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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 • HT) + (0.883 • SD) - (0.104 • SEX)

Age 2-5 years: 
BW = exp(0.773 + (0.0197 • HT) + (0.0880 • SD) - (0.0123 • SEX)

Age >5 years: 
BW = exp(2.335 + (0.00969 • AGE) + (0.153 • SD) - (0.00102 • 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 values using scaling factors generated specifically for each organ.

\[ \text{fBW} \times \frac{BW_{\text{org}}} {BW_{\text{org}}} = \text{fOW} \times \frac{OW_{\text{org}}}{OW_{\text{org}}} \]

- 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:

\[ \text{CO}_{\text{org}} = \frac{\text{CI} \times \text{BSA}_{\text{org}}}{\text{BSA}} \times \text{BF}_{\text{org}} = \frac{\text{BF}_{\text{org}}}{\text{OW}_{\text{org}}} \]

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

Results: PK predictions

I. Healthy adults

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 amphotropic compounds, e.g. ciprofloxacin.
- Application of this model to other drugs is now required in order to substantiate the predictive performance of the model.