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REVIEW

Population clinical pharmacology of children: general principles

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Abstract
Introduction Population modelling using mixed-effects models provides a means to study variability in drug responses among individuals representative of those for whom the drug will be used clinically.
Discussion The advantages of these models in paediatric studies are that they can be used to analyse sparse data, sampling times are not crucial and can be fitted around clinical procedures and individuals with missing data may still be included in the analysis. The introduction of explanatory covariates explains the predictable part of the between-individual variability. Simulations using parameter estimates and their variability can be used to investigate large numbers of children – many more than is possible in studies dealing with real children – for a fraction of the cost, which is an advantage when developing clinical trials. Paediatric population modelling has expanded greatly in the past decade and is now a routine procedure during the development and investigation of drugs. Children have benefitted and will continue to benefit from this approach.

Keywords Allometry · Children · Pharmacodynamics · Pharmacokinetics · Population modelling

Abbreviations

CL	clearance
ka	absorption rate constant
Ln	natural logarithm
NONMEM	Nonlinear mixed-effects model
PD	pharmacodynamics
PK	pharmacokinetics
Tabs	absorption half time
TDM	therapeutic drug monitoring
V	volume of distribution

Introduction

Children have been labelled therapeutic orphans. This is largely the consequence of their involvement in all of the major therapeutic catastrophes that have shaped modern drug development [8, 12, 25, 43], the result of which has been that pharmacokinetic (PK) and pharmacodynamic (PD) studies were not performed in children for many years because such studies were considered to be unethical. Unmonitored off-label use of medicines in children, extrapolated from adult data, has resulted in significant morbidity [8, 11, 29] that could have been avoided or

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minimised by the appropriate testing in children. However, the implementation of licensing laws that encourage paediatric studies [38, 44], improvements in drug assay techniques that allow small volume samples and advances in population pharmacokinetic modelling methods [33] have dramatically altered the scene for paediatric pharmacological studies. Pleas have been made to seize upon these initiatives and facilities as the means to further improve paediatric pharmacology knowledge within Europe [34].

Paediatric population modelling has been reported in the *European Journal of Pediatrics* [28] and other general paediatric journals, although a great many paediatricians remain suspicious of the methodology and are unfamiliar with how to interpret the results. While it is unnecessary to understand all of the mathematical details of the population approach, paediatricians should have a general appreciation of the subject, of the idiosyncrasies of modelling in children and of population modelling's potential to expand knowledge of developmental aspects of drug disposition and effects in the area of paediatrics. A number of in-depth reviews of general aspects of population modelling are currently available in the literature [26, 27, 33, 46, 47]. The use of explanatory covariates specific to children will be reviewed in the second of this two-part paper.

Population modelling

Clinical pharmacology studies often entail a series of measurements (e.g. serum concentration) in subjects at consecutive time points. The simplest way of analysing a sequence is by reducing the sequence into a small number of characteristics. For example, the reduction of a time-concentration profile into summary measures can be done without specific models (e.g. non-compartment models) or by estimating the parameters of mathematical models that describe that particular profile (e.g. compartment models). The one-compartment, first-order input and first-order elimination model is commonly used to describe medications given orally

$$C(t) = \frac{Dose \cdot F}{V \cdot (ka - CL/V)} \cdot \left(e^{-CL/v \cdot t} - e^{-ka \cdot t}\right) \quad (1)$$

The parameters required to be estimated in order to predict concentration (C) at any time (t) are the volume of distribution (V), clearance (CL) and an absorption rate constant (ka). The ka parameter can also be expressed as an absorption half-life [Tabs=Ln(2)/ka]. F is the bioavailability. This mathematical model can then be used to predict the time-concentration profiles of other doses. Attempts to predict what will happen in a further subject often become unstuck because a factor accounting for variability between subjects is missing. If the variability between patients is modelled, then it is possible to predict the magnitude of the difference between predictions and the observations in the next subject. It may be possible to explain the variability on the basis of physiological differences; in which case, predictions are improved because unexplained residual variation is reduced.

There are three common approaches to modelling data collected from a group of subjects.

Naïve pooled data approach

In this approach, time concentration data are pooled together as if all doses and all observations pertain to a single subject. In Fig. 1a, the mean concentration at each time point is used to calculate parameter estimates. No information is available on individual subject profiles or parameters. This approach may be satisfactory if data are extensive for each subject and if there is only minor between-subject variability, but misrepresentation may result if data are few. Problems also arise in the interpretation of the results when data are missing from some subjects (e.g. there are fewer data in the later time points in Fig. 1). No information can be gathered about the magnitude of between subject variability and its causes.

