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Population Pharmacokinetic Studies in Pediatrics: Issues in Design and Analysis

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ABSTRACT

The current review addresses the following 3 frequently encountered challenges in the design and analysis of population pharmacokinetic studies in pediatrics: (1) body size adjustments during the development of pharmacostatistical models, (2) design and validation of limited sampling strategies, and (3) the integration of historical priors in data analysis and trial simulation. Size adjustments with empiric approaches based on body weight or body surface area have frequently proven as a pragmatic tool to overcome large size differences in a pediatric study population. Allometric size adjustments, however, provide a more mechanistic, physiologically based approach that, if used a priori, allows delineation of the effect of size from that of other covariates that show a high degree of collinearity. The frequent lack of dense data sets in pediatric clinical pharmacology because of ethical and logistic constraints in study design can be overcome with the application of D-optimality-based limited sampling schemes in combination with Bayesian and nonlinear mixed-effects modeling approaches. Empirically based dose selection and clinical trial designs for pediatric clinical pharmacology studies can be improved by applying clinical trial simulation techniques, especially if they integrate adult and pediatric in vitro and/or in vivo data as historic priors. Although integration of these concepts and techniques in population pharmacokinetic analyses is not only limited to pediatric research, their application allows researchers to overcome some major hurdles frequently encountered in pharmacokinetic studies in pediatrics and, thus, provides the basis for additional clinical pharmacology research in this previously insufficiently studied fraction of the general population.

KEYWORDS: population pharmacokinetics, pediatrics, body size, sparse sampling, clinical trial simulation

INTRODUCTION

One of the major areas of the application of population pharmacokinetic (POPPK) approaches is the analysis of drug concentration measurements in pediatric populations. The first POPPK analyses in pediatric patients were performed not long after introduction of the nonlinear mixed-effects modeling methodology to clinical pharmacology.¹⁻³ The subsequent widespread application of this modeling technique in pediatric pharmacokinetic (PK) studies can particularly be ascribed to its ability to analyze studies with sparse and unbalanced PK data collection, which are frequent features in pediatrics because of ethical, as well as logistic constraints in the conduct of these studies. An extensive use of this approach has additionally been spurred by the recent regulatory incentives for the conduct of pediatric PK studies during clinical drug development.⁴ Pediatric POPPK studies are now explicitly recommended in the draft guidance documents on pediatric PK studies by the US Food and Drug Administration.⁵

There are numerous challenges in the design, conduct, and analysis of POPPK studies in pediatric populations that are distinctively different from the problems encountered in similar studies for adult populations. This article will focus on the following 3 issues that the authors think are of particular importance: (1) body-size adjustments during the development of pharmacostatistical models in pediatrics, (2) design and validation of limited sampling strategies in pediatric PK studies, and (3) the integration of historical priors (adult and pediatric data) into pediatric POPPK and clinical trial simulation (CTS) models.

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SIZE ADJUSTMENTS IN POPPK STUDIES

Populations in pediatric PK studies frequently cover a much wider relative range in body size than comparable studies in adults. It is not unusual, for example, that the

Figure 1. Example for collinearity in a pediatric covariate data set ($n = 40$; age range 12 days to 2 years). Creatinine clearance (CreaCL) was estimated based on serum creatinine, height, and age according to Schwartz et al.⁸⁸

body weight (BW) of the smallest-sized individual is $<10\%$ of the BW of the largest-sized individual in the study.^{6,7} Because PK parameters like clearance and volume are usually functions of body size, the effect of body size overlays and may potentially even mask the effects of other covariates, which are usually phenotypic, genotypic, or demographic patient characteristics that are tested for their value in predicting PK parameters. To identify covariates other than body size, it is, thus, highly desirable to standardize or adjust these parameters to an appropriate body size measure. This is crucial in screening potential covariate effects at the beginning of a covariate model development exercise via a visual or mathematical data analysis of structural-based, model-derived PK parameters.^{8,9}

Another, even more potentially important reason for size correction being a necessity in POPPK analyses of pediatric data is the frequently observed collinearity between covariates. Collinearity refers to a situation where, within a set of covariates, some of the covariates are highly correlated with others, that is, some of the covariates are nearly totally predicted by the others. In this situation, it becomes extremely difficult to estimate the contribution of individual covariates on a PK parameter, because no reliable estimates for individual regression coefficients can be determined. In pediatric PK data sets, size parameters, like

BW, height, and body surface area (BSA), are frequently highly correlated with other development- or maturation-related parameters, for example, renal function or age in newborns and infants. An example for the collinearity of these parameters in a pediatric study population is shown in Figure 1. Collinearity among covariates in pediatric PK data sets is usually more pronounced the wider the size range included in the study.

The implications of collinearity in covariates on the model-building process in nonlinear mixed-effect modeling have been explored by Bonate.¹⁰ He concludes that models that include covariates showing a high degree of correlation ($r > 0.5$) when included in the model at the same time may indicate that one or both are not relevant to the structural model even when, in fact, they are. Thus, collinearity is a potential source for errors in identifying covariates that are predictor variables for PK parameters.

Allometric Versus Empirical Body Size Adjustments

The methodology used to adjust PK parameters for body size in POPPK analyses can mainly be differentiated into allometric versus empirical approaches. The latter ones have traditionally focused on BW and BSA but could also include other size descriptors, such as ideal BW, lean body

mass, fat-free mass, body cell mass, or liver weight.¹¹⁻¹³ In the following sections we will only focus on BW and BSA.

Allometric Size Adjustments

Allometry is a methodology used to relate morphology and body function to the size of an organism. Allometric scaling of PK has found wide application in drug development, especially to predict PK parameters in humans based on data from several animal species during the transition from pre-clinical to clinical drug development.¹⁴⁻¹⁶ The science of allometry is well established¹⁷⁻¹⁹ and has been repeatedly suggested for size standardization in PK.²⁰⁻²² In the allometric size adjustment approach, PK parameters are related to the BW of an individual subject via a power model:

$$P_i = P_s \cdot BW^b \quad (1)$$

where BW is the BW of the individual in kg, P_i is the PK parameter of the individual subject, and P_s is the intercept on a log-log scale. The standard parameter P_s represents P_i for an individual with the (theoretical) weight of 1 kg. The allometric coefficient b tends to have a value of 0.75 for clearance terms, 1 for volumes terms, and 0.25 for half-lives.²²⁻²⁴

Although allometric relationships were initially derived based on empirical observations,²⁵ physiologists have provided mechanistic frameworks supporting the quarter-power allometric scaling laws, including the relationship between whole-organism metabolic rate and BW ²⁶ and, more recently, a general model of transport of essential materials through space filling fractal networks of branching tubes as encountered in the vascular system of mammalian species.^{17,18}

To obtain a more meaningful, readily interpretable standard parameter P_s , as well as to increase numerical stability during the optimization procedure with a population analysis software package, it has been suggested to express BW relative to a standard weight BW_s . In this case, P_s may be used as the standard parameter for a 70-kg reference individual (if BW_s is 70 kg), a typical or representative individual in the studied population (if BW_s is the BW of the typical or representative individual), or the mean or median weight of the population (if BW_s is the mean or median BW).²⁷ Hence, equation 1 can be rewritten as

$$P_i = P_s \cdot \left(\frac{BW}{BW_s} \right)^b \quad (2)$$

although it should be noted that P_s in equation 1 is not the same as in equation 2.

