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Tailor-made drug treatment for children Creation of an infrastructure for data-sharing and population PK–PD modeling

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Rational dosing guidelines for drugs in pediatrics are urgently needed. To develop these guidelines, we use population pharmacokinetic–pharmacodynamic (PK–PD) modeling and simulation by: (i) optimization of clinical trial designs based on preliminary data; (ii) development and internal validation of population PK–PD models using sparse data; (iii) external validation using independent data; and (iv) prospective clinical evaluation. Optimized dosing regimens for specific drugs may then serve as a basis to develop dosing guidelines for existing or newly developed drugs with similar disposition and/or effect. In addition to modeling of drug disposition (PK) pathways, we emphasize the need for modeling of effect (PD) pathways and the use of a multidisciplinary infrastructure for data-sharing.

Problem definition for medicines in children: role of the dose

Well-known differences exist in disposition of, and response to, drugs between children and adults and between children of different ages [1]. Yet, because well-designed clinical studies in children are scarce, dosing schemes in children are usually derived in an empirical manner from clinical trials in healthy volunteers and/or restricted adult patient groups, and often based on a linear extrapolation on the basis of bodyweight [2]. To account for differences in drug disposition and/or drug response between children of different ages, higher or lower dosages per kilogram bodyweight are regularly recommended in different age groups. The scarcity of dedicated studies in children is explained by the ethical, practical and financial constraints of clinical trials in this patient population [1,3,4].

At present, approximately 70% of drugs prescribed to children in general, and more than 93% of drugs prescribed to critically ill neonates, are unlicensed or used in an off-label manner [5–7]. As a result, therapeutic failure, adverse events and sometimes, even fatalities may occur. Examples are chloramphenicol causing the grey baby syndrome [8] and the intravenous formulation of vitamin E causing the death of 38 neonates [9]. Neonates receiving a combination of penicillin and sulphisoxazole had a significantly higher mortality than those receiving oxytetracycline [10]. Also, the drug interactions of commonly used drugs in children may be unknown. Only recently, the concomitant administration of ceftriaxone and calcium has been reported to cause fatal reactions in the lungs and kidneys in neonates (see: http://www.fda.gov/cder/drug/InfoSheets/HCP/ceftriaxone.html; http://www.rocheusa.com/products/rocephin/rocephin-hcp-letter.pdf). These, and other, unknown reactions to drugs in children have important implications for the efficacy and/or safety of pharmacotherapy in this population. This lack of information is a problem not only for clinicians but also for the pharmaceutical industry. Given the new Paediatric Law, which has come into force in Europe in 2007, the information on drug disposition and effect in children is of great importance because, already at the end of Phase I of the development of a new drug, a pediatric investigational plan (PIP) has to be submitted to the European

regulatory authorities (EMEA). With a final reward for this effort of a six-month patent extension and because the studies in children are now a prerequisite for labeling of drugs in Europe, more information and guidance to develop dosing guidelines for drugs used in children is of great value.

What information in children is needed?

Instead of an empiric-dosing regimen based on bodyweight alone, pediatric dosing regimens should be based on an understanding of the pharmacokinetic–pharmacodynamic (PK–PD) relationship of the drug in children. Therefore, to define effective and safe dosing regimens for children of different ages, detailed information is needed on the PK (the drug-concentration versus time profile) and the PD (the drug-concentration versus effect relationship and the time-dependent transduction mechanism that governs the time course of the response) [11].

Both the PK and PD may change over the continuum of a child's life [1]. Age-related differences in PK may be caused by the differences in absorption, distribution, metabolism and/or excretion [1]. For example, profound developmental changes in the activity of the isoforms of drug metabolizing enzyme CYP3A have been shown to occur in the neonatal period and through infancy [12]. Also, the developmental changes in renal function can dramatically alter the plasma clearance of compounds with extensive renal elimination [1]. For example, ceftazidime, which is excreted primarily by the glomeruli, shows a plasma drug clearance that correlates with maturational changes in renal function [13]. The differences in PD can be caused by different pathogenesis in children compared to adults [14]. They can also result from age-related changes in receptor expression causing differences in target tissue sensitivity and age-related changes in the function of *in vivo* transduction and homeostatic feedback mechanisms governing the intensity of the response [1]. For example, children appear to respond differently to adults to antihypertensive drugs [15], despite similar PK in the age-range studied. Traditionally, the studies on PD have received less attention than PK studies, although it is generally accepted that the variability in PD is much larger than the variability in PK [16]. Although there is a lack of validated PD endpoints in children, it is of utmost importance to study the PD relation in children as well. Clinical trials in children should therefore consider age-related variability in PK and PD simultaneously, to be able to develop rational dosing schemes [1].

