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Does size matter? : bridging and dose selection in paediatric trials

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Chapter 7

Dosing recommendation rationale for fixed-dose combinations in children: a shoot from the hip?

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Abstract

In this investigation we evaluate the relevance of a model-based approach for pharmacokinetic (PK) bridging and dose selection of drug combinations in children. The fixed-dose combination of atovaquone and proguanil was used for illustration purposes. A population pharmacokinetic model was developed for each compound using plasma concentration data from adult and paediatric patients. PK parameter estimates were subsequently used to simulate drug exposure in children following different dose levels. In contrast to common practice, we show that in order to achieve comparable target exposure across both populations, different dose ratios may be required across age groups. Moreover, this example illustrates the consequences of covariate interactions, as determined for the effects of body weight and ethnicity on pharmacokinetics. A model-based approach is critical for dose selection and rational use of drug combinations in children. Flexible rather than fixed dose ratios may be needed to ensure comparable target exposure in bridging studies.

7.1 Introduction

DRUG DEVELOPMENT IN CHILDREN is still dominated by empiricism and by the lack of consensus on suitable methodologies for the selection of doses and dosing regimens for paediatric indications. Among many of the deep-rooted practices in paediatric medicine, the choice of the paediatric doses assumes a linear relationship between dose and body weight (BW) or age [1]. In this paper we look at the implications of another commonly used assumption for the selection of the paediatric dose, i.e., that the same ratio between two (or more) drugs in a fixed dose ratio combination yields comparable exposure in children and can therefore be considered as effective and safe as in adults. Often enhanced efficacy, enhanced safety or tolerability, convenience and improved compliance are amongst the common reasons for the development of a combination drug product [2]. In recent years, such combinations, administered both as a single or separate dosage form, have gained acceptance in clinical practice and have become first-line therapy in various therapeutic areas. In adults, the choice of the ratio between the active moieties in a fixed dose combination is determined by extensive clinical trials. How these studies are conducted and how efficacy and safety are defined in the evaluation of combination therapy is beyond the scope of this paper. However, once the dosing regimen of each moiety has been identified, the dose ratio is fixed and subsequently used as basis for the regimen in other populations, such as renally or hepatically impaired patients. Likewise, the same dose ratio has been used as basis for the dose rationale when extrapolating the dosing regimen from adults to children, irrespective of whether comparable exposure levels are maintained or whether comparable pharmacokinetic-pharmacodynamic (PKPD) relationships can be assumed to make inferences about efficacy and safety.

Considerations about target exposure are critical if ICH E11 guideline is to be applied as basis for bridging in paediatric drug development. Paediatricians, clinical researchers and regulators should realise that pharmacokinetic bridging may not only prevent the unnecessary assessment of efficacy, but can also be used to optimise dose selection when efficacy trials are required [3]. The implementation of a bridging strategy requires that

- the pathophysiological processes underlying the disease in adults do not differ significantly from those in children;
- the endpoint used for the assessment of efficacy in clinical trials is the same in both populations;
- the exposure-effect relationship does not vary due to age differences.

In the current investigation, we propose the selection of paediatric doses and dose ratios according to differences in pharmacokinetic parameter distributions, rather than using fixed ratios across populations without prior understanding of the potential differences in pharmacokinetics.

As demonstrated previously for abacavir, a model-based approach is required to allow accurate estimation of parameter distributions in both populations of

interest [4]. In addition, the use of non-linear mixed effects modelling also enables better characterisation of parameter-covariate correlations and hence accurate dose adjustment due to the effect of developmental growth. When dealing with drug combinations, it is unlikely that such a correlation remains exactly the same for both compounds across the range of covariate values (e.g. neonates to adults). Furthermore, different covariates may determine changes in the exposure to each compound, depending on their physicochemical properties. This situation has important consequences for the dose rationale and for the implementation of bridging protocols. In fact, multiple scenarios can be hypothesised, in which the correlation between parameter and covariate:

1. can be described as a continuous function over the full range of a covariate for both compounds;
2. cannot be described as continuous function across the range of interest for one of the drugs;
3. cannot be described as a continuous function across the range of the covariate of interest for both drugs or the covariates affecting the pharmacokinetics of each drug are different.