Allometric size adjustments using fixed allometric coefficients of 0.75 for clearance terms and 1 for volume terms

have repeatedly been used in pediatric PK analyses and have especially been reported in more recent publications. Rajagopalan and Gastonguay,⁶ for example, applied allometric size adjustment to characterize the POPPK of ciprofloxacin in a pediatric population with a wide age range of 0.27 to 16.9 years. Similarly, Anderson et al²¹ used this approach to investigate the effect of age on the PK of acetaminophen (paracetamol) in pediatric patients ranging from 1 day to 15 years after allometric adjustment of size differences.

A major advantage of the allometric size adjustment is that it is a mechanistic approach that is based on a well-described scientific framework that can be related to basic physiologic functions.^{17,18} As such, allometric size adjustments are often not used as variables to be estimated during the data modeling process but are fixed as an underlying theoretical basis, thereby allowing researchers to delineate secondary covariate effects from the effect of size. Using this approach, however, careful consideration has to be given to the fact that the strong assumptions associated with allometric size adjustments may not hold for all of the studied populations,²⁰ and concerns have been raised recently about the validity and limitations of the underlying scientific basis, especially the values used for allometric coefficients.²⁸ Hu and Hayton,²² for example, suggested the use of an allometric exponent of 0.75 for the clearance of drugs that are eliminated mainly by metabolism or by metabolism and excretion combined, whereas an exponent of 0.67 might be more appropriate for drugs that are eliminated mainly by renal excretion. Other researchers^{19,29} suggested that the 0.75 power law is only applicable for the relationship between weight and basal metabolic rate but not maximum metabolic rate, which requires an allometric exponent of 0.86. The implications for this observation on allometric size adjustments in PK are, so far, unclear.

In addition, the clearance of subjects with unusual body composition by obesity or pathophysiological conditions, for example, may not fit an allometric model using total BW with an exponent of 0.75 derived from "healthy" individuals. Ideal or lean BW and/or a different allometric coefficient may in this case be more appropriate to describe the relationship between size and clearance. Nevertheless, the allometric approach may offer in this case the opportunity to quantify the effect of "obesity" as an additional categorical or continuous covariate (eg, via body mass index), thereby allowing to better characterize the PK of a drug in this special population compared with the healthy population and to derive adequate dosing adjustments compared with standard dosing.

Empiric Size Adjustments

BW and BSA are most frequently used for empirical size adjustments in pediatric POPPK analyses, generally using

linear relationships. The decision to use one or the other, however, seems to be arbitrary.³⁰

Bailey et al,³¹ for example, used BW-adjusted clearance expressed as milliliters per hour per kilogram to describe the effect of age on this parameter for milrinone in the treatment of low cardiac output syndrome in pediatric patients after cardiac surgery. The same approach was also used in the characterization of the POPPK of digoxin in pediatric patients.³² For the PK of ciprofloxacin in cystic fibrosis patients, Schaefer et al³³ did not follow this direct proportionality approach but, rather, modeled a linear relationship between clearance and weight by using a slope and intercept. Although less frequently used, more complex relationships, such as a second-order polynomial function to describe the apparent clearance of sumatriptan in children as a function of BW, have been applied.³⁴

BSA, especially in oncology, but also pediatrics, has been used for size-based dosage adjustments to account for the fact that many physiologic processes are slower in larger individuals or animals than in smaller ones and that smaller species are generally more tolerant of drug treatment than larger species when doses are calculated on a unit BW basis. BSA is generally predicted based on BW and height via the classic Dubois equation³⁵ or the methods by Gehan and George³⁶ or Mosteller.³⁷

Shi et al,³⁸ for example, related oral clearance and volume of distribution of sotalol in pediatric patients with tachyarrhythmias to BSA via a linear relationship. Sallas et al³⁹ used BSA as a predictor for oral clearance of the anticonvulsant oxcarbazepine in children using a power model with an exponent of 0.9. The rationale for using BSA rather than BW for size adjustments was, in both cases, a better model fit during the covariate building step of the POPPK analysis. Although this may be inherently related to the fact that BSA is a better size measure than BW to predict PK parameters for these drugs, it may also be caused by BSA being more highly correlated with pediatric maturation-related developmental changes in the PK of these compounds not solely produced by size changes.

An advantage of empirical size adjustments for PK parameters using BW, especially if they have a simple structure, is their easy translation into BW-based dosage recommendations familiar to clinicians, such as milligrams per kilogram of BW. Volume terms may be adequately represented by a linear relationship to BW, which is identical to the allometric approach for BW ($b = 1$). However, it is well known that the clearance of drug-eliminating organs is usually not linearly related to BW.^{30,40} BSA may generally be a better predictor for clearance values than BW, because a linear BSA adjustment is approximately equivalent to an allometric size-adjustment approach using BW with a coefficient of $b = 0.67$, which is relatively close to

the coefficient of $b = 0.75$ used with the allometric approach. BSA, however, is not directly measured, but is a secondary covariate estimated from BW and height via empirical relationships,³⁵⁻³⁷ thereby introducing additional error into size-based predictions of PK parameters.

It has been shown previously that for clearance terms, the difference between allometric size adjustments and empiric size adjustments based on linear relationships to BW or BSA is only minor at higher weights in the adult range around 70 kg but shows progressively increasing deviations at lower BWs typical for pediatric subjects, especially those in the first years of life.^{20,30} Thus, the methodology of size adjustments becomes particularly relevant for PK data analysis in pediatric populations.

