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Innovative clinical trial design for pediatric therapeutics

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Abstract

Until approximately 15 years ago, sponsors rarely included children in the development of therapeutics. US and European legislation has resulted in an increase in the number of pediatric trials and specific label changes and dosing recommendations, although infants remain an understudied group. The lack of clinical trials in children is partly due to specific challenges in conducting trials in this patient population. Therapeutics in special populations, including premature infants, obese children and children receiving extracorporeal life support, are even less studied. National research networks in Europe and the USA are beginning to address some of the gaps in pediatric therapeutics using novel clinical trial designs. Recent innovations in pediatric clinical trial design, including sparse and scavenged sampling, population pharmacokinetic analyses and 'opportunistic' studies, have addressed some of the historical challenges associated with clinical trials in children.

Keywords

clinical trial simulation; opportunistic study; pediatrics; pharmacodynamics; pharmacokinetics; pharmacometrics; therapeutics

Children have long been 'therapeutic orphans', which has resulted in off-label use of the majority of drugs prescribed to children [1]. This practice places children at risk of adverse events and therapeutic failures because of the lack of appropriate safety, pharmacokinetic (PK), pharmacodynamic (PD) and efficacy studies [2,3]. In addition, 'pediatrics' is simply an age-based designation, whereas pediatric disease or pediatric subpopulations represent a diverse and complex clinical landscape. The lack of clinical trials is partly due to the

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specific challenges in conducting studies in these populations of children. Recent innovations in pediatric clinical trial design have addressed some of these challenges. National funding agencies are now providing support for initiatives such as the UK Medicines for Children Research Network (MCRN), the Global Research in Pediatrics (GRIP) and the recently developed US National Institute of Child Health and Human Development (NICHD) Pediatric Trials Network (PTN). These networks are incorporating novel clinical trial design to improve dosing, safety and efficacy in pediatric therapeutics. In this article, we will identify some of the clinical trial challenges in children and review examples of successful solutions to these challenges.

Off-label prescribing & PK/PD parameters in children

Off-label prescribing has been cited as a common source of adverse events among hospitalized children [4]. Data for infants with respect to drug safety, PK, PD and efficacy are even more limited than in older children [5–7]. Improper dosing in children leads to higher rates of treatment failures, adverse events, mortality and long-term morbidities.

Unfortunately, the relationship between drug action and drug exposure in children often cannot be completely understood by extrapolating information from adult patients. Using adult data as a means of designing an initial pediatric PK trial is an appropriate starting point, as advocated by the US FDA and the European Medical Agency (EMA) [101]. However, when pediatric PK studies are performed, the results do not often reflect the predictions based on adult data [8]. Drug clearance is often highly variable in children, particularly infants, because the processes responsible for drug biotransformation and elimination are under active development. When drugs are studied in children, dosing requirements are often substantially different from adults or significant safety discrepancies are identified (Table 1) [9–11]. For example, fluconazole dosing requirements for invasive candidiasis in young infants are two-times higher than adult dosing (12 mg/kg/day vs 6 mg/kg/day)[12] and the micafungin dosing requirement is five-times higher than adult dosing (10 mg/kg/day vs 2 mg/kg/day) [13–15]. Consequently, for these two examples, simple allometric scaling applied in an effort to predict drug clearance across the continuum of development [16] would probably have limited accuracy consequent to true maturational differences in the pathways responsible for drug clearance. PK/PD trials need to be conducted in children in order to address these issues.

State of pediatric labeling

For the majority of the 20th century, drug development was focused on adults, with <25% of drugs marketed in the US and Europe labeled for pediatric use. The passing of the FDA Modernization Act in 1997 and the Best Pharmaceuticals for Children Act (BPCA) in 2002 were designed to address this knowledge gap by providing incentives to drug manufacturers to study on-patent medications and providing funding for study of off-patent medications in children. The study of off-patent medications in children established under BPCA provided a collaborative setting between the NICHD and the FDA. The Pediatric Research Equity Act of 2003 required drug manufacturers to submit pediatric studies for products that might have substantial use in the pediatric population, even in instances where the drug manufacturer was only seeking an indication in adults.

In Europe, laws introduced in January 2007 (EU Directive 2001/20/EC) sought to increase the number of trials of therapeutics in children. In addition, new applications for therapeutics in Europe require a Pediatric Investigation Plan in which the sponsor and EMA outline pediatric populations where trials are needed prior to market authorization, populations where trials are deferred to a later time point and populations in which the sponsors are not

obligated to perform trials. These legislative efforts have given rise to an increase in the number of clinical trials performed in children in Europe and the USA.