It can be anticipated that in scenarios 2 and 3, the choice of a fixed ratio between the two compounds will not warrant comparable exposures when the dose is scaled across populations. The clinical relevance of such differences should therefore be carefully considered before defining the rationale for fixed ratios in paediatric drug combinations.

Given the importance of pharmacokinetic bridging in paediatric drug development, the ultimate objective of our analysis is to demonstrate the feasibility and advantages of a model-based approach for assessing dosing requirements for drug combinations in children. Atovaquone (ATV) and proguanil (PGN) were selected as a paradigm combination for the evaluation of the proposed methodology. The marketed product has a lower dose strength available for the paediatric indication (62.5/25 mg *vs.* 250/100 mg in adults), but the ratio between the two active compounds remains the same (2,5:1). The recommended oral dose of ATV and PGN for treatment of malaria in adults is 4 tablets (1000 mg and 400 mg respectively) as a single dose for three consecutive days. In children, the dosing regimen is based on body weight [5].

Atovaquone is a potent and selective inhibitor of the mitochondrial electron transport chain within the cytochrome *bc₁* complex in the protozoa. Several metabolic enzymes which are linked via ubiquinone to the electron transport system are thus inhibited, resulting in the disruption of adenosine 5'-triphosphate (ATP) and nucleic acid synthesis [6]. Proguanil itself is a weak inhibitor of plasmodial dihydrofolate reductase, but in vivo it is metabolised into cicloquanil, which in turn is a potent inhibitor of that enzyme [7]. Proguanil was selected to be co-administrated with atovaquone based on the evidence of a pharmacodynamic interaction, but the mechanisms underlying the so-called synergistic effect remain

unexplained [8]. In addition, no pharmacokinetic interaction is observed between ATV and PGN [9, 10].

ATV is highly lipophilic with low aqueous solubility and is therefore poorly absorbed unless administered after a fatty meal. 94% of the administered ATV is recovered unchanged in the faeces, 0.6% in urine [11, 12]. Body weight and ethnicity are known to be correlated with pharmacokinetic parameters [13]. In contrast, PGN is rapidly absorbed from the gastrointestinal tract and achieves peak plasma concentrations in 2-4 h. Between 40 and 60% of PGN is excreted renally, whilst the rest is mainly metabolised by both cytochromes CYP4503A and CYP2C19 to the active moiety cycloguanil [14]. CYP2C19 is known to be polymorphic, with Caucasians (3-5%) and especially Orientals (15-20%) considered poor metabolisers [15, 16]. BW and ethnicity are known to affect PGN pharmacokinetics [17].

Moreover, ATV and PGN meet the requirements for bridging: the pathophysiological processes subsequent to infection in adults do not differ significantly from those observed in children; the endpoint for efficacy in clinical trials is the same in both populations, as indicated by the elimination of parasitemia after the treatment and no recrudescence during 28 days of follow-up [18]; based on the mechanism of action of ATV and PGN, the exposure-effect relationship can be assumed to be independent of age.

7.2 Methods

Clinical studies

Data from 12 different clinical trials (three phase I: MAL10907, MAL10908, MAL10909; one phase II: MAL115-005; seven phase III: MAL115-120, MAL115-123, MAL115-131, MAL115-134, MAL115-135, MALB3003, MAL30013; and one phase IV: MAL30015) were retrieved from GlaxoSmithKline's clinical database. Concentration profiles from a total of 783 subjects (adults: 301, children: 482) were available for the analysis of ATV, whilst data from 726 subjects (adults: 278, children: 448) were available for PGN. Clinical protocols included a wide range of doses under different conditions (different ratios between the compounds, different competitors in cross-over trials, different disease conditions). Blood sampling for pharmacokinetics ranged from 1 to 19 samples per subject, although the average number of samples collected in paediatric patients was only 2.2 for ATV and 1.9 for PGN. A summary of the demographic variables and treatment allocation is provided in Table 7.1. Further details of these trials can be found at GSK clinical trial register (<http://www.gsk-clinicalstudyregister.com>).

