Chapter 6
Population Pharmacokinetics in Pediatric Drug Development

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6.1 Introduction

Pediatric product development initiatives in the United States have resulted in improved product labeling, increased identification of adverse events, and development of new pediatric formulations. However, a substantial number of pediatric trials have failed to establish either safety or efficacy, leading to an inability to label the product for use in children. An important consideration is drug dosing with resulting inadequate drug exposure, which was found to be a possible contributing factor to pediatric trial failures in nearly a quarter of failed pediatric drug development programs reviewed by the US Food and Drug Administration (FDA) between 2007 and 2014 [1]. A number of scientific tools are now being applied in pediatric drug development to improve pediatric dosing and increase the success rate of pediatric trials. Population pharmacokinetics (POPPK), broadly defined as the quantitative approach to describe pharmacokinetic (PK) data and identify and characterize sources of variability in drug disposition, is one such tool that has made a significant contribution to understanding PK and drug exposure linked to clinical outcomes in the pediatric patient population. POPPK is a robust tool that can handle sparse and

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unbalanced PK data, which is common in pediatric studies secondary to the logistical and ethical considerations of studying drugs and biologics in children. Additionally, the pediatric population is highly diverse with respect to body size, renal and metabolic maturation, and hormonal status, and the population approach can be used to understand how these factors impact variability in drug disposition and response. The objective of this chapter is to provide an overview of POPPK in pediatric drug development.

6.2 Regulatory Considerations for Pediatric PK Studies

The pediatric drug development approach for regulatory approval and dosing recommendations depends upon evidence-based assumptions regarding disease progression, response to intervention, and exposure-response relationships [2]. A thorough understanding of pharmacokinetics in the pediatric population allows researchers and drug developers to make rational dosing decisions to optimize patient outcomes. The relationship between concentration and pharmacodynamic effect must be either characterized directly or extrapolated from adults. In instances where full extrapolation of efficacy is applied, such as when the disease progression, response to intervention, and exposure-response relationships are expected to be similar between adults and pediatrics, the goal of the pediatric PK study should be to sufficiently characterize PK in order to design a regimen that matches adult drug exposure in the pediatric population of interest. This approach is practically more straightforward because, as discussed by Anderson and Holford, far more research is available on pediatric pharmacokinetics than pharmacodynamics [3]. HIV infection is one therapeutic area that has used this pathway, as the effectiveness of antiretroviral drugs for HIV infection can be extrapolated from adequate and well-controlled studies in adults when supplemented with safety and pharmacokinetic studies conducted in children [4]. In many situations, a reasonable assumption can be made that exposure-response relationships will differ between adults and pediatrics. Examples include antihypertensives [5] or anti-infectives in neonates (immune-compromised, by definition) where drug exposure may need to be greater than in adults in order to achieve similar clinical outcomes. In these situations, pediatric studies should aim to characterize both the PK parameters and the PK-PD relationship to support dose selection [2]. In all cases, pediatric PK studies should be designed by taking into account all available information, such as knowledge about the drug's PK in adults, experience with products in the same class or with a similar elimination pathway, and PK studies that have been conducted in other age groups or for different indications. Meibohm et al. have reviewed the importance of prior adult data on PK parameter estimation in pediatrics and point out that priors greatly influence the fit of a pediatric POPPK model [6].

As discussed in FDA's Guidance for Industry on General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, the two common approaches used to obtain PK information are a traditional noncompartmental analysis and a population analysis [7]. A dedicated traditional PK study with rich sampling (>8 samples) in a relatively small number of patients after a single dose or multiple doses is often conducted as the first study. Noncompartmental analysis can be used to provide preliminary estimates of PK parameters such as clearance (CL) and volume of distribution (V) for subsequent POPPK analyses. In some cases, traditional PK studies may not be necessary because of the limited value of data generated. For example, in adolescent patients (12–16 years of age), PK parameters can be reasonably estimated from adults using weight-based scaling approaches [7]. A recent study showed that for 27 drug products, prediction of drug clearance in adolescents using allometric scaling resulted in a mean absolute percentage error (MAPE) of 16.7 and 17.1 % for IV drugs and oral drugs, respectively [8]. Further, because actual adolescent clearance averaged 93.2 % of adult values for the drugs studied, the same doses are approved for the vast majority of these products [8]. Traditional PK studies may also be impractical due to blood sampling limitations in vulnerable populations like neonates. Regardless of whether initial PK parameters are obtained from prediction or a traditional noncompartmental PK study, POPPK can be applied to sparse PK samples obtained from later efficacy and/or safety studies in order to estimate population and individual means, intra- and inter-subject variability, and the impact of covariates. Data are evaluated using nonlinear mixed-effects modeling, meaning that drug or metabolite concentrations are not necessarily related to model parameters in a linear fashion.