Several limitations to legislative efforts and labeling exist. Despite incentives, pharmaceutical companies are not obliged to pursue pediatric labeling. One recent example is oseltamavir, which was used with an emergency-use authorization without pediatric PK/PD and dosing data during the H1N1 epidemic. The PK trial of oseltamivir used an opportunistic study design (see later) to examine data in premature infants [17]. More than 300 label changes for children have occurred since these acts have become law, but few have included infant-specific labeling. Infants (<1 year of age) and premature infants represented only 0.2 and 0.01%, respectively, of all children studied in trials submitted to the FDA through the pediatric exclusivity program in 1998–2005. Furthermore, PD end points, which are often necessary to obtain labeling by both European and American regulatory organizations for drugs in the pediatric population, are not always clear. Unique and diverse PD end point measurement tools are often needed across the pediatric age continuum, and developmental changes in normal values hamper pediatric PD assessments and interpretations. Finally, the extent to which labeling guidance is valued by the caregiver remains unclear.

Understudied pediatric populations where innovative clinical trial design is needed

We present three examples of pediatric populations where there is a dearth of clinical pharmacology and PK information.

Premature infants

Despite neonatal medicine's long history of catastrophic adverse events resulting from inadequate study of drugs prior to their widespread use [18–21], the majority of drugs used in infants have undergone insufficient study to receive FDA labeling [5–7,22,23]. Nine out of the ten most commonly used therapeutics in the neonatal intensive care units are not labeled for use in premature infants (Table 2). The difficulties associated with infant Phase I PK trials have forced investigators to rely on extrapolation of PK data obtained in older children and adults to estimate PK parameters and dosing recommendations in premature infants. However, this approach underestimates the complicated physiology of premature infants, which differs greatly from other populations, especially when it is modulated by concurrent disease. These differences include a larger extracellular fluid volume, immature renal and hepatic function (e.g., ontogeny of glomerular filtration, active tubular secretion and drug metabolizing enzyme activity), and a unique blood–brain barrier, all of which can alter drug disposition significantly [24]. Neonatal infants also represent a difficult population to assess CNS drug affects and are extremely vulnerable to harmful perturbations to normal development. In addition, categorizing the level of prematurity is challenging, owing to issues such as postnatal age versus gestational age versus post-menstrual age. Although PK data exist for some therapeutics (e.g., midazolam [25], morphine [26], penicillins [27] and propofol [28,29]), more PK and safety studies specifically designed for premature infants are needed.

Children receiving extracorporeal life support

Extracorporeal life support (ECLS) provides life-saving support for children with refractory cardiorespiratory failure. ECLS is a cardiopulmonary bypass device that provides complete respiratory and cardiac support and is used in intensive care units when conventional modes of support have failed. Mechanically, blood is drained from the venous system, pumped through an artificial lung where oxygen is added and carbon dioxide removed, and then,

depending on the configuration of the circuit, returned to either the venous or arterial circulation. ECLS is used successfully for multiple pediatric disease states, including meconium aspiration syndrome, acute respiratory distress syndrome, pneumonia, post-cardiac surgery, post-heart and lung transplant with graft failure, fulminant myocarditis and sepsis [30–35]. PK data collected to date suggest that the ECLS circuit has the potential to significantly alter the PK of drugs, including changes in clearance and apparent volume of distribution [36–44]. In addition, the ECLS circuit itself also has the potential to increase the apparent volume of distribution through the adsorption of drug as demonstrated by *in vitro* and *ex vivo* studies [45–49]. Most studies evaluating the PK of drugs in patients supported with ECLS are limited to small PK trials and case reports, with most of the emphasis on antimicrobials [36] and sedatives [50].

