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Review Article

Theme: Team Science and Education for Pharmaceuticals: the NIPTE Model
Guest Editors: Ajaz S. Hussain, Kenneth Morris, and Vadim J. Gurvich

Pediatric Formulations: Knowledge Gaps Limiting the Expedited Preclinical to Clinical Translation in Children

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Abstract. Traditionally, drug discovery and development research have been primarily focused on the mitigation of disease treatment for the general adult population, often overlooking the medical needs of pediatric patients. While remarkable progress toward the discovery of better medicines has been made, the pharmacological differences between children and adults are often neglected as part of the translation process. In fact, until recently, children have been considered therapeutic orphans due to the lack of significant drug discovery, formulation development, and dosage form design specifically tailored for pediatric patients. Perhaps the least understood is the significant physiological changes that occur during the maturation process from birth to adulthood. It requires careful considerations to achieve age-specific-desired therapeutic outcomes with minimal toxicity. This introduces considerable risk into the preclinical and clinical testing of new medicaments, which until recently, was avoided based on the conventional approach where a demonstration of safe and efficacious use in adults over several years potentially would minimize the chance of adverse juvenile responses. However, the lack of appropriate drug products for children has led to off-label use of adult medicines with potential life-threatening adverse reactions and health complications. Recent developments and future considerations regarding pediatric drug discovery and development using a patient-centric approach in the context of ontogenic biopharmaceutical considerations are discussed below.

KEY WORDS: pediatric; neglected; therapeutic orphans; recent developments; patient centric.

INTRODUCTION

Rapid development occurs from birth to adulthood creating a spectrum of physiological conditions in the pediatric population (1,2). This leads to the further classification of multiple subgroups at different stages of maturity, namely newborns or neonates, infants, children, and adolescents (Table I). Despite the apparent differences between multiple pediatric subgroups, the ontogeny-driven effects are often not delineated or well examined in clinical trials (3,4). For example, a large variability in the age of patients was found in the pediatric studies published by the Cochrane Central Register of Controlled Trials (CENTRAL) during the year 2007, but an age-group analysis was performed in only 25% of the studies (5). This may be due to the limited availability of participants enrolling in pediatric clinical trials, however, there does need to be an increasing awareness of the importance of age-based striation placed in the field. Furthermore, in our literature search, we did not uncover studies where gender differences in drug response were considered, although it is not clear how significant this would be prepubescent. Extrapolation of data from pediatric clinical trials to guide drug development is also confounded by the fact that, to our knowledge, there has never been a clinical trial conducted in a healthy childhood population. In part, this arises from safety considerations regarding exposing children to unpredictable risks (6). In an attempt to overcome these ethical issues, changes in current regulations have created a paradigm shift in the public point of view from "protecting children from research" to "protecting children through research" (7,8).

Given the issues with traditional approaches and our limited knowledge of drug discovery and development for pediatric populations, there has been a concerted focus on improving therapeutic outcomes through incentivizing

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Table I. Approximate Age Range for Each Pediatric Subpopulation Based on (1) the FDA/CDRH and (2) the WHO

Pediatric subpopulation	Age range	
	(1) FDA/CDRH	(2) WHO
Newborns	Birth to 1 month	0 to 28 days
Infants	1 month to 2 years	>28 days to 23 months
Children	2 to 12 years	2 to 11 years
Adolescents	12 to 21 years	12 to 16 or 18*

**Depending on the region*
FDA, Food and Drug Administration; CDRH, Center for Devices and Radiological Health; WHO, World Health Organization
The ranges provided by FDA/CDRH (Pediatric Expertise for Advisory Panels—Guidance for Industry and FDA Staff, 2003) are based on the usage of medical device in pediatric subgroups. In a document (Promoting Safety of Medicines for Children, 2007) published by WHO Press, the age ranges are indicated based on internationally agreed classification that can be found in ICH E 11 clinical investigation of medicinal products in the pediatric population

