JPPT | 2024 Yaffe Award Lecture

Creativity in Pediatric Clinical Pharmacology: Study Design and Oral Dosage Forms

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ABBREVIATIONS AUC, area under the concentration-time curve; BPCA, Best Pharmaceuticals for Children Act; C_{max}, maximum concentration; C_{min}, minimum concentration; CYP, cytochrome P450; FDA, US Food and Drug Administration; GA, gestational age; IND, investigational new drug application; MIC, minimum inhibitory concentration; NDA, new drug application; NEC, necrotizing enterocolitis; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; NICU, neonatal intensive care unit; PK, pharmacokinetics; PMA, post-menstrual age; PNA, post-natal age; PREA, Pediatric Research Equity Act

KEYWORDS Best Pharmaceuticals for Children Act; neonatal; pediatric; pediatric clinical trials; population pharmacokinetic modeling

J Pediatr Pharmacol Ther 2024;29(6):564–569

DOI: 10.5863/1551-6776-29.6.564

The Best Pharmaceuticals for Children Act[1] (BPCA) and the Pediatric Research Equity Act[2] (PREA) are companion legislations enacted to improve pediatric labeling. BPCA has 2 sections, for on-patent and for off-patent drugs. The BPCA on-patent process provides an additional 6 months of marketing exclusivity to the pharmaceutical manufacturer/new drug application (NDA) holder in exchange for performance and submission of pediatric labeling studies. The off-patient process was delegated to the National Institutes of Health (NIH), and then to the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development[3] (NICHD). The NICHD role consists of prioritization of drugs in need of improved labeling, performance of studies in accord with the Written Request negotiated with and issued by the US Food and Drug Administration (FDA), and submission of those data to the FDA for consideration of labeling change. The purpose of this paper to talk about some of those labeling studies performed under the BPCA legislation by NICHD.

The NICHD, and the Obstetric and Pediatric Pharmacology and Therapeutics Branch, has developed and overseen the studies under BPCA for pediatric labeling. The complete listing of the off-patent labels developed by NIH/NICHD are available online.[4–6]

Specific issues with pediatric clinical trials include: need for competent, trained pediatric clinical investigators and study staff familiar and comfortable in working with children and their families, need for minimally invasive procedures, small volume blood draws and potential development and expansion of dried blood spot analyses, maximal use of sparse sampling techniques, population pharmacokinetic (PK) analyses, age-appropriate study procedures and study endpoints, study procedures that are developed in consideration of the child (e.g., missed school) and the child's family (e.g., missed work), and age-appropriate formulations. All clinical trial activities should be compliant with current Good Clinical Practice guidelines,[7] making all results auditable by regulatory agencies, to be included in product labeling.

Neonates have been a particularly difficult population to study, for all of the above reasons as well as: medical frailty, conditions in neonates that occur only in neonates, and small blood volume for sampling. For reference, total blood volume is ~ 80 mL/kg, or 40 mL in a 500 g premature neonate, 3% of which can be drawn over a 24-hour period, which translates to 1.2 mL. There is a pressing need for neonatal-appropriate clinical outcome measures. Pulmonary arterial hypertension would be a classic example, where the 6-minute walk test is the clinical outcome measure as a biomarker of pulmonary artery pressure in ambulatory patients, whereas in neonates an invasive pulmonary pressure is required. Incorporation of pediatric extrapolation principles simplified several of the clinical trials, eliminating the need to prove efficacy while requiring dosing and safety data.[8]

Full Efficacy, Safety, and Dosing Studies

A blinded, active comparator trial comparing lorazepam and diazepam for status epilepticus was performed, using exception from informed consent for the first time in children.[9] In 273 children aged 3 months to 17 years of age from 11 US sites, "Cessation of status epilepticus for 10 minutes without recurrence within 30 minutes occurred in 101 of 140 (72.1%) in the diazepam group and 97 of 133 (72.9%) in the lorazepam group. Twenty-six patients in each group required assisted ventilation. There were no statistically

significant differences in secondary outcomes except that lorazepam patients were more likely to be sedated."[10] These results have been incorporated into the evidence-based treatment guidelines of the American Epilepsy Society.[11]

A double-blind, placebo-controlled trial of lithium for bipolar I disorder in 81 children and adolescents aged 7 to 17 years showed efficacy, as measured by improvement of the Youth Mania Rating Scale,[12] in children randomly assigned to lithium compared with placebo. Overall Clinical Global Impression-Improvement scores were also significantly better with lithium than placebo. Thyrotropin was increased in the lithium group, which is a known side effect of lithium treatment. The FDA label for lithium[13] is available online.