Size Adjustments A Priori Versus as Part of Covariate Modeling

Independent of the approach used, allometric or empirical, body size adjustments in POPPK analysis can be performed either a priori within the development of the structural base model before other covariates are evaluated or can be performed as part of the covariate model-building procedure. The latter approach has been used more frequently for empirical size adjustments but can also be applied to the allometric approach.

Incorporating the allometric size adjustments in the model-building procedure can be accomplished in 2 different ways, either by fixing the allometric exponent thereby creating a nonnested model or by estimating it as parameter of a nested model during the covariate model building. Yukawa et al,⁴¹ for example, used the latter approach to investigate the effect of concomitant administration of carbamazepine and valproic acid on the oral clearance of clonazepam in a pediatric and adult population of 160 patients with an age range of 0.3 to 28 years. In their final model, estimates for the allometric exponent ranged between -0.181 and -0.231 for clearance expressed in the unit milliliter per hour per kilogram dependent on the concurrent medication, which is equivalent to exponents of 0.769 to 0.819 for clearance expressed in the unit milliliter per hour. The advantage of this approach is that no assumptions on the relationship between the size measure and the parameters are made, and a superior description of the analyzed data is frequently achieved.

The incorporation of the size adjustment in the covariate model building procedure, however, may have severe limitations if collinearity between size measures and other covariates is present in the data set. In this case, the effect of size and other correlated covariates on PK parameters may become indistinguishable from each other, and some covariates may appear to be irrelevant for the model although they are mechanistically relevant. In such a situa-

tion, it appears advantageous to first perform an allometric size adjustment of affected PK parameters a priori in the base model using fixed allometric coefficients, thereby excluding the effect of size from the covariate model building procedure. This modified base model can then be used to delineate the effect of other potential covariates, for example, using previously described covariate model building strategies.⁴² This approach is, of course, a tradeoff between the potential identifiability of secondary covariates other than size and the strong and potentially erroneous assumption of the validity of the allometric size adjustments with fixed exponents, and the individual modeler has to decide whether its application is justified based on a comprehensive review of the information that is relevant for the data set.

Investigating the PK of zidovudine in HIV-infected infants and children, Capparelli et al⁴³ provided a prime example for the application of a priori size adjustments to detect the effect of secondary covariates. Because of the noted collinearity of several potential covariates, allometric size adjustments with fixed coefficients of 0.75 for clearance and 1 for volume of distribution were incorporated in the base model before other potential covariates were evaluated. Concurrent antiretroviral medication, age, liver enzyme measurements, and repeated versus single-dosing status were identified as significant covariates for allometrically scaled zidovudine oral clearance, whereas gender, total bilirubin, and serum creatinine were without significant effect on zidovudine PK.

LIMITED SAMPLING METHODS IN PEDIATRIC PK

Limited sampling studies are becoming more common because of many factors, including the availability of POPPK analysis software. They are attractive because of their ability to determine important clinical PK information accurately and without bias while providing convenient schedules with minimal blood draws and reduced load on clinical laboratories. This is accomplished by first determining the optimal sparse sampling times given the constraints of the study (eg, time of day, number of samples that can be obtained, and convenience to the patient and clinical laboratory) and, second, by using the most appropriate techniques to analyze these results. These issues become even more important in pediatrics where, in many cases, limited sampling PK studies are the only option.⁴⁴

One example of a drug where a limited sampling model was shown to be relevant is etoposide, used in the treatment of pediatric acute lymphocytic leukemia, which has shown a relation between the PK parameters and efficacy and toxicity.⁴⁵⁻⁴⁹ A limited sampling model with just 2 samples (at 3 and 5.5 hours after dosing) was developed for this drug that had very little bias (percent error <3%)

and very good accuracy (percent absolute error <8%).⁵⁰ Therefore, the authors were able to study questions on efficacy and toxicity of the drug while only needing 2 samples per subject at reasonable times, which made this study acceptable for both the patient and the clinical staff.

Development and Implementation of Sampling Strategies

The most important aspect to consider when developing a limited sampling strategy is the prior information available on the drug in the specific patient population. For example, drugs for which the PK are functions of either age and/or BSA (eg, temazolomide⁵¹) would require either an age/BSA-specific population or a priori knowledge of the relation between age/BSA of the 2 different populations so as not to bias the results. A good set of prior data (informatively sampled data from a statistically reasonable-sized population of subjects) allows first developing and then validating of the limited sampling model.

First, strategies are considered for developing limited sampling models in individual PK studies. The general technique is to use the prior PK data along with D-optimality sampling methods^{50,52,53} to define a sequence of sampling times that provide the most information for the PK model parameter estimates (eg, clearance or volume of distribution) by minimizing their standard error estimates. In D-optimality, this is accomplished by minimizing with respect to sample times the negative determinant of the Fisher Information Matrix (of which the inverse is the variance/covariance matrix of the parameter estimates). Once the sampling times are determined, a Bayesian parameter estimation method is implemented, which uses the prior parameter distribution as a form of constraint on the parameters being estimated, to estimate the parameters in the sparsely sampled data set. Bayesian methods are available in a variety of programs, including ADAPT II.⁵⁴ In general, the more informative the data (either more samples or more optimally placed samples), the less of an effect the prior distribution has on the estimation.

Hypothetical examples of several cases of informative and noninformative data are given in Figure 2. Here it can be observed that in the cases where the data are informative, the model description of the data is reasonable even when it was fit using an inappropriate set of prior data, thus indicating that the prior data has little influence in these cases. But, in the case of less-informative data, the prior data has a strong influence on the model fit, and the importance of using an appropriate set of priors is observed. In particular, when the model was fit to the noninformative data using an inappropriate set of prior data, the results were poor.

