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

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Bridging strategies for drug combinations in paediatric indications

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submitted for publication

Abstract

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 evaluation. Population pharmacokinetic models were developed for ATV and PGN using historical data in adults. Target exposure values for ATV and PGN were considered comparable in adults and children. Using simulations, a paediatric population ($n=40$) was evaluated according to a range of scenarios in which clearance varied from 20% to 100% of the adult values, or was allometrically correlated with body weight. The same initial dose was administered in all scenarios and the simulated concentration time profiles were then fitted using the SAEM method in NONMEM 7. Doses were adapted, if necessary, based on the individual AUC estimates. The accuracy of parameter estimation after the first dose and after the adapted dose was compared. Systemic exposure expressed as AUCs (geometric means + 90th percentile) was significantly different across scenarios. Despite the evidence for higher exposures when the clearance was lower than in adults and high variability in drug disposition across the population, adaptation (titration)

procedures were effective in ensuring target exposure was achieved in each individual patient. An adaptive trial protocol is critical for accurate paediatric dose selection when evaluating drug combinations. It enables implementation of bridging concepts, taking into account the impact of covariates and other sources of variability on systemic exposure, which cannot be factored in a typical fixed design protocol. In contrast to current beliefs regarding the use of allometric methods only, flexible trial protocols are required to ensure target exposure is achieved for both active moieties.

9.1 Introduction

DESPITE THE PRIMARY FOCUS OF DRUG DEVELOPMENT on single therapeutic agents, very often effective therapy relies on the use of multiple drugs. In clinical practice, prescription of more than one drug is commonly referred to as polypharmacy [1]. In certain indications, where the concomitant prescription of drugs is further defined by therapeutic guidelines, the use of drug combinations is highly desirable and advantageous [2–4]. 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. In addition to the clear impact that such dosage forms can have on patient compliance, there is also evidence of improved outcome [5, 6].

Whilst different technologies may be considered for the delivery of drug combinations, they all rely on the assumption that

1. the same doses recommended for each therapeutic agent are required when the moieties are administered as a combination, or
2. pharmacokinetic or pharmacodynamic interactions occur which impose different doses or dosing regimens as compared to the use of the single therapeutic agents [7–9].

In either case, in adult indications the rationale for the use of drug combinations often translates into the so-called fixed dose formulations or devices. The same rationale has been further extended to paediatric indications without careful consideration of the implications that developmental growth and maturation can have on drug exposure and that such differences are unlikely to be exactly the same for two different drugs.

In fact, the empiricism underlying the choice of the dose for children arises among other things from the lack of understanding of how physiological function (e.g., blood flow, enzymatic maturation) changes over time (with age) and consequently how such differences alter pharmacokinetics and pharmacodynamics. We have shown in previous investigations that the use of a model-based approach enables the characterisation of parameter-covariate correlations and hence accurate dose adjustment due to the effect of developmental growth [10]. Our findings suggest that when dealing with drug combinations, it is unlikely that such a correlation is comparable for both compounds across the range of covariate values. Furthermore,

different covariates may determine changes in the exposure to each compound, depending on their physicochemical properties [11]. 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.

This prerequisite has important consequences for the dose rationale and for the implementation of bridging protocols for drug combinations. We are aware of the technical and ethical difficulties in performing clinical trials in children. However, quantitative methods are available that permit the assessment of drug exposure to drug combinations, whilst accounting for the role of developmental growth. Given the importance of pharmacokinetic bridging in paediatric drug development, the ultimate objective of the current investigation is to demonstrate the feasibility and advantages of adaptive rather than fixed-dose protocols to select the dose and dose ratio for paediatric indications. More specifically, a randomised concentration-controlled trial (RCCT) design is proposed as framework for protocols in early clinical development. In contrast to a randomised dose-controlled trial (RDCT), where patients are randomly assigned to a predefined fixed dose, in a RCCT patients are randomly assigned to predefined drug exposure ranges or values. During the study, each patient's dose is adjusted to bring drug exposure to the pre-specified randomisation range or value. This adjustment is normally made using an algorithm, the complexity of which may depend on the compound being studied, the population and the objectives of the study [12]. Based on a learn-confirm paradigm, the selection of a fixed-dose ratio can be made *a posteriori* taking into account the effect of covariates on relevant pharmacokinetic parameter distributions. Kraiczi et al. [13] suggested that a RCCT should be considered when the studied drug shows

- high pharmacokinetic variability in relation to pharmacodynamic variability of the investigational drug,
- narrow therapeutic range, and
- the possibility of a clinically important correlation between kinetic and dynamic parameters.