A randomized, double-blind, parallel group, dose-ranging, effect-controlled multicenter study on the effects of sodium nitroprusside in pediatric patients requiring controlled hypotension was performed. The sodium nitroprusside trial[14] demonstrated dose-dependent blood pressure reduction in 203 children less than 17 years of age who were randomized to 0.3, 1, 2 and 3 µg/kg/min. There were no measurable cyanide concentrations in the enrolled patients, which has been a safety concern as sodium nitroprusside is metabolized to cyanide. A starting infusion rate of 0.3 µg/kg/min appears reasonable.[14] The sodium nitroprusside label[15] is available online.

Neonatal and Infant Trials using Full Extrapolation

Neonates are newborns aged from birth to 28 days, and a full-term gestation is 40 weeks. Frequently, neonatal conditions are related to prematurity, some as young as 23 weeks. Premature infants have immature and/or poorly functioning organs; premature and immature kidneys and their liver cannot eliminate drugs as quickly as mature organs, leading to the delayed elimination of drugs cleared through those organs. The immature neonatal brain may not properly innervate the breathing center in the brainstem, leading to apnea of prematurity. The neonatal gut is prone to necrosis (necrotizing enterocolitis [NEC]), of unclear etiology but possibly related to infection. An immature immune system leads to systemic bacterial, viral, and fungal infections.

Associated issues include: how to do a PK study in a neonate weighing 500 g, how to minimize the blood volume removal, what kind of sampling strategy can be used (e.g., sparse sampling, use of scavenged blood/urine samples), and development of highly precise quantitative, reproducible assays capable of accommodating a very small volume of plasma (10–25 µL). As noted above, neonatal total blood volume is approximately 80 mL/kg, or 40 mL in a 500 g premature neonate, 3% of which can be drawn over a 24-hour period, which translates to 1.2 mL. Very small volume, less than 100 µL assays are therefore necessary for PK studies in neonates.

Infants in the neonatal intensive care unit (NICU) are often treated with many medications, most not FDA labeled for neonates, so doses are a best estimate. Several BPCA studies have addressed this question, leading to new labels for neonatal and infant dosing.

Our first neonatal study was for meropenem to treat complicated, or suspected, intra-abdominal infections (the labeled indication), leading to the first neonatal dosing recommendations in a label (see Table 1). Two hundred pre-term and term infants less than 91 days of age were enrolled from 24 NICUs.[16] The safety question, seizure incidence, was resolved by data from a large data collection from NICUs, showing that meropenem was not associated with an increase in seizure frequency from baseline.[17,18]

PK sampling consisted of sparse sampling and scavenged samples (samples which were drawn for other purposes). An assay was developed for 50 µL of plasma.[19] PK data were then analyzed and stratified by gestational age to develop dosing guidelines to achieve a time above minimum inhibitory concentration (MIC) for multiple neonatal ages. The meropenem label is available online.[20]

Ampicillin is administered as standard of care for potentially infected neonates, which has lacked neonatal labeling for dosing in the premature neonate, and possible increased seizure frequency.

An opportunistic study design was used: enrolling 75 neonates who were already receiving ampicillin for

Table 1. Recommended Meropenem for Injection Dosage Schedule for Pediatric Patients Less Than 1 Month of Age With Complicated Intra-Abdominal Infections and Normal Renal Function

Age Group	Dose (mg/kg)	Dose Interval
Infants less than 32 wk GA and PNA less than 2 wk	20	Every 12 hr
Infants less than 32 wk GA and PNA 2 wk and older	20	Every 8 hr
Infants 32 wk and older GA and PNA less than 2 wk	20	Every 8 hr
Infants 32 wk and older GA and PNA 2 wk and older	30	Every 8 hr
There is no experience in pediatric patients with renal impairment.		

