Comparative analysis of scaling methods for dose selection in paediatric indications

Massimo Cella, Frank L. Kloprogge, Meindert Danhof, Oscar Della Pasqua

Introduction

Dose selection for paediatric indications remains a major challenge in early clinical development. Despite understanding of the role of developmental growth on pharmacokinetics and pharmacodynamics, medical practice often assumes a direct, linear relationships between body size, physiological function and clinical response. This assumption may lead to inappropriate dose selection in children.

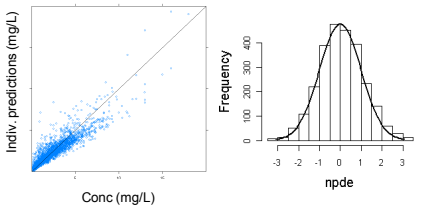
In the current investigation, we compare the accuracy of PK predictions obtained by two different approaches to scale pharmacokinetics from adults to children. The objective is to identify which methods are best suited for the assessment of drug exposure in small populations.

Methods

The antimalarial drug atovaquone (ATV) is used as paradigm compound for our analysis. Nine clinical trials from GlaxoSmithKline's clinical database were used for pharmacokinetic modelling. Different doses were available (62.5 to 1000 mg).

	CHILDREN (mean and range)	***ADULTS*** (mean and range)
Africans	**423**	**106**
Orientals	**59**	**195**
Body weight (Kg)	**26.5** (5.4 – 68)	**55.6** (39 – 110)
Age (years)	**8.8** (0.3 – 17)	**29.2** (18 – 65)
Blood samples per subject	**2.2** (1 - 13)	**5.1** (1-15)

ATV pharmacokinetics was characterised by a one-compartment model with 1st order absorption and 1st order elimination. The effect of body weight (BW) on clearance (CL) was described by the following equation: $CL = CL_{RACE} * (BW/70)^{EXP}$. The coefficients were affected by ethnicity. In addition, a linear correlation was found between BW and volume of distribution (V).



Fixed effects	***Estimate***
CL, Africans (L/h)	3.9
CL, Orientals (L/h)	11.8
Exp on CL	0.801
V (L)	10.4
KA (1/h)	0.24
IIV	
CL	25.9 %
V	27.8 %
KA	94.4 %
Residual variability	
Proportional error	11.2 %
Additive error (mg/L)	0.01

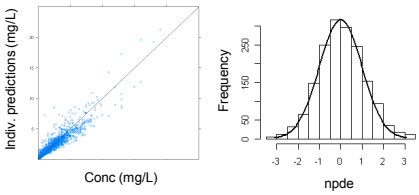
Diagnostics and model parameter estimates for ATV. Results are based on data from adults and children.

To estimate the individual systemic exposure (AUC), simulations were performed using the model parameter estimates. 200 replicates were obtained for each patient. Additional sampling points were included to mimic serial sampling in this population.
Taking into account the weight groups defined in the label of ATV, AUC distributions were summarised as median, 25th and 75th percentiles. For the sake of clarity, only data from Africans patients are presented here.
Based on a procedure analogous to the posterior predictive check, model performance was compared using two scaling methods. This evaluation is meant to support prospective data analysis in paediatric drug development, when availability of PK data in children is limited:

→ *ALLOMETRIC SCALING*. A dataset was created using 301 adults and 58 children stratified for all significant covariates. The same structural model was used as for the total population, with the exception of the exponent on CL, which was fixed at 0.75.
→ *PRIORS FROM ADULTS*. A dataset was created using the same 58 children used above, i.e., stratified for all significant covariates. ATV parameter estimates in adults were used as priors in the analysis of the paediatric dataset, as implemented by $PRIOR statement in NONMEM. In contrast to the full dataset, a linear correlation was found between CL and BW.

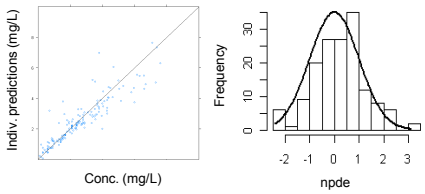
Goodness-of-fit and parameter estimates

ALLOMETRIC SCALING



Fixed effects	***Estimate***
CL, Africans (L/h)	3.90
CL, Orientals (L/h)	11.80
Exp on CL	0.750
V (L)	9.87
KA (1/h)	0.25
IIV	
CL	25.7 %
V	23.9 %
KA	95.7 %
Residual variability	
Proportional error	10.2 %
Additive error (mg/L)	0.02

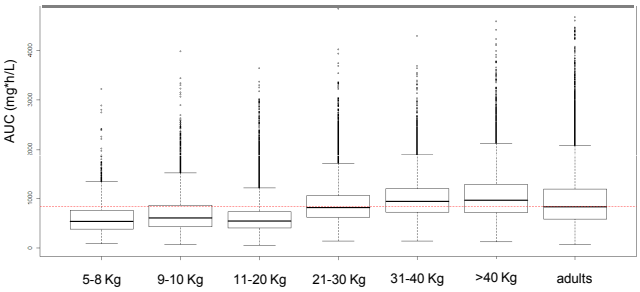
PRIORS FROM ADULTS



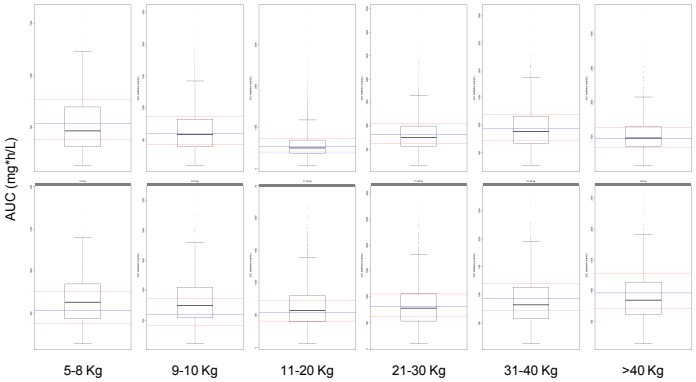
Fixed effects	***Estimate***
CL, Africans (L/h)	1.8
CL, Orientals (L/h)	4.25
V (L)	10.2
KA (1/h)	0.28
IIV	
CL	43.5 %
V	58.3 %
KA	87.4 %
Residual variability	
Proportional error	8.7 %
Additive error (mg/L)	0.03

Results

Predicted AUC distributions stratified by BW category from the model built on all data, following current dosing regimen recommendations.



Predicted AUC distributions stratified by BW category, as calculated by allometric scaling (top) and using adult priors (bottom). The blue line represents the median reference AUC, the red lines represent the 25th and 75th percentiles.



Conclusions

Incorporation of parameter distributions from pharmacokinetics in adults as priors for the modelling of paediatric data provides an alternative, valid method to evaluate drug exposure in children.

In contrast to allometric scaling, which assumes a predefined relationship between body weight, CL and V, the use of priors enables the assessment of the correlation between parameters and covariates in the absence of rich data.

Leiden /Amsterdam Center for Drug Research
GlaxoSmithKline
Universiteit Leiden