6.3 Considerations for Pediatric POPPK Study Design and Analysis

The goal of PK studies for both adults and pediatrics is to obtain information on drug absorption, distribution, metabolism, and elimination (ADME) and to identify sources of variability in these processes. For pediatrics, important considerations include the ontogeny of drug-metabolizing enzymes and transporters, growth characteristics, genetics, and other covariates that affect drug disposition, such as liver and kidney function. These unique aspects make children physiologically different from adults and can affect the ability to predict PK based solely on adult data. For example, predictions based on scaling by body weight alone are unlikely to provide accurate predictions in the youngest children (e.g., neonates and infants) due to differences in the expression of enzymes and transporters. For example, hepatic CYP3A7 expression is higher than CYP3A4 at birth until at least 6 months of age [9]. Considerations for the design of analysis of pediatric POPPK studies are discussed below.

6.3.1 Study Design

6.3.1.1 Sample Size

Pediatric research must be conducted within the ethical framework of scientific necessity and sample size for PK studies must be derived to conform to those considerations. These pediatric subject protection requirements are driven by Subpart D of 21 CFR 50, which provides additional safeguards for children in clinical research. FDA has proposed one such approach to derive the sample size for pediatric PK studies, which prospectively targets a 95 % confidence interval within 60 and 140 % of the geometric mean estimates for clearance and volume of distribution in each pediatric age subgroup with at least 80 % power. These precision criteria, which are applicable to both noncompartmental analysis and POPPK study designs, propose a simulation-based approach to justify the sample size for pediatric studies [10]. Alternate approaches to justify the size of pediatric PK studies can be considered. In the setting of pediatric drug development, the sample size is an important topic of consideration for pediatric Written Requests under the Best Pharmaceuticals for Children Act (BPCA), such that a sponsor must enroll the specified number of patients in order to meet the terms of the Written Request and receive additional patent exclusivity.

6.3.1.2 Sampling Scheme and Innovative Sampling Approaches

The timing of sparse samples obtained in clinical trials can bias estimates of PK parameters and therefore the sampling scheme should be carefully considered in order to design studies that are as informative as possible. For example, if samples are obtained too late after a dose is given, the disposition from the first compartment can be missed. Unnecessary samples that are below the limit of quantification for the assay can also be avoided by performing preliminary simulations. Several methods to derive optimal sampling are available and will not be reviewed here [11].

Two innovating sampling approaches being utilized for the pediatric population are scavenged sampling and dried blood spots [12]. Scavenged sampling accompanied by POPPK is a relatively new approach to obtain PK data in vulnerable pediatric populations, particularly neonates. This approach measures drug concentrations in residual blood or plasma left over from samples taken for other tests within the scope of routine clinical care. As discussed by Laughon et al., scavenged sampling offers several advantages, including avoiding vascular puncture specifically for PK sampling allowing for higher rates of parental consent [13]. Potential disadvantages include drug stability problems associated with inappropriate sample storage and inaccurate recording of sample collection time. Small volumes of residual blood or plasma may also be problematic for drug assays, although the use of more sensitive analytical techniques, such as mass spectrometry, may overcome this challenge.

Recent investigations employing scavenged sampling with population pharmacokinetics have successfully characterized the PK of metronidazole [14], piperacillin [15], and fluconazole [16] in preterm infants.

