

Scaling of fixed-dose combinations in children

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Introduction

Drug combinations with a fixed dose ratio are standard therapy for various infectious diseases. In these cases, dose adjustment is often based on the assumption that the effect of developmental growth on pharmacokinetics, pharmacodynamics and risk : benefit ratio for each agent is comparable across populations. Such an assumption may however be inappropriate for many drugs.

Here we demonstrate the relevance of a model-based approach for the purposes of pharmacokinetic bridging and selection of paediatric doses for drug combinations. The antimalarial drugs atovaquone (ATV) and proguanil (PGN), which are prescribed in the ratio 2.5:1 in adults and children, are used as paradigm compounds.

Methods

In a bridging study, dose adjustments are aimed at target exposure equivalent to that observed in a reference population. In this investigation the predicted median exposure (AUC) in adults was obtained from a population PK model for ATV and PGN. The parameter estimates from the PK model were then used to simulate drug exposure in children following different dose levels. Dose selection was based on a threshold value for AUC in at least 80% of the paediatric population. Simulation datasets included patients across a wide range of weights (5, 10, 15, 25, 35, 70 kg).

Nine clinical trials from GlaxoSmithKline's clinical database were used for pharmacokinetic modelling. Different doses and dosing regimens were available for ATV (62.5 to 1000 mg) and PGN (25 to 400 mg).

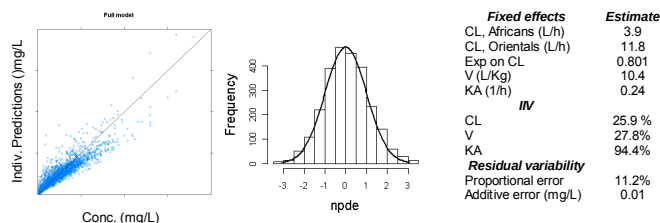
	atovaquone		proguanil	
	CHILDREN (mean / range)	ADULTS (mean / range)	CHILDREN (mean / range)	ADULTS (mean / range)
Africans	423	106	402	105
Oriental	59	195	46	174
Body weight (Kg)	26.5 (5.4 – 68)	55.6 (39 – 110)	26.8 (5.4 – 68)	62.5 (39 – 110)
Age (years)	8.8 (0.3 – 17)	29.2 (18 – 65)	9.0 (0.3 – 17)	40.5 (18 – 79)
Sex (m/f)	247/234	268/33	225/222	207/72
Blood samples per subject	2.2 (1 - 13)	5.1 (1-15)	1.9 (1 - 13)	6 (1-19)

Pharmacokinetics of atovaquone

A one-compartment model with 1st order absorption and 1st order elimination was used to describe the PK of atovaquone. Body weight and ethnicity (Africans or Orientals) were covariates on clearance (CL). The effect of BW on CL was characterised by an exponential model:

$$CL = CL_{\text{RACE}} * (BW / 70)^{\text{EXP}}$$

BW was also linearly correlated with volume of distribution (V).



PK modelling - Diagnostics and parameter estimates for atovaquone.

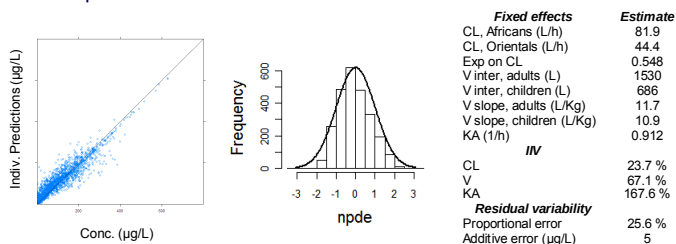
Pharmacokinetics of proguanil

The PK of PGN was also described by a one-compartment model with 1st order absorption and 1st order elimination.

The correlation between BW on CL was similar to the one used for ATV, whilst the effect of BW on V was expressed in the following equation:

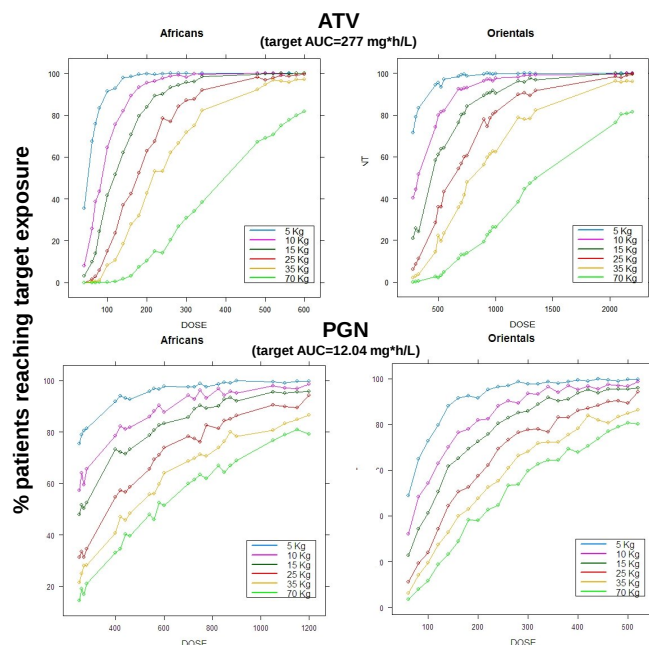
$$V = INT_{\text{AGE}} + SLOPE_{\text{AGE}} * BW$$

Where INT_{AGE} and $SLOPE_{\text{AGE}}$ indicate respectively a different intercept and slope for adults and children.



PK modelling - Diagnostics and parameter estimates for proguanil.

Results



DOSE REQUIRED TO ACHIEVE TARGET EXPOSURE

Body weight (Kg)	AFRICANS			ORIENTALS		
	ATV (mg)	PGN (mg)	ratio	ATV (mg)	PGN (mg)	ratio
5	80	270	1 : 3.5	280	120	2.5 : 1
10	140	420	1 : 3	500	200	2.5 : 1
15	180	560	1 : 3	700	240	3 : 1
25	280	775	1 : 2.75	975	360	2.75 : 1
35	340	875	1 : 2.5	1350	420	3.25 : 1
70	580	1150	1 : 2	2100	500	4.2 : 1

Conclusions

- Our analysis shows how differences in exposure ratios can be estimated when scaling fixed-dose ratios from adults to children. Whilst data on efficacy and safety support the use of a fixed dose-ratio for ATV and PGN, this is not generalisable to all drugs.

- The effect of covariates on drug disposition cannot be assumed constant for different compounds, age and ethnic groups.

- Appropriate bridging and dose selection for drug combinations in children should therefore be based on exposure ratios rather than dose ratios.