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Population pharmacokinetics of abacavir in infants, toddlers and children

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The pharmacokinetics of abacavir has been previously investigated in children. However, these studies were based on a small number of patients, sparse sampling or a narrow age range of children, which renders assessment of the role of developmental factors on drug disposition difficult.
- The recommended paediatric dose of abacavir is 8 mg kg^{-1} twice daily up to a maximum of 300 mg twice daily.

WHAT THIS STUDY ADDS

- In contrast to descriptive data analysis often used in clinical reports, in which the evaluation of covariate effects on pharmacokinetics occurs in restricted populations or subgroups, the availability of patient data across a wide range of ages enabled identification of accurate relationships between abacavir pharmacokinetic parameters and covariates in children.
- Meta-analytical concepts are required to ensure thorough understanding of pharmacokinetic differences in paediatric patients.
- There were no pharmacokinetic differences between the two formulations of abacavir (tablet and solution).

AIMS

To characterize the pharmacokinetics of abacavir in infants, toddlers and children and to assess the influence of covariates on drug disposition across these populations.

METHODS

Abacavir concentration data from three clinical studies in human immunodeficiency virus-infected children ($n = 69$) were used for model building. The children received either a weight-normalized dose of 16 mg kg^{-1} day^{-1} or the World Health Organization recommended dose based on weight bands. A population pharmacokinetic analysis was performed using nonlinear mixed effects modelling VI. The influence of age, gender, bodyweight and formulation was evaluated. The final model was selected according to graphical and statistical criteria.

RESULTS

A two-compartmental model with first-order absorption and first-order elimination best described the pharmacokinetics of abacavir. Bodyweight was identified as significant covariate influencing the apparent oral clearance and volume of distribution. Predicted steady-state maximal plasma concentration and area under the concentration–time curve from 0 to 12 h of the standard twice daily regimen were 2.5 mg l^{-1} and 6.1 mg h l^{-1} for toddlers and infants, and 3.6 mg l^{-1} and 8.7 mg h l^{-1} for children, respectively. Model-based predictions showed that equivalent systemic exposure was achieved after once and twice daily dosing regimens. There were no pharmacokinetic differences between the two formulations (tablet and solution). The model demonstrated good predictive performance for dosing prediction in individual patients and, as such, can be used to support therapeutic drug monitoring in conjunction with sparse sampling.

CONCLUSIONS

The disposition of abacavir in children appears to be affected only by differences in size, irrespective of the patient's age. Maturation processes of abacavir metabolism in younger infants should be evaluated in further studies to demonstrate the potential impact of ontogeny.

Introduction

Abacavir is a potent nucleoside reverse transcriptase inhibitor, prescribed in combination with other antiretroviral agents (nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of human immunodeficiency virus (HIV) infection in both paediatric and adult patients [1, 2]. It is marketed for paediatric patients from 3 months to 16 years at the dose of 8 mg kg^{-1} twice daily, up to a maximum of 300 mg twice daily.

Abacavir is well absorbed following oral administration and distributed into body tissues, including the central nervous system. It is extensively metabolized by the liver, and less than 2% is excreted as unchanged drug in the urine. The two major catabolic pathways include oxidation by alcohol dehydrogenase and conjugation by uridine diphosphate glucuronyltransferase, resulting in inactive carboxylate and glucuronide metabolites [3, 4]. The antiviral activity of abacavir results from its intracellular activation to carbovir triphosphate. Carbovir triphosphate competes with the endogenous nucleotide 2′-deoxyguanosine triphosphate for incorporation into the nucleic acid chain and terminates the DNA chain by preventing addition of new bases [5]. The end-point for efficacy, as indicated by the change from baseline in viral load (plasma HIV-1 RNA) and increase in $CD4^+$ T-cell count, was significantly correlated with the area under the concentration–time curve (AUC) [6]. The AUC from 0 to 12 h (AUC_{0-12}) value of 6.02 mg h l^{-1} was set as target exposure in both adults and children [7].

The pharmacokinetics of abacavir has been previously investigated in children [8–15]. However, these studies were based on a small number of patients, sparse sampling or a narrow age range of children, which renders assessment of the role of developmental factors on drug disposition difficult. Accurate characterization of these factors may allow not only further assessment of the individual dosing requirements across different age groups, but also insight into processes determining maturation and metabolic capacity, which may be deemed drug independent. In this investigation, we make use of a model-based approach to analyse three different studies in children across a wide age range, with the objective of obtaining more reliable prediction of pharmacokinetic profiles in individual patients. In addition, given the availability of tablet and solution formulations, this analysis offered us the opportunity to explore the potential influence of formulation on paediatric pharmacokinetic parameters.

Methods

Clinical trials

The data were obtained from the following three studies: PENTA (Pediatric European Network for the Treatment of AIDS) 13, PENTA 15 and a pharmacokinetic substudy within the main ARROW (AntiRetroviral Research fOr Watoto) trial [8–10]. Briefly, the primary objectives of these studies were to compare the pharmacokinetics of once daily *vs*. twice daily dosing of abacavir and lamivudine in HIV type-1-infected children. The European studies PENTA 13 and PENTA 15 were conducted in children aged from 2 to 13 years and from 3 months to 3 years, respectively. The ARROW pharmacokinetic substudy was conducted in Uganda with children aged 3–12 years.

In total, 69 children were included in this population pharmacokinetic meta-analysis. The mean (SD) age was 5.74 (3.40) (range 0.42–12.84) years and the mean (SD) weight was 18.7 (8.0) (range 7.6–60.9) kg. Pharmacokinetic samples were obtained at steady state at time T0 (immediately before administration) and T1, T2, T3, T4, T6, T8 and T12 h after administration for the twice daily regimen and an additional sample at T24 h for the once daily regimen. A summary of trial design, dosage regimens and patient characteristics is presented in Table 1.