In this paper, we apply the concept of RCCT as a tool for the selection of the paediatric dose for drug combinations. Atovaquone (ATV) and proguanil (PGN) were chosen as a paradigm combination for the evaluation of the proposed methodology. Currently, the fixed 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 [14]. In children, the combination is available at a lower dose strength, with a dosing regimen based on body weight (62.5/25 mg *vs.* 250/100 mg in adults), but the ratio (2.5:1) between the two active compounds remains the same. Here we perform clinical trial simulations to illustrate the implementation of a bridging study using an adaptive protocol design in which the doses are adjusted for each patient with the objective of reaching the pre-defined target exposure range.

The main assumption underlying our exercise is that the mechanisms of action and exposure-response relationships of both compounds are age-independent. 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 [15]. On the other hand, proguanil itself is a weak inhibitor of plasmodial dihydrofolate reductase, but in vivo it is metabolised into cicloguanil, which in turn has potent inhibitory activity [16]. Proguanil was selected to be co-administrated with atovaquone based on its pharmacodynamic interaction, even though the mechanisms underlying the so-called synergistic effect remain unexplained [17]. From a methodological perspective, the choice of these two compounds is further justified by the absence of pharmacokinetic interactions [18, 19].

9.2 Methods

Clinical studies

Data from seven different clinical trials (three phase I: MAL 10907, MAL 10908, MAL 10909; one phase II: MAL115-005 and three phase III: MAL115-120, MAL115-134, MAL115-135) were retrieved from GlaxoSmithKline's clinical database. Concentration profiles from 301 subjects were used for the assessment of ATV pharmacokinetics in adults, whilst data from 278 adults were available for PGN. Most of the subjects received both ATV and 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). Further details of these protocols can be found at GSK clinical trial register (<http://www.gsk-clinicalstudyregister.com>).

Pharmacokinetic analysis

Given the objectives of this investigation, data were modelled in two steps, in such a way that the proposed bridging concepts can be applied for prospective 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-estimated 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, concentration profiles for each adult subject were simulated 500 times, 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.

Non-linear mixed effects modelling was used to analyse the pharmacokinetic data, using the first-order conditional estimation method in NONMEM VI (release 1.0) [20].

For both compounds, the pharmacokinetics after oral administration was best described by a one-compartment model using the ADVAN2 TRANS2 subroutine. The models were parameterised in terms of absorption rate constant (K_a), clearance (CL) and volume of distribution (V). 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. A parameter value of an individual i (*post hoc* value) is therefore given by the following equation:

$$\theta_i = \theta_{TV} \cdot e^{\eta_i} \quad (9.1)$$

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, which comprises measurement and model error, was described with a proportional error model. This yields the relation (Y_{ij}) for j^{th} observed concentration of the i^{th} individual:

$$Y_{ij} = F_{ij} + \epsilon_{ij} \cdot W \quad (9.2)$$

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) [21] *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.

An exploration of the relationship between parameters and demographic variables was based on a stepwise covariate analysis. The following covariates were explored: body weight (BW), ethnicity, age, gender and co-administration with tetracycline (TC) or pyrimethamine (PYRM). Significant correlations between covariates and parameters were incorporated using an exponential relationship for continuous variables, according to the formula:

$$\theta_i = \theta \cdot \left(\frac{COV_i}{median} \right)^{EXP} \quad (9.3)$$

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 [22]. 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 [23]. 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 [24]. Therefore, in addition to bootstrapping, normalised prediction distribution errors (NPDE) [25] were computed using the NPDE add-on package in R [26]. 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.

Clinical Trial Simulation (CTS)

Simulations of a RCCT were performed according to an adaptive protocol design, in which patients are expected to reach a target exposure range. Protocol procedures include monitoring of drug concentrations at pre-defined intervals after the beginning of therapy. Based on the observed exposure at these intervals, if necessary, the total dose is adjusted using model parameter estimates, as determined by the non-linear mixed effects modelling. An overview of the protocol procedures and adaptation rules is presented in Figure 9.1.

