp(2.335 + (0.00969 \cdot AGE) + (0.153 \cdot SD) - (0.00102 \cdot SEX)$$

where BW is body weight (kg), HT is height (cm), SD is Z-score value, SEX is gender (0=male, 1,=female), and AGE is age of the child (months)

- Organ volumes in malnourished children were scaled from normal (healthy) values using scaling factors generated specifically for each organ.

$$fBW = \frac{BW_M}{BW_H}$$

$$OW_{M,i} = fOW \cdot OW_{H,i}$$

*f*BW = body weight fraction
*f*OW = organ weight fraction
H = healthy
M = malnutrition

Table I Equations for predicting *f*OW of each organ

Organs	Equations
Adipose	*f*OW = (1.9 · *f*BW) – 0.9
Bone	*f*OW = (0.2 · *f*BW) + 0.8
Heart	*f*OW = (0.5384 · *f*BW) + 0.3824
Kidney	*f*OW = (0.5368 · *f*BW) + 0.4092
Liver	*f*OW = (0.7436 · *f*BW) + 0.2254
Muscle	*f*OW = (1.3571 · *f*BW) – 0.3401
Skin	*f*OW = (1.5945 · *f*BW) – 0.5945
Spleen	*f*OW = (0.8942 · *f*BW) + 0.0269
Lungs	*f*OW = (0.7027 · *f*BW) + 0.2836

- Cardiac output (CO) was estimated using body surface area (BSA) and cardiac index (CI), and was subsequently used to calculate organ blood flows (BF) as follows:

$$CO_M = \frac{CO_H \cdot BSA_M}{BSA_H} \qquad BF_{M,i} = \frac{BF_{H,i} \cdot OW_{M,i}}{OW_{H,i}}$$

- Kp values were predicted using the models proposed by Poulin & Theil [1], Rodgers et al. [2] and Jansson et al. [3].

[1] Poulin P, & Theil FP. Prediction of pharmacokinetics prior to in vivo studies. 1. Mechanism based prediction of volume of distribution. J Pharm Sci 2002;91:129–156.
[2] Rodgers T, Leahy D, Rowland M. Physiologically based pharmacokinetic modeling 1: Predicting the tissue distribution of moderate-to-strong bases. J Pharm Sci 2005;94:1259–1276.
[3] Jansson R, Bredberg ULF, Ashton M. Prediction of drug tissue to plasma concentration ratios using a measured volume of distribution in combination with lipophilicity. J Pharm Sci 2007;97:2324-2339.