pharmaceutical companies to investigate the use of drug products in children. The World Health Organization (WHO) and international regulatory agencies have worked to raise awareness and promote pediatric research activities in both academic and industrial settings (9). The Best Pharmaceutical for Children Act (BPCA) was established by the Food and Drug Administration (FDA) to provide an additional 6 months of market exclusivity for drug products that have been clinically evaluated in pediatric patients. The Pediatric Research Equity Act (PREA) is another legislation that requires the pediatric clinical assessments to be conducted by the pharmaceutical companies, unless there is a strong justification for bypassing testing, *e.g.*, aging-based disorders. The enactment of BPCA and PREA and other regulatory changes have been proven to be effective based on the increase in the number of pediatric drug labeling in recent years (10,11). Similarly, the European Medicines Agency (EMA) also enforced the integration of pediatric studies at an early stage of drug development. In addition to regulation enforcement, working groups were formed with representatives from academic, industrial, and governmental institutes to identify major issues in pediatric drug development and determine appropriate solutions (12). One of the prevalent gaps identified across the board as hindering further facilitation of pediatric drug discovery and development was the understudied preclinical modeling of ontogenic-based changes during the different stages of growth and their relevance in guiding new and repurposed formulation development.

Safety- and efficacy-oriented preclinical animal models used to assess the pharmacokinetic (PK) and pharmacodynamic (PD) in the drug development process have yet to be established for pediatric research (8,13). There are many cases where the traditional animal models have been demonstrated to not be adequate for predicting adult PK/PD, thus suitable pediatric models would be even harder to establish. Differences in drug absorption, distribution, metabolism, excretion, and toxicity (ADMET) should be incorporated in animal studies to help determine the potential changes in the age groups and the potential implications on dosage tailoring for a dynamic safe and efficacious dose range. Absorption is one key aspect as the rate of absorption needs to balance disposition-driving ontogenic changes in order to ensure a safe and efficacious response. For pediatric oncology patients, the failure to understand the rate determining mechanisms of dosage form performance that effects absorption is also predicated on a more comprehensive understanding of the ontogenic changes in gastrointestinal transporter and enzyme expression. Without the fundamental background knowledge across species and the relationship to pediatric and adult populations, the knowledge gaps may significantly limit the ability of the therapeutic agent to reach a systemic exposure and has been theorized to be one of the main causes of the high attrition rate in the development of drugs such as anticancer agents (14–16).

INADEQUACY OF PRECLINICAL MODELS

The lack of clinical knowledge, albeit in diseased children, presents an inordinate increase in safety concerns comparative to adults (17–19). The disparity in pediatric clinical results further justifies the necessity of validating clinically relevant animal models that can accurately predict risk and potential efficacy. This is further justified by the fact that many age-related effects on disease characteristics and drug responses have also been observed in children, where preemptive screening may have minimized these unintended outcomes (20–22). In this regard, the physiological barriers associated with *in vivo* models may better mimic the systemic changes across pediatric age ranges that would not be adequately reflected in studies using current *in vitro* and more established adult *in vivo* animal models.

The translation of hits to leads almost universally begins in rodents (mice and rats primarily), which are the most studied preclinical models (23,24). However, the difference in their developmental physiology from humans is a major disadvantage, particularly in areas like organogenesis (25). This is particularly important for pediatric drug development, which requires a similar body maturation rate to assess its impact on ADMET. The life span of mice and rats are also shorter, and therefore, extended pediatric therapeutic toxicity is not easily obtained using these traditional early toxicity screening models.

There have been a number of studies contrasting the utility of larger animal models due to translational advantages allowing extensive analyses that are not possible in small animals (26,27). One model of interest for our laboratory has been the swine (porcine) model, which has been utilized for drug studies in pediatric populations (28–30). The porcine model shares several similarities with humans with respect to anatomical, physiological, and biochemical properties, making them suitable for pediatric pharmacokinetic studies (31). For example, the Jaeger laboratory has demonstrated that developmental maturation in the porcine intestine parallels humans and is largely completed by parturition, whereas the rat intestine still matures into infancy (32,33).