In practice, this age-related variability in PK and/or PD must be considered in the context of all other sources of intra- and inter-individual variability resulting from genetic-, environmental- and disease-related factors and drug interactions [1]. For example, the role of pharmacogenetic (PGx) factors on treatment effect or PK should not be evaluated independently, but should be studied together with all other clinical covariates [17]. In a recent example on CYP2D6 polymorphisms in newborns, the influence of age, body weight and CYP2D6 polymorphisms classified as 2D6 activity score were simultaneously investigated. Each of the three variables was shown to affect the formation of tramadol to its main metabolite significantly [18,19], with size and age as major contributors to the variability (52.7%) while CYP2D6 activity score contributes 6.4% to this variability [18]. In our opinion, this study provides a sophisticated example on how to study

different covariates such as age-related and genetic factors in a quantitative manner.

Recently, Alcorn *et al.* identified population PK, allometric scaling and physiologically based clearance scaling models as principal approaches to estimate pediatric systemic clearance in the absence of comprehensive age-group-specific data [20]. In addition to modeling of drug disposition (PK) pathways, we emphasize that a similar approach for modeling of effect (PD) pathways should be undertaken to predict expected effects and safety over the developing age continuum.

How should this information be gathered?

Properly designed studies in children aiming at the development of PK–PD models are difficult to perform. Specific challenges are not only the availability of limited patient numbers but also ethical and practical restrictions to the volume and frequency of blood sampling and the number of PD observations, particularly in neonates. Modern technologies involving sampling and laboratory analyses have, however, been developed and can be used in pediatric populations. LC–MS/MS, for example, is highly sensitive and allows the use of very small volume samples for drug-concentration analyses [21]. Also, the use of saliva to monitor drug concentrations noninvasively [22], the use of dried blood spots from heel-prick samples [23] and the use of breath tests to study drug metabolism are examples of methods that may facilitate drug studies in children [24]. In addition to these novel approaches, the application of the so-called 'population approach' opens new avenues for drug studies in children. Population PK–PD modeling involves the application of concepts of 'non linear mixed effects modeling', where PK and/or PD parameters are simultaneously estimated in all individuals. The final results are population PK and/or PD parameters and estimates for the interindividual variability (variance) as well as intraindividual variability or residual error (variance). Following this characterization of the variability in PK and PD, the next step is the so-called covariate analysis, in which demographic and pathophysiologic (e.g. weight, age, liver and kidney function, disease severity and genetics) predictors of the variability are identified. If these predictors are associated with clinically significant shifts in the therapeutic index, they may serve as the basis for the design of individualized dosing schedules.

The most important advantage of the population approach is that it allows for the utilization of infrequently obtained samples and observations from actual patients at time points compatible with clinical care, rather than in a specific experimental setting. The approach allows for the analysis of relatively dense data, combinations of sparse and dense data or combinations of observations from experimental settings and clinical practice. Moreover, because the population approach is able to handle 'missing data' in individual patients, it greatly facilitates PK and/or PD studies in young children [23]. Finally, this approach ensures that the obtained information can indeed be directly applied in clinical practice and that the burden to the individual patient can be kept to a minimum [25].

Role of modeling and simulations in pediatric clinical dosing studies

The development of evidence-based dosing schedules using population PK–PD modeling involves several steps (Fig. 1). First, for the

design of novel prospective clinical trials, the amount and quality of existing data from the literature or databases from industry or regulatory authorities need to be considered. These data are preferably obtained not only from children of the same age, but also from other age groups, from adults or even *in vitro* data (e.g. from the population-based PK modeling and simulation program SIM-CYP^{TM} that includes extensive *in vitro* libraries [26]) may be considered. These preliminary data are then used to simulate the concentration and effect versus time profiles and their variability in the (individual) patients in the trial. The simulations allow for the determination of an optimal sampling scheme, thereby minimizing the burden for the individual child and, at the same time, ensuring maximum information content. For example, a population PK model was developed by Rubino *et al.* [27] to describe the PK of gatifloxacin in children, for which data of an existing study were used [28]. The developed model can be used to estimate exposure in future studies and to perform simulation experiments for defining appropriate dosing regimens as well as to evaluate the comparative utility of anti-infective agents [27].

