The Newborn Drug Development Initiative

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ABSTRACT

The Best Pharmaceuticals for Children Act (BPCA; Pub L 107-109) was enacted in January 2002 and will sunset in October 2007. The BPCA established processes for studying off-patent and on-patent drugs that are used in pediatric population. Although some drugs have been successfully developed for the neonate (eg, surfactant, nitric oxide), drug development for the youngest, least mature, and most vulnerable pediatric patients is generally lacking. Most drugs are empirically administered to newborns once efficacy has been demonstrated in adults and usefulness is suspected or demonstrated in the older pediatric population. Unfortunately, this process undermines the ability to perform the appropriate studies necessary to demonstrate a drug's short- and long-term safety and efficacy and establish appropriate dosing in neonates. The Newborn Drug Development Initiative Workshop I (held March 29–30, 2004) specifically addressed scientific, clinical, and ethical concerns in the development of trials of pediatric therapeutic agents for neonates. Implementation of the BPCA for all pediatric populations will foster collaboration among federal agencies and academic institutions on scientific investigation, clinical-study design, and consideration of the weight of evidence and address ethical issues related to the performance of drug studies.

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The views presented in these supplement articles do not necessarily reflect those of the Food and Drug Administration (FDA) or the National Institute of Child Health and Human Development. The supplement articles reflect discussions of designing clinical trials in newborns and should not be construed as an agreement or guidance from the FDA. Drug development and clinical-trial design should be discussed with the relevant review division within the FDA.

Key Words
clinical research/trials, neonatology, clinical-trial design

Abbreviations
BPCA—Best Pharmaceuticals for Children Act
FDA—Food and Drug Administration
NIH—National Institutes of Health
NICHD—National Institute of Child Health and Human Development
NDDI—Newborn Drug Development Initiative

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ALTHOUGH SOME DRUGS have been successfully developed for the neonate (eg, surfactant, nitric oxide), drug development for the youngest, least mature, and most vulnerable pediatric patients is generally lacking. Most drugs are empirically administered to newborns once efficacy has been demonstrated in adults and usefulness is suspected or demonstrated in the older pediatric population. Unfortunately, this process undermines the ability to perform the appropriate studies necessary to demonstrate a drug's short- and long-term safety and efficacy and establish appropriate dosing in neonates.

The Best Pharmaceuticals for Children Act (BPCA; Pub L 107-109) was enacted on January 4, 2002, and will sunset in October 2007. The BPCA established processes for studying off-patent drugs and an alternative process for studying on-patent drugs that are used in the pediatric population. These trials of pediatric therapeutic agents will address inadequate or absent pediatric safety, efficacy, and dosing information on drug labels, including information for the neonate. Implementation of the BPCA will foster collaboration among federal agencies and academic institutions on scientific investigation, clinical-study design, and consideration of the weight of evidence and address ethical issues related to the performance of drug studies on children.

The BPCA directs the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) via the off-patent written-request process to review available literature and, when appropriate, publish a request for contract to conduct clinical studies on children for selected older drugs that are already approved and marketed for adults. Within the NIH and FDA, this task has been delegated to the National Institute of Child Health and Human Development (NICHD) and the Center for Drug Evaluation and Research, respectively.

As part of the activities implementing BPCA provisions, the NICHD and FDA are collaborating with neonatal experts and colleagues, representing industry and academia, as well as practitioners, on the Newborn Drug Development Initiative (NDDI). The NDDI will explore innovative approaches to improving clinical-trial design for preterm and term neonatal populations with the goal of facilitating the study and ultimately labeling more drug therapies in these heterogeneous and complex populations.[1]

NDDI

Several compelling reasons prompted the establishment of the NDDI. Perhaps the most important is the fact that few drugs have been tested or labeled for use in newborns, especially premature infants. Studies regarding drug usage in neonatal intensive care units (NICUs) suggest that 90% of neonates in these units received at least 1 drug without adequate labeling to guide its use in this special population.[2] Recent surveys demonstrated that 47% to 59% of prescribed drugs that are used in a NICU were used off-label, primarily because the drugs were not approved for either the population or the prescribed indication.[2,3] The paucity of adequate trials in neonatal populations is due in part to the unique physiology and developmental diversity of newborns, which may impact both the efficacy and toxicity of the drugs.[4]