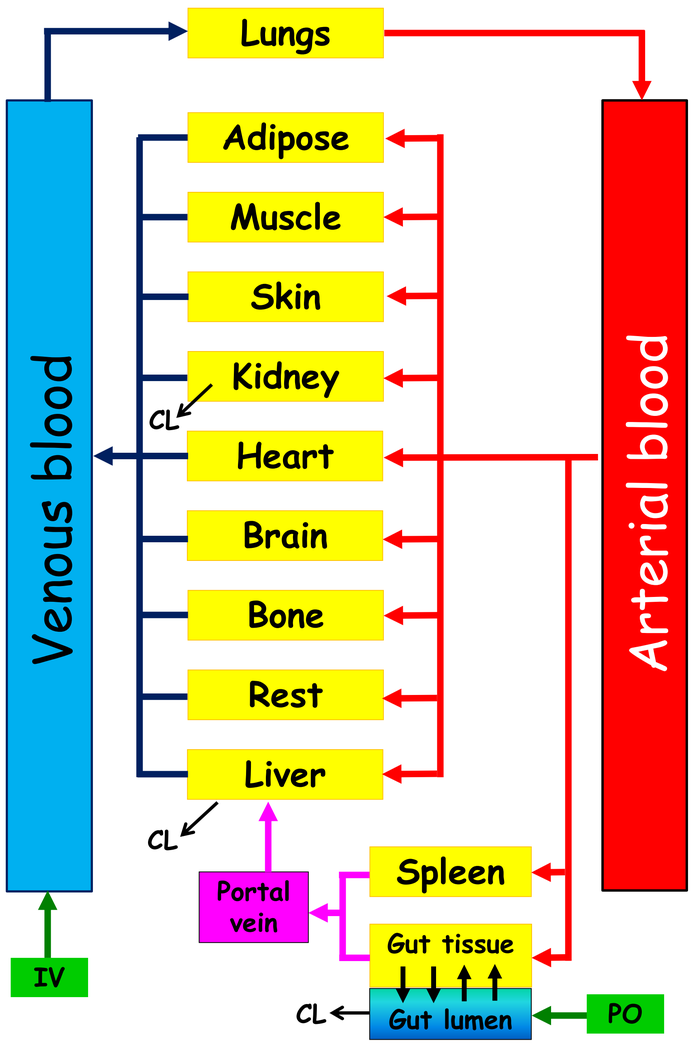


Figure I (above) Structure of the PBPK model

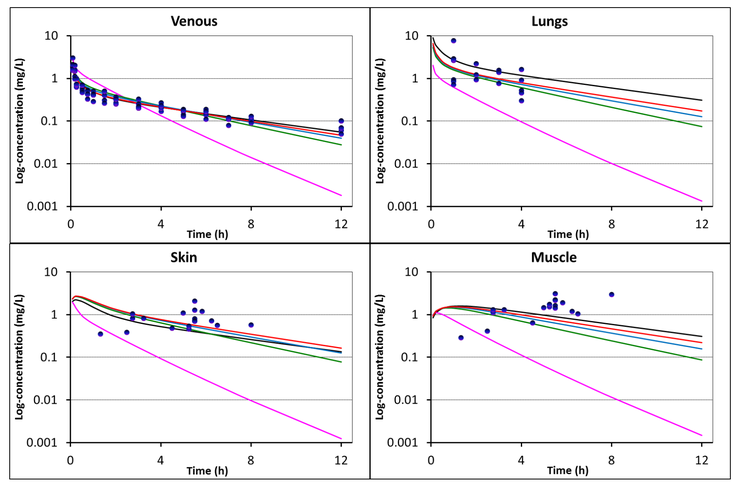
Figure II (right) Concentration-time profile generated using Kp values predicted from Poulin model (pink line), Rodgers model (black line) and the empirical method (green, blue, and red lines).

Results: Kp predictions

Table II Kp values predicted from Poulin model, Rodger model, and the empirical method

Organs	Poulin model	Rodgers model	Empirical method		
			Vss=1.74 L/kg (M/F)	Vss=2.0 L/kg (M/F)	Vss=2.4 L/kg (M/F)
Adipose	0.12	0.64	0.35/0.43	0.40/0.49	0.48/0.59
Bone	0.50	1.29	1.33/1.79	1.65/2.17	2.13/2.75
Brain	0.82	1.27	0.18/0.21	0.20/0.23	0.22/0.26
Gut	0.76	3.77	2.93/3.28	3.18/3.56	3.53/3.96
Heart	0.72	3.57	3.05/3.66	3.48/4.19	4.13/4.99
Kidney	0.72	7.10	7.27/7.83	7.66/8.26	8.21/8.85
Liver	0.72	6.52	2.79/3.11	3.01/3.35	3.32/3.70
Muscle	0.67	3.79	3.17/3.94	3.71/4.62	4.54/5.68
Skin	0.65	2.26	3.14/3.63	3.48/4.03	3.99/4.62
Spleen	0.75	4.80	3.17/3.94	3.71/4.62	4.54/5.68
Lungs	0.71	5.68	3.65/4.33	4.13/4.91	4.84/5.78

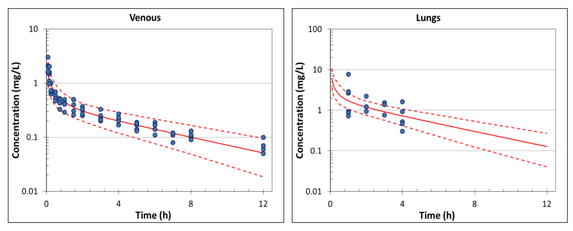
Vss = volume of distribution at steady state, M = male, F = female