Obese children

Approximately 20% of children in the USA are obese and the prevalence of childhood obesity is rapidly increasing [51]. This population has been largely excluded from pediatric drug trials, with the exception of those targeting pediatric hypertension. The PK of drugs used in obese individuals can be markedly different and specific dosing recommendations for this population are likely to be required. Perfusion of lean tissues is more rapid in obese than in normal subjects, leading to a more rapid distribution of compounds into tissues [52]. The apparent volume of distribution for many drugs is typically larger in obese patients than in normal subjects, but the apparent volume of distribution expressed per kilogram of total body weight may also differ between the two populations owing to the different tissue composition [52]. It remains unclear how generalizable studies in obese adults are with respect to obese pediatric populations. A recent study evaluating the survival of obese children after in-hospital cardiopulmonary resuscitation showed that obesity was an independent risk factor for death [53]. This might have resulted from subtherapeutic dosing of resuscitation drugs and emphasizes the need to conduct studies in the obese population. On the other hand, it is not clear how to dose children in situations where the per-kilogram dosing exceeds the recommended adult dose. Since the impact of obesity on drug clearance appears compound-specific, it is important to have a well-validated weight descriptor (e.g., BMI). However, there is presently no weight descriptor that can be used to characterize drug clearance in this population [54].

Clinical trial challenges with children & innovative trial design solutions

Performing clinical trials in children is challenging and is limited by: low study consent rates for parents of vulnerable children; limited blood volume available to conduct PK studies; lack of pediatric population PK/PD analysis expertise; difficulties associated with blood sampling timing; and the relative absence of microanalytical techniques sufficiently sensitive to enable accurate determination of drug concentration from specimens of very small volume. In addition, it is important to consider the ethical issues in pediatric trial design to ensure that conduct of pediatric trials is safe and appropriate. This involves experts with pediatric knowledge of therapeutics, pediatric clinical trial methodology and physiologic developmental issues, as well as those of assent and consent, as recently reviewed [55]. In the following section, we present innovative trial design solutions that address some of these problems.

Sparse and scavenge sampling approaches can reduce the overall blood volume needed for PK trials. Sparse sampling uses a lower number of samples per patient compared with traditional PK sampling methods. Traditional PK studies in adults involve the collection of multiple (10–15 samples per subject) high blood volume (>3 ml) samples. Children, particularly infants, have a reduced blood volume when compared with adults and this limits the conduct of intensive PK sampling. Therefore, investigators have evaluated the use of

sparse sampling (two-to-three samples per subject) with ultra-low sample volume to describe the PK of antimicrobials in this population [12,56,57]. Scavenged sampling paradigms rely upon the use of residual blood/plasma samples remaining after the performances of laboratory tests obtained in the course of medical care and thus, it poses essentially no risk for the child. The use of scavenged samples for PK studies in children offers several advantages over traditional timed PK trials. These include avoiding the need for vascular puncture specifically for the study; higher rates of parental consent; availability of several samples per infant; and avoidance of time-specific sampling. Possible disadvantages include drug stability problems associated with inappropriate sample storage; unsuitable draw times not useful for PK analysis; less accurate recording of sample collection time; and low volume of surplus blood. Most of these limitations can be overcome by the availability of several samples per patient and the use of new methodologies for estimating PK parameters such as population PK analyses. The salient point with both of these approaches is that careful consideration be given to the design of informative sampling schemes that leverage opportunistic sampling with informative sampling that is evaluated *a priori* via modeling and simulation.

Given that a limited sampling scheme can potentially affect the PK characterization of a drug, investigators have used novel PK analysis techniques to avoid PK misspecification of drugs, such as population PK methods [12]. Population PK methods, whereby samples are attributed to a population rather than an individual, can be used to analyze sparse sampling data collected for pediatric studies, either with or without physiologic-based PK modeling [58]. Physiologic-based PK modeling uses the anatomic and physiological structure of various organs in the body to model and predict drug disposition and tries to incorporate maturational changes in liver mass, organ blood flow and enzymatic activity. Commercially available software has recently incorporated developmental modules to allow the use of physiologic-based PK modeling in pediatrics [59]. The sparse sampling with the population PK approach, with or without physiologic-based PK modeling, has been increasingly endorsed by governmental agencies (the FDA and EMA) and industry [101].