The physiologic characteristics of low birth weight infants may affect the pharmacokinetics of drugs. Factors affecting the oral bioavailability of drugs include decreased acid secretion,[5] prolonged intestinal transit time,[6] and a decreased bile acid pool.[7] Skin permeability is increased in very low birth weight infants, favoring the dermal absorption of topically applied drugs.[8] The relatively small muscle mass and decreased muscle blood flow in low birth weight infants may slow the absorption rate of drugs administered by the intramuscular route.[9] Decreased plasma protein binding of drugs[10,11] and sparse amount of body fat in low birth weight infants compared with term infants[12] affects the distribution of lipid-soluble drugs. Similarly, the distribution of water-soluble drugs may be increased in low birth weight infants because of their larger extracellular volume compared with term infants.[13] Low renal blood flow[14] and patent ductus arteriosus[15] during the first few days can markedly influence drug distribution through the body. Moreover, the low glomerular filtration rate in low birth weight infants[16] may lead to the accumulation of those drugs that are eliminated primarily by the kidneys, necessitating dose adjustment.[17] At birth, renal tubules exhibit significant functional immaturity. The major renal tubular transport systems are less developed in infants of <34 weeks of gestation.[18]

In addition to the developmental differences, the pathophysiologic changes associated with the various neonatal conditions and diseases can markedly affect the biodisposition and pharmacologic effect of drugs. Drug studies in the neonatal population are performed frequently after the pathophysiologic abnormalities revert to normal and may not be generalizable to sick infants. Validated outcome measures in neonatal populations are frequently absent. Specifically, the relationship between clinical end points and outcomes, particularly outcomes linked to meaningful benefits, has not been well characterized. Moreover, variable study designs in the few trials that have been performed do not permit comparison between studies and/or meta-analysis. Finally, few suitable neonatal formulations have been licensed, which may promote dosing errors that lead to adverse events[19,20] and the use of extemporaneous formulations, which lack bioavailability information.[21]

The concern about lack of knowledge of adverse drug reactions in pediatric populations, and especially in neonatal age groups, is well-founded. For example, the review by Impicciatore et al[22] suggests that adverse drug reactions in pediatric populations are a significant public

health problem. In this systematic review, a significant proportion (39%) of the adverse drug reactions that led to hospitalization was fatal or severe in children. The potential risk for adverse drug reactions and medication errors in the newborn population has long been recognized.[23,24] Multiple factors may contribute to an increased susceptibility to adverse drug reactions in this population. These factors include immature-drug detoxification mechanisms,[25–27] multiple drug exposures, coexistence with multiple organ dysfunction, use of concentrated drug solutions, and the presence of toxic excipients or adjuncts in injectables[28,29] and/or formulations for oral use.[30] The information on adverse drug reactions in the preterm infant population is quite limited; some experts recommend the need for an active surveillance system.[31]

Several research requirements have been identified in the preclinical and clinical phases of the drug-development process in neonates and preterm infants. Although, for example, some cell cultures can be used to define the mechanism of action of some drugs, how these systems mature in neonates and how maturation affects pharmacodynamics needs to be determined. Identifying juvenile animal models that are analogous to both mature and premature human infants for all aspects of pharmacokinetics and pharmacodynamics is challenging. Indeed, animal models may yield conflicting information because of species-dependent variations in pharmacologic or toxic effects. The current controversy over the significance in humans of neuronal apoptosis found in neonatal rats after exposure to ketamine and other general anesthetics[32,33] illustrates the difficulty in using animal data to predict toxicity in human newborns.

