A PBPK Framework to Predict Drug Exposure in Malnourished Children

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Objectives

To develop and evaluate a physiologically based translational framework for prediction of drug disposition and PK characteristics in children with severe protein energy malnutrition.

Background

Protein energy malnutrition in children is a global health problem, particularly in developing countries. The effects of nutritional status on body composition and physiological functions may have implications for drug disposition and ultimately affect the clinical outcome in this already vulnerable population. Physiologically based pharmacokinetic (PBPK) modeling can be used to predict the effect of protein starvation as it links physiological changes to pharmacokinetic (PK) consequences. When established, this approach can be used to guide dose recommendations in malnourish pediatric populations were it can be expected that no PK information is available. Still, the absence of detailed information on body composition and the scarce availability of controlled clinical trials in malnourished children, has so far impeded the establishment and evaluation of a generic PBPK model in this population.

Methods

Changes to body composition and plasma protein concentrations due to protein energy malnutrition were derived for adults from the literature and implemented in PK-Sim® (v7.4.0) [1-3]. To accommodate the differences between a healthy and a malnourished population in PK-Sim, compiled physiological data were converted to a set of physiology scaling parameters (PSP). Malnourished pediatric populations (MPP) were acquired by applying the PSP to healthy pediatric populations generated via the population algorithm in PK-Sim®, including maturation of biological systems, e.g., metabolic enzymes and plasma proteins.

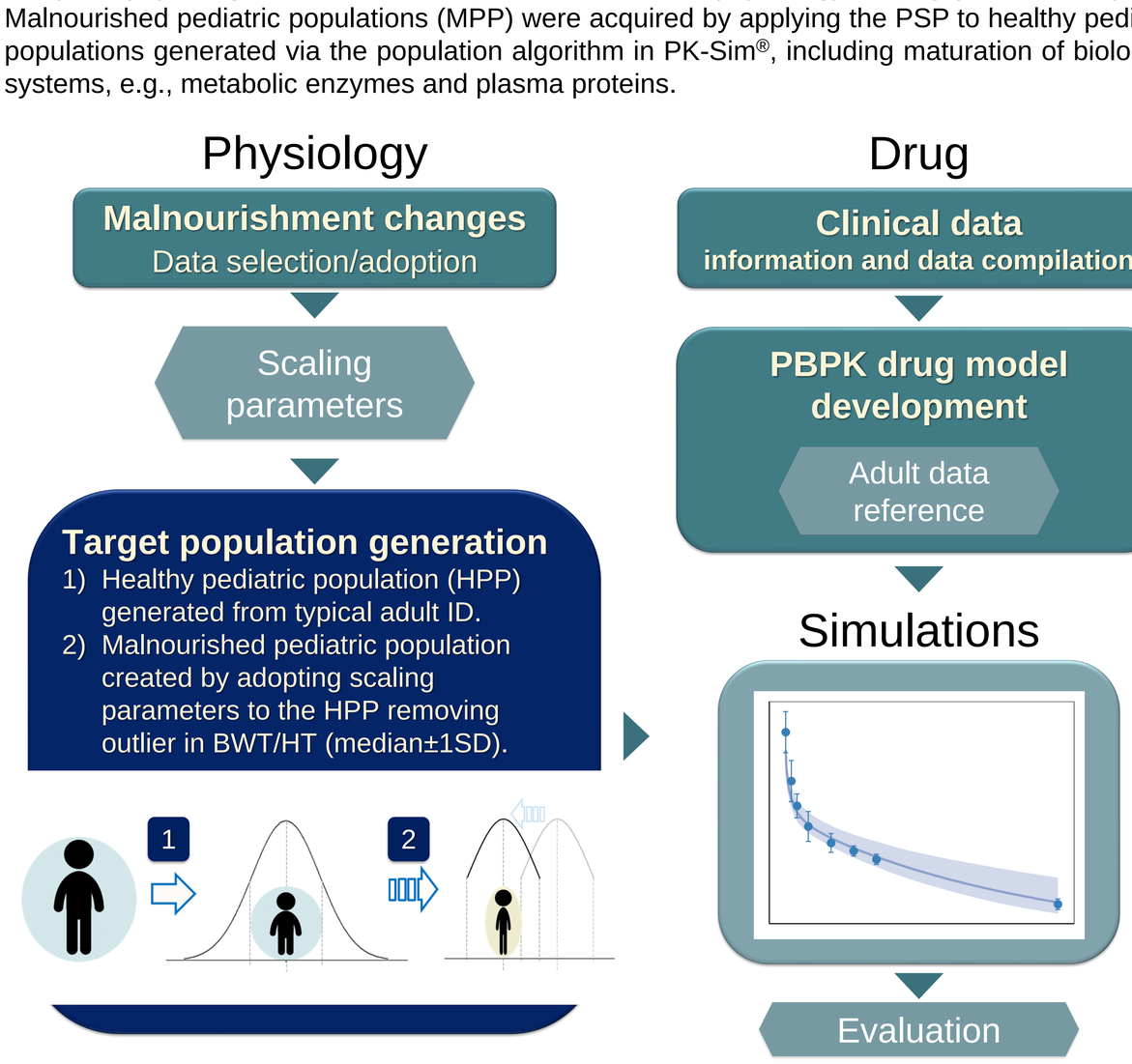

Figure 1. *Project workflow. Physiology scaling parameters established based on publications, PBPK modeling and generation of healthy virtual populations performed in PK-Sim (v7.4.0)*