Study population

A paediatric population with a broad range of weights and ages was simulated. Age distribution included children and adolescents from 2 to 17 year. Weight distribution was calculated according to growth charts available from the National Center for Health Statistics (http://www.cdc.gov/growthcharts/cdc_charts.htm). To ensure appropriate assessment of the covariate effect and prevent the potential confounders due to imbalance in the population, a total of 40 subjects were simulated, with the objective of obtaining 4 patients per stratification level, which included 5 categories for body weight categories and 2 ethnicities (African and Orientals).

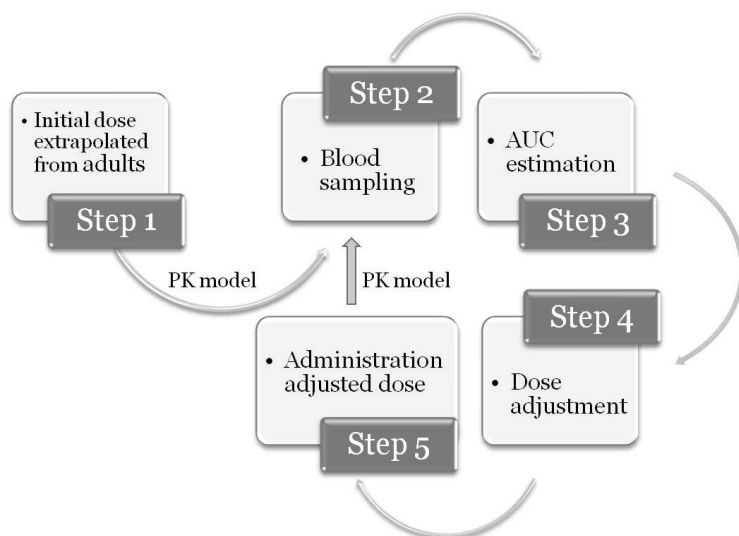


Figure 9.1: Diagram depicting protocol procedures and adaptation rules. The loop on the right-hand side (steps 2 to 5) can be repeated as required

Dosing regimen and adjustment criteria

The initial doses of ATV and PGN to be administered to the subjects were extrapolated using the adult pharmacokinetic models taking into account the covariates effects observed in that population. The same dose was administered in each simulation scenario, irrespective of the putative differences in pharmacokinetics. 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 value
2. CL of both drugs in children is 50% of the adult value
3. CL of both drugs in children is comparable to the adult value
4. CL of both drugs in children is allometrically correlated with body weight, with an allometric exponent of 0.75.

For the sake of simplicity, the magnitude of the differences in pharmacokinetics was set to be comparable for both compounds. Furthermore, all other parameters (V, K_a and IIV) were fixed to the adult values. In reality, the differences in pharmacokinetics can vary considerably across compounds and in some cases

even show highly correlated values. Nevertheless, it should be noted that these assumptions do not hamper the primary objective of this exercise, which is to illustrate the implementation of an adaptive protocol design for the evaluation of drug combinations in children.

Based on a sparse sampling schedule, individual dose adjustment is subsequently performed with the objective of reaching the target exposure. A third monitoring step allows confirmation of the results and further dose titration if necessary. Individual doses are calculated according to the formula:

$$\text{adjusted dose} = \frac{\text{first dose} \cdot \text{target AUC}}{\text{individual AUC}} \quad (9.4)$$

Simulation and dose adaptation procedures

Individual concentration data were simulated at pre-defined sampling times according to the scenarios indicated above. The simulated concentration *vs.* time profiles were subsequently analysed using non-linear mixed effects modelling. This procedure allowed individual pharmacokinetic parameters to be estimated for each patient. The dose adjustment required to achieve the pre-defined target exposure was based on the individual parameter estimates and consisted in up or down-titration relative to the starting dose. Finally, the distribution of doses administered after the adaption procedures was summarised by ethnicity and body weight. Dosing regimens for ATV and PGN were derived for each of the four different scenarios based on the median values observed for these distributions.

Pharmacokinetic parameter estimation in children

The stochastic approximation expectation maximisation (SAEM) [27] method in NONMEM VII was used to fit the simulated paediatric data. The pharmacokinetic parameters obtained after the first and second adaptation steps were compared with the values initially used to simulate the concentration *vs.* time profiles.

All calculations included in the statistical and graphical analysis were performed in R.