Previous investigators have successfully used sparse sampling combined with the population PK approach to describe the PK of antimicrobials in children. The most extensively studied agents include vancomycin and gentamicin because these agents are routinely assessed in the clinical setting during therapeutic drug monitoring. The PK of vancomycin was evaluated in infants at 24–41 weeks gestational age with peak and trough concentrations measured per standard of care (approximately two samples per patient). The most important predictor of PK parameters (clearance and volume of distribution) was bodyweight, and the best therapeutic target was reached using a dose of 30 mg/kg/day divided every 8 h [56]. A study in Spain evaluated the population PK estimates of gentamicin in premature infants (mean gestational age: 32 weeks) using more than 400 serum drug concentrations. They determined that creatinine clearance was the most important predictor of gentamicin clearance and developed dosing recommendations of gentamicin based on gestational age [57]. Population PK methods were used to determine the optimal dose for a PK/safety trial of meropenem [60], which avoided the need for a dose-escalation trial. Other drugs in which this type of analysis has proven successful in premature infants include fluconazole [12], cefepime [61] and ampicillin [62] These studies demonstrate the important role of novel methodologies, such as sparse sampling and the population PK approach, in the estimation of drug clearance in children.

Sparse sampling without population PK techniques has been used to examine therapeutics at a steady state in pediatric therapeutic trials. Investigators examined micafungin using sparse sampling when this therapeutic was at steady state using traditional PK methods [63,64]. Investigators used the population PK strategy to characterize valganciclovir steady-state PK

in young infants with congenital cytomegalovirus infection [65]. Thus, using a sparse sampling strategy while a therapeutic is at steady state has moved pediatric PK knowledge forward without using traditional larger sample sizes.

Two novel clinical trial tools offer the possibility of improving the field of PK trials in children: multiple-drug assays and dried blood spot sampling (DBS). Over the last two decades, advances in technology have provided tools to measure drug concentration in biological matrices accurately, selectively and with increased sensitivity. Optimized methods using high-performance liquid chromatography and the incorporation of mass spectrometry in the evaluation of biological samples have revolutionized the field of analytical science. This progress has resulted in the ability to measure drug concentrations in ultra-low plasma samples (<100 μl). Given the ability of these instruments to separate compounds efficiently, it is now possible to measure several compounds in the same sample simultaneously [66]. This methodology has been successful in several settings, including the measurement of 17 antiretroviral drugs from different drug classes in 50 μl of human plasma [67] and simultaneous measurements of five β-lactam antibiotics (cefepime, ceftazidime, cefuroxime, meropenem and piperacillin) and seven antimicrobials (cefuroxime, cephalexin, ceftazidime, ampicillin, benzylpenicillin, metronidazole and chloramphenicol) of different classes using high-performance liquid chromatography with ultraviolet detection [68,69]. In children, the multiplex-assay approach is attractive because they are often treated with several therapeutics (particularly antimicrobials) concomitantly. More importantly, in the setting of clinical trials where each infant receives a different agent, a single multiplex assay increases the efficiency of the trial by measuring drug concentrations of all agents without the need to develop and validate multiple individual assays specific for each drug.

Dried blood spot sampling may also improve the design of PK studies in children. Traditional PK sampling involves collection of plasma or whole blood in a sample collection tube. However, when plasma is the desired biological matrix, blood needs to be centrifuged to extract the plasma. As such, the blood volume required per sample is usually double the amount of plasma needed for analysis, thereby increasing the amount of sample collected unnecessarily. In addition, sample processing times and personnel training are required to maintain a controlled sample collection environment. Over the past few years, a novel sample collection method using DBS has emerged and is increasingly employed by the pharmaceutical industry in drug development [70]. This method involves the collection of 15–30 μl of whole blood on blotting paper. Potential advantages of this methodology include low sample volume, minimal personnel training, no sample processing (sample is collected as is at the patient bedside), room temperature storage and simple bioanalytical analysis. These properties make DBS sampling a potentially attractive technology for accomplishing PK analyses in children.

Although DBS sampling has been used in the newborn metabolic diseases screening program over the past five decades, its application in pediatric clinical PK trials is limited. Several investigators have evaluated the predictability of DBS (which uses whole blood) compared with traditional plasma drug concentrations in clinical trials. Investigators employed patient-derived DBS sampling in tacrolimus therapeutic drug monitoring using 108 paired samples from 36 patients. They demonstrated a high linear correlation ($r^2 > 0.97$; $p < 0.001$) between whole blood and DBS tacrolimus concentrations, as well as equal $AUC_{0–12}$ estimations between both biological matrices [71]. Partitioning in blood cells types needs to be determined as some drugs concentrate into blood cells, resulting in a higher DBS concentration, while others penetrate poorly into cells and have lower DBS concentrations than plasma, resulting in matrix-dependent PK parameters. Other investigators have demonstrated excellent correlation between plasma and DBS concentrations and PK parameter estimation of rifampin ($r^2 > 0.92$) [72] and theophylline ($r^2 > 0.98$) [73]. Recently,

investigators developed DBS technology for metronidazole [74] and used DBS to successfully examine the population PK of metrodinazole in preterm infants [75].