The studies have been conducted in full conformance with the principles of the Declaration of Helsinki and with the local laws and regulations concerning clinical trials. The protocol and the informed consent documents for each study have been formally approved by the relevant research ethics committee of each clinical site and by a national ethics body.

Bioanalysis

For the PENTA 13 and PENTA 15 studies, plasma concentrations of abacavir were determined by high-performance liquid chromatography assay with ultraviolet detection (HPLC-UV). The details of the analytical method have been reported [8, 9]. The lower limit of quantification was 0.015 mg l^{-1}. Within-day and between-day variability were 1.1–1.9 and 0.16–2.3%, respectively. For the ARROW study, plasma concentrations of abacavir were determined using a validated HPLC–tandem mass spectroscopy method by GlaxoSmithKline (Research Triangle Park, NC, USA). The lower limit of quantification was 0.0025 mg l^{-1} [10].

Pharmacokinetic modelling

Pharmacokinetic analysis was carried out using the nonlinear mixed effects modelling program NONMEM VI (version 2.0; Icon Development Solutions, Ellicott, MD, USA). The first order conditional estimation method with interaction option was used to estimate pharmacokinetic parameters and their variability.

Interindividual variability of the pharmacokinetic parameters was estimated using an exponential model and could be expressed as follows:

$$\Theta_i = \theta_{mean} \times e^{\eta_i}$$

Table 1

Summary of three pharmacokinetics studies and characteristics of patients

Clinical trial	PENTA 13	PENTA 15	ARROW			Total
Number of patients	14	18		37		69
Number of pharmacokinetic profiles	28	36		74		138
Steady state	Yes	Yes		Yes		
Age (years)						
Mean ± SD	5.94 ± 3.43	1.76 ± 0.76		7.61 ± 2.41		5.74 ± 3.40
Median (range)	5.10 (2.14–12.84)	1.93 (0.42–2.81)		7.70 (3.62–12.54)		5.66 (0.42–12.84)
Weight						
Mean ± SD	23.9 ± 13.2	11.5 ± 2.3		20.3 ± 4.0		18.7 ± 8.0
Median (range)	19.2 (14.0–60.9)	11.6 (7.6–15.8)		20.5 (14.0–29.8)		17.6 (7.6–60.9)
Dosage regimen						
Once daily	16 mg kg^{-1}	16 mg kg^{-1}	300 mg	450 mg	600 mg	
Twice daily, a.m.	8 mg kg^{-1}	8 mg kg^{-1}	150 mg	300 mg	300 mg	
Twice daily, p.m.	8 mg kg^{-1}	8 mg kg^{-1}	150 mg	150 mg	300 mg	
Formulation	Tablet and solution	Solution		300 mg scored tablet		

where θ_i represents the parameter value of the i^{th} subject, θ_{mean} the typical value of the parameter in the population and ηi the variability between subjects, which is assumed to follow a normal distribution with a mean of zero and variance $\omega 2$.

Covariate analysis followed a forward and backward selection process. Stepwise covariate modelling [16] and the likelihood ratio test were used to test the effect of each variable. Model validation was based on graphical and statistical criteria, including goodness-of-fit plots, mirror plots, bootstrap, visual predictive check (VPC) and normalized prediction distribution errors (NPDEs). The detailed process of covariate analysis and model validation is described in the online Supporting information.

Clinical application in therapeutic drug monitoring

Given our interest in the clinical application of model-based approaches, the performance of the final model to support therapeutic drug monitoring and dosing adjustment was tested via simulation scenarios. To assess its predictive value, we have extensively evaluated whether the final model could be used to predict accurately the observed drug exposure with current dosing regimens. For this purpose, the time course of abacavir concentrations was simulated 100 times in each subpopulation (infants, toddlers and children) and for each dosing regimen (once *vs*. twice daily). The area under the concentration *vs*. time curve (AUC_{0-24}) was selected as the end-point for the purposes of this evaluation, and AUC_{0-24} ($2 \times AUC_{0-12}$ for twice daily) was calculated using the trapezoidal rule. The simulated AUC_{0-24} was then compared with the median observed AUC_{0-24}.

The feasibility of a model-based approach in therapeutic drug monitoring was evaluated by considering two main scenarios in which pooled population data and sparse pharmacokinetic sampling are used as the basis for predicting drug exposure in new patients, as follows.

1 To assess model performance in new patients, 10 children were randomly removed from the original data set. The parameters for the remaining 59 children were re-estimated. The model parameters were then used to predict individually the pharmacokinetics of the 10 children excluded from the analysis, taking into account the effect of covariates in each patient. Predictions were compared with the observed data graphically by means of visual predictive check plots (1000 simulations per patient).

2 To assess the impact of empirical sparse sampling on model predictions, data from new patients using only three samples (T0, T1 and T3) were added in a stepwise manner to the data set (i.e. initial population, $n = 59$). Model parameters were then re-estimated for all 60 children (of whom 59 had the frequent sampling scheme). The new model was used to predict the full pharmacokinetic profile of single patients with sparse samples. Results were compared graphically with the original data using visual predictive check plots (1000 simulations per patient). This approach was selected as an initial step to the use of a full Bayesian analysis, in which model parameter values from a historical population (instead of the data) are used as priors to anchor the estimation of the parameters of interest for a new subject or population.

