

Extrapolating abacavir doses from children to babies and vice-versa: a case study

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Introduction

Paediatric pharmacology practice suggests that linear correlations can be assumed between body weight (BW) and dose, with dosing recommendations in children often expressed as mg/kg. These views imply that drug exposure can be interpolated within and extrapolated between populations.

Aim

The objective of the current investigation was to evaluate the predictive value of a model-based approach to establish dosing requirements in infants and toddlers using pharmacokinetic parameter distributions obtained from the analysis of exposure data in adults and children, and vice-versa. The proposed approach is illustrated for the antiviral drug abacavir.

Methods

→ **PK model in children (Mod1)**: the PK of abacavir in adults and children was described by a one-compartment model with 1st order absorption and 1st order elimination. NONMEM prior based on adult parameters was used to stabilize the parameter estimation in children.

→ **PK model in babies (Mod2)**: in parallel, PK in infants and toddlers was characterised by another one-compartment model with 1st order absorption and 1st order elimination.

In both cases, BW was a covariate on clearance (CL), whilst BW was a covariate on volume only in *Mod1*.

	INFANTS / TODDLERS (mean and range)	CHILDREN (mean and range)
Age (years)	1.8 (0.4 – 2.9)	5.9 (2.1 – 12.8)
Weight (Kg)	11.6 (7.4 – 15.9)	23.8 (13.7 – 60.5)
N	22	14
Weight distribution in the simulated population (N=70)	11.3 (5.9 – 15.5)	23.8 (12.9 – 40.3)

The effect of this covariate was characterised by an exponential model:

$$\theta = \theta_{TV} * (BW / 70)^{EXP}$$

where θ represents the parameter estimate, θ_{TV} the typical value for the parameter, 70 is the median weight of the population and EXP the exponent.

Given the skewed distribution of BW in the original dataset, resampling (n=70) was performed to obtain a population distribution of BW representative of the whole population within that age range, according to growth charts available from the National Center for Health Statistics.

Challenging models predictive power

Drug exposure was estimated as AUCs within the dosing interval by integration of predicted plasma concentrations. The AUC proven to be effective in adults is 6.02 $\mu\text{g}^*\text{h/mL}$.

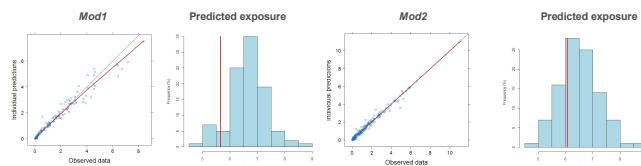
Simulations were performed for patients groups of n=70. These groups also comprised the population in the original datasets. For each sample the median and the 95% confidence interval were calculated.

Using *Mod1*, we evaluated whether exposures (AUC) in babies can be predicted accurately under the assumption of common PK parameter distributions.

The same methodology was applied to *Mod2* with the objective of predicting exposures in children aged 2 to 12 years.

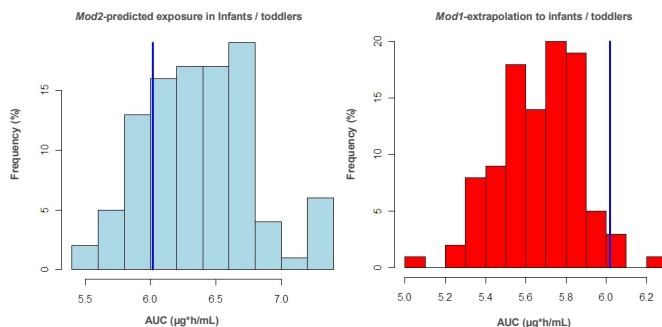
Results: goodness-of-fit

Both PK models accurately describe plasma concentration and systemic exposure (AUCs) observed in the original data sets.

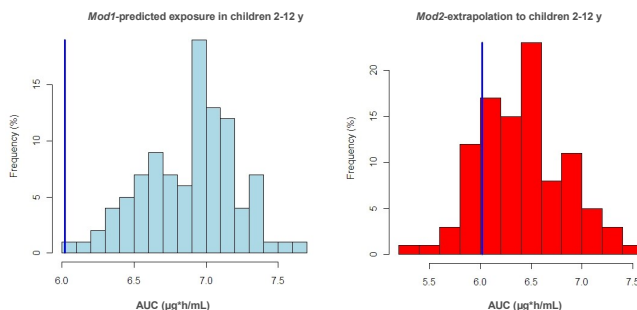


Results: AUC predictions

Exposure distribution in infants and toddlers, as estimated by *Mod2*, had a median of 6.36 $\mu\text{g}^*\text{h/mL}$ (4.26 – 8.45). 79% were above the target AUC observed in adults. In contrast, predictions by *Mod1* were generally lower: the median was 5.69 $\mu\text{g}^*\text{h/mL}$ (3.63 – 7.69). Only 4% of the values reached the efficacy threshold.



Exposure distribution in children aged 2 -12 years, as estimated by *Mod1*, had a median of 6.94 $\mu\text{g}^*\text{h/mL}$ (4.83 – 8.94), whilst predictions from *Mod2* were of 6.42 $\mu\text{g}^*\text{h/mL}$ (4.29 – 8.49). 100% of values are above the efficacy threshold in adults. In contrast, predictions by *Mod2* show that only 81% of the values reach target exposure.



Conclusion

The estimated covariate-parameter correlation doesn't describe the influence of developmental growth in infants and toddlers.

Extrapolation of exposure across different populations or groups cannot rely on the assumption that covariate-parameter interactions are constant beyond the range of observations.

These differences have implications for the rationale for dose selection, particularly in early drug development.



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