Implementation of pharmacokinetic bridging for drug combinations in children

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Introduction

Very often effective therapy relies on the use of drug combinations. Consequently, to facilitate prescription, formulations have been developed which allow compounds with different physicochemical and pharmacokinetic properties to be combined into a single dosage form or device.

The aim of this investigation is to show the relevance of adaptive protocols for dose selection of drug combinations for paediatric indications. A randomised concentration-controlled trial (RCCT) design is proposed as framework for protocols in early clinical development. The combination of antimalarial drugs atovaquone (ATV) and proguanil (PGN) was used as paradigm for the purposes of our analysis.

Methods

Population pharmacokinetic models were developed for ATV and PGN using historical data in adults. For the purpose of pharmacokinetic bridging, target exposure ($AUC_{0-\infty}$) comparable to adult values were assumed to be required in children.

Assuming the same pharmacokinetic model structure across populations, concentration vs. time profiles of ATV and PGN were simulated for the paediatric population according to four different scenarios:

1. CL of both drugs in children is 20% of the adult values
2. CL of both drugs in children is 50% of the adult values
3. CL of both drugs in children is comparable to the adult values
4. CL of both drugs in children is allometrically correlated with body weight, with an allometric exponent of 0.75.

For the sake of clarity, all other parameters (V, Ka and BSV) were fixed to the adult values.

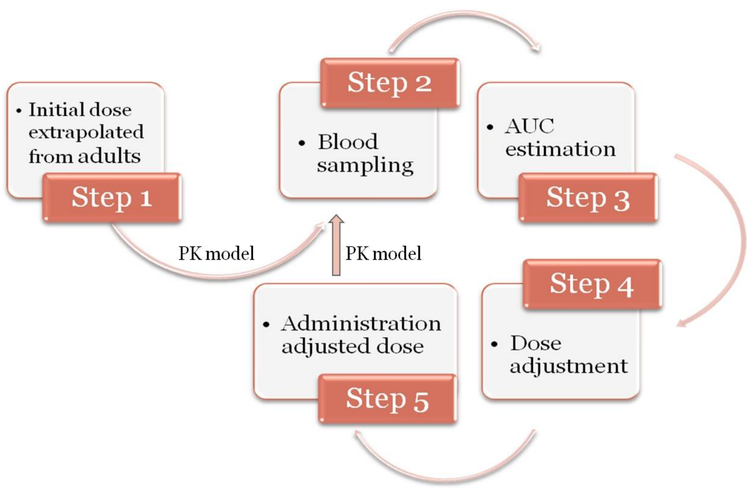


Diagram depicting protocol procedures and adaptation rules

The same initial dose was administered in all scenarios and the simulated concentration time profiles were then fitted using the SAEM method in NONMEM version 7.1.

A dose adjustment criterion was used to correct for differences in clearance, as predicted from the individual AUCs:

$$adjusted dose = \frac{first dose \times target AUC}{individual AUC}$$

Results

PK analysis

A one-compartment model with first-order absorption and elimination was found to best describe the pharmacokinetics of both compounds in adults. Between-subject variability was identified on CL, V and Ka. Residual variability was described using a combined error model.

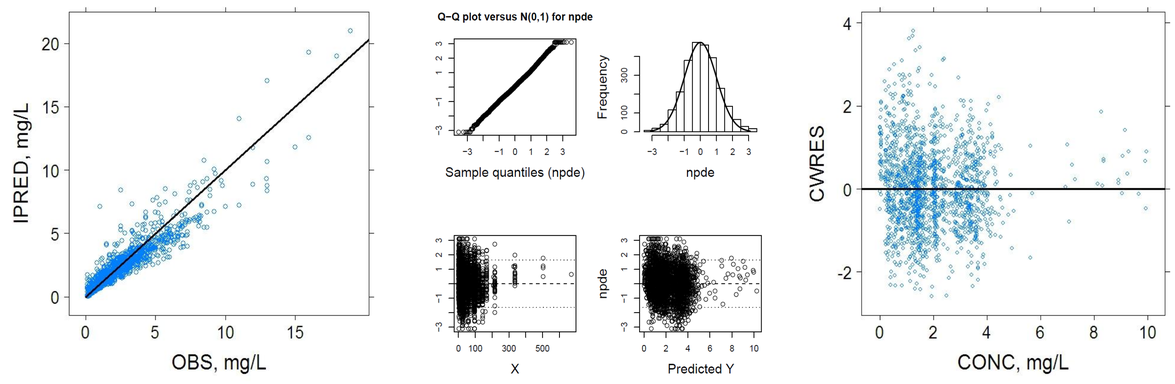
For ATV, ethnicity (Africans or Orientals) was found to be a covariate on clearance, whilst body weight was linearly correlated with the volume of distribution.