Dried blood spots (DBS) have been used as an alternative to plasma or whole blood to characterize the PK of several drugs in pediatric patients [17–19]. The primary advantage of DBS in pediatric PK studies is that only micro-blood volumes are required (≤50 μL), which are collected into capillary tubes and spotted directly onto filter paper for analysis [20]. DBS-based techniques have shown accuracy and precision comparable to assays using large volumes of plasma [21]. When combined with POPPK, this approach is well-suited for pediatric populations that are traditionally difficult to study due to blood sample volume limitations, such as neonates and preterm infants. For example, a recent study reported the use of DBS to characterize the POPPK of metronidazole in preterm infants undergoing treatment or prophylaxis for necrotizing enterocolitis [18]. The derived PK model allowed for the design of specific dosage recommendations for the management of anaerobic infections associated with the disease in this population. Although the regimen requires prospective validation, this study offers valuable PK information for a drug that is commonly used in neonatal intensive care units on an empiric basis. However, as discussed by Rowland and Emmons, important considerations exist for the use of DBS in PK studies, and particular attention should be paid to the distribution kinetics of the drug of interest within whole blood [22]. For drugs with a high variability in either the fraction unbound in plasma or the blood cell-to-unbound plasma concentration ratio, caution should be exercised when using DBS as an alternative to plasma. In addition, the stability of drugs on the filter paper matrix of the DBS (including temperature-related stability), needs to be considered when assessing reliability compared with plasma sampling.

6.3.2 POPPK Analysis

6.3.2.1 Body Size

The pediatric population is extremely diverse with respect to body size. A study that includes patients across the pediatric age continuum from birth to adolescence will include a very broad range of body weights, which is in contrast to many adult studies where the weight of the smallest size individual often does not differ by more than onefold from the largest size individual. Weight can reflect the development of organ systems involved in drug disposition and therefore often exhibits a high degree of colinearity with other covariates such as indices of renal or hepatic function. The correlation between weight and other predictor variables may bias PK parameter estimates if both are included in the model simultaneously [23]. For this reason, a priori size adjustments are common for pediatric POPPK analyses prior to evaluation of secondary covariates. Size adjustments are often performed using an allometric power model where the coefficient may be either fixed (e.g., 0.75 for

clearance, one for volume of distribution) or estimated. The use of fixed exponents was derived empirically but has been supported by the relationship between physiologic variables and animal size across species. A number of readings are available for the origin, application, and limitations of the power law [24–32]. The allometric scaling approach dictates 0.75 power for clearance and a linear relationship (raised to the power of 1.0) for volume of distribution, as follows:

$$\mathrm{CL_i} = \mathrm{TVCL} \times \left(\frac{\mathrm{WT_i}}{\mathrm{StdWT}} \right)^{0.75}$$

and

$$V_\mathrm{i} = \mathrm{TVV} \times \left(\frac{\mathrm{WT_i}}{\mathrm{StdWT}} \right)$$

where $\mathrm{CL_i}$ and V_i are clearance and volume of distribution estimates in an individual, TVCL and TVV are typical values of estimates or estimates for an individual with body weight (WT) that equals the standardized weight (StdWT). Some of the reasons to include the standardized weight are the numerical stability and ease of interpretation of typical values. Using median weight or an average weight of 70 kg have both been used in modeling pediatric data.

In some cases, allometric scaling with a fixed exponent of 0.75 does not adequately describe the apparent observed relationship between clearance and body weight. For this reason, some researchers have used empirical body weight adjustment either by estimating the exponent or assuming a linear relationship between clearance and body weight. The underlying true relationship between clearance and size may possibly be dictated by allometric scaling and through the influence of a confounder, and consequently the apparent relationship does not conform to basic expectations. Some investigators have argued that allometric scaling with an estimated rather than fixed allometric coefficient more accurately predicts PK for some drugs [33, 34].