Pharmacokinetic analysis

Given the objectives of the current investigation, data were modelled in two steps, in such a way that the proposed bridging concepts can be applied for prospective

Table 7.1: Study characteristics and patient demographics. Mean and (range) are shown for age and body weight

	Atovaquone		Proguanil	
	<i>Children</i>	<i>Adults</i>	<i>Children</i>	<i>Adults</i>
Africans	423	106	402	105
Orientals	59	195	46	173
Body Weight (kg)	26.5 (5.4-68)	55.6 (39-110)	26.4 (5.4-68)	60.1 (39-110)
Age (years)	8.8 (0.3-17)	29.2 (18-65)	8.8 (0.3-17)	36.4 (18-79)
Sex (m/f)	247/234*	268/33	225/222*	207/71
Blood samples per subject	2.2 (1-13)	5.1 (1-15)	1.9 (1-13)	6.0 (1-19)

* = the gender of one paediatric patient was unknown.

purposes. First, adult data were modelled separately for each compound. Model building included the evaluation of all relevant covariates in the adult population. Assuming comparable exposure-response relationships across populations, model-predicted exposures in adults were subsequently set as target for bridging purposes. The area under the curve ($AUC_{0-\infty}$) was deemed as the most suitable measure of exposure to ATV and PGN, due to the short dosing regimen (q.d. dosing for three consecutive days) and the delay of approximately one month between drug administration and response (i.e., clearance of protozoa from the body). Using the final model parameters, 500 concentration profiles were simulated for each adult subject and the AUCs were then calculated according to the trapezoidal rule. To prevent underestimation of the exposure in these subjects due to the limited sampling scheme in original data set (i.e., 5.1 and 6.0 samples on average for ATV and PGN, respectively), a denser sampling scheme was used in the simulations. Subsequently, instead of utilising priors on parameter distributions for characterising changes in pharmacokinetics in the paediatric population [4], a pooled analysis of paediatric and adult data was performed for each drug. Given the availability of patient data across a wide range of values for influential covariates, this approach was deemed more suitable for accurate estimation of the parameter-covariate correlations.

A brief description of the model building and evaluation procedures for ATV and PGN is provided in the following paragraphs. The same statistical modelling criteria were applied to the analysis of ATV and PGN pharmacokinetics in adult subjects and in the combined population (adults and children).

Pharmacokinetic and covariate model building

Non-linear mixed effects modelling was used to analyse the pharmacokinetic data in adults and children. The first-order conditional estimation method in NONMEM VI (release 1.0) [19] was used to fit the data to the pharmacokinetic models described later in this section. For both compounds, pharmacokinetics was best described

by a one-compartment model using the ADVAN2 subroutine. The models were parameterised in terms of clearance (CL), volume of distribution (V) and absorption constant (Ka). Fixed and random effects were introduced into the model in a stepwise fashion. Inter-individual variability in pharmacokinetic parameters was assumed to be log-normally distributed. The parameter value of an individual i (*post hoc* value) is therefore given by the following equation:

$$\theta_i = \theta_{TV} \cdot e^{\eta_i} \quad (7.1)$$

in which θ_{TV} is the typical value of the parameter in the population and η_i is assumed to be random variable with zero mean and variance ω^2 . Residual variability was described with a proportional error model. This yields the relation (Y_{ij}) for j^{th} observed concentration of the i^{th} individual:

$$Y_{ij} = F_{ij} + \epsilon_{ij} \cdot W \quad (7.2)$$

where F_{ij} is the predicted concentration and ϵ_{ij} the random variable with mean zero and variance δ^2 . W is a proportional weighing factor for ϵ .

The minimal objective function value (OFV; equal to $-2 \log$ likelihood) determined by NONMEM was used as a diagnostic criterion with a decrease in OFV of 3.84 points corresponding to a statistically significant difference between hierarchical models ($P = 0.05$, χ^2 distribution with one degree of freedom). In addition, goodness-of-fit plots, including observed (OBS) *versus* individual prediction (IPRED), OBS *versus* population prediction (PRED), conditional weighted residuals (CWRES) [20] *versus* time and CWRES *versus* OBS were used for diagnostic purposes. The confidence interval of the parameter estimates, the correlation matrix, and visual improvement of the individual concentration *versus* time plots were also used as diagnostic criteria during model building.