Standard two-stage approach

Individual profiles are analysed (Fig. 2), and the individual structural parameters (e.g. V, CL) are then treated as variables and combined to achieve summary measures (Table 1 shows the arithmetic mean). If the estimates are not based on a similar number of measurements for each individual, or if the response in one individual is much more variable than in another, some form of weighting is required. The time-concentration profiles for the two individuals shown in Fig. 2 are clearly different. The

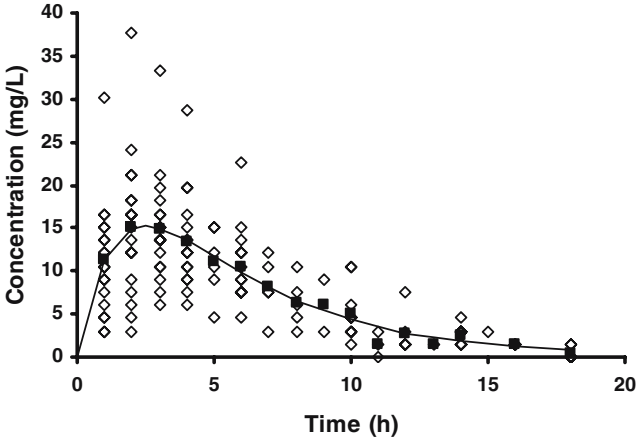

Fig. 1 Concentrations at discrete time points are averaged to obtain a single time-concentration profile. Data were collected from 20 children given a paracetamol 40 mg/kg PR, and a one-compartment, first-order input and elimination model was used to fit the data

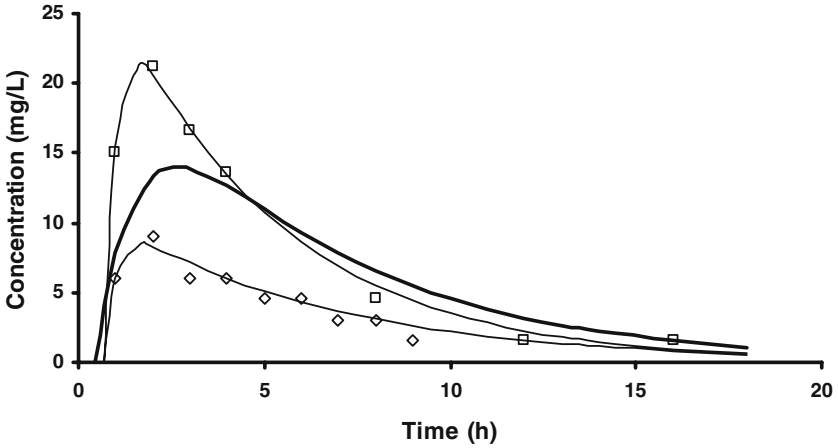

Fig. 2 The predicted time-concentration profiles from two of 20 children given paracetamol 40 mg/kg PR have been plotted with their observations. Parameter estimates from all 20 individuals are averaged to obtain a mean population profile (*bold line*)

between-subject variability can be estimated from the standard deviation of the individual estimates, but it is an overestimate of the true variability because each estimate also has variability due to the imprecision of the estimate. It may be possible to identify covariates to explain some of the variability, but this possibility depends on having relatively good individual estimates of the parameters.

Mixed-effects models

Mixed-effects models provide a means to study variability in drug responses among individuals representative of those in whom the drug will be used clinically. The naïve and standard two-stage approaches rely on "rich" data from a small group of subjects and, consequently, parameter estimates may be very similar to those estimated using mixed-effects models if data are rich [24]. In contrast, mixed-effects models can be used to analyse "sparse" (two to three samples) data from a large number of subjects. These models are "mixed" because they describe the data using a mixture of fixed and random effects. Fixed effects predict the average influence of a covariate – such as weight – as an explanation of part of the between-subject variability in a parameter such as clearance. Random effects describe the remaining variability between subjects that is not predictable from the fixed-effect average. Explanatory covariates (e.g. age, size, renal function, sex, temperature) can be introduced that explain the predictable part of the between-individual variability.