6.3.2.2 Age

In general, it is preferable to incorporate size as an initial covariate prior to evaluating additional covariates to explain variability. Age may be an important secondary covariate for pediatric POPPK analyses because it is linked to maturation of clearance pathways, such as hepatic cytochrome P450 expression or development of renal filtration and secretion. Others have argued that the requirement for age in pediatric POPPK analyses is due to the use of fixed exponents rather than direct estimation of the allometric exponent [35, 36]. For example, Wang et al. report that the scaling of propofol clearance with a fixed exponent of 0.75 is inferior to estimation of the allometric exponent [37]. The limitation of this approach is that the

effects of growth (weight) and maturation (age) on pharmacokinetic parameters cannot be separated [38]. Separation of these factors is particularly important when considering the youngest pediatric patients (neonates and infants) in whom dramatic development is taking place that cannot be accounted for by weight alone. For instance, from a pharmacokinetic point of view, a premature infant will likely be different than a full-term infant of the same body weight due to differences in the maturation of clearance pathways. Incorporation of age into the POPPK model can therefore help to optimize dosing recommendations in these circumstances. The type of model best suited to describe maturation as a function of age depends largely on how wide of an age range is included in the data. A linear model is appropriate for a narrow age range while an exponential model often better describes clearance over a wide age range (e.g., birth through adolescence) [38]. When modeling age as a potential covariate in young patients, it is also useful to separately evaluate gestational age (conception until birth), postnatal age (chronological age since birth), and postmenstrual age (gestational age plus postnatal age). When more than one of these covariates is significant for clearance or volume, a forward-addition, backward-elimination approach can be used to refine the model. For example, a recent study of fluconazole pharmacokinetics in premature infants found that postmenstrual age performed better than either gestational age or postnatal age alone as covariates for clearance [39]. It is also important to consider which age definition will be easiest to integrate into practical dosing guidelines for clinical practice. A study of ampicillin POPPK included postmenstrual age in the final PK model, although dosage recommendations were stratified by gestational age and postnatal age, similar to dosing recommendations in the past, in order to simplify dosing for clinicians [40].

The inclusion of POPPK into neonatal trials has become more pertinent since the FDA Safety and Innovation Act (FDASIA), which places emphasis on studying the neonatal population. Prior to FDASIA, less than 6 % of over 400 FDA label changes related to pediatric information involved neonates and less than 1 % of greater than 120,000 trials listed on clinicaltrials.gov involved neonates. Traditional densely sampled PK studies are virtually impossible to perform in these patients. However, POPPK is one of the tools that will allow for the successful inclusion of neonates in pediatric drug development studies.

6.3.3 Physiologically Based PK (PBPK) Modeling

Physiologically based PK (PBPK) modeling is used to build models from the basic principles of physiology and can incorporate knowledge of drug-specific parameters from in vitro studies, phase 1 adult studies, and anatomical and physiological changes in pediatric populations [41]. The complexity of these models can make it challenging to use within a population-based framework [42]. While it may be logical to attempt to use these complex model-based approaches for study design and initial dose selection, evidence has yet to be developed that these approaches are better able to predict exposures and resulting outcomes than conventional approaches

such as simulation using a POPPK model derived from adults with allometric scaling [43]. This would be particularly true in the older pediatric populations where there are fewer problems with the accuracy of allometric scaling.

6.4 Future Challenges and Application of POPPK

Prior to FDASIA in 2012, pediatric studies were usually deferred until after the approval of the adult application. This situation created a scenario where approvals for pediatric use lagged behind adult approvals by nearly a decade. FDASIA Title V stipulates that planning for pediatric studies will begin at the end of phase II, and therefore pediatric studies may now occur with less adult data to inform the trials. Early planning allows for sponsors and regulatory agencies to determine a pathway for pediatric drug development while adult studies are still underway, with the intent of faster pediatric approvals and less off-label use. Unfortunately, earlier initiation of pediatric studies poses a challenge because important decisions need to be made with limited prior adult data. Many pharmaceutical sponsors seeking drug approval in both the USA and the EU need to present a pediatric investigation plan to the European Medicines Agency even earlier, after phase I adult studies. In pediatrics, POPPK offers the ability to refine dose selection in pediatric sub-populations and provide the highest probability of successful trials.

Population pharmacokinetics has made a significant contribution to understanding PK in the pediatric patient population. POPPK has great potential for applications for the most understudied of the pediatric patients, the neonates, and for new advances in therapeutics. For this potential to be realized, POPPK in pediatric patients must rigorously adhere to the best standards of the scientific and drug development community. The sampling schemes and numbers of pediatric patients required to make precise estimates of PK parameters that then provide appropriate dosing information are critical. Regulators and drug developers must work together to ensure that POPPK is utilized appropriately to improve the success of pediatric drug development programs.

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