In fact, several studies have also suggested that the porcine model is the best large animal model for studying

digestive diseases and superior to rodent models (26,34–36). Swine models for cancer studies have also been established using various technologies including targeted gene editing (37–39). Such models could potentially serve as significantly better surrogates for investigating the PK/PD of anticancer therapies for pediatric oncology patients. In addition, accumulating information regarding tolerability of different excipients used for oral, parenteral, and dermal formulations in minipig and other swine species can be readily accessed for drug development studies without performing extensive tolerability tests (40).

Domesticated swine weighing up to 50 kg have been used in research studies in our laboratories, and miniature pigs have also been utilized in preclinical testing because they are easy to handle (41). In a comparative PK study of glipizide, pig and dog models were used for immediate and modified release formulations (42). For the 10 mg modified release formulation, pigs showed a more consistent exposure with a coefficient of variance of 54% which was lower compared to dogs (80%). The absorption PK parameters and bioavailability value obtained in pigs more closely resembled the data reported for humans.

Juvenile porcine models were assessed for their potential to serve in preclinical pharmacokinetic testing as a human pediatric surrogate (43). Juvenile (20 kg) and adult pigs (40 kg) were administered with rifampin in a capsule form at an equivalent dose of 14.5–14.7 mg/kg as recommended by WHO (43). A lower level of exposure was observed for juvenile pigs with an AUC value of 58.1 μg h/mL comparing to 188.4 μg h/mL in adult animals. The ontogeny-related changes between the two groups were also seen in the maximum plasma concentration (C_{max}), which was lower in juvenile pigs (7.0 *versus* 28.8 μg/mL) while the T_{max} values were the same (2.0 h). Both the C_{max} and T_{max} values from juvenile porcine models fell within the range reported for pediatric humans in literature after dose normalization was applied in the comparison. In a separate study in our laboratory, an oral buccal film strip formulation containing a measles vaccine was tested to assess if it would elicit a systemic immune response in juvenile pigs (44). The results of these studies revealed that antibody titers, as determined by ELISA, against the vaccine were visible after the initial administration and increased with additional dosing.

INNOVATIVE ORAL DOSAGE FORM FOR PEDIATRIC MEDICINES

Many innovative approaches that have been studied for the general adult population do not focus on overcoming the challenges in pediatric drug administration, which is often associated with swallowing difficulty, mouth-feel, and taste preferences. In terms of oral administration, mini-tablets (Fig. 1), granules, and pellets have been proven to be the most acceptable solid dosage forms for pediatric patients (45–47). Liquid formulations such as syrup have been commonly used for children, but stability and drug loading may be an issue rendering its application for a wide range of API's. On the other hand, mini-tablets have gained increasing interests because they can provide ease of administration and dose flexibility similar to the oral liquid dosage form. In addition,

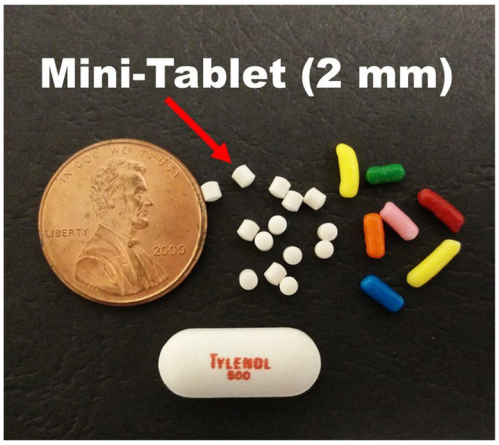

Fig. 1. Display of mini-tablets (red arrow), ice cream sprinkles, a conventional tablet (Tylenol®), and the US penny for size comparison. Note that the ability to dose multiple mini-tablets, perhaps in smaller aliquots, to achieve the desired dose can be achieved with minimal dysphagic response from the child

improved stability, high drug loading, and reduced transportation cost can also be achieved with the use of mini-tablets. To further increase the compliance in younger pediatric populations, oral disintegrating mini-tablets are also a viable option.