Simulations were performed in PK-Sim® for ciprofloxacin, caffeine and cefoxitin based on the information provided in selected reference studies and using developed or adopted drug models [4-9]. Observed and simulated plasma concentration versus time profiles and PK parameters in malnourished pediatric populations were compared to evaluate the aptness of the suggested modelling approach. A prediction error (PE) (predicted/observed) within the range of 0.5-2.0 were considered as adequate predictive performance.

References

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Conclusions

The results demonstrate that the proposed PBPK modelling strategy may be appropriate for predictions of drug disposition and PK in malnourished children.

Results

A set of PSP was established which, together with the in-built virtual population algorithm in PK-Sim®, was adopted to generate MPPs. The change in total body weight generated a population with z-score representative for a population with severe malnourished (Figure 2). A representation of changes in physiological parameters for a generic population (males, age = 2 yr, n=100) is shown in Figure 3. Plasma concentration-time profiles, as well as the inter individual variability, in malnourished children were well captured by the model predictions applying the suggested PBPK framework (Figure 4). Adequate predictions of model drug exposure were achieved for all investigated cases (Table 1).

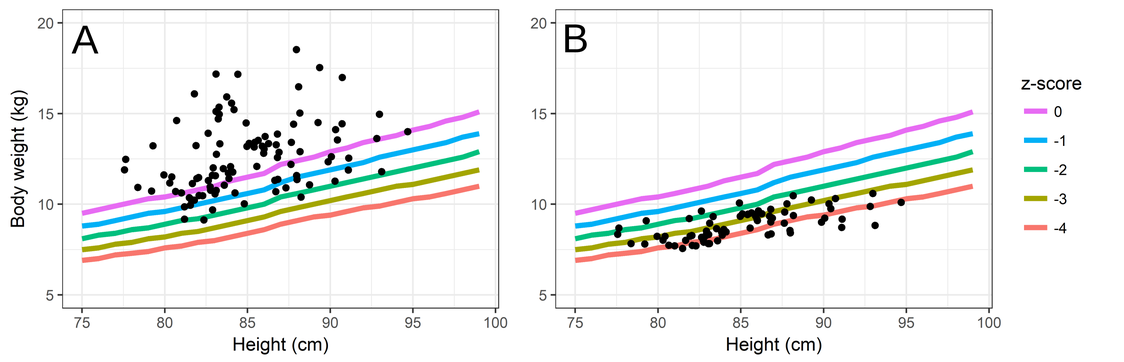

Figure 2. *Distribution of body weight and height for a virtual population (males, age=2 yr) before, i.e., healthy (panel A, [n=100]), and after, i.e., malnourished (Panel B, [n=71]), applying proposed scaling strategy to generate a malnourished population. The WHO z-scores for body weight per height are indicated by colored lines.*