Additional important components in the clinical development of drugs for neonates include developing age-appropriate formulations for both oral and intravenous drugs, identifying appropriate measures to use in pharmacokinetic and pharmacodynamic studies,[34] validating surrogates that correlate with clinical end points or outcomes in neonatal populations, and characterizing adverse events in a highly confounded population. The pharmacokinetics of drugs in both large- and small-for-gestational-age infants is likely to differ from that exhibited by their appropriate-for-gestational-age counterparts. These subpopulations have not been studied adequately. Finally, technical limitations in small infants (eg, small blood volume, unavailability of appropriate catheter sizes) may influence the feasibility of performing trials.

FDA requirements regarding the collection of data to characterize safety and effectiveness for labeling products for newborns must be considered in the design of clinical trials for newborns. Safety and effectiveness usually need to be proven by 2 adequate, well-controlled multicenter trials. Occasionally, 1 trial will suffice when other evidence, such as published medical literature or approval of the product for a similar condition in another age group, supports safety and effectiveness. Although extrapolation from older populations is permissible when the disease process is the same and the effect of the drug is similar, it is unfortunate that many neonatal conditions are unique; therefore, extrapolation is not appropriate (eg, necrotizing enterocolitis, intraventricular hemorrhage, patent ductus arteriosus, respiratory distress syndrome, bronchopulmonary dysplasia).

The NDDI is envisioned as an opportunity for experts in neonatal pediatrics, clinical-trial design, pathophysiology, and pharmacology to guide and inform the design of clinical trials for drugs in newborns under the BPCA. This initiative provides a unique opportunity to bring together pediatric researchers and federal regulators to harmonize academic studies of drugs in newborns, thereby promoting research and innovation in newborn therapeutics.

THE NDDI WORKSHOP I (MARCH 29–30, 2004)

The NICHD and FDA convened the first NDDI workshop to help frame issues and challenges in the design and conduct of clinical trials of drugs in preterm infants and neonates. Neonatologists, pediatric subspecialists, pediatric clinical pharmacologists, ethicists, biostatisticians, representatives of industry, and representatives of the 2 sponsoring agencies gathered to provide input in the first step of a continuum of activities designed to help the NICHD and FDA implement the BPCA.

The NDDI Workshop I was the first in a series of meetings that will examine the state-of-the-science and define research priorities for drug development for specific diseases and conditions in neonates. The first phase of the NDDI began with the formation of discussion groups in February 2003 and concluded with the workshop on March 29 and 30, 2004. This workshop addressed ethical issues and drug prioritization in neonates (to be reported later) as well as 4 therapeutic areas: (1) pain control; (2) pulmonology; (3) cardiology; and (4) neurology. Subsequent phases will involve additional groups and workshops that are focused on other therapeutic areas as well as a final evaluation phase. The goal for the final evaluation will be to identify and prioritize specific issues in neonatal drug development.

Objectives for the NDDI Workshop I included:

- categorizing diseases and conditions that are unique to neonates in etiology, pathophysiology, clinical manifestations, and clinical or laboratory measurements in the fields of cardiology, pulmonology, neurology, and pain control;
- recognizing which newborn conditions within these specialty areas differ in response to therapy from that in older children and adults;

- identifying drugs to treat these conditions for which no appropriate formulation is available for term and preterm infants; and
- harmonizing the design, methodology, performance, and monitoring of academic and industry-sponsored studies to allow the use of the data generated to support the labeling of these drugs.

An additional objective for the groups was to develop publications as resources for the FDA, industry, NIH, and non-NIH networks that desire to conduct clinical trials in neonatal populations. These publications will serve as the scientific underpinnings of such studies by providing:

- definitions for the most common neonatal conditions and diseases, with inclusion and exclusion criteria;
- state-of-the-art reviews that identify gaps in the scientific knowledge base for the treatment of these conditions;
- outcome measures (eg, primary and secondary clinical efficacy end points) and potential biomarkers of efficacy and toxicity; and
- consideration of extrapolation issues (eg, the applicability of outcome measures for similar conditions in older children and adults).