9.3 Results

Pharmacokinetic analysis

A one-compartment model with first-order absorption and elimination was found to best describe the pharmacokinetics of both compounds. Inter-individual variability was identified on CL, V and Ka. Residual variability was described using a proportional plus additive error model. For ATV, ethnicity (Africans or Orientals) was found to be a covariate on CL, whilst body weight was linearly correlated with V. For PGN, ethnicity had a significant effect on CL and V. An overview of the pharmacokinetic parameters along with the corresponding coefficients of variation

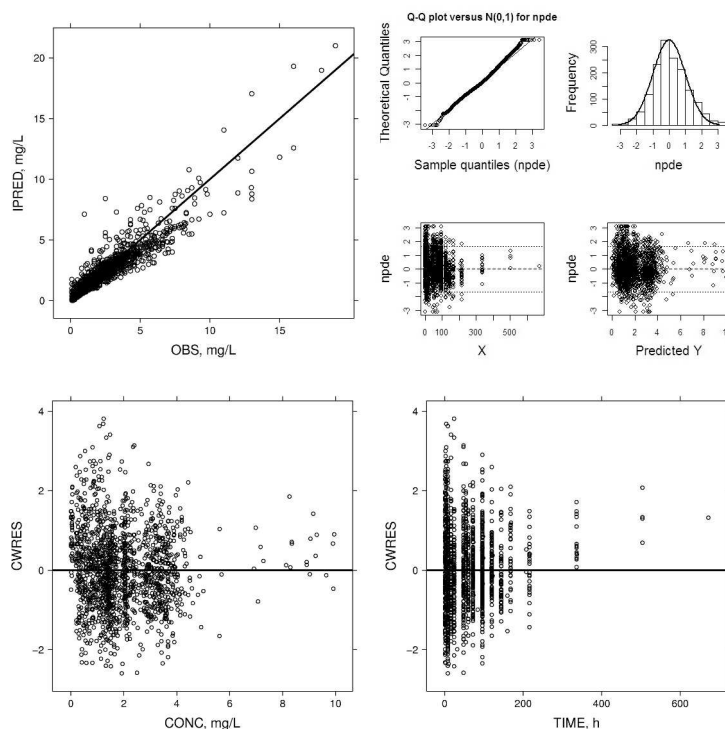


Figure 9.2: *Pharmacokinetic modelling of ATV adult data. Goodness-of-fit and diagnostic plots for adult subjects: (top left) post hoc predictions vs. observed concentrations; (top right) NPDE; (bottom left) CWRES vs. predicted concentrations; (bottom right) CWRES vs. time*

(CV%) is summarised in Table 9.1. The precision of the estimates was confirmed by nonparametric bootstrapping. In addition, NPDE reveals that the normality assumption cannot be rejected. The diagnostic plots for ATV and PGN are shown in Figures 9.2 and 9.3, respectively.

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

Clinical Trial Simulation

For each scenario, the individual exposure to ATV and PGN observed following the initial dose extrapolated from adults was compared to the target exposure. The implications of the putative differences in pharmacokinetics between adult and

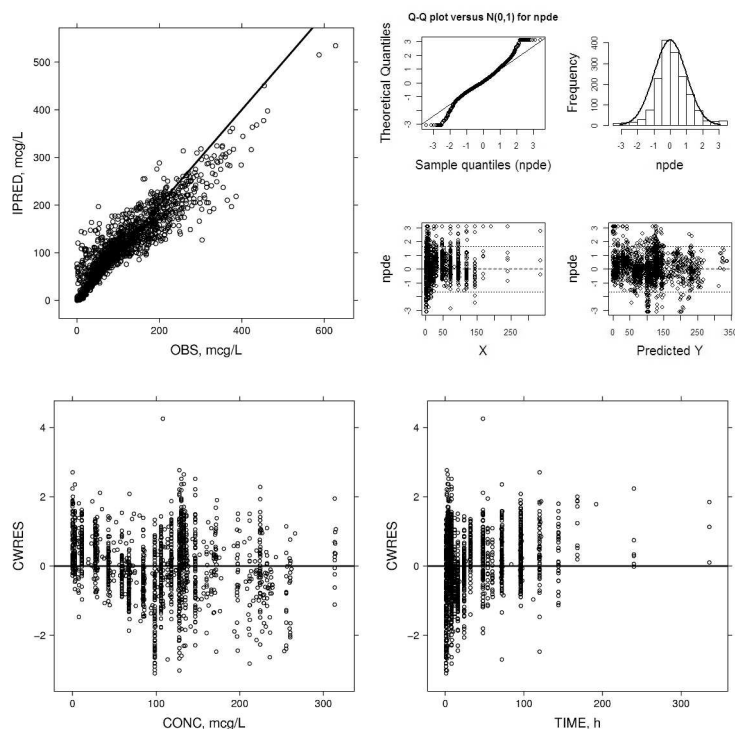


Figure 9.3: Pharmacokinetic modelling of PGN adult data. Goodness-of-fit and diagnostic plots for adult subjects: (top left) post hoc predictions vs. observed concentrations; (top right) NPDE; (bottom left) CWRES vs. predicted concentrations; (bottom right) CWRES vs. time