Results

Population pharmacokinetic modelling

A total of 1065 plasma abacavir concentrations were available for population modelling. Data fitted using a

Table 2

Population pharmacokinetic parameters of abacavir and bootstrap validation

Parameter	Final model		Bootstrap (n = 1000)	
	Final estimate	Relative standard error (%)	Median	5th–95th confidence interval
Absorption rate constant, K_a (h^{-1})	0.913	4.1	0.909	0.842–0.985
Apparent systemic clearance, CL/F (l h^{-1})				
$CL/F = CL/F_{ref} \times (WT_i/17.6)^{\theta 1}$				
CL/F_{ref}	20.1	3.8	20.1	18.7–21.4
θ1	0.802	11.6	0.796	0.651–0.954
Apparent central volume of distribution, V_1/F (l)				
$V_1/F = V_1/F_{ref} \times (WT_i/17.6)^{\theta 2}$				
V_1/F_{ref}	13.0	11.7	12.8	9.3–15.5
θ2	0.810	23.3	0.793	0.330–1.090
Apparent peripheral volume of distribution, V_2/F (l)	13.5	10.7	13.4	11.0–16.0
Intercompartment clearance, Q/F (l h^{-1})	2.0	9.9	2.0	1.7–2.4
Interindividual variability (%)				
Q/F	42.5	41.7	41.0	27.5–62.1
V_1/F	47.7	33.6	46.2	29.7–66.4
V_2/F	57.5	40.5	55.8	38.3–76.4
CL/F	21.9	38.4	21.0	13.7–28.6
Interoccasion variability (%)				
CL/F	20.4	25.3	20.2	15.7–24.8
Residual proportional (%)	38.2	8.2	38.1	35.7–40.9

CL/F, apparent systematic clerance; Q/F, intercompartment clearance; V_1/F, apparent central volume of distribution; V_2/F, apparent peripheral volume of distribution; WTi, individual weight.

two-compartment model with first order absorption and elimination. Interindividual variability was best described by an exponential model and was then estimated for intercompartment clearance, apparent central volume of distribution (V_1/F), apparent peripheral volume of distribution (V_2/F) and apparent systematic clerance (CL/F). Interoccasion variability on CL/F was coupled to interindividual variability by an additive model. Residual variability was best described by a proportional model.

During covariate model building, the inclusion of age, bodyweight and formulation on CL/F and weight on V_1/F all separately produced a significant decrease in objective function value (OFV). However, following the backward exclusion process, only the effect of bodyweight on CL/F and V_1/F was found to be significant (ΔOFV > 7.88, $P < 0.005$, χ^2 distribution); therefore, the influence of weight on CL/F and V_1/F was retained in the model as follows:

$$CL/F_i = CL/F_{ref} \times (WT_i/WT_{ref})^{\theta 1}$$

$$V_1/F_i = V_1/F_{ref} \times (WT_i/WT_{ref})^{\theta 2}$$

where CL/F_i and V_1/F_i are, respectively, the CL/F and V_1/F of the i^{th} individual, WT_i the bodyweight of the i^{th} individual, and WT_{ref} the reference weight. The subscript 'ref' indicates the individual with a reference weight. In our study, the reference weight was the median value of our population, 17.6 kg. The allometric exponents were estimated to be 0.802 for CL/F and 0.810 for V_1/F.

Model diagnostics indicated acceptable goodness of fit for the final model. As shown in Figure S1 (online Supporting information), population and individual predictions are unbiased. In addition, the mean parameter estimates resulting from the bootstrap procedure agreed very closely with the respective values from the final population model, indicating that the estimates for the population pharmacokinetic parameters in the final model were accurate and that the model was stable. The results of 1000 bootstrap replicates are summarized in Table 2.

Mirror plots reveal that the variance–covariance structure was well characterized, because the simulated data sets reproduced a similar dispersion pattern to that observed in the original data (Figure S2, online Supporting information). The VPC (Figure 1) of the final model with all patients shows that observed concentrations were well predicted by the model (exact binomial test, 7.4% out of limits observed, 95% confidence interval 5.9–9.2%). Visual predictive checks for each subpopulation (infants, toddlers and children) and each dosing regimen (once and twice daily) are also shown in Figure 1. The NPDE distribution and histogram indicates that the assumption of normal distribution of the differences between individual predictions and observed data is acceptable (Figure 2). No trends were observed on the diagnostic plots of NPDE *vs.* time or predicted concentrations.

Predictive performance in clinical applications

To assess the performance of the final model for therapeutic drug monitoring and dose adjustment,