Second, on the basis of data of the prospective clinical trial alone, or in combination with data obtained retrospectively from clinical practice, the population PK–PD models are developed (Fig. 1). In general, when building a PK and/or PD model, the first step is the identification of a structural model (e.g. a two-compartment model for the PK or an E-max model to characterize the concentration–effect relationship). The next step is the development of a statistical model to describe the interindividual as well as residual variability (e.g. log-normal distribution of PK-parameters). The final step is the exploration of the influence of covariates on the values of the PK and/or PD parameter, such as body weight, age and renal function, where they are incorporated in the model as predictors with potential clinical relevance [29,30]. Because the three submodels are interrelated, the choice of the structural (and statistical) model may affect the choice of covariate model and vice versa. The process of finding a model that adequately describes the data is thus an elaborate task, where model refinement/checking is performed in several steps [11,31,32]. As an example for this step, we discuss a study where Peeters *et al.* used nonlinear mixed effects modeling to develop a model for dose estimations of propofol in nonventilated children after major surgery [29]. In that study, the choice of the structural model was made by a comparison of the objective function. In addition, the diagnostic plots for examining

bias and precision, the confidence interval of the parameter estimates, the correlation matrix and visual improvement of the individual plots were used to evaluate the model. This resulted in a two-compartment model for the PK and a simple E-max model for the PD relationship. The interindividual variability was best characterized by a log-normal model for the parameters. Thereafter, in the covariate model, covariates such as body weight, age, body surface area and body mass index were plotted independently against the individual post hoc parameter estimates and the weighted residuals to identify their influence. Body weight incorporated as a power function was found to be a significant covariate for elimination clearance, thereby reducing the interindividual variability (CV%) in clearance from 27% to 20%, which further refined the models.

An important issue is the validation of population PK–PD models. This concerns the internal validation, the external validation, the prospective validation and ultimately the cross-validation. Cross-validation tests the ability of the PK–PD model to predict the disposition and effect of drugs that share similar PK and/or PD pathways. Although it was recently reported that only 17% of published pediatric PK and PD models are validated [33], we believe that all models should be at least fully internally validated. This includes the presentation of not only standard diagnostic measures, such as model-predicted versus observed plots, but also the results of advanced internal modeling, such as bootstrap resampling, visual predictive checks or normalized prediction discrepancy errors (NPDE) [34] (Fig. 1). In our example, Peeters *et al.* used a bootstrap resampling method, which involves repeated random sampling to produce another dataset of the same size but with a different combination of individuals, to assess the stability of the parameter estimates and the robustness of the final model. Although not always feasible owing to a lack of pertinent data, external validation is important to address the accuracy of a model in patients from a different but plausibly-related population [35,36]. The methodology of external validation is technically similar to internal validation [37]. The model-based individualized dosing regimens that result from the internally and also externally validated population PK–PD model should be evaluated in a prospective clinical trial. Although not performed in the study of Peeters *et al.* [30] the PK–PD model based dosing regimen can be tested in such a prospective clinical trial, to evaluate whether the proposed dosing regimen indeed leads to the expected concentrations and/or effects, which
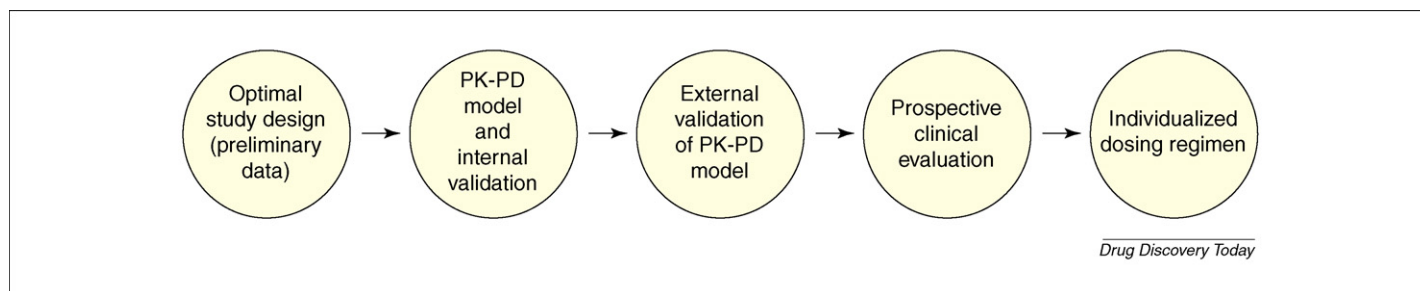

FIGURE 1

Proposed multi-step approach for modeling and simulation using nonlinear mixed effects modeling for the optimization of drug dosing in children. The four steps that are proposed are (1) optimization of clinical trial designs based on simulations using preliminary data; (2) development and internal validation of population PK–PD models using sparse data; (3) external validation of the population PK–PD models using independent data; and (4) prospective clinical evaluation of the PK–PD model based dosing regimen. PK, pharmacokinetics; PD, pharmacodynamics.

finally results in refining the dosing regimen for specific individuals in this population if needed. After these prospective trials, individualized dosing schemes will lead to a predictable efficacy and safety profile for each child of a certain age, bodyweight and genetic background.