The assessment of relationship between parameters and demographic variables (i.e., parameter-covariate correlation) was based on a stepwise covariate analysis. The following covariates were explored: body weight, ethnicity, age and gender. Significant correlations between covariates and parameters were described by an exponential relationship for continuous variables, according to the formula:

$$\theta_i = \theta \cdot \left(\frac{COV_i}{median} \right)^{EXP} \quad (7.3)$$

in which θ_i represents the individual value for the parameter, θ the population parameter estimate, COV_i the individual value of the covariate, *median* is the median value of the covariate in the population, and *EXP* the exponent. The change in objective function value was used as a diagnostic criterion for covariate inclusion (Δ OFV = 3.84, $P = 0.05$, χ^2 distribution). The contribution of each covariate was confirmed by a stepwise backward deletion (Δ OFV = 6.89, $P = 0.01$, χ^2 distribution).

The precision of model parameters was evaluated by means of a stratified nonparametric bootstrap procedure [21]. 500 bootstrap samples were generated by

re-sampling with replacement. Each model was fitted repeatedly to the replicate bootstrap samples based on the standard options in PsN [22]. Results were used to assess model stability and obtain estimates for the coefficient of variation for relevant model parameters. The mean and standard errors of the parameters obtained from bootstrapping were subsequently compared with those from the original dataset. Furthermore, given the purposes of our analysis, simulated data are expected to be comparable to actual patient data. Hence, it is important that not only model parameters are unbiased, but that the variability is accurately described. Standard goodness-of-fit criteria do not take the variance characteristics into account and may not indicate the best model [23]. Therefore, normalised prediction distribution errors (NPDE) [24] were computed using the NPDE add-on package in R [25]. Briefly, this method determines whether simulated data sets are interchangeable with the original data set using graphical diagnostics and statistical tests. To calculate NPDEs, each observation (i.e., plasma concentration) was simulated 1000 times.

Rationale for dosing regimen and choice of the dose ratio

The final parameter estimates from the pooled data analysis were used to simulate ATV and PGN concentration *versus* time profiles in children. Datasets were created, each consisting of individuals of 5, 10, 15, 25, 35 and 70 kg. A range of 24 different doses were evaluated. The weight groups were selected in such a manner that our results could be compared with the currently recommended dosing regimen. AUC values were subsequently calculated for each patient based on the predicted concentration *vs.* time profile. Each scenario was simulated 500 times. Results were then summarised graphically and dosing recommendations for ATV and PGN were derived based on a threshold with at least 80% of the individuals reaching the pre-defined target exposure. Dose ratios for each weight category were subsequently proposed in such a way that exposure comparable to adults is warranted for both compounds across all patients, irrespective of differences in body weight.

7.3 Results

Pharmacokinetic analysis (adult data)

Separate models were developed for ATV and PGN using the adult data only. A one-compartment model with first-order absorption and elimination best described the pharmacokinetics of each compound. Ethnicity (Africans or Orientals) was found to be a covariate on the clearance of ATV. The effect of BW on volume of distribution was characterised by a linear correlation. For PGN ethnicity was found to be the only covariate affecting both CL and V. Inter-individual variability was estimated for all fixed effects parameters, i.e., CL, V and Ka. All diagnostic measures (diagnostic plots, NPDE and bootstrap, data not shown) indicated