children are summarised as histograms in Figures 9.4 and 9.5 (left hand-side). The geometric means of the AUCs and their 90th percentile were very diverse across scenarios (Table 9.2). As expected, when the clearance in children is lower than in adults (scenarios 1 and 2), the exposures are generally higher than the target. This implies that children are being treated with a dose which is higher than necessary. Most importantly, as indicated by the 90th percentile, the distribution of the exposures is very large.

The wide differences across scenarios practically disappear in the second round of simulations. Following dose adjustment according to the pre-defined target exposure criteria, the concentration *vs.* time profiles as well as the distribution of the corresponding AUCs were comparable across scenarios (Figures 9.4 and 9.5, right hand-side). The AUC values resulting from the adaptation procedures were centred at the target exposure (Table 9.2).

Based on the aforementioned findings, fitting of the simulated concentra-

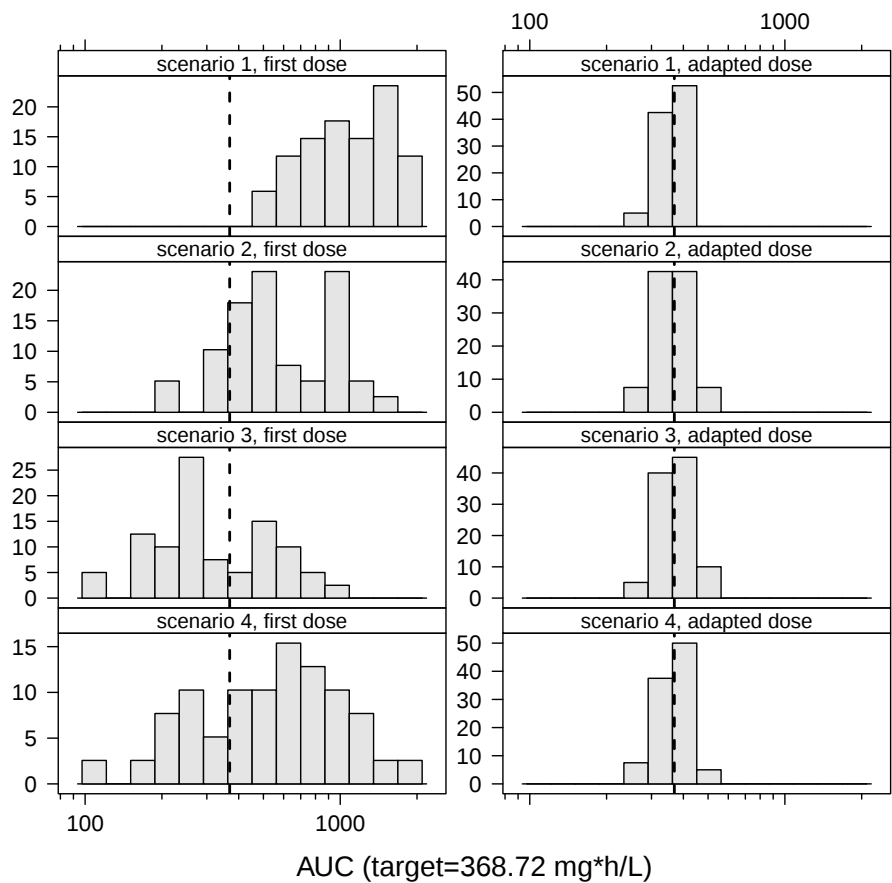


Figure 9.4: AUC distributions for ATV after the initial dose (left) and after the adaptive procedures (right). The dashed line represents the target exposure (i.e., mean AUC values in adults). Scenarios 1, 2, 3 and 4 are depicted from top to bottom