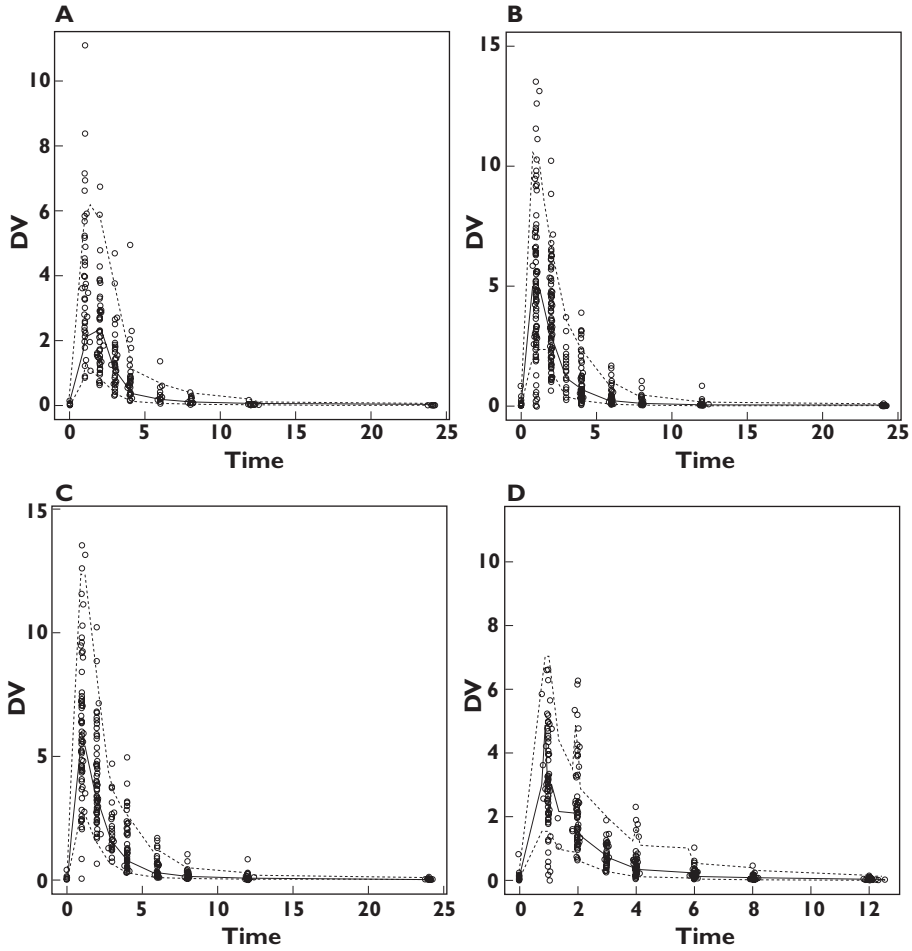

Figure 1

Visual predictive check in infants and toddlers (A) and children (B), following once daily (C) and twice daily dosing regimen (D); observed data are plotted using an open circle (○). The dashed lines represent the 5th and 95th percentiles of simulated data (n = 1000). The continuous lines represent the 50th percentile of simulated data (n = 1000)

pharmacokinetic parameter estimates were also used to simulate drug exposure, expressed as AUC_{0-24}, in different subpopulations (infants and toddlers, n = 21, age range 0.42–2.81 years; and children, n = 48, age range 3.58–12.84 years) and for currently used dosing regimens (once and twice daily dosing). As shown in Figure 3, considerable overlap was observed in the simulated and observed AUC_{0-24} values in the infants and toddlers and the children. The model-predicted maximal plasma concentration and AUC_{0-12} (geometric mean) of the standard dose regimen (8 mg kg^{-1} twice daily) were 2.5 mg l^{-1} and 6.1 mg h l^{-1} in toddlers and infants, and 3.6 mg l^{-1} and 8.7 mg h l^{-1} in children, respectively. These values were in agreement with the observed values in the original studies. In fact, the observed maximal plasma concentration and AUC_{0-12} (geometric mean) were, respectively, 2.3 mg l^{-1} and 5.8 mg h l^{-1} in toddlers and infants and 3.6 mg l^{-1} and 8.2 mg h l^{-1} in children. Likewise, drug exposure was not different after once or twice daily doses of abacavir.

Moreover, the assessment of the predictive performance of the model included scenarios in which drug exposure was predicted in new patients, taking sparse sampling schemes into account. In both cases, estimates of parameter accuracy and precision were acceptable. As shown in Figure 4, accurate predictions can be made of individual patient profiles using this model, despite some evidence of overestimation of residual variability.

Discussion

In the present study, we have shown the use of population pharmacokinetic meta-analysis of abacavir based on data obtained by a rich sampling strategy in 69 children from three pharmacokinetic studies. We believe that pooling of data offers the opportunity to evaluate drug disposition across a wide age and bodyweight range. Such an evaluation may be essential for assessment of the suitability of