Mechanism-based PK–PD modeling in children

Obviously, if this approach needs to be applied to every single drug in pediatrics, large costs and significant time will be needed to develop evidence-based dosing schedules for each drug. An intriguing question is, to what extent does a mechanism-based PK–PD model constitute a basis for the development of dosing guidelines for drugs other than those that have actually been studied? A pertinent feature of mechanism-based PK–PD models is the strict distinction between drug-specific and biological system-specific parameters to characterize the time course of the drug effect [38]. In this respect, the kinetics of age-related changes in renal function, the functionality of drug metabolizing enzymes, drug transporters, as well as the expression function of pharmacological receptors, are patient-specific or biological system-specific properties. These system-specific properties, derived from one 'model' drug, could in principle serve as a basis for the prediction of age-related changes in the PK and PD of other drugs (the so-called cross-validation). Using simulations for drugs other than those used to generate biological system-specific information may significantly reduce the time and costs needed to develop drug-dosing guidelines for individual drugs. For example, because CYP3A is involved in the metabolism of many clinically prescribed drugs [12], the developmental pattern of CYP3A activity can be studied *in vivo* using surrogate marker drugs that are specific for these pathways [4]. Similarly, because the renal elimination of drugs in children is dependent on the maturation of physiological parameters such as renal blood flow, glomerular filtration and renal tubular function, an approach to model the age-dependent changes in renal clearance using a surrogate marker drug such as ceftazidim, which is almost completely renally eliminated [39], may provide a good basis for the estimation of renal drug clearance in pediatric populations [20]. Next, the information gained from these 'model' drugs, may be used for the development of evidence-based dosing regimens for other drugs sharing similar pathways [38]. Using this approach, however, different potential limitations should be considered. An example is the use of a population PK model for CYP3A activity that is developed using midazolam as a model drug, for cross-validation to the immunosuppressant tacrolimus, which is also a substrate for CYP3A. Because tacrolimus is not only a CYP3A substrate but also a substrate for the P-glycoprotein (Pgp), the use of this model can result in misleading estimations. Additionally to the use of accessory pathways of the new drug compared to the drug that was used to build the model, the differences in receptor affinity of the different drugs should be taken into account, when developing dosing or sampling schemes using models that have been developed using a similar acting drug. Despite these limitations, however, we believe that cross-validation should at least be further explored to determine the exact value of this type of approach, because such an approach will significantly decrease the burden to the pediatric population.

Our approach in practice: current project in the Netherlands

In the Netherlands, a multidisciplinary research platform on mechanism-based population PK–PD modeling for the design of individualized dosing regimens in children has been established. Partners in this platform comprise four academic institutions and six leading international pharmaceutical industries (http://www.tipharma.com). The platform operates on the basis of a so-called 'matching fund' principle, which implies that the academic institutions and the industries each provide 25% of the budget; the Dutch government provides the other 50%.

The platform has a unique infrastructure for sharing anonymized data in a secure environment. There is restricted access for authorized investigators and there are extensive data checks and strict data management rules created for each research project (Table 1). This allows for data-sharing needed for initial analyses (step 1), and also for external validation or cross-validation of developed models. This data-sharing of existing data and potential data of newly developed drugs or studies does not only account for academia but also for the (competing) industry. In the platform, the supervision of the modeling is provided by academia and industry and the final population PK–PD models will be available for all partners.

Concluding remarks

In conclusion, we propose the use of population PK–PD modeling and simulation to develop evidence-based dosing schemes for children, with the ultimate goal to improve drug safety and efficacy in this population. This approach will allow for sparse sampling in children and reduce the burden for the individual child. The PK–PD data analyses of our platform will result in novel paradigms not only for individualized dosing in children but also

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TABLE 1

Main objectives for data management.

1. Data upload from academia and industry	(a) Proposal data handling (access restrictions)
	(b) Anonymized raw dataset
2. Data handling with tracking	Checking and validation of dataset (controlling and organizing data)
3. Data merge with tracking	Merge of validated anonymized raw datasets
4. Population PK–PD modeling	Model building
	(a) Experimental model + parameters
	(b) Finalized model + parameters
5. Data extraction	(a) Model + parameters
	(b) Report consisting of project proposal data handling finalized models + parameters

allow for the characterization of the biological system, by a distinction between drug-specific and system-specific determinants of drug effect. Ultimately, each 'model drug', reflecting specific developmental drug disposition and effect pathways, can then be used as a scientific basis to develop evidence-based dosing regimens for other existing or newly developed drugs, sharing the same pathways. In addition to modeling of drug disposition (PK) pathways, we emphasize the need for modeling of effect (PD) pathways and the use of a multidisciplinary infrastructure for data-sharing.

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