Pharmacogenomics

The study of multiple agents currently underway in the Pediatric Trial Network will involve a focused (i.e., compound-specific) application of pharmacogenomics. The strategy used for this specific application of technology will be a systematic assessment of the relative contributions of ontogeny and genetic variation on the disposition of a given compound [76]. Proof-of-concept for this approach is found in the context of classical PK trials of both omeprazole [77] and pantoprazole [78]; both collected DNA for the purpose of CYP2C19 genotyping. While the results from each of the aforementioned studies revealed concordant CYP2C19 genotype–phenotype (as reflected by drug plasma clearance) results, a subsequent reanalysis of the genotype data expanded to include the *CYP2C19*17* allele demonstrated that an apparent gene–dose effect was present for pantoprazole and absent for omeprazole [79]. Collectively, these data illustrate that focused application of pharmacogenomics (i.e., when gene polymorphisms are shown to be functionally important determinants of drug clearance) can inform the results of a clinical PK trial in a significant fashion (e.g., providing an explanation for apparent outliers for drug plasma clearance/elimination) and potentially provide evidence to support apparent compound-specific variability in drug disposition during development (Table 3).

Opportunistic studies in children

An opportunistic study is one where a child is receives a therapeutic as part of standard-of-care and, after informed consent, investigators collect PK samples at the time of routine laboratory draws, use scavenged samples or collect a low number (sparse blood sampling) of low-volume samples. Studies capitalizing on standard-of-care procedures, such as biological sample collection from children already receiving drugs of interest, have produced meaningful PK data, resulting in improved dosing recommendations in infants and children. As described later, these studies did not administer drugs to children, but rather collected samples from children who were already receiving drugs as standard-of-care as prescribed by the local caregiver. In addition, preliminary data obtained through opportunistic studies have helped to design Phase I–III trials in children, and have supported applications for extramural research.

A variation on the opportunistic approach is to use real-time monitoring to facilitate clinical care of the infants for drugs where dosing has not been established. This promotes sample collection at informative collection times and encourages enrollment as the subjects' caregivers see a direct benefit from feedback of drug concentrations. However, this approach requires additional resources to provide rapid sample analysis and interpretation in a clinically certified laboratory. An opportunistic real-time study design was used to determine the PK and safety of zidovudine (ZDV) in preterm infants [80]. In this multicenter trial, HIV-exposed infants were started on ZDV prophylaxis to prevent transmission of HIV from their mothers by their caregivers. Infants received ZDV at a reduced dose to account for immature renal function and glucuronidation. Two to three blood samples were collected at 1, 2 and 4 weeks of age with PK analysis of ZDV and ZDV–glucuronide. Doses were adjusted for individual subjects based on ZDV drug concentrations. The longitudinal design provided robust PK analysis that found large differences between preterm (including differences between <30 weeks and 30–35 weeks gestation) and full-term infants. Infants born at <30 weeks also acquired ZDV clearance capacity more slowly and require a delay in ZDV dose increase [80]. This study demonstrates that integration of study design into

clinical care in an opportunistic manner can generate robust neonatal PK and dosing information.

Fluconazole as a proof-of-concept from opportunistic study to Phase III trial

The NICHD Pediatric Pharmacology Research Unit (PPRU) conducted an Antimicrobial PK in High-Risk Infants trial, a prospective, open-label study that involved 13 neonatal intensive care units across the USA. Neonatologists at participating sites administered antimicrobials to infants as standard-of-care based on therapeutic indications. Once informed consent was obtained, PK samples were collected in a timed and scavenged fashion from infants <33 weeks gestational age following a predetermined sampling schedule deemed appropriate for each drug based on its known/suspected PK profile. These patients were divided into three groups: <26 weeks gestational age; 26–29 weeks gestational age; and 30–32 weeks gestational age. Over 360 premature infants were enrolled in the study (Table 4).