GA, gestational age; PNA, postnatal age

clinical care, a PK sampling approach to minimize the volume of blood draws and to coincide with already-scheduled blood draws, and an assay using 10 µL plasma. A PK model was developed for gestational age groups to assure that the time above MIC (8 µg/mL for *Escherichia coli*) was greater than or equal to 90%.[21–24] The dosing regimens for ampicillin, now in the label,[25] are in the Table 2. Using electronic health records, greater ampicillin exposure was associated with seizures.

Acyclovir

Neonatal herpes simplex virus (HSV) infections are life-threatening, and can cause long-term neurodevelopmental disability. Acyclovir is the drug of choice for treatment, but optimal dosing has been unknown. In a study of 28 infants less than 31 days postnatal age, a PK model was developed to achieve an acyclovir concentration greater than or equal to 3 µg/mL for greater than or equal to 50% of the dosing interval.[26] Safety of acyclovir was assessed using electronic medical records, acyclovir exposure was not related to adverse events.[27,28] The dosing guidelines for acyclovir are in the Table 3 and in the label,[29] demonstrating the increase in clearance with gestational age.

Fluconazole

Fluconazole, an antifungal agent, is used to treat premature neonates with suspected or confirmed fungal infections.[30] Because there is a delay in achieving therapeutic fluconazole concentrations, a loading dose has been used in children and adults, but has not been tested or used in neonates and infants. Nine infants requiring antifungal treatment received a 25 mg/kg loading dose of fluconazole, and PK sampling was performed in 8 of the infants. Five infants achieved therapeutic concentrations on day 1 of dosing, and there were no safety signals.[31] Recommended fluconazole dosing, from the updated label, is shown in Table 4.[32]

Table 2. Ampicillin Dosage in Neonates (Less Than or Equal to 28 Days of Postnatal Age) for Bacterial Meningitis and Septicemia

Gestational Age (wk)	Postnatal Age (days)	Dosage
Less than or equal to 34	Less than or equal to 7	100 mg/kg/day in equally divided doses every 12 hr
Less than or equal to 34	Greater than or equal to 8 and less than 28	150 mg/kg/day in equally divided doses every 12 hr
Greater than 34	Less than or equal to 28	150 mg/kg/day in equally divided doses every 8 hr

Clindamycin

Clindamycin is an antibacterial agent commonly used to treat gram-positive (including methicillin-resistant Staph aureus) and anerobic infections, among others. Two studies were performed with clindamycin, in neonates and in children with obesity. Optimal dosing and safety in infants drove this study, along with a safety assessment. Clindamycin is metabolized by CYP3A4, and its clearance would be expected to be reduced in neonates and infants of a younger gestational age. A population PK study was performed in 62 infants with a median gestational

Table 3. Acyclovir Pharmacokinetics in Neonates Aged from Birth to 3 Months

Post-Menstrual Age (PMA)	n	IV Dose*
< 30 wk	13	500 mg/m² every 8 hr or 10 or 20 mg/kg every 12 hr
30 to <36 wk	9	500 mg/m² every 8 hr or 10 or 20 mg/kg every 12 hr or 20 mg/kg every 8 hr
36 to 41 wk	6	500 mg/m² every 8 hr

IV, intravenous

* Administered over 1 hr.

Table 4. Recommended Fluconazole Dosing Regimens for the Treatment of Systemic Candida Infections in Pediatric Patients

Patient Age	Dosing Regimen
3 mo and older	A loading dose of 25 mg/kg on the first day (not to exceed 800 mg), followed by 12 mg/kg once daily (not to exceed 400 mg)
Birth to 3 mo postnatal age and gestational age 30 wk and above	25 mg/kg on the first day, followed by 12 mg/kg once daily
Birth to 3 mo postnatal age and gestational age less than 30 wk	25 mg/kg on the first day, followed by 9 mg/kg once daily

age of 28 weeks and postnatal age less than or equal to 120 days, from 8 sites. Modeling and simulation, from PK data from three pediatric trials, provided dosing recommendations based on post-menstrual age to achieve an adequate concentration to treat methicillin-resistant Staph aureus.[33,34] The updated clindamycin labeling for neonatal dosing is available in the label, and in Table 5 (below).[35]