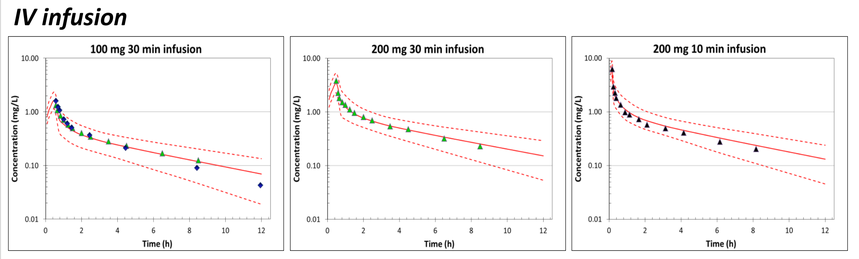
Results: PK predictions

I. Healthy adults

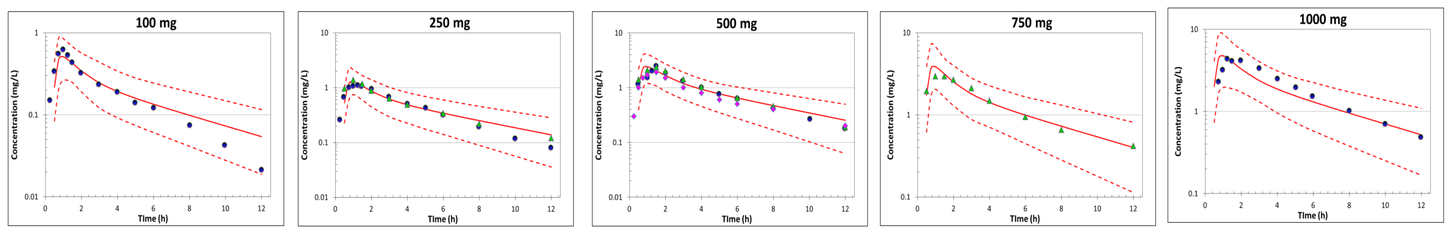
IV bolus



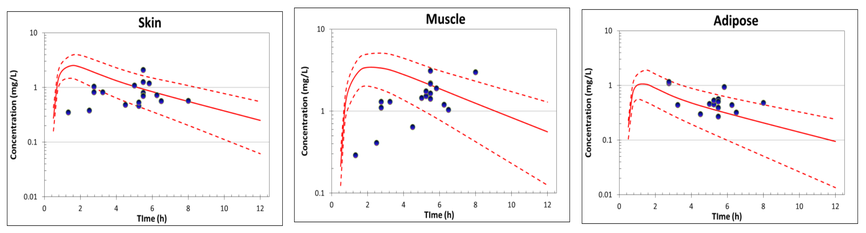
IV infusion



Oral

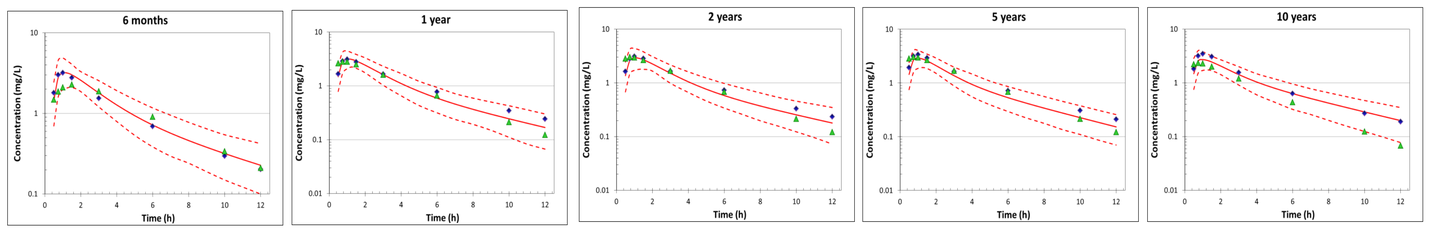


Tissue concentrations

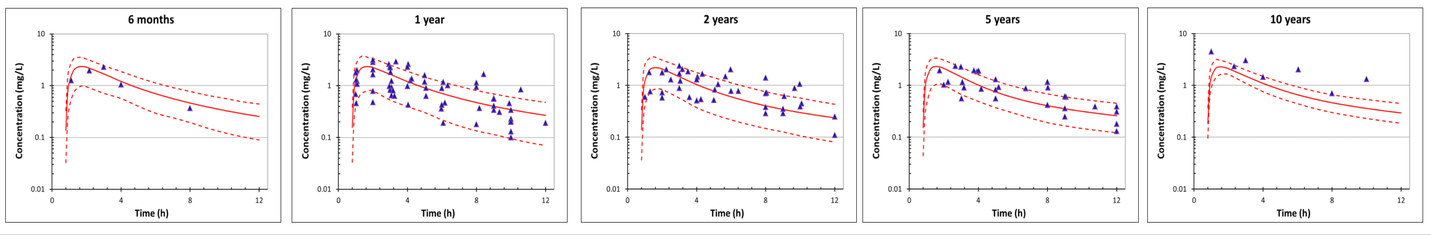


- The red solid line is the mean prediction and the red dashed lines are the 2.5th (lower) and 97.5th (upper) percentiles of prediction based on 1,000 simulations, assumed an equal proportion of male (*n*=500), and female (*n*=500).
- The symbols are the observed data taken from various human studies.

II. Healthy children



III. Malnourished children



Conclusions

- A PBPK model was created for healthy adults, healthy children and malnourished children (6 month to 10 years)
- The predictions derived from the model were in agreement with observed data.
- The Rodgers model and the empirical method were more suitable for predicting Kp for amphoteric compounds, e.g. ciprofloxacin.
- Application of this model to other drugs is now required in order to substantiate the predictive performance of the model.