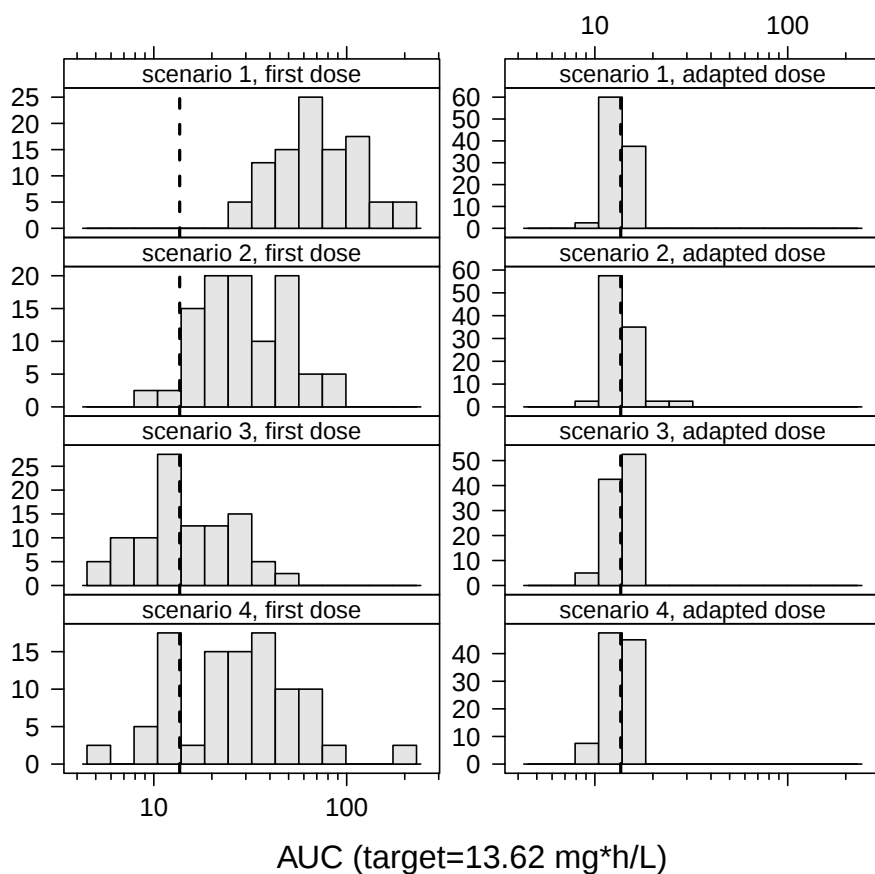


Figure 9.5: AUC distributions for PGN after the initial dose (left) and after the adaptive procedures (right). The dashed line represents the target exposure (i.e., mean AUC values in adults). Scenarios 1, 2, 3 and 4 are depicted from top to bottom

Table 9.1: Pharmacokinetic parameter estimates for ATV (left) and PGN (right) in adults. During the bootstrap analysis 98.2% and 100% of the runs were successful for ATV and PGN, respectively

Parameters (units)	Atovaquone		Proguanil	
	mean	bootstrap mean (%CV)	mean	bootstrap mean (%CV)
<i>Fixed effects</i>				
CL/F, Africans (L/h)	3.12	3.11 (13.9)	74.4	74.3 (4.9)
CL/F, Orientals (L/h)	8.23	8.26 (4.5)	71.7	72.8 (12.3)
V/F (L/kg)	10.3	10.2 (5.0)	-	-
V/F, Africans (L)	-	-	2130	2149 (9.1)
V/F, Orientals (L)	-	-	1270	1281 (17.5)
Ka (h ⁻¹)	0.262	0.261 (11.3)	1.04	1.04 (7.9)
<i>Inter-individual variability %</i>				
CL	52.8	52.3 (12.1)	50.9	50.7 (18.6)
V	53.8	53.2 (14.3)	38.2	38.0 (15.5)
Ka	96.1	96.9 (20.4)	65.6	66.1 (26.5)
<i>Residual variability</i>				
Proportional error (%)	31.2	31.2 (7.5)	33.2	33.1 (8.1)
Additive error	0.13	0.13 (96.7)	5.3	5.3 (42.1)

tion *vs.* time data obtained after the initial dose was performed to demonstrate that the discrepancies in drug exposure observed across scenarios did reflect the nominal differences in clearance. The differences in parameter estimates obtained from data fitting and the initial values were trivial. With just a very few exceptions, differences were below 15% and therefore not considered as clinically relevant. A similar procedure was applied to evaluate the data obtained after dose adjustment. Intriguingly, parameter estimates were less accurate than one would expect. Almost all parameter values deviated slightly more from the nominal values, as compared to the values observed prior to dose adjustment. This is particularly evident in scenario 4, in which clearance estimates were considerably different (Tables 9.3 and 9.4). This discrepancy may be explained by the “clamping” effect of the protocol procedures, which makes the identification of covariate effects (e.g., body weight) more difficult.