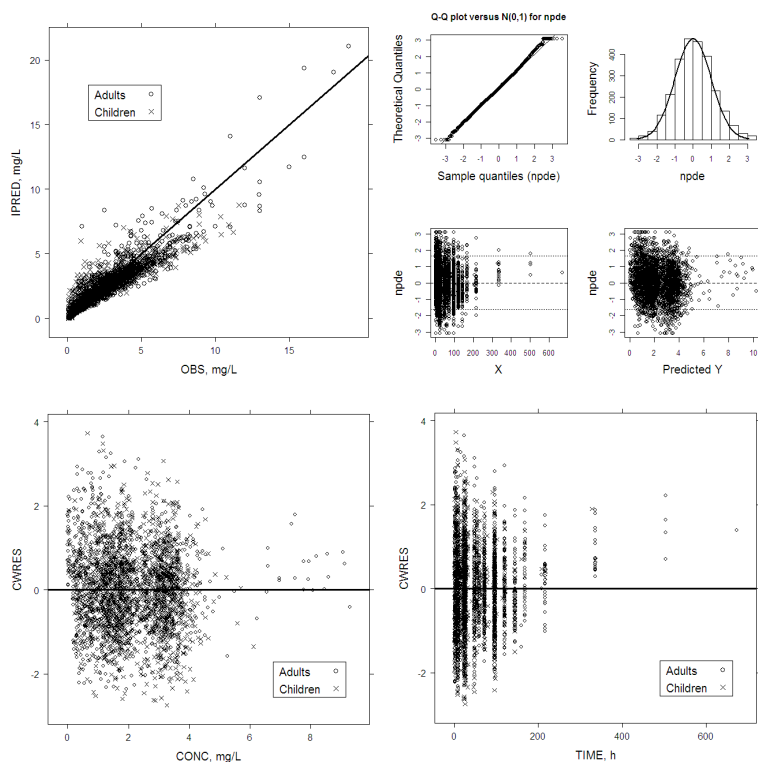


Figure 7.1: Goodness-of-fit and diagnostic plots for the final pharmacokinetic model of ATV using pooled adult and paediatric data. (Top left) Post hoc individual predictions vs. observed concentrations; (top right) NPDE summary; (bottom left) CWRES vs. predicted concentrations; (bottom right) CWRES vs. time

acceptable goodness-of-fit and model performance. The area under the curve ($AUC_{0-\infty}$) was then calculated and used as target exposure for the purposes of bridging. Mean estimates were 368.7 mg·h/L for ATV and 13.6 mg·h/L for PGN.

Pharmacokinetic analysis (pooled data)

Atovaquone

Similarly to the model based on adult data only, a one-compartment model with 1st order absorption and elimination accurately described the pharmacokinetics of ATV in children and adult patients. BW and ethnicity (Africans or Orientals) were found to be covariates on CL. The effect of BW on CL was characterised by

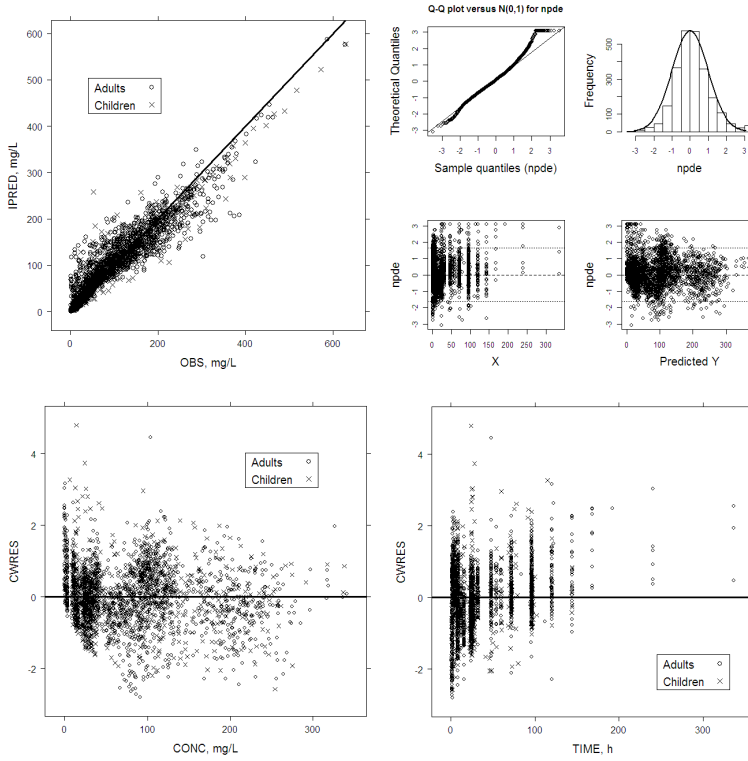


Figure 7.2: Goodness-of-fit and diagnostic plots for the final pharmacokinetic model of PGN using pooled adult and paediatric data. (Top left) Post hoc individual predictions vs. observed concentrations; (top right) NPDE summary; (bottom left) CWRES vs. predicted concentrations; (bottom right) CWRES vs. time

an exponential model:

$$CL_i = CL_{RACE} \cdot \left(\frac{BW_i}{70} \right)^{EXP} \quad (7.4)$$

BW was linearly correlated with V. Inter-occasion variability (IOV) was included on CL and V to distinguish between steady-state and non steady-state conditions.

