Pharmacokinetic Considerations for Pediatric Drug Development

Studying pharmacokinetics (PK) and pharmacodynamics (PD) in pediatric populations presents unique challenges to drug developers due to the plethora of ethical, clinical study design, feasibility, and safety and efficacy considerations that accompany this regulatory space. Importantly, FDA guidance for pediatric studies are intended to both promote fairness in the development of drugs for our pediatric populations and protect them from undue risk.

Historically, PK studies in children have lagged behind studies conducted in adults because of the complexity of designing clinical trials for children. However, with the passage of the Best Pharmaceuticals for Children Act (BPCA) in 2002 and the Pediatric Research Equity Act (PREA) in 2003 the laws promoting the inclusion of pediatrics in clinical research have become stronger. Since then, several guidances have been developed that describe the expectations for pediatric studies in various patient populations. Most recently the expectations around drugs treating adult oncology indications and how these relate to pediatric oncology indications have been revised.

Despite the profound need for an increased understanding of PK in younger people, there are also unanimous concerns about children participating in clinical trials. Even minors who are willing to participate in medical research may not fully grasp its inherent risks, which requires that parents and guardians provide written informed consent. Clinical trials in pediatric populations that do not provide direct therapeutic benefit are required to pose no more than minimal health risk to be approved by the FDA, highlighting the Agency's policy of preventing dangerous adverse effects (AEs) in pediatrics.

These limitations not only affect exposure-response (PK/PD) determinations related to the study drug itself, but also the interventions that are used to collect this data, like blood draws and imaging techniques. With these restrictions, however, comes the opportunity for the use of alternative sampling technologies, modeling and simulation, and in silico tools, like pharmacologically based pharmacokinetics (PBPK). Here we outline some of the key details of PK and PD in pediatric populations and additional considerations that may help optimize the development of your drug for pediatrics.

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Clinical Pharmacology Differences in Pediatric Age Groups

Clinical pharmacology studies in pediatric populations are generally conducted in patients receiving therapy for a particular indication or disease. The Center for Drug Evaluation and Research (CDER) divides the pediatric population into the following four groups:

- Adolescents (12 up to 16 years)
- Children (2 up to 12 years)
- Infants (1 month up to 2 years)
- Neonates (birth up to 1 month)

Identifying the appropriate ages for clinical studies and deciding how to stratify data by age are drug-specific questions that require scientific justification, which takes into consideration developmental biology, pharmacology, and epidemiology of the disease. Pediatric pharmacology is not simply "adult pharmacology for small adults," which we explain in more detail in our webinar, "Pharmacogenomics and Pediatric Drug Development: When Are Children Not Little Adults and Why?" The reality is that some, but not all, differences between adults and pediatrics can be explained by accounting for size, whether that be weight or body surface area (BSA).

Differences in PK between adolescents and adults are minor and mainly driven by differences in weight or BSA. However, with adolescence also comes changes in hormonal homeostasis which can unpredictably impact PK. As Carr and Ensome (2003) point out, hormonal steroids that are secreted in high amounts during puberty may affect the metabolism of some drugs by competing with oxidation and hydroxylation enzymes. Furthermore, periods of rapid growth during puberty may result in suboptimal dosing of some drugs if adjustments for size are not accounted for. Proposing a single dose level for adolescent studies may be particularly difficult due to wide variations in size and level of maturity. Many times, a weight cutoff may be used to ensure safety in the subjects, with weight-based dosing below this cutoff.

We know that ADME evolves with age in children, and while normal adult PK may not be reached until later in life, most children possess the requisite metabolic enzymes and physiology to be safely administered many medicines, often with dosing modifications.

Differences in PK between adults, adolescents, and children 2 to 12 years are typically a function of the patient's weight and can usually be described using an allometric equation.

The PK of drugs in children between the ages of 2 and 12 years are not always as straightforward as one would hope. It is imperative to consider the drug metabolizing enzymes of interest and when these enzymes reach maturity. There are also pharmacogenomic (PG) differences in the drug metabolizing enzymes that need to be considered. The disease itself (e.g., cystic fibrosis) may affect PK, as well. If the disease is linked to well-known changes in PK, then PBPK modeling can provide insight and help predict the optimal dose in children. In general, children 2 to 12 years old will likely require weight-based dosing or doses based on BSA-related bands (e.g., 30-40 kg given dose X) in clinical studies. If there are reasons to expect that the exposure-response relationship differs from adults, a range of doses may be studied in pediatric clinical trials.

Below age 2 years old, there are many changes in PK that are not just based on differences in weight. While there is still a lot to learn about drug metabolism in neonates and infants, we know that in these age groups the levels of many enzymes can be very different from those in adults. In fact, as described by O'Hara et al. (2015), some cytochrome P450 enzymes (CYPs) are not even expressed until weeks or months after birth. Many other CYPs are expressed in very low levels early in life and full activity may not be achieved until 6 weeks, 3 months, or even 2 years of age.