In addition to the changes in clinical responses to the active pharmaceutical ingredient (API), the effects of excipients added in the formulation must also be considered (48–50). Several studies have suggested that acceptable excipients levels used in adult formulations have been suggested to be toxic in children at the same concentration. For example, benzyl alcohol is an excipient that is commonly used as a preservative has been suggested to be causative of gasping syndromes in neonates (51). The side effects of neonatal exposure to high levels of benzyl alcohol are severe and include neurological deterioration, contribution to organ failures, metabolic dysfunction, and respiratory distress. In 2011, a safety labeling change was required for the presence of ethanol and propylene glycol, at a relevant amount in the Kaletra® formulation of the anti-HIV drug combination of lopinavir/ritonavir, due to excipient toxicity reported in newborns (52). Several other cases have been reported and resulted in a need to collect additional toxicity data for excipients in children. In response to these toxicity issues resulting from excipient use in pediatric drug formulation, the Safety and Toxicity of Excipients for Pediatrics (STEP) database was created to provide access to information on excipient usage for children (53–55).

Several studies demonstrated the suitability of mini-tablets for pediatric age groups including infants and neonates (56–58). A higher acceptability of mini-tablets compared to liquid formulation was observed for children from 6 months to 6 years of age (59). In neonates, the acceptability of mini-tablets was similar to a syrup with an even higher swallowability (60). Food particle size distribution ranges from 0.82 to 3.04 mm, according to studies conducted on mastication, prompting the FDA to recommend the target bead size of drug products that are labeled for administration by sprinkling to be at 2.5 mm maximum (61–63).

EFFECTS OF ONTOGENY ON PHARMACOKINETIC

Gastric Conditions

The gastric volume is over fivefold smaller during infancy compared to adulthood (64). The final concentration of the drug should be taken into consideration, especially for oral liquid dosage forms, due to limited functional volume in the stomach. Feeding frequency and tendency for gastric reflux can also affect the delivery of the drug. In a fasted state, a similarity between gastric volumes of children and adult was obtained with weight normalization. Gastric emptying is prolonged and the time to reach maximum drug plasma concentration is longer in neonates. An increasing trend in the drug absorption rate of phenobarbital, sulfonamides, and digoxin was found in pediatric patients from 3 weeks to 1 year old (65). The secretion of gastric acid is low due to immature parietal cells, thus creating a neutral pH environment in the stomach of neonates until 20 to 30 months old (66). This can influent the pH-dependent solubility and availability of acid-labile drugs.

Intestinal Barriers

The functional surface area of the small intestine undergoes an increase of over 40-fold during human development. The intestinal mobility does not differ between children and adults when tested with the same method, and the pH level is also not affected by age. In addition to physical and mechanical barriers, the absorption of the drug is subjected to biochemical processes in the small intestine. The expression of multidrug resistant protein 1 (MDR1), also known as p-glycoprotein (P-gp), was found to be lower in neonates, while the organic anion transporting polypeptide (OATP)2B1 is highly expressed in this age group (67,68).

Intestinal transporters and enzymes play an important role in the patient's response to drug treatment (69). Cytochrome P450 refers to a superfamily of enzymes present in the hepatocytes and at a lesser extent in the enterocytes (70). The expression of cytochrome P4503A (CYP3A) subfamily was confirmed at 80% in the small intestine (71). In a study using Western blotting and immunohistochemistry, the expression level of duodenal CYP3A4 was found to be significantly lower in neonates (72). The CYP3A4 enzyme residing in the gut wall is responsible for a significant reduction in oral bioavailability of some compounds during first-pass metabolism (73,74). Docetaxel, tacrolimus, and sirolimus are known to be susceptible to intestinal CYP3A drug metabolism. The effects of age on CYP3A metabolic capacity was observed in a clinical trial with patients having neurofibromatosis, in which children had a lower ratio of the metabolites (*i.e.*, 16-O-demethylsirolimus and 24-hydroxysirolimus) to sirolimus compared to adult patients (75).

