

Dose Bridging in Paediatric Indications

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Introduction

Dose selection for paediatric indications remains a major challenge in early clinical development. The rationale for dosing regimen in clinical trials is often determined by empiricism. Most importantly, medical practice assumes direct, linear relationships between body size, physiological function and clinical response. There is, however, sufficient clinical evidence to revisit this assumption.

In the current investigation, we explore the feasibility of a sequential approach for dose adjustment in early paediatric trials. Conceptually, we evaluate whether parameter distributions in the paediatric population are significantly different from adults and whether such differences may have clinical implications. A model-based covariate search was used to identify a descriptor of developmental changes. The proposed approach is illustrated for the antiviral drug abacavir.

Objectives

- Predict PK parameter distribution in children based on pharmacokinetics in adults
- Assess whether BW describes developmental changes accurately enough to be used as covariate for dose adjustment of abacavir in children
- Illustrate how to evaluate dosing recommendation using a model-based approach

Methods

A total of 111 subjects from Phase I studies were used as adult population. All subjects were Caucasians. The paediatric trial consisted of 14 African children, aged 2-12 years. Data were retrieved from GSK's clinical database and from the PENTA13 research network.

a) Data pooling

In this analysis, adults and children are assumed initially to belong to the same parameter distributions for CL and V. Using a stepwise covariate search, explanatory factors are tested for differences between the two populations are explored covariates. Arbitrary (grouping) and random dichotomisations (mixture model) of the study population were evaluated.

1. **Basic model:** The basic model fitted all the data with no demographic covariates.
2. **Mixture model:** Random dichotomisation of the population into adult (P1) and children (P2)
3. **Arbitrary dichotomisation:** Study population was categorised into 2 groups.
4. **Stepwise covariate search:** influence of demographic covariates BW, AGE, HT, BMI, CLCR was evaluated across the overall study population. The effect of covariates was characterised by an exponential model:

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

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.

b) Use of the Prior Subroutine

Since population size in paediatric studies is usually too small for accurate estimation of IIV, in this analysis priors were used to stabilise parameter estimation. Estimates of fixed (CL, V and KA) and random (η_{CL} , η_{TV} , η_{KA}) effects in adults were used as priors in the analysis of the paediatric data.

c) Simulations for dose selection

Based on the final PK model, a bridging strategy is proposed that accounts for steady-state exposure in adults as reference target exposure.

Results

A one-compartment model with oral absorption best described the data. A fixed lag time of 0.2 hours and a fixed bioavailability of 0.83 with IIV were included. The interindividual variability in PK parameters was assumed to be log-normally distributed. The residual variability was described with a proportional error model.

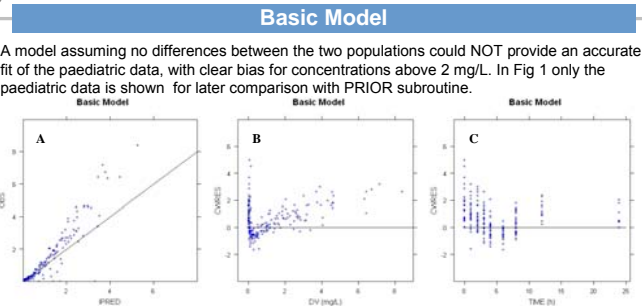


Fig 1. Diagnostic plots for the basic model.

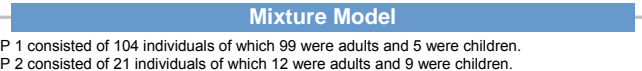


Fig 2. Diagnostic plots of the model with the BW as covariate on CL and V

Mixture Model

P 1 consisted of 104 individuals of which 99 were adults and 5 were children.
P 2 consisted of 21 individuals of which 12 were adults and 9 were children.

Parameters	Mean P1	Mean P2	% IIV
CL (L/h)	31.7	12.1	28
V (L)	54.2	27.9	10
KA (h ⁻¹)	2.7	2.7	136

Table 1. Parameter estimates of the mix model. Ka was assumed to be the same for P1 and P2

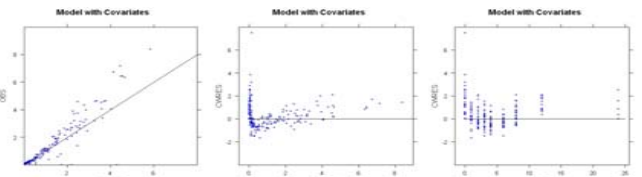
Dichotomisation

Parameters	Mean (%CV)	% IIV (%CV)
adult CL (L/h)	37.5 (6.1)	31 (27)
children CL (L/h)	18.3 (18)	
adult V (L)	64.7 (3.7)	13 (50)
children V (L)	32.6 (16)	
KA (h ⁻¹)	1.90 (13)	1.0 (20)

Table 2. Parameter estimates after dichotomisation of the population. Ka and IIV were assumed to be the same in adults and children.

Covariate Data Analysis

Inclusion of BW as covariate on clearance and volume using a power model showed the highest drop in objective function (Δ -37.5 points). This however has not eliminated the bias in parameter estimates for the paediatric population. Improvements occurred primarily in adults.



Prior Subroutine (Final Model)

Parameters	Mean (%CV)	BS mean (%CV)	% IIV (%CV)	BS % IIV (%CV)
Fixed effects				
CL (L/h)	37.7 (19)	38.5 (6.3)	27 (27)	27 (10)
V (L)	67.6 (11)	66.2 (4.8)	11 (34)	11 (4.4)
KA (h ⁻¹)	3.43 (34)	3.94 (47)	93 (32)	94 (13)
F (%)	0.83	0.83	55 (73)	52 (70)
Exponent on CL	0.693 (22)	0.705 (11)		
Exponent on V	0.802 (13)	0.804 (10)		
Residual error %				
ϵ	3.5 (16)	3.7 (32)		
Objective function				
-2LL	-668.4	-679 (6.7)		

Table 3. Summary of PK parameter estimates

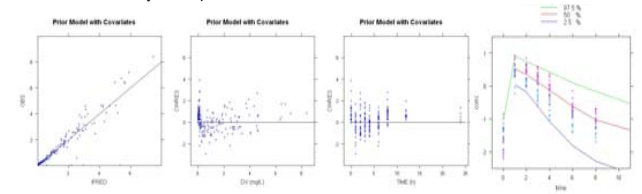


Fig 3. Diagnostic plots and VPC of the model using the PRIOR subroutine with inclusion of BW as covariate weight on clearance and volume.

Dosing Rationale

In a bridging study, dose adjustments are aimed at achieving exposure equivalent to the reference population (i.e., adults). Fig 4 shows model-predicted exposure (AUC) for doses of abacavir, which are required to achieve the median exposure of 6.02 mg*h/L.

Weight (Kg)	Recommended dose (mg)	Predicted dose (mg)
10	80	120
20	160	200
30	240	260
40	300	320

Fig 4. Frequency of AUC higher than 6.02 mg*h/L

Conclusions

- There is no justification to empirically define doses in early clinical trials by assuming linear correlations between dose and BW.
- Pooling of data from phase I studies in adults with data from efficacy trial in children does not allow accurate estimation of PK differences in children. The impact of imbalance in data is being further evaluated.
- A sequential protocol, enabling estimation of PK parameter distribution prior to completion of an efficacy trial is essential to ensure appropriate bridging studies in paediatric indications.