This difference in maturation can present unfortunate challenges because neonates often require lifesaving drugs soon after birth. Off-label use of drugs is a common and necessary practice in neonatal intensive care units in order to treat sick newborns. There are also large differences in the total body water content of neonates and infants relative to older children and adults that likely affect the volume of distribution in addition to clearance mechanisms. For infants and neonates, the key is to utilize PBPK modeling approaches that can account for differences in the age-related changes in volume and clearance. Simulations from such models allows for a much more accurate prediction of potential doses. Taken with the safety profile of the drug, decisions can be made to study infants and neonates using a dose-escalation designs.

Three Recognized Pediatric Study Design Approaches

There are three recognized approaches to provide evidence to support safe and effective use of drugs in pediatric populations. The three different scenarios listed below each require a different approach:

1. Pediatric programs where the pediatric indication is very different from the approved indication in adults
2. Pediatric programs where the pediatric indication is the same indication used in adults
3. Pediatric programs where the indication, drug, and its effects are already assumed to be very similar in pediatrics and adults

The first approach uses evidence from adequate, well-controlled studies of a pediatric indication that is very different from the approved indication in adults. This approach generally requires a large pediatric development program to fill in the knowledge gaps.

The second approach uses evidence from modeling and simulation to select potential doses that can be studied in pediatric patients in a well-controlled dose-response Phase 2 study. Depending on the safety profile of the drug, the importance of these safety issues, and the ages of patients being studied, further studies may need to be conducted (e.g., dose-escalation approaches for common AEs and larger Phase 3 studies for rarer AEs). This approach utilizes prior disease and exposure-response from adult studies and relevant pediatric information to design and analyze new pediatric studies.

The last approach uses evidence from adequate, well-controlled adult studies, bolstered by additional information for the specific pediatric population. This assumes that the course of the disease and effects of the drug are sufficiently similar in the pediatric and adult populations. With this approach, modeling and simulation is used to determine the dose that provides similar drug exposure in the pediatric population as observed in the adult population. Then small pediatric studies may be conducted utilizing that dose in patients with various patient age groups.

For each approach, the extent of required additional pediatric safety investigations may take into account:

- Prior experience with similar drugs in pediatric populations
- Seriousness of the AEs in adults or pediatric populations
- Feasibility of conducting studies in pediatric patients

Typically, pediatric studies start with adolescents. Then, when there is sufficient safety and PK data, children ages 2 to 12 years old are studied. Similarly, when there is sufficient safety and PK data from children ages 2 to 12 years old, studies in infants may begin, and lastly, when sufficient safety and PK data from infants are available, studies in neonates can begin.

Important Aspects in Pediatric Clinical Trials

Pediatric differences in pharmacology can only be characterized if they can be accurately measured in a timely manner. Therefore, safely administering the investigational product is only half of the equation. Special attention must be paid to the challenges of collecting data from children. Aside from the use of smaller gauge butterfly needles to accommodate thinner veins, the volume of each sample needs to be smaller in children, infants, and neonates because their total blood volume is much lower than that of adults. Indwelling intravascular catheters should also be considered to avoid repeated venipuncture, which can cause discomfort and bruising.

Sparse sampling is an important design feature to consider in pediatric studies, particularly in neonates, infants, and children. The timing and number of blood samples must balance the need for gaining appropriate information with the risks and inconvenience of the blood samples themselves and any timing issues (e.g., having children stay at a physician's office all day). Collecting PK samples when safety labs have to be collected will ease the burden on these pediatric patients and their families. In addition, home health nurses can collect PK blood samples from small children, infants, and neonates in a setting that makes study participation more convenient, increasing the likelihood of parents consenting to the study.

To further minimize the loss of blood, micro-volume drug assays that only require a finger prick can be utilized when possible. In situations where blood sampling for PK or PD analysis poses too great a risk, saliva and urine may be collected non-invasively if there is evidence to suggest that they can adequately characterize the drug/metabolite concentrations or biomarkers of interest. Moreover, efficacy biomarkers should be chosen with the pediatric study limitations in mind wherever possible.

Modeling and simulation are essential in pediatric drug development because of their ability to accurately predict drug concentrations, PD or efficacy, and leverage safety data to recommend the optimal dose in pediatric patients of all ages. Modeling and simulation can also help in the design of pediatric studies by determining the number of patients that need to be studied and the optimal sparse sampling scheme. PBPK is essential to predicting doses in neonates and infants and may also be useful to account for disease-related changes in older pediatric patients.

Conclusions

Pediatric drug development is not just drug development for little adults. Clinical studies for pediatrics present several unique challenges, from physiological differences to distinctive study design elements, that must be carefully considered. Additionally, pediatric clinical studies are notoriously difficult to enroll. Many parents do not like the idea of signing their children up for "experiments," no matter how noble the cause, especially when the design of the study is impractical for their child. There are also many genetic disorders for which there are likely only a handful of children in the world to study them, making recruitment nearly impossible.

However, with these challenges come many opportunities to leverage the available data and technology to expedite drug development while still ensuring safe and effective treatments for pediatric patients. Nuventra has experience and expertise in predicting pediatric doses through modeling and simulation and PBPK as well as designing pediatric studies to help maximize your chances of success. Contact one of our pediatric study design experts today to learn more.

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