Table 1 Paracetamol parameter estimates from the naive pooled data and simple two-stage approaches. A one-compartment, first-order input and first-order elimination model was used. Clearance (CL) and volume of distribution (V) are compounded by the bioavailability (F), which is unknown from this single-dose study

Parameter	Naive pooled data approach	Simple two-stage method	
	Estimate	Estimate	Standard deviation
CLF (l/h/kg)	0.334	0.35	0.14
V/F (l/kg)	1.52	1.90	0.88
Tabs (h)	1.05	0.71	0.66
Tlag (h)	0	0.44	0.35

Tlag is lag time to first detectable serum concentration

The approach treats the population as the unit of analysis rather than the individual. Consequently, rather than obtaining rich data from each individual, sparse data from many individuals can be analysed, and a more representative sample of the target population is thereby obtained. Interpretation of truncated individual sets of data or missing data is also possible with this type of analysis. The population information may be used to improve predictions for individuals for whom there is only a small amount of information.

The appropriate number of patients for a population study is difficult to determine and will depend on the number of covariates under examination [36]. Approximately 50 subjects are often used in a population study, but covariate investigation in a study investigating children ranging from neonates to adults requires large numbers. Fewer subjects are typically used in a discrete population, such as neonates, but little can be learned about covariate relationships in such a population. Population modelling also allows data to be pooled across studies to provide a single robust PK analysis [3, 6, 45] rather than requiring a comparison of separate smaller studies that are complicated by different methods and analyses.

There are a number of statistical programmes available to undertake such analyses, but the most commonly used and versatile is that implemented in the nonlinear mixed-effects model (NONMEM) [39–41] Nonlinear regression is

performed by an iterative process to find the curve of best fit by maximising the likelihood [31, 32], which is an extension of the line that is fit through minimising the residuals (difference between observation and prediction).

Model-building process

The first step for any population modelling is determining the most appropriate structural model (e.g. one-compartment, two-compartment). The type of model used will depend on the available data. Sparse data, for example, may not support a two-compartment model. The number and timing of observations recorded may also influence the number of parameters that can be reliably estimated. For example, a simple one-compartment model (Eq. 1) is commonly used to investigate the PK of paracetamol administered enterally [6], while rich early data obtained following the administration of an intravenous paracetamol formulation would support a two-compartment model [5]. A model for the residual unexplained variability can then be considered. Assay error may be a consistent error throughout the assay range (additive) or may increase as the assay substrate increases (proportional).

Estimates from preliminary analyses can be graphed against likely covariates (age, weight, renal function, disease states) in a search for trends that can be incorporated into the covariate models. Figure 3 has been obtained from a study which investigated paracetamol PK [7] and shows increasing clearance with weight. Weight is clearly important and should be explored as a covariate, although age may confound the interpretation of weight because the two are linked. A figure demonstrating bimodal CL distribution may indicate pharmacogenomic influences [23]. A bimodal distribution of the isoniazid acetylation has been shown in children suffering from tuberculosis, thereby differentiating children into fast and slow acetylators [30]. Inclusion of potential covariates may reduce between-individual variability of the structural parameters (e.g. CL, V). These potentially important covariates are judged by NONMEM's objective function (a number that evaluates the probability of seeing the observed data given the model and its parameters). Hypothesis tests can be used to compare different models by using the chi-squared distribution of the objective function difference between the models. The number of degrees of freedom is equal to the difference in the number of parameters between two nested models. Models are "nested' when one model is a simpler case of the other.

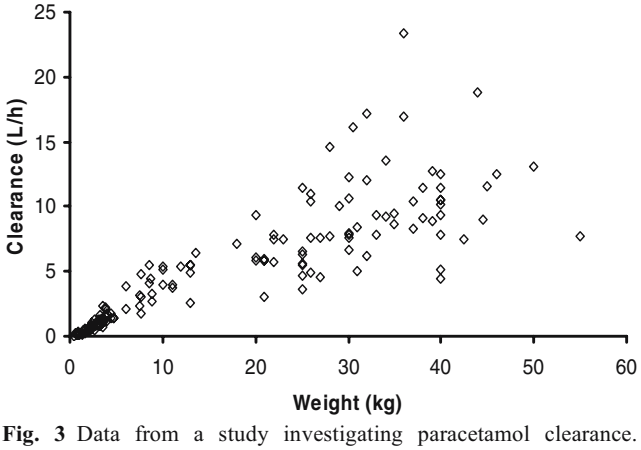

Fig. 3 Data from a study investigating paracetamol clearance. Clearance increases with weight. Individual predicted paracetamol clearances, from the NONMEM post hoc step, are plotted against weight

Model validation

Validation of the model should follow its evaluation. The model should be as simple as possible and the results creditable. It should produce clinically significant findings. Parameter estimates should be reliable. The model should perform well when used to predict new data sets. Covariate effects must be assessed to be clinically relevant of predicted dose individualisation.