The clinical-trial–issues papers developed by group members from February 2003 through March 2004 formed the foundation for both the publications and workshop discussions. Each group was asked to propose a framework for potential clinical-trial designs based on their background papers. The proposed clinical-trial frameworks were to include information such as the suggested study population (eg, stratification, age at study), biomarkers (eg, for diagnosis, efficacy, and toxicity), drug prioritization and formulations, ethical and feasibility issues, treatment end points, outcome variables, and long-term outcomes. However, it was acknowledged that not all groups would be able to identify or agree on all aspects of the clinical-trial design for their therapeutic area. Moreover, the goal was not to achieve consensus but to suggest strategies for designing and conducting clinical trials, which would help build a better understanding of drug development and therapeutic approaches for both preterm and term neonates.

On the first day of the workshop, each therapeutic work group gave a plenary presentation on the clinical-trial issues and potential clinical-trial frameworks to be addressed during the breakout sessions. Each group then met in concurrent breakout sessions. Participants in breakout sessions included reactors to the clinical-trial–issue papers, representatives of the ethics and drug-prioritization groups, representatives from the NIH and FDA, and members of the general public. On the second day of the workshop, the 4 therapeutic work groups presented highlights of their discussions of clinical-trial issues. The ethics group summarized major themes that emerged from the breakout discussions. The drug-prioritization group suggested factors that could help identify which drugs are most important for study in neonates.

GROUP RECOMMENDATIONS

The 4 discussion groups focused on the therapeutic areas of pain control, pulmonology, cardiology, and neurology. This supplement summarizes the issues, proposed clinical-trial frameworks, and other suggestions presented by the groups to the full assembly of workshop participants (see pages iv–ix of this supplement for a listing of the membership of the work groups). Experts in the areas addressed by the 4 discussion groups that were not involved in the preworkshop discussions were invited to serve as reactors during the deliberations. The reactors reviewed the articles and made editorial suggestions. The articles in this supplement describe in more detail the background factors that provided the context for discussion, the proposed clinical-trial frameworks, study-design issues, and the deliberations that occurred during the workshop.

Cardiology

The cardiology group's mandate was to focus on the use of inotropes (eg, dopamine and dobutamine) in low birth weight neonates. The group considered 2 neonatal populations: (1) very low birth weight infants with cardiac instability and (2) neonatal postoperative cardiac patients.

- The cardiology group proposed 2 potential frameworks for clinical trials in these populations: (1) a placebo-controlled trial with rescue for symptomatic infants and (2) a targeted blood-pressure study. In the blood-pressure–target study, infants would be assigned randomly to 1 of 2 target blood pressures and receive infusions of selected inotropic agents to maintain the target blood pressure. The group concluded that it needed more input from neonatologists concerning the feasibility of each trial. The major unresolved issues included whether a placebo-controlled study, although preferred scientifically, would be acceptable given the widespread use of dopamine and dobutamine in combination throughout US NICUs. Selection of appropriate blood-pressure targets (permitting discrimination between groups without creating toxicity in the upper target) was the issue for the targeted–blood-pressure study. The role of rescue therapy and steroids, which are given empirically to treat presumed adrenocortical insufficiency in very low birth weight infants, is a problematic area for both study designs. The group concluded that the most informative study of inotropes in neonates would be a prevention trial, with the primary recommended out-

come of survival without evidence of intraventricular hemorrhage or periventricular leukomalacia. The trial would enroll premature infants with birth weights of 500 to 1000 g.

- The cardiology group presented a general framework of study-design considerations for neonatal postoperative cardiac patients. The members agreed that a design for studying vasoactive agents would be a superiority trial that would compare 2 established agents (eg, dopamine or epinephrine, combination therapy) without using a placebo. Alternatively, a randomized withdrawal study was proposed. The group decided to discuss an appropriate primary end point with members of the Pediatric Cardiac Intensive Care Society at their biannual meeting.

Neurology

The neurology group focused its discussion on 2 areas: (1) seizures in the newborn and (2) hypoxic-ischemic encephalopathy and neuroprotection. The group presented the following suggestions about clinical-trial frameworks.