Dose recommendations

In contrast to current practice, the recommended doses and dose ratios varied considerably across scenarios due to the differences in drug disposition. In scenario 4, doses were proposed for four arbitrary ranges of body weight, namely, children

Table 9.2: *AUC distribution for ATV and PGN (geometric means and 90th percentile) following the initial dose and adaptation procedures for each scenario*

Scenario	AUC distribution after initial dose (mg·h/L)	AUC distribution after adapted dose (mg·h/L)	Target AUC (mg·h/L)
<i>ATOVAQUONE</i>			
1	1220.2 (564.9-2961.4)	328.6 (277.4-438.9)	368.7
2	602.3 (310.1-1366.2)	363.6 (288.4-458.7)	368.7
3	319.5 (157.5-755.5)	370.1 (292.9-469.8)	368.7
4	554.3 (209.4-1609.8)	365.1 (278.5-447.8)	368.7
<i>PROGUANIL</i>			
1	70.0 (35.9-151.4)	13.4 (10.9-16.2)	13.6
2	29.3 (14.3-70.5)	13.9 (10.7-17.2)	13.6
3	14.7 (7.1-36.2)	14.0 (10.6-17.6)	13.6
4	26.3 (9.5-74.5)	13.7 (10.1-17.0)	13.6

weighing less than 15 kg, between 15-25 kg, 25-35 kg and above 35 kg. An overview of the different dosing regimens is shown in Table 9.5. The dose ratios for ATV:PGN range from as low as 1.1:1 in Africans (scenario 4) to 4.5:1 in Orientals (scenario 3).

9.4 Discussion

Over the last several years significant efforts have been made towards the development of adult fixed-drug combination (FDC) tablets to help simplify therapy and improve long-term drug adherence in different therapeutic areas [28–30]. Such efforts have expanded to paediatric diseases partly due to the lack of affordable

Table 9.3: *Atovaquone: accuracy of model parameters, defined as the difference (in %) between parameter values estimated during the CTS and the corresponding values used to simulate the concentration profiles*

Atovaquone								
	<i>Africans CL</i>		<i>Orientals CL</i>		<i>V</i>		<i>Ka</i>	
	Initial dose	Adapted dose	Initial dose	Adapted dose	Initial dose	Adapted dose	Initial dose	Adapted dose
1	+18	+23	+5	+5	+8	+8	-8	-11
2	+13	+17	+7	+6	+3	+5	-24	-22
3	+7	+11	+7	+8	+4	+6	-11	-14
4	+11	-43	+8	-39	+5	+9	+4	+35

Table 9.4: Proguanil: accuracy of model parameters, defined as the difference (in %) between parameter values estimated during the CTS and the corresponding values used to simulate the concentration profiles

Scenario	Proguanil											
	Africans CL			Orientals CL			Africans V			Orientals V		
	Initial	Adapted	dose	Initial	Adapted	dose	Initial	Adapted	dose	Initial	Adapted	dose
1	+10	+15	+6	+6	+6	+4	+8	+8	+3	+5	+5	-8
2	+9	+15	+5	-1	-1	+8	+13	+13	-5	-5	-5	-1
3	+9	+15	+1	-1	-1	+14	+21	+21	0	-6	-6	+14
4	+10	-34	+4	-42	-42	+12	+18	+18	-2	-7	-7	+16

Table 9.5: *Proposed dosing regimen for each simulated scenario. Scenario 4 was divided into arbitrary body weight ranges to better illustrate the impact of covariates on the dose ratio of the two moieties*