When working with a population study with only sparse data per subject, a similar technique as described above

Figure 2. Hypothetical concentration versus time curves describing (A) informative data with full sampling, (B) informative data with limited sampling, (C) noninformative data with limited sampling. In all of the cases, the simulated data are represented by the diamonds ($\blacklozenge$), the simulated model curve is represented by the solid line (—), the Bayesian fit curve with appropriate priors is represented by the dashed line (---), and the Bayesian fit curve with inappropriate priors is represented by the dotted line ($\cdots$).

can be used if a prior data set already exists. Specifically, each individual's PK parameters should be first estimated using Bayesian methods, and then the population parameters and measures of variability (interindividual and intraindividual variability) should be estimated via a linear mixed-effects modeling approach. This technique is referred to as the 2-stage approach.⁵⁵

Although this is a good method for handling problems where reasonable sets of prior PK parameters exists, it is not appropriate in the more challenging case where there is not a prior set of data in the particular patient population. Whereas this is not as desirable a setting for limited sampling modeling, there are methods to allow studies of this type. First, assumptions on the POPPK must be made to develop an acceptable sparse sampling scheme. For example, the PK from a prior adult study could be used preliminarily in a pediatric study. Then, once some pediatric PK data become available, the prior distribution results can be updated. A similar D-optimality approach to the one described above is used to determine appropriate sampling times, although in this case, the Fisher Information Matrix of the population parameters is used.⁵⁶ This method is flexible, because all of the subjects do not necessarily need to be sampled at the same times, but, rather, they can be divided into several groups, and each group can be sampled at a different sequence of times so that the sampling for the full population is more complete. Once the sparse sampling scheme is determined, the next step is to analyze the data by nonlinear mixed-effects modeling methods available in programs such as NONMEM (GloboMax LLC, Hanover, MD) or S-PLUS (Insightful Corp, Seattle, WA). These methods give both estimates of the POPPK parameters and their measures of variability, along with estimates of each subject's parameters.

Limited Sampling Model Validation

The validation of limited sampling models is a critical aspect to their development. One of the most straightforward methods of validation is through an independent set of data with complete sampling where the limited sampling scheme is a subset of the complete sampling scheme. In this case, model parameters are first estimated using the full set of data, and then these results are compared with estimates determined only using the subset of samples in the limited sampling scheme. By estimating the accuracy (absolute percent error) and bias (percent error),⁵⁷ we can determine whether the PK parameter estimates generated by the limited sampling model are acceptably close to those estimated with the densely sampled data.

Another option for validation is Monte-Carlo simulations. Here, a data set is simulated, based on the known distribution of the PK parameters, at the proposed limited sampling times. The advantage of the simulated data set is that the actual PK parameters for each individual are known a priori. Therefore, the PK parameters estimated for the simulated limited sampling data set can be compared with the known parameters, and bias and accuracy can be assessed in the same manner as described above.

A more indirect approach to describing the accuracy and bias of a sampling scheme is through the D-optimality methods,^{52,56} which generate predicted estimates of the variability for the parameter estimates given a sampling scheme and a prior distribution of parameters. Thus, assuming the prior PK are reasonable representations of the limited sampling study, this gives a measure of the error associated with the estimated parameters.

One drawback to limited sampling studies in the past has been the difficulty and availability of the computational

methods needed. But these limitations have been overcome with the current accessibility of powerful desktop computing and user-friendly PK software, which can perform Bayesian parameter estimation and D-optimality. These software programs are used by clinical pharmacists to efficiently generate a patient's individual PK parameters, which are then used to effectively adjust the individual patient's dosages to target specific drug plasma levels.⁵⁸⁻⁶⁰ As more limited sampling methods become available and larger populations are studied, this type of dose adjustment will become more common.

INTEGRATING PRIORS INTO PEDIATRIC POPPK AND CTS

Clinical Translation: Adult to Pediatric Assumptions

Although the current climate for pediatric investigations is certainly much improved amid more heightened sensitivity to the "therapeutic orphans" of the past, there are still limited opportunities to assess drugs, both new chemical entities and existing, approved medicines, in pediatric populations.⁶¹ Likewise, given the need to assess dose finding, safety, and efficacy in the fewest drug exposures, pediatric investigators must depend a great deal on the knowledge obtained from the adult drug development. Pediatric research often relies on the following assumptions derived from the adult drug development experience: (1) the disease etiology is similar between adults and pediatric subpopulations, that is, in vivo pharmacology models still provide a rationale for drug use in pediatric settings; (2) the exposure-response and concentration-effect relationships established in adults are similar to those in pediatric populations; and (3) the safety and efficacy conferred from a recommended adult regimen can be conferred to pediatric populations, assuming that comparable drug exposure can be achieved.

The clinical setting for pediatric pharmacotherapy is similar to that for adult drug utilization. A key assumption in this linkage is that drug exposure can be measured in pediatrics and a scale established to match that attained in adults. This mandates the performance of PK studies—the measurement and tracking of relevant, active molecular species (the parent and relevant metabolites) at the site of action or a surrogate of the active site resulting from administration of a drug to children. Under those situations in which potential alterations of the activity of an agent in children are observed, pharmacodynamic (PD) studies must also be undertaken. PK-PD models then allow the exploration of dose and regimen scenarios that can be used in the "scaling" exercise.

Extension of PK-PD and POPPK Models for CTS

The extension of PK-PD relationships to predict clinical trial outcomes has been advocated,⁶² and several examples

Figure 3. Incorporation of modeling and simulation into CTS construct.

exist that demonstrate the ability to use prior assumptions to define CTS scenarios ultimately used to defend study designs. Most commonly, this work has focused on industrial applications with the intention of screening drug candidates, defining clinical trial designs and predicting drug performance.⁶²⁻⁶⁷ A key element to this process is the identification and assembly of the relevant "prior knowledge," as well as the construction of intermediate relationships and/or models that can serve as elements in the larger clinical trial construct (see Figure 3). These models are, likewise, evolutionary in that they continue to develop as new experimental data are generated and made available.

CTS can be used for dose selection and clinical trial design optimization in a number of adult indications. For dose selection, CTS has been described for pregabalin,⁶² darbe-poetin α ,⁶⁸ and docetaxel.⁶⁹ For the anticancer drug docetaxel, a series of CTS were initiated to test whether a specific subset of adult patients with non-small cell lung cancer might benefit from dose intensification. PK and PD models for time-to-progression, death, and dropout were developed and validated with the use of phase II data from 151 patients with non-small cell lung cancer. The simulation process was evaluated by comparison of the original phase II data with the predicted results. Simulations were undertaken for the evaluation of whether a phase III trial of 2 different doses of docetaxel in these patients would result in improved survival. In the simulated phase III trial, although median survival was slightly longer in the 125-mg/m² docetaxel group than in the 100-mg/m² group, the difference was significant in only 6 of 100 trials. Hence, given the small likelihood that a meaningful

difference in clinical outcomes would actually exist, the simulation was the basis for not conducting such a trial.