- After exploring 3 possible frameworks for clinical trials of phenobarbital in the treatment of electroencephalographic neonatal seizures, the group proposed a multicenter, placebo-controlled, blinded prevention trial of phenobarbital versus placebo in a homogeneous population of term infants (≥37 weeks' chronological age) who are at high risk for electroencephalographic neonatal seizures. The study would use continuous video-electroencephalographic monitoring to establish the presence and number of seizures (subclinical or clinical).
- The neurology group was unable to develop a definitive framework for the study of neuroprotective strategies for neonatal encephalopathy. However, they identified key elements for a potential clinical-trial framework comparing hypothermia to hypothermia plus additional therapies for moderate to severe encephalopathy.

Pain Control

The pain-control group identified 3 prioritized areas of pain control in newborns: (1) procedural pain, (2) perioperative pain, and (3) pain associated with mechanical ventilation. Potential study designs for evaluation of a drug for treatment of pain occurring in various settings were discussed and evaluated. Emphasis was placed on the need for better outcome measures to evaluate pain in neonates. Recommendations for clinical-trial frameworks included:

- For procedural-pain studies, a blinded, randomized, controlled trial to investigate the efficacy, safety, and pharmacokinetics of a study drug for heel-stick pain was discussed. The proposed design included 3 study groups stratified according to gestational age (23–42 weeks). The comparator therapies discussed for the proposed randomized, controlled trial included the role of placebo therapy (for the youngest gestational-age group) and the role of sucrose therapy.
- Proposals for clinical trials for perioperative pain included designs for postoperative analgesia and general anesthesia. The ethical constraint encountered is the inability to have a placebo study arm that withholds analgesia for extended periods of time. Trials for postoperative analgesia may include 1 group that receives placebo and 1 group that receives single or multiple doses of the study drug. However, both arms of the study would require immediate access to rescue analgesia with titratable incremental doses. Studies of general anesthesia could compare an older agent with a newer agent with outcome measures to include determination of minimum alveolar concentration, intraoperative hemodynamic stability, postoperative respiratory function, and time course of recovery from a surgical intervention.
- The proposed design for the study of pain control in mechanically ventilated preterm newborns was a randomized, double-blind, placebo-controlled trial of an analgesic with or without sedation in premature newborn infants who are stratified into 3 groups according to birth weight. The hypothesis discussed by the group was the role of intravenous analgesia with or without sedation in decreasing pain experience and opiate need in mechanically ventilated preterm newborns.

Pulmonary

The pulmonary group divided into separate breakout sessions on apnea of prematurity and bronchopulmonary dysplasia. The group presented the following recommended frameworks.

- A randomized, blinded, multicenter, placebo-controlled trial to study whether there is any difference in outcome between patients managed with a specific drug (eg, caffeine) for apnea of prematurity versus placebo. Neonatal groups would be stratified by birth weight, ranging from <800 to 1500 g.
- Components of the group's proposed bronchopulmonary dysplasia clinical-trial framework would vary according to the different phases of the disease. However, the overall design would include a placebo-controlled, randomized trial, without crossover, in infants of <32 weeks' gestational age.

Ethics

Members of the ethics group were integrated into the various therapeutic groups. Although issues and proposed study designs varied among the different groups,

the ethical issues involved in designing studies that seek to validate current or emerging medical practice were similar. The ethics group identified the following major themes emerging from the discussions of the other work groups:

- whether it is necessary to conduct a clinical-trial study in neonates (ordinarily, trials that can be conducted in a less vulnerable population should be performed before being brought to the NICU);
- how to balance risks and potential benefits to neonates in clinical trials (eg, component analysis of risks, equipoise and the choice of control group, ethics of "off-label" practice; risks and benefits may be particularly difficult to assess in a setting in which the patients are exquisitely vulnerable and much of the established practice has developed without controlled studies);
- the process of obtaining parental permission in a context of duress, sometimes under time pressure;
- efficiency and effectiveness of research oversight, including review by institutional review boards; and
- multicenter collaboration.