Proguanil

Proguanil concentrations profiles were also best described by a one-compartment model with 1st order absorption and elimination processes. In addition, ethnicity and body weight were identified as a covariate on CL. In contrast to atovaquone,

Table 7.2: Pharmacokinetic parameter estimates for atovaquone (left) and proguanil (right). In the bootstrap analysis, 96.8% and 100% of the runs were successful (respectively)

Parameters (units)	Atovaquone		Proguanil	
	mean	bootstrap mean (%CV)	mean	bootstrap mean (%CV)
<i>Fixed effects</i>				
CL/F, Africans (L/h)	3.9	3.9 (6.0)	77.7	77.7 (4.8)
CL/F, Orientals (L/h)	11.7	11.6 (4.7)	83.6	83.7 (81.2)
V/F (L/kg)	10.4	10.3 (3.8)	-	-
V/F (L)	-	-	1610	1605 (5.7)
Ka (h ⁻¹)	0.24	0.24 (9.7)	1.12	1.13 (7.8)
Exponent on CL	0.801	0.801 (7.5)	0.545	0.542 (13.2)
Exponent on V	-	-	0.640	0.632 (11.5)
<i>Inter-individual variability %</i>				
CL	25.9	25.4 (14.8)	26.0	25.7 (26.5)
V	27.7	27.5 (18.1)	25.1	25.5 (27.3)
Ka	94.4	93.6 (8.0)	69.3	70 (22.8)
Steady-state variability	22.6	22.1 (27.6)	21.7	21.5 (26.3)
Non steady-state variability	43.0	42.6 (6.2)	44.9	45.1 (14.0)
<i>Residual variability</i>				
Proportional error (%)	33.5	33.3 (5.4)	37.2	37.4 (15.4)
Additive error	0.14	0.14 (23.5)	6.41	6.25 (50.2)

the effect of BW on V was also characterised by an exponential model:

$$CL_i = CL_{RACE} \cdot \left(\frac{BW_i}{70} \right)^{EXP} \quad (7.5)$$

$$V_i = V \cdot \left(\frac{BW_i}{70} \right)^{EXP} \quad (7.6)$$

IOV was included on CL and V for the same reasons as above for ATV.

Table 7.2 summarises the results from this analysis along with the parameter estimation uncertainty, including coefficients of variation (CV%). These estimates were confirmed by nonparametric bootstrapping. Diagnostic plots for ATV and PGN are shown in Figures 7.1 and 7.2, respectively. NPDEs show that the normality assumption cannot be rejected.

Simulation scenarios and dosing recommendations

Paediatric dosing recommendations were proposed based on pooled data analysis. Final PK parameter estimates were used to simulate drug exposure in children

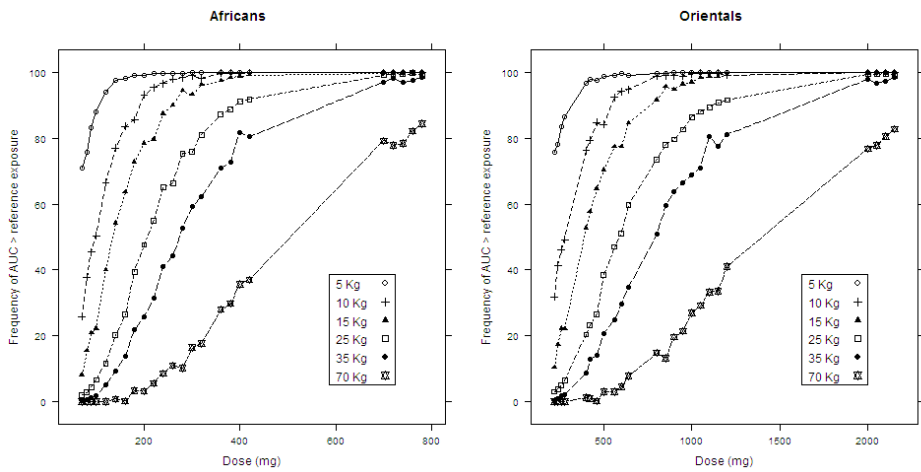


Figure 7.3: Model-based dose recommendations for ATV in children across the weight range from 5 to 70 kg. Left: Africans, right: Orientals. Note the non-linear relationship between dose and target exposure, as defined by $AUC_{0-\infty}$