The samples from the PPRU PK study of fluconazole in young infants trial and from an opportunistic antimicrobial PK trial conducted at Duke University (NC, USA) were combined and investigators described the PK of fluconazole using population PK analysis [12]. A total of 55 infants with 357 PK plasma samples were included: 217 out of 357 (61%) were collected prospectively at prespecified time intervals and 140 out of 357 (39%) were scavenged samples. Observed fluconazole concentrations from scavenged samples were indistinguishable from concentrations in timed PK samples; scavenging introduced variation (bias) of 4% (95% CI: −2–11%). This PK analysis led to the dose selection for a Phase III, randomized placebo-controlled trial of fluconazole prophylaxis in premature infants (clinicaltrials.gov identifier: NCT00734539) [102].

The analysis from the PPRU trial was also used to determine the fluconazole dosing for treatment of invasive candidiasis using population PK models [81]. Wade *et al.* examined the expected changes in fluconazole clearance based upon gestational age, post-natal age, weight and creatinine [81]. For the treatment of invasive candidiasis, a dose of at least 12 mg/kg/day in the first 90 days after birth is needed to achieve an area under the concentration curve of >400 mg per h/l in ≥90% of <30 weeks gestation infants and 80% of 30–40 weeks gestation infants. AUC >400 mg per h/l is the target exposure based on randomized trials in older patients.

Research consortiums: MCRN, GRIP & PTN

Research networks provide an opportunity to bring together different areas of expertise in pediatric therapeutics including PK/PD modeling and pharmacometrics, pharmacogenomics, conduct of pediatric trial design, pediatric formulations, and data coordination. The MCRN was created in 2005 to conduct well-designed studies of pediatric therapeutics [103]. The MCRN infrastructure includes a coordinating center, local research networks, clinical studies groups and a neonatal network, and supports both investigator-initiated and pharmaceutical studies.

Global Research in Pediatrics is scheduled to begin in 2012 and includes 21 institutions as partners and at least another 16 major networks that represent therapeutic in pediatrics [104]. Its main goal is to provide an infrastructure to stimulate and facilitate the development and safe use of medicine in children. GRIP also plans to validate and harmonize research tools specific for children and provide training in pediatric clinical pharmacology.

The PTN began in the fall of 2010 and is designed to conduct high-quality PK/PD trials in children [105]. The PTN consists of five cores: a clinical pharmacology core; a pharmacometrics core; a formulations core; an education core; and a device core. The PTN will conduct up to 30 trials in children over the next 7 years, and is specifically designed to fill the knowledge gaps in pediatric therapeutics, including an FDA label change.

The PTN is using an opportunistic trial design to examine the 'PK of Understudied Drugs Administered to Children per Standard of Care', which will target therapeutic drugs listed on the BPCA prioritization list. Another example of other opportunistic studies include a common PK trial being conducted by investigators at the University of North Carolina at Chapel Hill (NC, USA) – therapeutics include moxifloxacin, doxycycline and sildenafil. These protocols will enable investigators to provide valuable new information either not previously described or limited owing to the poor performance of small studies regarding the disposition of agents in the plasma, urine, CNS and potentially other body fluids obtained from infants and children. These studies will obtain PK data for products to better understand the impact of ontogeny and for some agents, pharmacogenetics, on producing variability in the dose–exposure relationship in drug development. Drugs to be evaluated will include newer as well as more commonly used older and off-patent antimicrobials, diuretics, chemotherapeutics, anticonvulsants and cardiac agents.

Clinical trial simulation in pediatric populations

While there are few published examples of clinical trial simulation (CTS) focused on pediatrics, the occasion to consider CTS has increased dramatically, largely due to motivation by regulatory considerations from the EMA and the FDA. The most common application is the standard PK/safety trial employed when adult and pediatric indications are perceived to be similar and there is information/data to support such assumptions. The primary goal in this setting is to ensure an adequate sample size and an informative sampling scheme that considers the potential shift in PK across age strata or temporal changes in PD response. More uncommon, but perhaps increasing, is the interest in pediatric efficacy trials. The approach, methodology and applications have recently been reviewed [82]. Certainly, CTS coupled with the other innovations discussed herein presents an important approach for the design and conduct of informative trials in children.