Bootstrap methods [17] provide a means to evaluate parameter uncertainty. A total of 200 iterations are suggested for a mean value and standard deviation of a statistic, while thousand iterations may be required to estimate 95% confidence intervals.

The posterior predictive check [16, 48] is a model evaluation tool that provides reassurance that the model can – at the very least – simulate the data that were used to build the model. Simulated data (posterior predictions) from the final model are compared to actual observations used to create the model. Graphically, 90% prediction intervals generated from the posterior predictions should encompass 90% of the observations.

Advantages to children of mixed-effects population modelling

Ethical concerns surrounding consent issues in children that include patient autonomy, physician beneficence, unforeseen future harm, the pain associated with venipuncture and the amount of blood required for drug assay are some of many factors that have limited paediatric data collection. However, the first "true" population PK studies were performed in adults using data from routine therapeutic drug monitoring (TDM) [42]. Interpretation of these routine clinical data was used to develop dosage guidelines that could be used for other patients. The benefits of using data without additional inconvenience in paediatric studies are obvious, and paediatric TDM data are now used extensively for population studies [2, 19–21]. TDM is routinely used in

neonates nursed in intensive care units, and the use of these TDM data has enhanced our practical use of aminogycosides in this population, thereby allowing the identification of covariates, such as age and weight, to determine dosing and the impact of nonsteroidal anti-inflammatory drug (NSAID) use on renal function and consequent clearance. For example, the use of a NSAID (either aspirin or ibuprofen) on the first day of life has been found to reduce amikacin clearance by 22% [2].

Sampling times are not crucial for population methods and can be fitted around clinical procedures or outpatient appointments. However, optimal sampling schedules can be determined through prior information and the Fisher Information Matrix [13, 14, 35]. Sampling time bands rather than exact times are equally effective [15] and allow flexibility in working with children. These approaches involve defining the PK model, inputting the parameter values and weighting scheme and specifying time ranges. Unfortunately, sampling cannulae may block or tissue, children or their parents may refuse repeat sampling and repeat venipuncture is frowned upon. Missing data, however, can still be used in a paediatric population analysis.

Growth and development are two major aspects of children not seen in adults. These aspects can be investigated using size and age as covariates. One advantage of population modelling programs such as NONMEM is the ability to investigate covariates. Problems exist because covariates can exhibit co-linearity. Clearance, for example, may increase with weight, height, age, body surface area and glomerular filtration rate. All of these covariates may show a high degree of correlation and they are not mutually exclusive [9]: any one covariate may or may not predict another.

Simulation

Simulation using parameter estimates and their variability can be used to investigate time-concentration profiles in large numbers of patients – many more than is possible using real patients – for a fraction of the cost. This technique has been used to predict paracetamol concentrations after an accidental overdose in young children [4]. The demonstration that elixir is absorbed more quickly in children than the ingestion of tablets in adults paved the way for earlier testing of concentrations in the emergency department and, subsequently, earlier discharge [10].

Paediatric clinical pharmacology studies can be improved by applying clinical trial simulation techniques to replace empirically based dose selection, thereby improving clinical trial designs. Integration of priors from adult data and paediatric in vitro data can be used to improve prognostication [27]. PK/PD modelling and simulation in drug development are considered to be valuable in the following situations: censoring because of assay limitation, characterisation of nonlinearity, estimation of exposure-response relationship, combined analyses, sparse sampling studies, special population studies, integrating PK/PD knowledge for decision making, simulation of Phase II trials, prediction of multiple-dose profile from single-dose, bridging studies and formulation development [1, 22, 37]. Many of these situations have direct applicability to paediatric patients.

Conclusion

Children differ from adults with respect to the immaturity of clearance pathways (PK), receptor functions, effector systems and homeostatic mechanisms that are not efficiently developed (PD), growth and development and altered pathology [18]. Population modelling can be used to explore each of these facets. Population analyses are able to describe variabilities in response and/or concentration, determine the dose that achieves a target concentration, derive maximum a posteriori Bayesian individual predictions during TDM and predict the best sampling protocols for future studies. The applications of paediatric population modelling have expanded greatly in the past decade, and paediatric population modelling is now a routine procedure during the development and investigation of drugs. Children have benefitted and will continue to benefit from this approach.

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