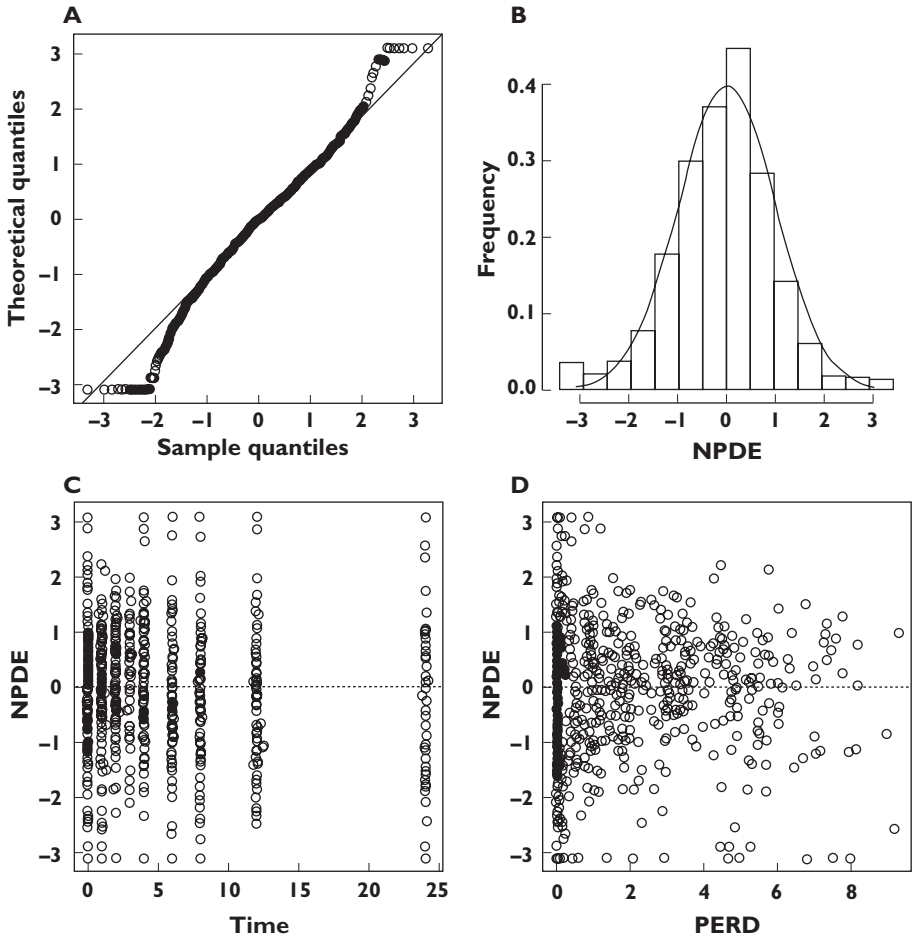

Figure 2

Normalized prediction distribution errors (NPDE) analysis. (A) QQ-plot of the distribution of the NPDE *vs*. the theoretical normal distribution. (B) Histogram of the distribution of the NPDE, with the density of the standard Gaussian distribution overlaid. (C) NPDE *vs*. time. (D) NPDE *vs*. population prediction concentrations (PRED)

dosing recommendations for children. Even though our analysis is limited to abacavir data, we anticipate that such considerations are necessary and applicable to most, if not all, compounds for paediatric indications.

From a methodological perspective, meta-analytical concepts are required to ensure thorough understanding of the implications of developmental growth on pharmacokinetics in paediatric patients. Despite attempts to describe changes in drug disposition by allometric models, it should be clear that the paediatric population encompasses a very heterogeneous group of patients. Inferences about pharmacokinetics in individual patients may be challenging with data arising from a very limited number of patients, especially when the objective is to predict individual exposure in prospective patients or to adjust dosing regimens in chronic treatment, as in the case of therapeutic drug monitoring. The scope of population pharmacokinetic modelling is to enable the description and prediction of absorption, distribution, metabolism, and excretion processes in a parametric manner, so that hierarchical parameters can be derived that can discriminate population from individual patient characteristics. In paediatric pharmacokinetics, however, discrimination between population and individual differences is further confounded by the role of maturation and other factors associated with developmental growth, including changes in metabolic capacity [17]. In a previous work [7], Cella *et al*. have shown that a model-based approach offers a suitable basis for estimation of pharmacokinetic parameters even when only sparse samples may be available. However, such models do not necessarily permit accurate prediction of the differences in pharmacokinetics for individuals whose characteristics are not represented in the population used during model-building and validation. As shown in a previous analysis [18], a model developed using data in older children cannot reliably predict exposure in infants and toddlers, and vice versa. This lack of predictive performance is partly explained by the fact that covariate–

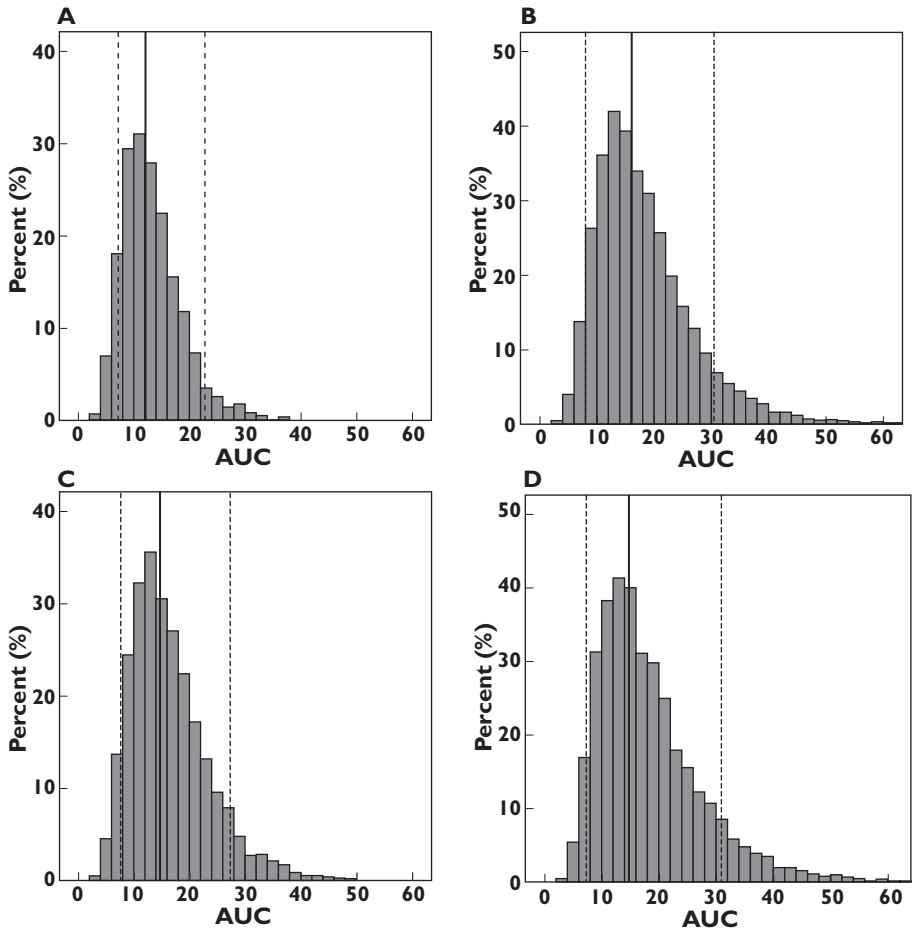

Figure 3

Exposure distribution of abacavir. Simulated area under the concentration–time curve (AUC) distribution, with median (continuous line) and 5th and 95th percentiles (dashed lines) of the observed AUC in infants and toddlers (A), in children (B), following once daily dosing (C) and following twice daily dosing (D)

parameter correlations may not remain constant beyond the range of observations. Estimation of covariate effects is therefore not sufficient to allow accurate extrapolation of pharmacokinetics from a reference population to another population.