Drug Prioritization

The goal of the drug-prioritization group was to determine factors that identify which drugs are most important for study in neonates, especially when resources are limited. A secondary goal was to develop a list of criteria that would help to inform the NIH listing process. The drug-prioritization group used 5 categories (ie, disease/indication, evidence, drug, feasibility, and ethics) to describe factors that it considered important for studying drugs in newborns.

Members of the ethics and drug-prioritization groups served as resources for the 4 therapeutic groups. These 2 groups are continuing their deliberations, and their recommendations will be published at a later date.

CONCLUSIONS

Workshop participants noted the areas of overlap among clinical-trial frameworks that were presented at the meeting. For example, several frameworks identified similar research questions, study-design issues, study populations, study drugs, and/or outcomes. Many common themes emerged from each group. Evidence-based information, even regarding commonly used therapies, is lacking. Thus, placebo-controlled trials may be both scientifically and ethically appropriate in certain situations in which the standard of care is undefined. One of the most challenging and pervasive aspects of performing trials in the newborn population is the existence of entrenched treatment practices that are not evidenced-based for either safety or efficacy. These practices frustrate efforts to design feasible studies and enroll study patients. Informed-consent issues must be addressed. All studies require long-term neurodevelopmental outcomes. Performing the studies will be challenging because of multiple confounding variables. Enrolling the same patients in multiple studies raises many practical, scientific, and ethical issues. Therefore, cooperation will be necessary, because many studies will be targeting a similar, limited population. One challenge for the NDDI will be to identify and address common elements among the groups' proposed frameworks to apply them to a broadly generalizable template for drug development. Alignment of vision among practicing neonatologists, academicians, and regulators is essential for further advances. Progress can only be made by the combined efforts of federal agencies that fund research in newborns, pharmaceutical companies, and research foundations. Determining the gaps in knowledge is the first step in solving the problem. Areas of additional research include the natural history of neonatal conditions, pathophysiology (eg, shock, hypotension in preterm infants), development of noninvasive pharmacodynamic measurements, and validated outcome measures of a number of drugs used for specific indications.

Another major challenge ahead will be to close the gap in the current understanding of the ontogeny of drug-metabolizing enzymes, transporters, and receptors in the early neonatal period and the identification of clinically significant long-term consequences of drug exposure in a critical phase of human development.

FUTURE AND ONGOING ACTIVITIES

The study-design frameworks and/or end points proposed by the initial groups will be considered by the NICHD in the requirements for BPCA contracts for the study of off-patent drugs in the newborn population. Other ad hoc groups will be convened when necessary to address frameworks for other therapeutic areas or indications.

The large number of patients needed to demonstrate the efficacy and safety of drugs and the limited number of newborns, particularly preterm infants, is a major obstacle for the performance of drug studies. Innovative study designs and additional development of small sample biostatistical strategies to prove efficacy are needed. The development of a new group in study design and biostatistics is currently being considered.

Another major impediment to drug studies in newborns is current therapeutic practices that are not evidence-based but have become de facto standards of care. Increased awareness by neonatologists of the need to prove the efficacy of drugs and to remove ineffective drugs from practice is urgently needed. Workshop participants proposed to evaluate practice standards and how they will impact the feasibility of conducting efficacy trials for BPCA-related trials.

Ethical concerns are of paramount importance, par-

ticularly when drugs are used in emergency conditions. Ethical principles in the neonatal population are evolving as newer approaches to study design are developed and as newer therapies, drug-delivery systems, and diagnostic imaging (eg, positron emission tomography scanning) are applied to newborn studies.[35,36] The ethics group will continue to serve as a resource to the other work groups.

The large number of drugs that require study, coupled with limited resources, dictates the need to prioritize the drugs for study in neonatal populations. Additional refinement of the prioritization scheme developed by the drug-prioritization group will be undertaken. The group is to survey practicing neonatologists to test the feasibility of using the weighted scale to identify key discriminating variables and simplify its use. Using the new prioritization system then can be incorporated in the drug-prioritization list process for off-patent drugs mandated by the BPCA and entrusted to the NIH in consultation with the FDA and other experts.