<i>Scenario</i>	<i>BW</i>	Africans		Orientals	
		<i>ATV (mg)</i>	<i>PGN (mg)</i>	<i>ATV (mg)</i>	<i>PGN (mg)</i>
1		150	80	300	100
2		270	190	690	200
3		500	380	1370	300
4	<15 kg	130	100	320	100
	15-25 kg	250	180	640	200
	25-35 kg	250	190	1000	300
	>35 kg	500	430	1650	520

paediatric formulations, as well as the convenience of FDC tablets, which have gained popularity, particularly in resource limited settings [31]. Our scenario analysis highlights the need to re-define the scientific and regulatory requirements for the rationale for fixed-dose drug combinations in children. There should be evidence for comparable exposure to the moieties in the patient populations of interest. This is particularly important for infectious diseases, where the drug target is an evolutionarily unrelated microorganism and the loss of efficacy produced by the emergence of drug-resistant strain may be a direct consequence of inappropriate exposure [32]. These conditions impose certain limitations, including the impossibility of individual dose adjustment without affecting the regimen of the other drug. It is clear that differing pharmacokinetics of constituent drugs also pose the problem of frequency of administration of the formulation.

In paediatric pharmacology one must acknowledge that differences in size do not necessarily reflect changes in function. The assumption that size can be a surrogate for function has been used as the basis for the development of fixed-dose combinations in children. Such an assumption is questionable, despite the therapeutic impact that drug combinations can have on clinical outcome [33]. Our analysis clearly shows that it is not size that drives the rationale for dose adjustment, but rather a comprehensive understanding of the changes in pharmacokinetics due to developmental growth as well as other relevant factors such as ethnicity and pharmaceutical formulation.

In a previous investigation we have concluded that defining the dose rationale for children based on extrapolation or interpolation procedures does not guarantee optimal dosing regimen at the individual patient level [11]. Adaptive procedures are required to tackle the uncertainty in model structure (i.e., parameter-covariate correlations), discriminating it from the uncertainty in parameter estimates (i.e., heterogeneity or differences in parameter distributions). Despite the challenges associated with the implementation of adaptive proto-

cols, these considerations are essential for the development of drug combinations. In contrast to a number of publications in which modelling and simulation have been applied retrospectively to clinical study data, here we illustrate how to progress with a compound in early clinical development for which no paediatric data is available. Our findings demonstrate that the use of a randomised concentration-controlled trial ensures the child's right to receive the right dose.

Based on adult data and making use of a bridging approach under the assumption that the PKPD relationships of ATV and PGN are age-independent, pharmacokinetic modelling has been performed to establish target exposure levels for both compounds. Clinical trial simulations were subsequently implemented taking into account a predefined number of "what-if" scenarios, which permits systematic assessment of model and parameter uncertainty. Most importantly, it enabled the assessment of the impact of extreme conditions, most of which would not be feasible in a real clinical trial.

A comparison between the proposed simulation scenarios and the current dosing recommendations for ATV and PGN is beyond the scope of this publication. However, the key message from this exercise is that parameter-covariate correlations may differ considerably from the adult population. Therefore, dose adjustments according to differences in size may result in inadequate drug exposure in children. Furthermore, the changes in drug disposition are unlikely to be similar for two different chemical moieties. It should be noted that in some cases, these changes may not even be of the same order of magnitude, given that other covariates may play a role in the paediatric population, which may not be evident in adults. In fact, these considerations are very pertinent to the current combination. We show that one may include covariates found to be significant in adults to define the starting dose in children. On the other hand, it has been shown that for ATV and PGN body weight correlates with CL in children but not in adults (chapter 7).

Irrespective of the strategy used to define an initial dose level, the use of RCCT allows adaptive procedures which limit the impact of any model misspecification or parameter uncertainty arising from pharmacokinetic data in adults. Obviously, the dose adjustment procedures imply the availability of suitable delivery and dosage forms. It is unfortunate that often are the cost of goods and the requirements associated with the development of pharmaceutical formulations that prevent accurate evaluation of the dose rationale in children.

In conclusion, we strongly recommend the introduction of adaptive protocols for the evaluation of drug combinations in early paediatric clinical trials. A model-based approach is necessary, but not sufficient to ensure accurate dose selection in children. We are fully aware of the implications that different dose strengths and dose ratios have in terms of manufacturing processes. It is therefore essential to foster closer collaboration between clinical pharmacologists and pharmaceutical scientists to define dosing requirements in a timely manner. Regulatory agencies have shown clear commitment to improve trial design and analysis of paediatric trials. Time has now arrived for industry and paediatricians to

make use of available quantitative tools to address relevant clinical questions and provide a scientific basis for the dose selection of drug combinations in children.

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