Our results indicate that it is not the overall number of patients that determines the predictive performance of a model, but rather the availability of data from the overall population, so that parameter distributions can be estimated accurately and imputations can be made about individuals belonging to any part of the population with adequate precision. Our results indicate that good predictive performance of a model can be achieved with a considerably limited number of individuals as long as the covariate distribution in the subjects used for model building represents the covariate distribution in the population described by the model. This is critical to ensure that differences driven by covariates are not captured as random effects nor that random effects are wrongly associated with covariates. This is illustrated by the difference in the magnitude of parameter estimates in our analysis and in estimated parameters for a single trial (Table 3).

While the focus of previous publication has been on the use of modelling as the basis for drug development (i.e. early paediatric trials), little attention has been paid to the implications of similar modelling requirements for accurate dosing adjustment and therapeutic drug monitoring in clinical practice [19, 20]. In the present study, we have assessed the predictive performances of the final model using several simulation scenarios, in which potential differences in individual exposure were evaluated. Our results indicated that the final model can accurately predict drug exposure with currently used dosing regimens in new patients, even in cases of sparse sampling.

Population pharmacokinetic and/or pharmacodynamic model validation is another key issue to consider when models are to be used for simulation purposes (i.e. dosage optimization or clinical trial simulation). Validation

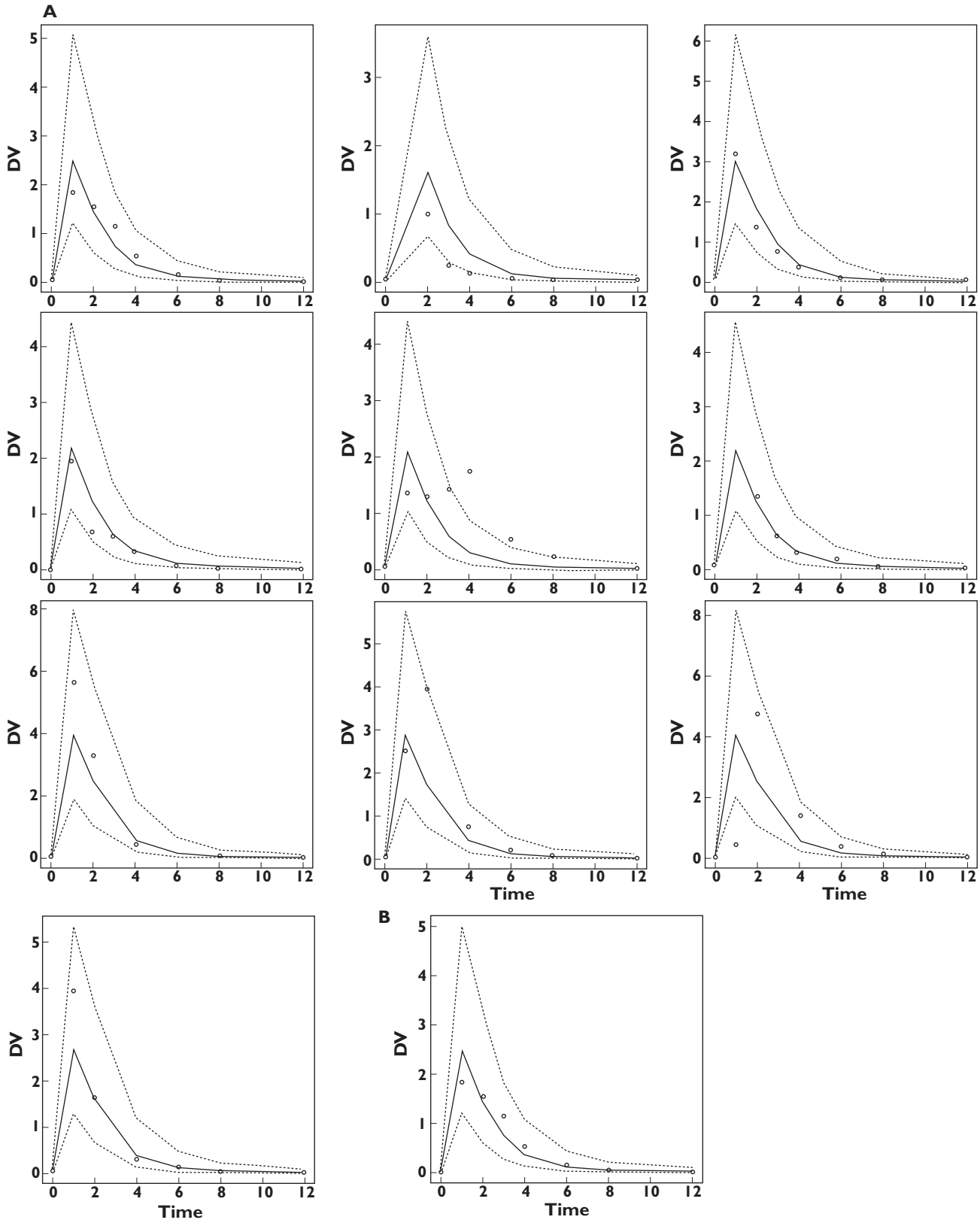

Figure 4

Individual visual predictive checks (VPCs) for new patients. (A) Scenario 1, VPC for 10 new patients. (B) Scenario 2, VPC for one patient with sparse sampling. Open circles (○) represent the observed values, whilst dashed lines depict the 5th and 95th percentiles of the simulated data ($n = 1000$). The continuous lines indicate the median obtained from the simulated data ($n = 1000$)