The lack of appropriate formulations for preterm and term infants will be addressed during a new pediatric formulation initiative currently in process at the NICHD. A workshop is being planned as part of this initiative that will identify scientific issues for the development of pediatric formulations, new methods of drug delivery (eg, use of dendrimers and inhalation devices for drug delivery in young infants,[37–39] economic barriers, research on taste and flavor preferences in infants and children, and methods to facilitate the development and approval of pediatric formulations.

Research needs identified by the work groups will be reviewed in a workshop planned for 2006. During the workshop, experts in the fields of neonatology, pediatric subspecialties, developmental biology, developmental toxicology, and pediatric clinical pharmacology will be gathered to issue recommendations on gaps in knowledge. The newly created Obstetric and Pediatric Pharmacology Branch at the NICHD will have a pivotal role in the conduct of necessary studies.

The NDDI illustrates the benefits derived from implementation of the BPCA. The emphasis on the study of off-patent drugs, including the newborn population, as outlined in the legislation may prove to be a powerful engine to ensure that newborns receive safe and effective drugs. This workshop represents the beginning of an ongoing process that will expand for several years.

REFERENCES

1. Villar J, Abalos E, Carroli G, et al. Heterogeneity of perinatal outcomes in the preterm delivery syndrome. *Obstet Gynecol.* 2004;104:78–87
2. Barr J, Brenner-Zada G, Heiman E, et al. Unlicensed and off-label medication use in a neonatal intensive care unit: a prospective study. *Am J Perinatol.* 2002;19:67–72
3. O'Donnell C, Stone R, Morley C. Unlicensed and off-label drug use in an Australian neonatal intensive care unit. *Pediatrics.* 2002;110(5). Available at: www.pediatrics.org/cgi/content/full/110/5/e52
4. McIntyre J, Choonara I. Drug toxicity in the neonate. *Biol Neonate.* 2004;86:218–221
5. Euler A, Byrne L, Cousins M, Ament E, Walsh J. Increased serum gastrin concentrations and gastric acid hyposecretion in the immediate newborn period. *Gastroenterology.* 1977;72:1271–1273
6. Berseth C. Gestational evolution of small intestine motility in preterm and term infants. *J Pediatr.* 1989;115:646–651
7. Boehm G, Braun W, Moto G, Minoli I. Bile acid concentrations in serum and duodenal aspirates of healthy preterm infants: effects of gestational and postnatal age. *Biol Neonate.* 1997;71:207–214
8. Barret D, Rutter N. Transdermal delivery and the premature neonate. *Crit Rev Ther Drug Carrier Syst.* 1994;11:1–30
9. Radde IC. Mechanisms of drug absorption and their development. In: McLeod SM, Radde IC, eds. *Textbook of Pediatric Clinical Pharmacology*. Littleton, MA: PSG Publishing; 1985:17–43
10. McNamara P, Alcorn J. Protein binding predictions in infants. *AAPS PharmSci.* 2002;4:E4
11. Pacifi GM, Viani A, Taddeucci-Brunelli G, Rizzo G, Carrai M, Schltz HU. Effects of development, aging, and renal and hepatic insufficiency as well as hemodialysis on the plasma concentrations of albumin and alpha 1-acid glycoprotein: implications for binding of drugs. *Ther Drug Monit.* 1986;8:259–263
12. Ellis KJ, Shypailo RJ, Shandler RJ. Body composition of the preterm infant. *Ann Hum Biol.* 1994;21:533–545
13. Hartnoll G, Betremieux P, Modi N. Body water content of extremely preterm infants at birth. *Arch Dis Child Fetal Neonatal Ed.* 2000;83:F56–F59
14. Kluckow M, Evans N. Low systemic blood flow in the preterm infant. *Semin Neonatol.* 2001;6:75–84
15. Williams BS, Ransom JL, Gal P, Carlos RQ, Smith M, Schall SA. Gentamicin pharmacokinetics in neonates with patent ductus arteriosus. *Crit Care Med.* 1997;25:273–275
16. Bueva A, Guignard J. Renal function in preterm infants. *Pediatr Res.* 1994;36:572–577
17. Van den Anker X. Pharmacokinetics and renal function in preterm infants. *Acta Paediatr.* 1996;85:1393–1399
18. Jones D, Chesney R. Development of tubular function. *Clin Perinatol.* 1992;19:33–57
19. Horn L, Kuhn R, Kanga J. Evaluation of the reproducibility of tablet splitting to provide accurate doses for the pediatric population. *J Pediatr Pharm Pract.* 1999;4:38–42
20. Edwards W, Goldmann D, Gray J, et al. Voluntary anonymous reporting of medical errors for neonatal intensive care. *Pediatrics.* 2004;113:1609–1618
21. Nahata M, Hipple T. *Pediatric Drug Formulations*. Cincinnati, OH: Harvey Whitney; 2000
22. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C. Incidence of adverse drug reactions in paediatric in/out patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol.* 2001;52:77–83
23. Aranda J, Portuguez-Malavasi A, Collinge J, et al. Epidemiology of adverse drug reactions in the newborn. *Dev Pharmacol Ther.* 1982;5:173–184
24. Knight M. Adverse drug reactions in neonates. *J Clin Pharmacol.* 1994;34:128–355
25. Blake M, Castro L, Leeder J, Kearns G. Ontogeny of drug metabolizing enzymes in the neonate. *Semin Fetal Neonatal Med.* 2005;10:123–138
26. Hines R, McCarver D. The ontogeny of human drug-metabolizing enzymes: phase I oxidative enzymes. *J Pharmacol Exp Ther.* 2002;300:355–360
27. Mc Carver DG, Hines RN. The ontogeny of human drug-