Genetically modified mouse models showed a dramatic decrease in the drug absorption for docetaxel when tissue-specific expression of CYP3A4 was introduced in the small intestine compared to the liver (76). It has been proposed that the overlap in substrate specificity of CPY3A enzymes and MDR1 transporter may be the cause of unexpectedly high intestinal first-pass metabolism that occurs in a synergistic manner (74,77,78). When tacrolimus was given to pediatric patients after a heart transplant, a higher amount of drug was required in CYP3A5 expressers to obtain the same blood concentration as the nonexpressers (79). A similar situation was also seen for different genotypes of MDR1 (*i.e.*, G2677 T *versus* C3435T) at 6 and 12 months but not during the earlier post-transplantation period.

Age-Related Changes in Drug Disposition

Dramatic changes in body composition occur during rapid growth and maturation. Total body water and extracellular water decrease and reach a stable level after the age of 1-year old, which can result in a decrease in the plasma concentration of hydrophilic drugs (80). While total body fat decreases in children as they progress into adulthood, the contents (lipid and water composition) of adipose tissues are different in neonates compared to adults. Lipid content was 40% in neonates and increases with age to 75% (81). The plasma concentration of albumin and α1-acid glycoprotein remains below the adult's level for the first year after birth (82). Neonates may be at risk when administered with highly plasma bound drugs at a standard dose due to a higher fraction of free drug in the systemic circulation, although the extent at which plasma protein binding can affect pharmacokinetic in pediatric patients remains to be clearly elucidated. Diazepam and cyclosporine had a three to fourfold higher of unbound fraction in children *versus* adults, but when deltamethrin was given in the same study, the unbound fraction was higher only during neonatal period at 0 to 1 month (83).

In hepatic metabolism, CYP3A4 enzyme has an opposite pattern of expression with CYP3A7 which is influenced by the maturation process (84). Newborns treated with sildenafil for persistent pulmonary hypertension had a threefold increase in clearance from day 1 to day 7 after birth (85). Due to immature metabolic capability of CYP3A4 in neonates, potential side effects can occur when drugs primarily metabolized by this enzyme are used. For example, cisapride caused pediatric gastroesophageal reflux when administered in neonates with nonfunctional CYP3A4 enzymes (86). It was later confirmed that cisapride does not get broken down by CYP3A5 and CYP3A7 that are often expressed at higher levels during the neonatal period before the transition takes place (87,88). The rapid maturation of enzymatic expression in the early stage of life makes it difficult to predict the pharmacokinetic parameters of the pediatric population based on individual levels. Leeder and Kearns demonstrated the changes in the activity of CYP2C19, which the authors referred to as a "moving target" due to the challenge associated with the variation in drug disposition and response in pediatric patients (89).

The ontogeny-related effects on enzymatic expression in pediatric patients *versus* adults are well defined in multiple sources in literature (90–92). It should be noted that the variation in the level of enzyme expression within the same age group may also exist, similar to the cases in adult patients (93). Multiple factors such as genetic heredity, diet, environment, and health conditions may also play a role in the individual expression level of transporter and enzymes (94,95).

CONCLUSION

In order to make better pediatric medicines and meet the high demand in this population, further research needs to be

conducted to understand the physiological conditions in pediatric patients affecting clinical outcomes and toxicity. Innovative dosage forms such as mini-tablets and other oral dispersible formulations should be investigated, in addition to liquid forms, to facilitate dose flexibility and patient adherence, which are a common challenge in pediatric drug administration. A more comprehensive understanding of the relationship between the ontogenic physiological similarities and differences between preclinical *in vitro*, *e.g.*, gastric dissolution testing for neonates and infants, and *in vivo*, *e.g.*, changes in transporter and enzyme expression in preclinical animals and children, models are also needed, Incorporation of ontogeny-related changes in preclinical testing is essential and requires additional attention to enable translation from the preclinical animal models to children, and the differences in patient necessities between different subgroups need to be considered to provide patient-centric medicines for pediatric patients.

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