Table 3

Covariate–parameter relationships identified for abacavir in previous population pharmacokinetic analyses

Study	Reference	Number of children	Age range (years)	Significant covariates in the model	Covariate–parameter relationship
PENTA 13	[7]	14	2.14–12.84	Bodyweight on *CL* and *V*	CL/F (l h^{-1}) = 37.2 × (BW/23.8)$^{0.553}$ V/F (l) = 64.8 × (BW/23.8)$^{0.537}$
PENTA 15	[12]	18	0.42–2.81	Bodyweight on *CL*	CL/F (l h^{-1}) = 13.4 × (BW/12)$^{1.14}$
PENTA 13 + PENTA 15 + ARROW	Present study	69	0.42–12.84	Bodyweight on *CL* and V_1	CL/F (l h^{-1}) = 20.1 × (BW/17.6)$^{0.802}$ V_1/F (l) = 13.0 × (BW/17.6)$^{0.810}$
Therapeutic drug monitoring data	[11]	105	0.0685–16	Bodyweight on *CL* and *V*	CL/F (l h^{-1}) = 24.3 × (BW/25)$^{1.0}$ V/F (l) = 42.9 × (BW/25)$^{0.95}$

procedures are lacking in many publications reporting the development of population pharmacokinetic and/or pharmacodynamic models [21]. In fact, advanced internal evaluations were performed on merely 16% of the models in children [22]. In the present study, the following five evaluation/validation criteria were included: (i) standard goodness-of-fit plots, which inform on model misspecification and allow assessment of trends or bias in the model predictions; (ii) mirror plots, which allow comparison of the variance structure between simulated and observed data; (iii) bootstrap, which provides information on the stability of the final model (a robust model is not affected by the contribution or influence of specific individuals in the data set); (iv) visual predictive check, which yields information on the presence of systemic bias or deviations (trends) in model predictions; and (v) NPDE, which provides details on the distribution of the differences between predictions and observations and is an important criterion for the validation of a model for subsequent simulation purposes. Even though each of the aforementioned diagnostic tools reveals different aspects of model performance, it is critical to point out that there is no guarantee that model predictions will be accurate unless the relevant covariates are included in the initial model.

Limitations

During this investigation, only bodyweight, age, gender and formulation were tested as potentially influential covariates on pharmacokinetic parameters. Information on ethnicity and other potential demographic factors was not available. Given that abacavir is metabolized primarily through alcohol dehydrogenase or glucuronyl transferase, metabolic information would have been useful to describe abacavir pharmacokinetics. Further studies are required to evaluate the ontogeny of abacavir metabolism.

Conclusion

In summary, we have shown that abacavir pharmacokinetics in children can be characterized by a two-compartment model with first order absorption. Bodyweight was identified as the primary covariate influencing the apparent oral clearance and volume of distribution. The availability of data across a wide range of ages and consequently across bodyweights enabled the identification of the accurate relationships between pharmacokinetic parameters and covariates in the paediatric population. These relationships may not be evident or may even be missed when analysing small data sets or when the relevant range of values for the influential covariates is not included in the overall population. The use of an integrated, meta-analytical approach is therefore essential to ensure accurate prediction of drug exposure in new patients or in clinical conditions different from the original trial setting.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf. W.Z. and E.J.-A. had support from PENTA LABNET for the submitted work, no financial relationship with any other organization that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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PENTA 15 Executive Committee: J.-P. Aboulker, C. Brothers, D. Burger, A. Compagnucci, C. Giaquinto, D. M. Gibb, E. Jacqz-Aigrain and W. Snowdon.

ARROW Steering Committee: I. Weller, E. Luyirika, H. Lyall, E. Malianga, C. Mwansambo, M. Nyathi, A. Wapakhabulo, D. M. Gibb, A. Kekitiinwa, P. Mugyenyi, P. Munderi and K. J. Nathoo. Observers: S. Kinn, M. McNeil, M. Smith, M. Roberts and W. Snowden.

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REFERENCES

1 Thompson MA, Aberg JA, Cahn P, Montaner JS, Rizzardini G, Telenti A, Gatell JM, Günthard HF, Hammer SM, Hirsch MS, Jacobsen DM, Reiss P, Richman DD, Volberding PA, Yeni P, Schooley RT, International AIDS Society-USA. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. JAMA 2010; 304: 321–33.

2 PENTA Steering Committee, Welch S, Sharland M, Lyall EG, Tudor-Williams G, Niehues T, Wintergerst U, Bunupuradah T, Hainaut M, Della Negra M, Pena MJ, Amador JT, Gattinara GC, Compagnucci A, Faye A, Giaquinto C, Gibb DM, Gandhi K, Forcat S, Buckberry K, Harper L, Königs C, Patel D, Bastiaans D. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. HIV Med 2009; 10: 591–613.

3 McDowell JA, Chittick GE, Ravitch JR, Polk RE, Kerkering TM, Stein DS. Pharmacokinetics of [(14)C] abacavir, a human immunodeficiency virus type 1 (HIV-1) reverse transcriptase inhibitor, administered in a single oral dose to HIV-1-infected adults: a mass balance study. Antimicrob Agents Chemother 1999; 43: 2855–61.

4 Yuen GJ, Weller S, Pakes GE. A review of the pharmacokinetics of abacavir. Clin Pharmacokinet 2008; 47: 351–71.

5 Faletto MB, Miller WH, Garvey EP, St Clair MH, Daluge SM, Good SS. Unique intracellular activation of the potent anti-human immunodeficiency virus agent 1592U89. Antimicrob Agents Chemother 1997; 41: 1099–107.