CTS for clinical trial designs has been described recently for naratriptan⁷⁰ and ivabradine,⁷¹ again in adults. Ivabradine is a new bradycardic agent that may be of use for stable angina pectoris. To investigate the optimal balance among efficacy, safety, drug regimen, and number of patients to include in a phase III study, Monte Carlo simulations were performed. Chest pain was simulated using a physiologic model in which the coronary reserve was derived from the heart rate. Safety was defined as being heart rate dependent. Using a PK-PD model established to predict drug effect coupled with the resampling of heart rate profiles from a historical database, 100 clinical trials were simulated for 5 oral doses (2.5, 5, 10, 20, and 40 mg once daily or twice daily) of ivabradine. Only 25% of the simulated trials showed a significant effect of ivabradine with doses up to 10 mg once daily, whereas >80% of the trials showed an effect with a 40-mg daily dose. The number of subjects to include in a future trial to obtain a 15% decrease in chest pain under the assumption of a 68% base risk was determined to be 239 subjects per group with 10 mg twice daily or 196 with 20 mg once daily.

The approach for CTS involves pooling all of the available prior knowledge deemed appropriate to define drug exposure-activity-outcome relationships into study designs that have been chosen based on their ability to address the medical needs of the given therapeutic area population combination. Functional relationships for these sequential relationships are connected based on defined dependencies, and Monte Carlo simulation is used to generate replicate outcomes for an individual study across the range of evaluable PK, PD, and design parameters. The process is repeated so that the likelihood that a particular design will yield the expected outcomes can be estimated. The principal methodology used at this stage is Monte Carlo simulation, as mentioned previously.⁷² The foundation of the drug exposure model is typically based on nonlinear mixed-effect representation, either via actual modeling or from historical parameter estimates. The analysis of replicates of virtual trials requires the same statistical methodology and consideration as the single occurrence of an actual trial. An empirical determination of error rate can be made via a likelihood ratio test (implemented in NONMEM). A variety of graphical techniques, including coplots, mean absolute error percentage versus sample size plots, histograms (ie, likelihood ratio χ^2 values for showing the percentage of trials falling within an interval), and box plots, can be used to summarize the results of simulated trials. There is no simple sample-size calculation for a population nonlinear mixed-effects modeling analysis. Simulation studies have shown that, in general, a sample size of approximately 100 subjects is necessary for accurate and precise

estimation of fixed-effect and random-effect parameters where interindividual variance is moderate.^{73,74}

Pediatric Experience and Regulatory Support

The use of CTS for the design of efficient clinical trials is not well developed in pediatrics. Modeling techniques, for the most part, are limited to studies that provide dose predictions based on PK data obtained previously from pediatric patients. Dose prediction based on pediatric priors necessitates repeated measures. Bayesian approaches for dose predictions based on prior PK data obtained in pediatric patients have been performed for imipramine and desipramine,⁷⁵ gentamicin,⁷⁶ theophylline,⁷⁷ cefuroxime,⁷⁸ chloramphenicol,⁷⁹ vancomycin,⁸⁰ and digoxin.³² These dose predictions, however, have not been tested in clinical trials nor have they been used in CTS settings to evaluate and/or optimize design elements. Another Bayesian approach-based dose prediction model that used prior pediatric and adult PK data was performed for the prediction of amikacin concentrations. In this study, the dose predictions were tested by comparing predicted values of plasma concentrations with actual concentrations of 12 patients who were not initially involved with the development of the model.⁸¹

Adult priors from a population PD model were also used as the basis of initial dosing guidance in children for the low molecular weight heparin tinzaparin.⁸² In this setting, a Bayesian forecasting model was used as a guide in the dosing of a prospective study of which the objectives were to determine the once-daily dose of tinzaparin required in children to achieve anti-Xa levels of 0.5 to 1.0 IU/mL 4 hours postdose, to determine the PK of the dose of tinzaparin in children with thromboembolism that achieves plasma anti-Xa concentrations similar to adults being treated for thromboembolism, and to obtain some long-term safety data for therapeutic doses of tinzaparin in children with thromboembolism.⁸³ An additional outcome of this trial was the development of a pediatric dosing rule that extended from neonates to adolescents. Most important was the prospective use of modeling and simulation for the following purposes: (1) to examine the information content of the sampling scheme, (2) to examine the time to dose stabilization during the "adjustment" phase, and (3) to examine the sensitivity of the model to changes in both PK properties and the variation about such properties.⁸⁴

Bayesian forecasting can facilitate the evaluation of clinical trial performance metrics and possibly outcomes for a proposed model. With a real-time application of Bayesian forecasting, it is possible to extend this type of feedback to consider study designs that may change based on in-process results as in the tinzaparin example. Willis et al⁸⁵ recently presented the results of a Bayesian forecasting

Figure 4. FDA-proposed decision tree for the evaluation of pediatric populations.

approach to examine the predictive capacity of POPPK models developed from adult transplant patients receiving tacrolimus to explain the variation in pediatric liver and adult kidney transplant recipients. This work serves as a good example of the potential for discrepancy between the adult priors and the data obtained in pediatric patients. Although there were several reasons cited for the discrepancy between the observed and predicted results, the major finding was that the extension of the adult models to pediatrics was not reasonable because of the imprecision in the adult parameter estimates (ie, drug clearance, specifically). Hence, the evaluation of the “priors” against expectations (and actual observations, in this case) in the critically ill pediatric population is a necessary step in this process,

especially if we seek to propose that an actual clinical trial be conducted in children. Previous clinical trials performed in critically ill children have not fully taken into account all of the possible estimates of drug exposure response. For example, POPPK studies have identified covariates such as renal failure, hepatic failure, and concomitant administration of CYP3A inhibitors as important predictors of altered midazolam and metabolite PK in pediatric intensive care patients,⁸⁶ and yet significant unexplained variability exists, prohibiting the management of individual patients.

The FDA provides guidance with respect to pediatric clinical trials in the way of a flowchart for determining whether such trials need to be conducted (Figure 4), and, assuming they do, another flowchart is used to define the nature of

Figure 5. FDA-proposed criteria for dose adjustments in pediatric populations.

the trial design(s) to fulfill regulatory requirements, as well as the necessity of dose adjustment for pediatric subpopulations (Figure 5). Although the approach may be somewhat minimalistic and does not ensure the generation of meaningful dosing guidance, it is a means to encourage pediatric investigation and, as such, is a step in the right direction. With respect to the operating characteristics of the flowchart (Figure 4), it is strongly dependent on assumptions about drug action, dose-exposure relationships, and clinical outcomes. Ironically and despite the recent efforts of FDA in this area, the Pediatric Guidance remains in draft form.⁵ In a recent communication,⁸⁷ the FDA has implored pharmaceutical sponsors to develop new tools to “identify successful products and eliminate impending failures more efficiently and earlier in the development process.” The plea from the FDA in this area is based on a request that sponsors identify ways to bridge between the laboratory and the whole organism and correlate early markers of safety and benefit with actual outcomes in patients. A likely outcome of model-based approaches in pediatric investigation is the compilation of information (data, models, and experimental design constructs) that will constitute a pediatric knowledge base. The FDA has particularly focused on such approaches for pediatric research citing the following:

Although the results of each individual trial have been informative for the particular drug studied, a significant opportunity now exists for analysis of what has been collectively learned about the PK, PD, safety, and efficacy of drugs in children. Such an analysis could begin to build a knowledge base to better inform pediatric trials.