metabolizing enzymes: phase II conjugation enzymes and regulatory mechanisms. *J Pharmacol Exp Ther.* 2002;300:361–366
28. Glasgow X, Boeck R, Miller M, MacDonald M, August G, Goodman S. Hyperosmolality in small infants due to propylene glycol. *Pediatrics.* 1983;72:353–355
29. Gershanik J, Boecler B, Ensley H, McClosky S, George W. The gasping syndrome and benzyl alcohol poisoning. *N Engl J Med.* 1982;307:1384–1388
30. Kumar P. Issues in the formulation of drugs for oral use in children: role of excipients. *Paediatr Drugs.* 2002;4:371–379
31. Carleton B, Lesko A, Milton J, Poole R. Active surveillance systems for pediatric adverse drug reactions: an idea whose time has come. *Curr Ther Res.* 2001;62:738–742
32. Jevtovic-Todorovic V, Hartman R, Isumi Y, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci.* 2003;23:876–882
33. Anand K, Soriano S. Anesthetic agents and the immature brain: are these toxic or therapeutic agents? *Anesthesiology.* 2004;101:527–530
34. Abdel-Rahman, Kauffman R. The integration of pharmacokinetics and pharmacodynamics: understanding dose-response. *Annu Rev Pharmacol Toxicol.* 2004;44:111–136
35. Field MJ, Behrman RE, eds. *Ethical Conduct of Clinical Research Involving Children.* Washington, DC: Committee on Clinical Research Involving Children, Board on Health Science Policy, Institute of Medicine of the National Academies; 2004
36. Ackerman T. The ethics of drug research in children. *Paediatr Drugs.* 2001;3:29–41
37. Kannan S, Raykoua M, Glibetec M, Kannan RM, Lieh-Lai M, Basset D. Dynamics of cellular entry and drug delivery by dendritic polymers into human lung epithelial carcinoma cells. *J Biomater Sci Polym Ed.* 2004;15:311–330
38. Kolhe P, Khandare J, Pillai O, Kannan S, Lieh-Lai M, Kannan R. Hyperbranched polymer-drug conjugates with high drug payload for enhanced cellular delivery. *Pharm Res.* 2004;21:2185–2195
39. Chan FK, Chew NY. Novel alternative methods for the delivery of drugs for the treatment of asthma. *Adv Drug Deliv Rev.* 2003;55:793–805

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