For PGN, ethnicity had a significant effect on CL and V.

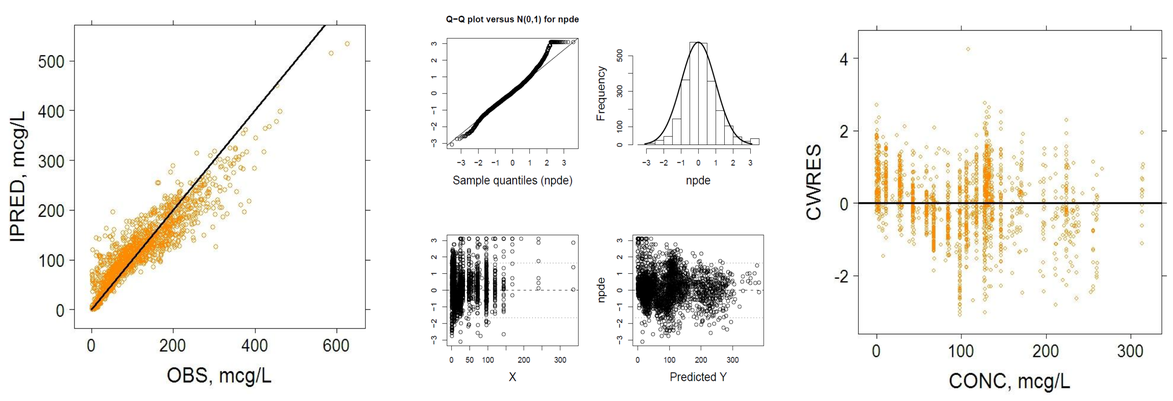
The adjustment of the dose during the CTS in children was based on the predicted concentration vs. time profiles. The (population) mean exposure, expressed as $AUC_{0-\infty}$, was estimated at 368.7 mg*h/L for ATV and at 13.6 mg*h/L for PGN.

CTS

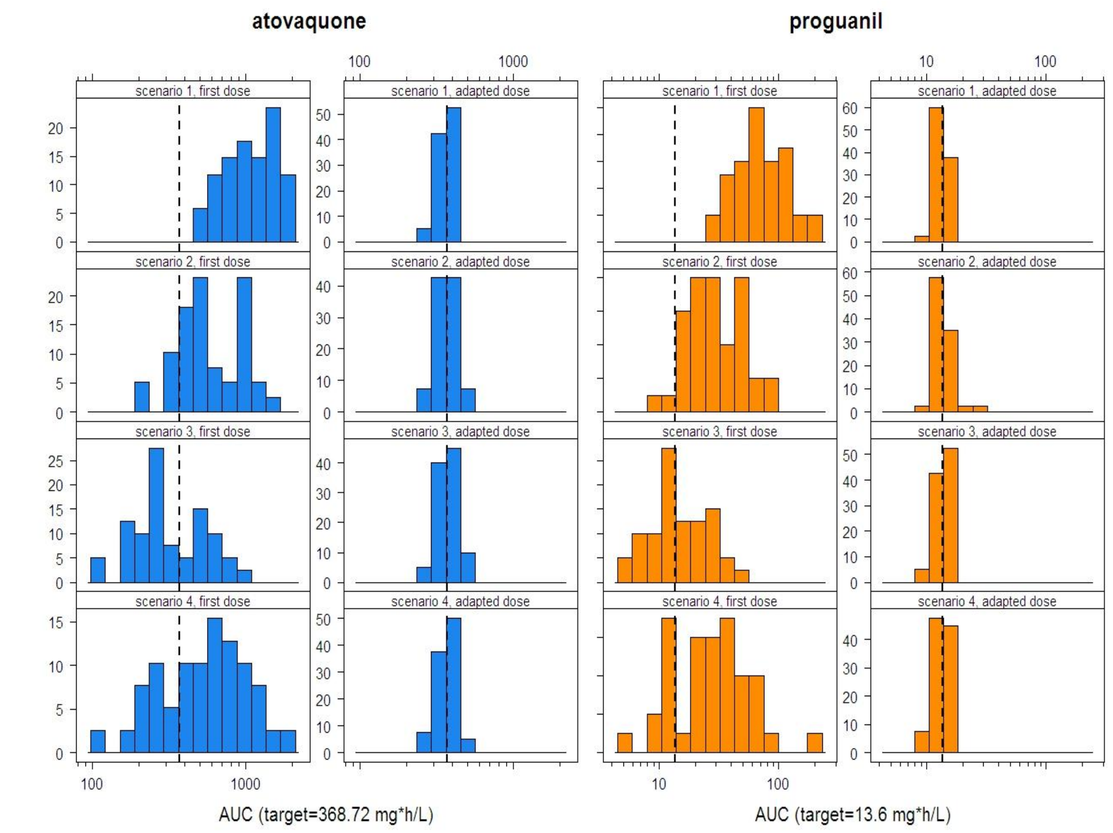
For each scenario, the individual exposure to ATV and PGN observed after the initial dose extrapolated from adults was compared to the target $AUC_{0-\infty}$ values. As expected, point estimates for the AUCs were very diverse across scenarios. Most importantly, the distribution of the exposures was found to be very large in the paediatric population (up to 100-fold, see Scenario 4).