There is clearly a need to identify methods by which efficient and informative pediatric clinical trials can be per-

formed. A requirement for such methods should be that they yield results to improve the safety and efficacy of pharmacotherapy. Many drug candidates lack pediatric dosing guidelines for critically ill children, specifically. The application of CTS techniques to this area would seem to be timely and in the best interest of our children.

CONCLUSIONS

We reviewed in the present article 3 issues that are frequently raised during the design, conduct, and analysis of POPPK studies in pediatric populations. Size adjustments based on allometric or empiric approaches have both been used in POPPK analyses, but the allometric approach seems to be more mechanistically and physiologically based, whereas the empiric approaches are more a pragmatic tool to overcome large size differences in a study population without providing additional insight into other mechanistically based covariates affecting the PK of the studied drug.

Limited sampling designs are a frequently used feature in POPPK analysis in pediatric populations. Sufficient methodology is currently available to allow for the design of D-optimality based sampling schemes and validation of these schemes. Furthermore, reliable and unbiased results can be obtained using various Bayesian and nonlinear mixed-effects modeling approaches.

In many instances, empiricism is the basis on which the administration of drugs to pediatric populations proceeds. The pursuit of relationships between systemic exposure and both response and toxicity, specifically in pediatric populations, is, likewise, rational. Despite the empiricism associated with many agents, including cancer chemotherapy administration, progress has been made in the derivation of such relationships and models and has been shown to have an impact on outcome. More studies are definitely needed to improve pediatric pharmacotherapy. The integration of model-based techniques as a tool in these investigations would also seem to be both rational and necessary.

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REFERENCES

- Grasela TH, Sheiner LB, Rambeck B, et al. Steady-state pharmacokinetics of phenytoin from routinely collected patient data. *Clin Pharmacokinet.* 1983;8:355-364.
- Grasela TH Jr, Donn SM. Neonatal population pharmacokinetics of phenobarbital derived from routine clinical data. *Dev Pharmacol Ther.* 1985;8:374-383.

3. Kelman AW, Thomson AH, Whiting B, et al. Estimation of gentamicin clearance and volume of distribution in neonates and young children. *Br J Clin Pharmacol*. 1984;18:685-692.
4. Roberts R, Rodriguez W, Murphy D, Crescenzi T. Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. *JAMA*. 2003;290:905-911.
5. CDER/FDA. General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products – Draft Guidance. Rockville: Food and Drug Administration, Center for Drug Evaluation and Research, 1998.
6. Rajagopalan P, Gastonguay MR. Population pharmacokinetics of ciprofloxacin in pediatric patients. *J Clin Pharmacol*. 2003;43:698-710.
7. Chatelut E, Boddy AV, Peng B, et al. Population pharmacokinetics of carboplatin in children. *Clin Pharmacol Ther*. 1996;59:436-443.
8. Ette EI, Ludden TM. Population pharmacokinetic modeling: the importance of informative graphics. *Pharm Res*. 1995;12:1845-1855.
9. Ette EI, Williams P, Fadiran E, Ajayi FO, Onyiah LC. The process of knowledge discovery from large pharmacokinetic data sets. *J Clin Pharmacol*. 2001;41:25-34.
10. Bonate PL. The effect of collinearity on parameter estimates in nonlinear mixed effect models. *Pharm Res*. 1999;16:709-717.
11. Gusella M, Toso S, Ferrazzi E, Ferrari M, Padriani R. Relationships between body composition parameters and fluorouracil pharmacokinetics. *Br J Clin Pharmacol*. 2002;54:131-139.
12. Kanamori M, Takahashi H, Echizen H. Developmental changes in the liver weight- and body weight-normalized clearance of theophylline, phenytoin and cyclosporine in children. *Int J Clin Pharmacol Ther*. 2002;40:485-492.
13. Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? *Br J Clin Pharmacol*. 2004;58:119-133.
14. Mahmood I. Allometric issues in drug development. *J Pharm Sci*. 1999;88:1101-1106.
15. Bonate PL, Howard D. Prospective allometric scaling: does the emperor have clothes? *J Clin Pharmacol*. 2000;40:335-340.
16. Mahmood I. Interspecies scaling: predicting oral clearance in humans. *Am J Ther*. 2002;9:35-42.
17. West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. *Science*. 1999;284:1677-1679.
18. West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. *Science*. 1997;276:122-126.
19. Weibel ER. Physiology: the pitfalls of power laws. *Nature*. 2002;417:131-132.
20. Holford NH. A size standard for pharmacokinetics. *Clin Pharmacokinet*. 1996;30:329-332.
21. Anderson BJ, Woollard GA, Holford NH. A model for size and age changes in the pharmacokinetics of paracetamol in neonates, infants and children. *Br J Clin Pharmacol*. 2000;50:125-134.
22. Hu TM, Hayton WL. Allometric scaling of xenobiotic clearance: uncertainty versus universality. *AAPS PharmSci*. 2001;3:E29.
23. Boxenbaum H. Interspecies scaling, allometry, physiological time, and the ground plan of pharmacokinetics. *J Pharmacokinet Biopharm*. 1982;10:201-227.
24. Anderson BJ, McKee AD, Holford NH. Size, myths and the clinical pharmacokinetics of analgesia in paediatric patients. *Clin Pharmacokinet*. 1997;33:313-327.
25. Kleiber M. Body size and metabolism. *Hilgardia*. 1932;6315-6353.
26. McMahon T. Size and shape in biology. *Science*. 1973;179:1201-1204.
27. Anderson BJ, Holford NH, Woollard GA, Chan PL. Paracetamol plasma and cerebrospinal fluid pharmacokinetics in children. *Br J Clin Pharmacol*. 1998;46:237-243.
28. Agutter PS, Wheatley DN. Metabolic scaling: consensus or controversy? *Theor Biol Med Model*. 2004;1-13.
29. Darveau CA, Suarez RK, Andrews RD, Hochachka PW. Allometric cascade as a unifying principle of body mass effects on metabolism. *Nature*. 2002;417:166-170.
30. Rodman JH. Pharmacokinetic variability in the adolescent: implications of body size and organ function for dosage regimen design. *J Adolesc Health*. 1994;15:654-662.
31. Bailey JM, Hoffman TM, Wessel DL, et al. A population pharmacokinetic analysis of milrinone in pediatric patients after cardiac surgery. *J Pharmacokinet Pharmacodyn*. 2004;31:43-59.
32. Martin-Suarez A, Falcao AC, Outeda M, et al. Population pharmacokinetics of digoxin in pediatric patients. *Ther Drug Monit*. 2002;24:742-745.
33. Schaefer HG, Stass H, Wedgwood J, et al. Pharmacokinetics of ciprofloxacin in pediatric cystic fibrosis patients. *Antimicrob Agents Chemother*. 1996;40:29-34.
34. Christensen ML, Mottern RK, Jabbour JT, Fuseau E. Pharmacokinetics of sumatriptan nasal spray in children. *J Clin Pharmacol*. 2004;44:359-367.
35. Dubois D, Dubois E. A formula to estimate the approximate surface area if height and weight be known. *Arch Int Med*. 1916;17863-17871.
36. Gehan EA, George SL. Estimation of human body surface area from height and weight. *Cancer Chemother Rep*. 1970;54:225-235.
37. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317:1098.
38. Shi J, Ludden TM, Melikian AP, Gastonguay MR, Hinderling PH. Population pharmacokinetics and pharmacodynamics of sotalol in pediatric patients with supraventricular or ventricular tachyarrhythmia. *J Pharmacokinet Pharmacodyn*. 2001;28:555-575.
39. Sallas WM, Milosavljev S, D'Souza J, Hossain M. Pharmacokinetic drug interactions in children taking oxcarbazepine. *Clin Pharmacol Ther*. 2003;74:138-149.
40. Reilly JJ, Workman P. Normalisation of anti-cancer drug dosage using body weight and surface area: is it worthwhile? A review of theoretical and practical considerations. *Cancer Chemother Pharmacol*. 1993;32:411-418.
41. Yukawa E, Satou M, Nonaka T, et al. Pharmacoeconomic investigation of clonazepam relative clearance by mixed-effect modeling using routine clinical pharmacokinetic data in Japanese patients. *J Clin Pharmacol*. 2002;42:81-88.
42. Mandema JW, Verotta D, Sheiner LB. Building population pharmacokinetic-pharmacodynamic models. I. Models for covariate effects. *J Pharmacokinet Biopharm*. 1992;20:511-528.
43. Capparelli EV, Englund JA, Connor JD, et al. Population pharmacokinetics and pharmacodynamics of zidovudine in HIV-infected infants and children. *J Clin Pharmacol*. 2003;43:133-140.
44. Panetta JC, Iacono LC, Adamson PC, Stewart CF. The importance of pharmacokinetic limited sampling models for childhood cancer drug development. *Clin Cancer Res*. 2003;9:5068-5077.
45. Desoize B, Marechal F, Cattani A. Clinical pharmacokinetics of etoposide during 120 hours continuous infusions in solid tumours. *Br J Cancer*. 1990;62:840-841.