Obesity has become a major health problem globally, and a challenge to determine appropriate drug dosing. PK samples were collected from children already receiving clindamycin for a clinical indication (an opportunistic study). A virtual PK model was developed incorporating US demographic data, lab data from multiple studies, and organ size and blood flow estimates to predict volume and clearance changes in the obese pediatric population. Of note, the Schwartz equation was similar to the simulated GFR in the model. The upshot of this project was that the current dosing recommendations achieved desired drug concentrations in children with obesity.[36]

Conclusions

The preciousness of these neonatal/pediatric resources, and the need to waste nothing in the course of these trials, is an ongoing theme. Embedded in these trials is clinical research/clinical trials training, so although one trial is being performed, clinical trials knowledge and infrastructure is being developed for future clinical trials. Training is also available through free on-line courses at the National Institutes of Health for clinical research (Introduction to the Principles and Practice of Clinical Research)[38] and clinical pharmacology (Principles of Clinical Pharmacology).[39]

The ongoing problem of a lack of pediatric dosage forms has not been solved. Doing the math for a neonatal dose of meropenem (commercially available in 500 mg and 1 g vials), 20 mg/kg × 0.5 kg = 10 mg. For the pharmacist, this requires serial dilutions and an acute need for accuracy. The lack of swallowable and palatable oral dosage forms in the correct pediatric dose remains a problem, despite the statistic that many adults also have difficulty swallowing large tablets and capsules, leading to at-home dosage form modifications.[37] The use of 3D printing, for smaller batches that tend not to be commercially viable, might be one technological solution. Levetiracetam, an antiepileptic agent, is the only 3D printed FDA approved, commercially available oral dosage form. Use of 3D printing to make isoleucine tablets for maple syrup urine disease produced tablets of various palatable round sizes, colors and flavors.[40] Increasing use of 3D printing technologies could provide new opportunities in polymer chemistry, pharmaceutics, and engineering.[41]

In summary, pediatric clinical trials sponsored by NICHD have improved pediatric labeling and the health of neonates and children. There is considerable room for improving swallowable, palatable dosage forms which will benefit children and adults.

Table 5. Predicted Drug Exposure (Mean ± SD) of Clindamycin in Adults and in Pediatric Patients with PMA ≤ 32 wk, or >32 to ≤ 40 wk

Age	Adult (70 kg)	PMA ≤32 wk	PMA >32-≤40 wk
Dose (every 8 hr)	600 mg	5 mg/kg	7 mg/kg
$AUC_{ss,0\text{-}8\ hr}$ mcg-h/mL	50.5 (30.95)	52.5 (17.0)	55.9 (23.55)
$C_{max,ss}$ (mcg/mL)	12.0 (3.49)	9.0 (2.02)	10.5 (2.79)
$C_{min,ss}$ (mcg/mL)	3.1 (3.34)	4.6 (2.00)	4.4 (2.77)

$AUC_{ss,0\text{-}8\ hr}$, area under the concentration-time curve during a dosing interval at steady state; $C_{max,ss}$, maximum drug concentration at steady state; $C_{min,ss}$, minimum or trough drug concentration at steady state; PMA, post-menstrual age

Article Information

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Disclosures. Anne Zajicek, MD, PharmD has retired from the National Institutes of Health effective July 31, 2024. The author declares no conflicts or financial interest in any product mentioned in the manuscript. The opinions stated are those of the author, and are not representative of the National Institutes of Health, the Department of Health and Human Services, or the US Government.

Acknowledgements. I would like to acknowledge the work of my colleague Perdita Taylor Zapata, MD, Program Director of the Best Pharmaceuticals for Children Act at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the editorial assistance of Rebecca Hwang.

Submitted. August 29, 2024

Accepted. August 29, 2024

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