Pharmacokinetic modelling of ATV. Goodness-of-fit and diagnostic plots for adult subjects



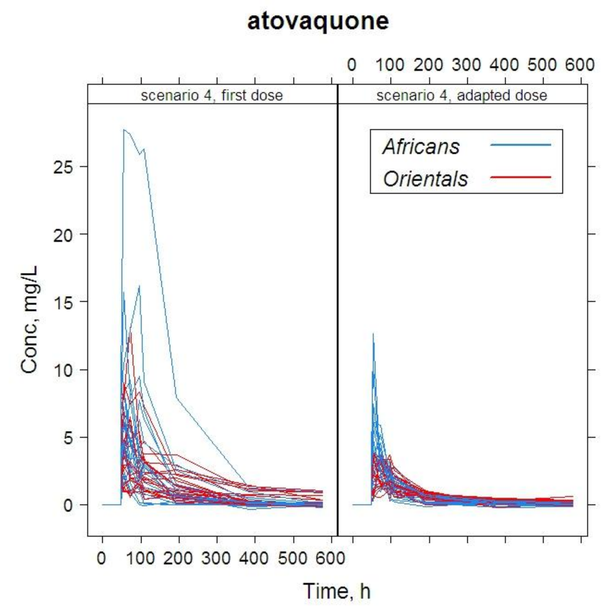
Pharmacokinetic modelling of PGN. Goodness-of-fit and diagnostic plots for adult subjects



AUC distributions for ATV and PGN after the initial dose and after the adaptive procedures. The dashed line represents the target exposure

	ATV	PGN
Parameters (units)	*mean*	*mean*
Fixed effects		
CL/F, Africans (L/h)	3.12	74.3
CL/F, Orientals (L/h)	8.23	71.7
V/F, (L/Kg)	10.3	-
V/F, Africans (L)	-	2130
V/F, Orientals (L)	-	1270
Ka (h^{-1})	0.262	1.04
Inter-individual variability %		
CL	52.8	50.9
V	53.8	38.2
Ka	96.1	66.1
Residual error		
proportional error (%)	31.2	33.2
additive error	0.13	5.3

PK parameters for ATV and PGN in adults



Concentration profiles for ATV. The adaptive procedure accounts for the impact of ethnicity on exposure

Conclusions

• Adaptive protocols are recommended for the evaluation of drug combinations in early clinical trials for paediatric indications. Dose titration criteria ensures that target exposure is achieved for both active moieties.

• The use of RCCT limits the impact on dose selection of any model misspecification or parameter uncertainty arising from pharmacokinetic data.

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