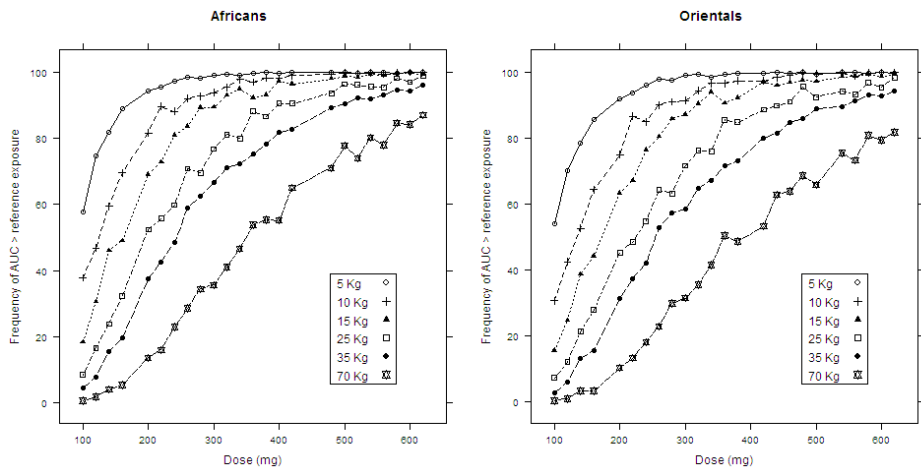


Figure 7.4: Model-based dose recommendations for PGN in children across the weight range from 5 to 70 kg. Left: Africans, right: Orientals. Note the non-linear relationship between dose and target exposure, as defined by $AUC_{0-\infty}$

Table 7.3: Total dose and ratios required to achieve target exposure in different ethnic groups, as defined by $AUC_{0-\infty}$. Note that dose ratios vary across age groups to account for linear and non-linear relationships between body weight and pharmacokinetic parameters

Africans				Orientals		
Body Weight	ATV (mg)	PGN (mg)	ratio	ATV (mg)	PGN (mg)	ratio
10 kg	160	200	1:1.25	460	220	2.1:1
15 kg	240	240	1:1	640	280	2.5:1
25 kg	320	320	1:1	950	360	2.6:1
35 kg	400	400	1:1	100	440	2.6:1
70 kg	760	580	1.4:1	2100	580	3.6:1

across a wide weight range following different doses of ATV and PGN. The dose of each compound and the corresponding dose ratio were then derived taking into account the number of simulations in which target exposure was achieved. Figures 7.3 and 7.4 show the dose range of ATV and PGN required to reach exposure levels comparable to adults according to different weight ranges and ethnicities.

The dosing recommendations for different weight ranges and ethnicities are summarised in Table 7.3.

7.4 Discussion

Our results clearly show the relevance of a model-based approach to support bridging and overcome some of the key challenges in the development of drug combinations for paediatric indications. As illustrated by the findings with ATV and PGN, empirical evidence of efficacy and safety does not necessarily warrant an accurate rationale for the paediatric dose where bridging concepts can be applied. In contrast, the use of modelling and simulation allows one to characterise and quantify the impact of developmental growth on the pharmacokinetics of each compound in a combination.

This preference for empiricism derives from the entrenched beliefs in paediatric clinical practice about the relationship between dose requirements and body size, which leads to a completely distorted view of how pharmacokinetics changes during developmental growth and how time-variant covariates affect systemic exposure. Although the consequences of such empiricism may always not be evident for a single drug, the potential impact for drug combinations cannot be overlooked. Empirical extrapolation of the dose from adults, based on linear scaling according to demographic covariates as descriptors of developmental changes concurs to poor estimates of the required paediatric dose. Recently, we have shown how a model-based approach in paediatric dose selection could be used to provide effective and safe dose recommendations in children [4]. We have also highlighted how modelling and simulation can be applied to quantify the implications of current paediatric prescription practice and support dose selection in early clinical development for

paediatric indications [1].

Atovaquone and proguanil, the two compounds analysed in this paper, do not show any interactions in their pharmacokinetics. This allowed us to consider them separately, and derive dose recommendations for both drugs independently. Using a model-based approach, we first found which covariates are actually affecting the exposure to ATV and PGN (i.e., ethnicity and body weight) and subsequently used simulations to define dosing recommendations accounting for the effect of covariates. Our analysis shows that, even before considering the requirements for pharmacokinetic bridging from adult data, clearance (and consequently systemic exposure to both drugs) is considerably affected by ethnicity. For example, for ATV the clearance in Africans is three times lower than in Orientals (3.9 *vs.* 11.8 L/h); for PGN, the difference in clearance is much smaller (77.7 *vs.* 83.6 L/h respectively). These differences cannot be accounted for if the dose rationale is purely based on the evidence from empirical data. In contrast to the current recommendations for dose adjustment in children, which considers the dose to be linearly correlated to body weight, modelling revealed that body weight does affect clearance, but not in a linear manner.