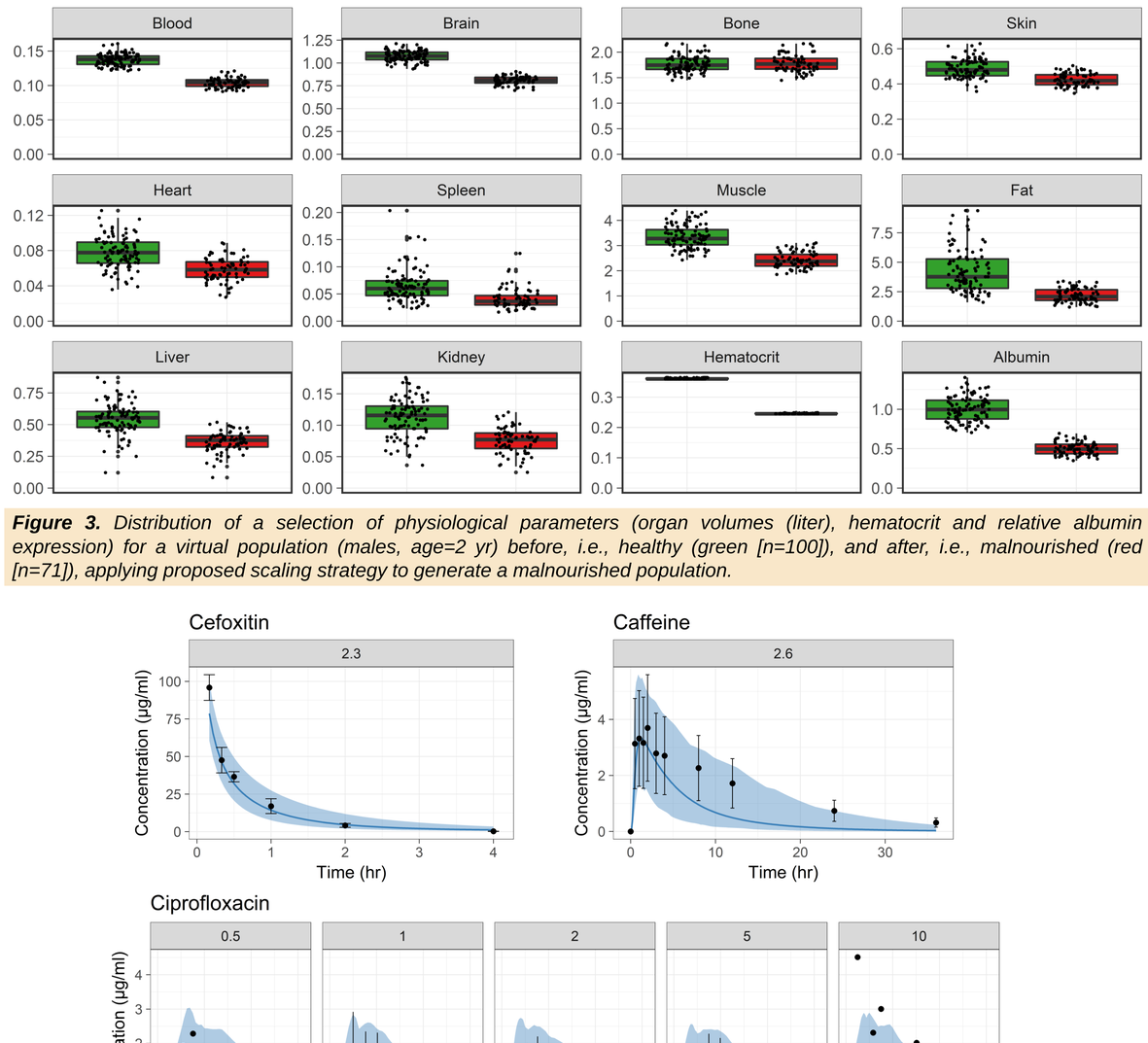

Figure 3. *Distribution of a selection of physiological parameters (organ volumes (liter), hematocrit and relative albumin expression) for a virtual population (males, age=2 yr) before, i.e., healthy (green [n=100]), and after, i.e., malnourished (red [n=71]), applying proposed scaling strategy to generate a malnourished population.*

Figure 4. *Observed and simulated plasma concentration-time profiles after administration of cefoxitin (intra venous, 40 mg/kg), caffeine (oral, 40 mg) and ciprofloxacin (oral, 10 mg/kg) in malnourished children. Simulations were performed for representative virtual populations (n~80) generated with the proposed scaling strategy (average age [years] indicated in plot header). Observations (mean±SD) are displayed as black dots and simulations as geometric mean (blue line) with CI95% (shaded area).*

Table 1. *Observed and simulated pharmacokinetic parameters (AUC_t, C_{max} and $t_{½}$) and prediction error (PE). Observed values are based on mean observations while simulated values represents the geometric mean (SD) of the population.*

	AUC_t			C_{max}			$t_{½}$		
Group	**Obs.**	**Pred.**	**PE**	**Obs.**	**Pred.**	**PE**	**Obs.**	**Pred.**	**PE**
Cefoxitin	43	50 (21)	1.17	96	80 (13)	0.83	0.47	1.3 (0.11)	2.77
Caffeine	49	28 (16)	0.57	3.7	3.8 (1.3)	1.03	10	6.8 (1.8)	0.69
Ciprofloxacin (0.5 yr)	7.8	9.3 (4.2)	1.24	2.3	1.5 (0.82)	0.65	-	3 (0.83)	-
Ciprofloxacin (1 yr)	9.7	9.3 (3.9)	0.95	1.8	1.5 (0.84)	0.83	3.7	3.6 (1.1)	0.97
Ciprofloxacin (2 yr)	9.0	10 (3)	1.14	1.5	1.8 (0.78)	1.20	3.0	3.4 (0.79)	1.13
Ciprofloxacin (5 yr)	8.6	11 (2.9)	1.25	1.6	1.7 (0.57)	1.06	2.8	3.3 (1)	1.19
Ciprofloxacin (10 yr)	16	11 (3.8)	0.71	4.5	1.8 (0.87)	0.41	5.7	3.6 (0.92)	0.63