46. Kobayashi K, Ratain MJ. Pharmacodynamics and long-term toxicity of etoposide. *Cancer Chemother Pharmacol*. 1994;34(suppl):S64-S68.
47. Minami H, Ratain MJ, Ando Y, Shimokata K. Pharmacodynamic modeling of prolonged administration of etoposide. *Cancer Chemother Pharmacol*. 1996;39:61-66.
48. Relling MV, McLeod H, Bowman L, Santana VM. Etoposide pharmacokinetics and pharmacodynamics after acute and chronic exposure to cisplatin. *Clin Pharmacol Ther*. 1994;56:503-511.
49. Sonnichsen DS, Ribeiro RC, Luo X, Mathew P, Relling MV. Pharmacokinetics and pharmacodynamics of 21-day continuous oral etoposide in pediatric patients with solid tumors. *Clin Pharmacol Ther*. 1995;58:99-107.
50. Panetta JC, Wilkinson M, Pui CH, Relling MV. Limited and optimal sampling strategies for etoposide and etoposide catechol in children with leukemia. *J Pharmacokinet Pharmacodyn*. 2002;29:171-188.
51. Kirstein MN, Panetta JC, Gajjar A, et al. Development of a pharmacokinetic limited sampling model for temozolomide and its active metabolite MTIC. *Cancer Chemother Pharmacol*. 2005;55:433-438.
52. D'Argenio DZ. Optimal sampling times for pharmacokinetic experiments. *J Pharmacokinet Biopharm*. 1981;9:739-756.
53. D'Argenio DZ. Incorporating prior parameter uncertainty in the design of sampling schedules for pharmacokinetic parameter estimation experiments. *Math Biosci*. 1990;99:105-118.
54. D'Argenio DZ, Schumitzky A. *ADAPT II User's Guide: Pharmacokinetic/Pharmacodynamic Systems Analysis Software*. Los Angeles: Biomedical Simulations Resource; 1997.
55. Steimer JL, Mallet A, Golmard JL, Boisvieux JF. Alternative approaches to estimation of population pharmacokinetic parameters: comparison with the nonlinear mixed-effect model. *Drug Metab Rev*. 1984;15:265-292.
56. Retout S, Duffull S, Mentre F. Development and implementation of the population Fisher information matrix for the evaluation of population pharmacokinetic designs. *Comput Methods Programs Biomed*. 2001;65:141-151.
57. Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. *J Pharmacokinet Biopharm*. 1981;9:503-512.
58. Stewart CF, Iacono LC, Chintagumpala M, et al. Results of a phase II upfront window of pharmacokinetically guided topotecan in high-risk medulloblastoma and supratentorial primitive neuroectodermal tumor. *J Clin Oncol*. 2004;22:3357-3365.
59. Santana VM, Zamboni WC, Kirstein MN, et al. A pilot study of protracted topotecan dosing using a pharmacokinetically guided dosing approach in children with solid tumors. *Clin Cancer Res*. 2003;9:633-640.
60. Evans WE, Relling MV, Rodman JH, Crom WR, Boyett JM, Pui CH. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. *N Engl J Med*. 1998;338:499-505.
61. Wilson JT. An update on the therapeutic orphan. *Pediatrics*. 1999;104:585-590.
62. Lockwood PA, Cook JA, Ewy WE, Mandema JW. The use of clinical trial simulation to support dose selection: application to development of a new treatment for chronic neuropathic pain. *Pharm Res*. 2003;20:1752-1759.
63. Anderson JJ, Bolognese JA, Felson DT. Comparison of rheumatoid arthritis clinical trial outcome measures: a simulation study. *Arthritis Rheum*. 2003;48:3031-3038.
64. Blesch KS, Gieschke R, Tsukamoto Y, Reigner BG, Burger HU, Steimer JL. Clinical pharmacokinetic/pharmacodynamic and physiologically based pharmacokinetic modeling in new drug development: the capecitabine experience. *Invest New Drugs*. 2003;21:195-223.
65. Thall PF, Lee SJ. Practical model-based dose-finding in phase I clinical trials: methods based on toxicity. *Int J Gynecol Cancer*. 2003;13:251-261.
66. Hausheer FH, Kochat H, Parker AR, et al. New approaches to drug discovery and development: a mechanism-based approach to pharmaceutical research and its application to BNP7787, a novel chemoprotective agent. *Cancer Chemother Pharmacol*. 2003;52:1S3-1S15.
67. Konski A, Sherman E, Krahn M, et al. Monte Carlo simulation of a Markov model for a phase III clinical trial evaluating the addition of total androgen suppression (TAS) to radiation versus radiation alone for locally advanced prostate cancer (RTOG 86-10). *Int J Radiat Oncol Biol Phys*. 2003;57:S215-S216.
68. Jumbe N, Yao B, Rovetti R, Rossi G, Heatherington AC. Clinical trial simulation of a 200-microg fixed dose of darbepoetin alfa in chemotherapy-induced anemia. *Oncology (Huntingt)*. 2002;16:37-44.
69. Veyrat-Follet C, Bruno R, Olivares R, Rhodes GR, Chaikin P. Clinical trial simulation of docetaxel in patients with cancer as a tool for dosage optimization. *Clin Pharmacol Ther*. 2000;68:677-687.
70. Nestorov I, Graham G, Duffull S, Aarons L, Fuseau E, Coates P. Modeling and stimulation for clinical trial design involving a categorical response: a phase II case study with naratriptan. *Pharm Res*. 2001;18:1210-1219.
71. Chabaud S, Girard P, Nony P, Boissel JP. Clinical trial simulation using therapeutic effect modeling: application to ivabradine efficacy in patients with angina pectoris. *J Pharmacokinet Pharmacodyn*. 2002;29:339-363.
72. Holford NH, Kimko HC, Monteleone JP, Peck CC. Simulation of clinical trials. *Annu Rev Pharmacol Toxicol*. 2000;40:209-234.
73. Ette EI, Sun H, Ludden TM. Balanced designs in longitudinal population pharmacokinetic studies. *J Clin Pharmacol*. 1998;38:417-423.
74. Ette EI, Sun H, Ludden TM. Ignorability and parameter estimation in longitudinal pharmacokinetic studies. *J Clin Pharmacol*. 1998;38:221-226.
75. Fernandez de Gatta MM, Tamayo M, Garcia MJ, et al. Prediction of imipramine serum levels in enuretic children by a Bayesian method: comparison with two other conventional dosing methods. *Ther Drug Monit*. 1989;11:637-641.
76. Kraus DM, Dusik CM, Rodvold KA, Campbell MM, Kecskes SA. Bayesian forecasting of gentamicin pharmacokinetics in pediatric intensive care unit patients. *Pediatr Infect Dis J*. 1993;12:713-718.
77. el Desoky E, Ghazal MH, Mohamed MA, Klotz U. Disposition of intravenous theophylline in asthmatic children: Bayesian approach vs direct pharmacokinetic calculations. *Jpn J Pharmacol*. 1997;75:13-20.
78. Lares-Asseff I, Lugo-Goytia G, Perez-Guille MG, Flores-Perez J, Juarez-Olguin H, Raquel Moreno MA. Cefuroxime Bayesian pharmacokinetics in severely ill septic children. *Rev Invest Clin*. 1998;50:311-316.
79. Lares-Asseff I, Lugo-Goytia G, Perez-Guille MG, et al. Bayesian prediction of chloramphenicol blood levels in children with sepsis and malnutrition. *Rev Invest Clin*. 1999;51:159-165.