6 Weller S, Radomski KM, Lou Y, Stein DS. Population pharmacokinetics and pharmacodynamic modelling of abacavir (1592U89) from a dose-ranging, double-blind, randomized monotherapy trial with human immunodeficiency virus-infected subjects. Antimicrob Agents Chemother 2000; 44: 2052–60.

7 Cella M, Gorter de Vries F, Burger D, Danhof M, Della Pasqua O. A model-based approach to dose selection in early pediatric development. Clin Pharmacol Ther 2010; 87: 294–302.

8 Bergshoeff A, Burger D, Verweij C, Farrelly L, Flynn J, Le Prevost M, Walker S, Novelli V, Lyall H, Khoo S, Gibb D. PENTA-13 Study Group. Plasma pharmacokinetics of once- versus twice-daily lamivudine and abacavir: simplification of combination treatment in HIV-1-infected children (PENTA-13). Antivir Ther 2005; 10: 239–46.

9 Paediatric European Network for Treatment of AIDS (PENTA). Pharmacokinetic study of once-daily versus twice-daily abacavir and lamivudine in HIV type-1-infected children aged 3-<36 months. Antivir Ther 2010; 15: 297–305.

10 Musiime V, Kendall L, Bakeera-Kitaka S, Snowden WB, Odongo F, Thomason M, Musoke P, Adkison K, Burger D, Mugyenyi P, Kekitiinwa A, Gibb DM, Walker AS, ARROW Trial team. Pharmacokinetics and acceptability of once- versus twice-daily lamivudine and abacavir in HIV type-1-infected Ugandan children in the ARROW Trial. Antivir Ther 2010; 15: 1115–24.

11 Jullien V, Urien S, Chappuy H, Dimet J, Rey E, Pons G, Blanche S, Tréluyer JM. Abacavir pharmacokinetics in human immunodeficiency virus-infected children ranging in age from 1 month to 16 years: a population analysis. J Clin Pharmacol 2005; 45: 257–64.

12 Zhao W, Cella M, Della Pasqua O, Burger D. Jacqz-Aigrain E, on behalf of Pediatric European Network for Treatment of AIDS (PENTA) 15 study group. Population pharmacokinetics and Bayesian estimator of abacavir: application of individualized therapy in HIV infected infants and toddlers. Br J Clin Pharmacol 2012; 73: 641–50.

13 Kline MW, Blanchard S, Fletcher CV, Shenep JL, McKinney RE Jr, Brundage RC, Culnane M, Van Dyke RB, Dankner WM, Kovacs A, McDowell JA, Hetherington S. A phase I study of abacavir (1592U89) alone and in combination with other antiretroviral agents in infants and children with human immunodeficiency virus infection. AIDS Clinical Trials Group 330 Team. Pediatrics 1999; 103: e47.

14 Hughes W, McDowell JA, Shenep J, Flynn P, Kline MW, Yogev R, Symonds W, Lou Y, Hetherington S. Safety and single-dose pharmacokinetics of abacavir (1592U89) in human immunodeficiency virus type 1-infected children. Antimicrob Agents Chemother 1999; 43: 609–15.

15 Cross SJ, Rodman JH, Lindsey JC, Robbins BL, Rose CH, Yuen GJ, D'angelo LJ. Abacavir and metabolite pharmacokinetics in HIV-1-infected children and adolescents. J Acquir Immune Defic Syndr 2009; 51: 54–9.

16 De Cock RF, Piana C, Krekels EH, Danhof M, Allegaert K, Knibbe CA. The role of population PK-PD modelling in paediatric clinical research. Eur J Clin Pharmacol 2011; 67: 5–16.

17 Cella M, Knibbe C, Danhof M, Pasqua OD. What is the right dose for children? Br J Clin Pharmacol 2010; 70: 597–603.

18 Cella M, Zhao W, Jacqz-Aigrain E, Burger D, Danhof M, Pasqua OD. Paediatric drug development: are population models predictive of pharmacokinetics across paediatric populations? Br J Clin Pharmacol 2011; 72: 454–64.

19 Neely M, Jelliffe R. Practical therapeutic drug management in HIV-infected patients: use of population pharmacokinetic models supplemented by individualized Bayesian dose optimization. J Clin Pharmacol 2008; 48: 1081–91.

20 Zhao W, Fakhoury M, Fila M, Baudouin V, Deschênes G, Jacqz-Aigrain E. Individualization of valganciclovir prophylaxis for cytomegalovirus infection in pediatric kidney transplant patients. Ther Drug Monit 2012; 34: 326–30.

21 Brendel K, Dartois C, Comets E, Lemenuel-Diot A, Laveille C, Tranchand B, Girard P, Laffont CM, Mentré F. Are population pharmacokinetic and/or pharmacodynamic models adequately evaluated? A survey of the literature from 2002 to 2004. Clin Pharmacokinet 2007; 46: 221–34.

22 Tod M, Jullien V, Pons G. Facilitation of drug evaluation in children by population methods and modelling. Clin Pharmacokinet 2008; 47: 231–43.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1
Diagnostic plots. (A) Observed (OBS) *vs*. population predicted concentrations (PRED). (B) OBS *vs*. individual predicted concentrations (IPRED). (C) conditional weighted residuals (CWRES) *vs*. time. (D) CWRES *vs*. PRED

Figure S2
Mirror plots. Observed (DV) *vs*. population prediction (PRED). Observed (DV) *vs*. individual prediction (IPRED)