Given the strong effect of ethnicity (Africans *vs.* Orientals) on the clearance of both drugs, it is not surprising that the exposure to fixed dose drug combinations cannot be determined by extrapolations of pharmacokinetic data across populations. In fact, despite the practical difficulties and ethical burden, the development of anti-malarial drug combinations still relies on the assessment of efficacy and safety. To meet bridging requirements, it should be the exposure, not the dose ratio of each compound that needs to be comparable across the various populations.

Based on bridging concepts, the dose ratios for the combination of ATV and PGN should vary from 1:1.25 to 1.4:1 for Africans and from 2.1:1 to 3.6:1 for Orientals, respectively, depending on body weight. Nevertheless, it must be highlighted that inferences about the current dosing recommendation for atovaquone and proguanil are beyond the scope of this article. After all, data on efficacy and safety strongly support the use of a fixed dose-ratio for the marketed drug combination.

The main lesson from this exercise is the need to account for a potential change in the benefit-risk ratio of a treatment when using fixed dose ratios in drug combinations in the presence of time-variant covariates. The effect of covariates such as body weight, age and ethnicity on drug disposition cannot be assumed constant for different compounds. Without careful assessment of the differences in pharmacokinetics across populations, inferences made about the efficacy and safety of drug combinations may be biased. One may consider drugs unsafe or ineffective, whilst the problem may be simply due to the wrong dose.

The scenarios described here do not reflect the complexity one may face if drug-drug interactions are considered. As mentioned previously, ATV and PGN show no liability for PK interaction, which allowed modelling of the two drugs separately. However, pharmacokinetic interactions may occur when two drugs are given in combination, which can lead to far more complicated scenarios [26]. Such an interaction may render difficult the characterisation of covariate-parameter correlations or alter these correlations considerably. In these circumstances, the

interaction must be included into the pharmacokinetic model. On the other hand, for some drug combinations the effect of demographic covariates on the pharmacokinetic parameters determining systemic exposure may be clinically and scientifically questionable, such as in the case of many drugs used for topical administration [27]. The clinical relevance of different dosing regimens is therefore paramount and should be considered in an integrated manner.

In summary, the proposed methodology is not meant to replace the evidence from clinical trials, but rather as a tool for protocol design and for the analysis and interpretation of early clinical data, so that accurate decisions can be made about dosing requirements for drug combinations. In fact, one may consider that some of the concepts presented here as an integral component of the concept of personalised medicines [28]. Nevertheless, one should also be aware of the implications of different dosing regimens for prescription errors [29]. Another issue are the practical problems associated with the use of different dose ratios, which imply the availability of multiple dosage strengths, which may not always be possible, especially if the dosage form cannot be prepared extemporaneously.

Although a comprehensive evaluation of the methodology applied here may be required for further generalisation of the concepts to a wide range of drugs and indications, we cannot anticipate theoretical limitations to the use of drug exposure as the basis for extrapolating pharmacokinetics combined dosage forms. The reader should realise that, as in any model-based analysis, the issue is the validity of model assumptions and the rationale for covariate model-building criteria.

Irrespective of the implications of pharmacokinetic bridging for paediatric drug development, clinical researchers and paediatricians cannot simply rely on perennial assumptions about dose requirements in clinical practice. A dosing regimen which warrants comparable exposure in adults represents a much safer and effective approach. This is particularly important for drugs which show narrow therapeutic windows (e.g. anticancer drugs). Assuming a constant ratio between the compounds may lead to unacceptable efficacy/safety profiles across different groups of patients. The dose rationale for drug combinations in children should therefore be based on exposure ratios rather than dose ratios.

We are aware of the technical and ethical difficulties in performing clinical trials in children. However, this should not be an excuse for allowing for poor science. Quantitative methods are available that permit one to address complex therapeutic problems such as the assessment of drug exposure to drug combinations, whilst accounting for the role of developmental growth. On the other hand, one should not draw conclusions about the efficacy/safety profiles of drug combinations without further understanding of pharmacokinetics and of the underlying PKPD relationships.

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