80. Wrishko RE, Levine M, Khoo D, Abbott P, Hamilton D. Vancomycin pharmacokinetics and Bayesian estimation in pediatric patients. *Ther Drug Monit.* 2000;22:522-531.
81. Bressolle F, Gouby A, Martinez JM, et al. Population pharmacokinetics of amikacin in critically ill patients. *Antimicrob Agents Chemother.* 1996;40:1682-1689.
82. Barrett JS, Gibiansky E, Hull RD, et al. Population pharmacodynamics in patients receiving tinzaparin for the prevention and treatment of deep vein thrombosis. *Int J Clin Pharmacol Ther.* 2001;39:431-446.
83. Andrew MV, Mitchell DJ, Barrett JS, Hainer JW. Design aspects of dose-finding trials in pediatric patients with severe TE: Tinzaparin pediatric study [abstract]. *Thromb Hemostasis.* 2001;86.
84. Gastonguay MR, Gibiansky E, Gibiansky L, Barrett JS. Optimizing a Bayesian dose-adjustment scheme for a pediatric trial: a simulation study. In: Kimko HC, Duffull SB, eds. *Simulation for Designing Clinical Trials.* New York: Marcel Dekker; 2002;369-390.
85. Willis C, Staatz CE, Tett SE. Bayesian forecasting and prediction of tacrolimus concentrations in pediatric liver and adult renal transplant recipients. *Ther Drug Monit.* 2003;25:158-166.
86. de Wildt SN, de Hoog M, Vinks AA, van der Giesen E, van den Anker JN. Population pharmacokinetics and metabolism of midazolam in pediatric intensive care patients. *Crit Care Med.* 2003;31:1952-1958.
87. CDER/FDA. *Innovation and Stagnation: Challenge and Opportunity on the Critical Path to New Medicinal Products.* Rockville, MD: Food and Drug Administration, Center for Drug Evaluation and Research, 2004.
88. Schwartz GJ, Haycock GB, Spitzer A. Plasma creatinine and urea concentration in children: normal values for age and sex. *J Pediatr.* 1976;88:828-830.