Discussion

The majority of therapeutic drugs used in children are off-label, and in many instances, the knowledge concerning the impact of development on their disposition and action is lacking, due to either absent or insufficient study. Novel pediatric trial designs, including opportunistic PK studies of off-label therapeutics used as part of clinical care, provide a stepping stone for further pediatric research, including Phase I and Phase III trials. A successful example of an opportunistic study moving the field of pediatric therapeutics forward is fluconazole in premature infants, where an opportunistic study informed the dose for a prophylactic candidiasis Phase III trial and the dose for the treatment of invasive candidiasis. Other advantages of opportunistic studies include enrollment of: the population of interest (vs healthy volunteers), intensive care patients with comorbid conditions, children with many concomitant medications that might affect PK parameters (vs healthy volunteers), subtypes of pediatric populations (e.g., obese, renal transplant and premature infants) and pediatric patients presenting during 'disaster' situations. Other innovations in pediatric clinical trial design include sparse and scavenged PK sampling and population PK methods. The future of pediatric trial design includes incorporating relevant pharmacogenomics, metabolomics and proteomics coupled with CTS as potentially informative 'tools' into pediatric pharmacologic studies so as to provide greater mechanistic

insights into the reasons associated with variability in drug disposition and response during development.

Expert commentary & five-year view

Over the next 5 years, the MCRN, GRIP and the PTN, as well as many other investigators will use these principles of innovative pediatric trial design to conduct a range of pediatric therapeutic trials. These will involve an array of pediatric clinical trials including traditional PK studies, bioavailability studies, sparse sampling and population PK studies and device-validation studies, as well as safety and efficacy studies. A mixed-model approach using traditional and innovative clinical trial design tools will be implemented in order to improve the knowledge of off-label therapeutics in children.

Key issues

- Legislation has begun to address the issue of children as ‘therapeutic orphans’, although more work in pharmacodynamic end points needs to be performed in children.
- Innovative pediatric trial designs using sparse and scavenged pharmacokinetic (PK) samples, along with population PK techniques, reduce the amount and number of PK samples needed in children.
- Research networks, such as the Medicines for Children Research Network and the Pediatric Trials Network, have the necessary expertise and resources to address the knowledge gaps in pediatric therapeutics.
- Opportunistic studies, which capture PK samples from children receiving therapeutics as part of clinical care, represent a low-risk and high-yield innovative study design that is efficient and palatable to parents and institutional review boards.

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Table 1

Pediatric or infant dosing compared with adult dosing of commonly used antimicrobials.

Drug	Preferred adult dosing (mg/kg/day)	Pediatric or infant dosing (mg/kg/day)	Pharmacokinetic data available in infants <28 weeks gestation	Ref.
Ampicillin	30–50	50	None	[83]
Ciprofloxacin	10	30	None	[84]
Daptomycin	4–6	12	None	[85]
Metronidazole	30	15	Limited (>7 days of life)	[86]
Fluconazole	3–6	12	Yes	[12]
Micafungin	2	10	Yes	[14,15,87]

Table 2

Most common therapeutics reported among 253,651 infants in the intensive care nursery.

Medication	% exposed	US FDA labeling for premature infants
Ampicillin	74	None
Gentamicin	68	None
Cefotaxime	36	None
Caffeine citrate	19	None <29 weeks
Furosemide	19	None
Vancomycin	17	None
Beractant	14	Yes
Metoclopramide	11	None
Aminophylline	11	None
Dopamine	10	None

Data taken from [88].

Table 3

Summary of selected genetic polymorphisms in pediatric diseases.

Childhood disease	Genetic polymorphisms	Clinical effects
Transplantation	*MDR1 (ABCB1)*	Drug concentration
Leukemia	*CYP1A1, CYP2E1, GSTT1, GSTM1, GSTP1TMPT, MTHFR, MTHFD1*	Drug response and toxicity
Asthma	*B2AR, CRHR1, TBX21, 5-LO, LTC4S, LTA4, MRP1, ALOX5*	Drug response
ADHD	*DAT1, DRD4, DRD5, NET, SNAP25, ADRA2A*	Drug response

ADHD: Attention-deficit/hyperactivity disorder.

Data taken from [89].

Table 4

Pediatric Pharmacology Research Unit antimicrobial pharmacokinetics study: number of subjects in each group.

Drug	Number in each EGA group			Total
	<26 weeks EGA	26–29 weeks EGA	30–32 weeks EGA	
Acyclovir	8	14	9	31
Ampicillin	49	102	75	226
Metronidazole	14	13	5	32
Piperacillin/tazobactam	40	28	11	79

Scavenged plasma samples are collected from subjects treated with antimicrobials, as per standard of care.

An average of three plasma samples per antimicrobial are obtained at steady state.

EGA: Estimated gestational age.

Data taken from [106].