The Need for Rigorous Evidence on Medication Use in Preterm Infants

Is It Time for a Neonatal Rule?

Jonathan M. Davis, MD
Edward M. Connor, MD, MBE
Alastair J. J. Wood, MB, ChB

APPROXIMATELY 200 000 INFANTS BORN ANNUALLY IN the United States require admission to a neonatal intensive care unit for treatment of prematurity, costing more than $26 billion per year.[1] Preterm infants are at substantial risk of death or developing serious morbidity that can affect them for life. Unlike treatments used in other fields of medicine, most medications administered to preterm infants lack convincing data to support their safety and efficacy with more than 90% not approved by the US Food and Drug Administration (FDA) for the prescribed indication. No new medications have substantially improved outcome for preterm infants since the introduction of antenatal corticosteroids and surfactant 15 to 20 years ago. Infants admitted to the neonatal intensive care unit may be exposed to more than 60 separate drugs, with the most premature infants receiving the greatest number of medications.[2] Serious adverse drug reactions from single or multiple agents can significantly increase mortality and serious morbidity resulting in short- and long-term adverse consequences.[3] It is important to solve this knowledge gap and define systems for drugs to be adequately studied. Without this, each preterm newborn is essentially being enrolled in an uncontrolled and unapproved clinical trial that will not yield data of substantial value.

Congress passed the Best Pharmaceuticals for Children Act (BPCA) in 2002 (reauthorized in 2007 and 2012) to stimulate the study of pediatric therapeutics. The BPCA authorizes the FDA to offer drug manufacturers an extra 6 months of patent protection (exclusivity) for testing their products in children, although no specific age range is mandated. In the past 14 years, the FDA has updated the labeling of 434 drugs following completed studies in children, but only 1 involved premature infants.[4] This is primarily due to certain disincentives to conducting research in preterm infants. Many institutional review boards and the FDA struggle with this vulnerable population, with some suggesting that it is unethical to conduct any research in newborns.[5] Preterm infants also represent a relatively small market and can develop permanent injuries, which can be associated with large malpractice awards whether the adverse outcome is caused by the drug or not. Many companies understandably limit their studies to older children, an approach that still permits extended exclusivity under the BPCA. The BPCA also requires the National Institutes of Health to prioritize therapeutics in need of study (eg, pediatric formulations), to sponsor necessary pediatric clinical trials, and to submit the data to the FDA for labeling changes. While the National Institute of Child Health and Human Development has effectively prioritized and sponsored a number of clinical trials in neonates, no funds have actually been appropriated for this program. This severely limits the number, type, and quality of studies that can be performed.

The decision to use a drug in neonates is often based on a number of factors, including the clinical impression of the prescribing physician, an expert opinion, studies in older children, or a pilot study in newborns. In the absence of definitive information, it is imperative that initial safety and pharmacokinetic studies are followed by trials of sufficiently rigorous design and power to establish whether the benefits of using the drug in neonates exceed the risk. Because of the considerable morbidity and mortality intrinsic to preterm infants, and their complex physiology, randomized, masked, placebo-controlled trials are essential and should be designed to assess the superiority of one drug over another (vs no treatment at all). Although initial studies can use short-term outcomes, these studies must be followed by continued surveillance at least until the child reaches school age to more accurately define outcomes. For example, caffeine was initially shown to significantly reduce apnea, bronchopulmonary dysplasia, and cerebral palsy in preterm infants. However, follow-up at 5 years of age demonstrated that caffeine was no longer associated with significantly improved rates of survival without disability.[6] Determining long-term responses to therapy administered to infants shortly after birth will be challenging, expensive, and will require commitment and novel approaches by all key stakeholders.

The most important required change is that unapproved medications used in preterm infants should be assessed in randomized controlled trials to establish short- and longer-term safety and efficacy. Rigorous evaluation of complex therapies used in infants and children is possible. For ex-

Author Affiliations: Department of Pediatrics, Floating Hospital for Children at Tufts Medical Center, Boston, Massachusetts (Dr Davis); Children's National Medical Center, Washington, DC (Dr Connor); Symphony Capital LLC, New York, New York (Dr Wood); and Department of Medicine and Pharmacology, Weill Cornell Medical College, New York, New York (Dr Wood).
Corresponding Author: Jonathan M. Davis, MD, Tufts Medical Center, 800 Washington St, Box 44, Boston, MA 02111 (jdavis@tuftsmedicalcenter.org).

ample, the Children's Oncology Group has been successful in organizing multisite clinical trials for the treatment of infants and children with cancer resulting in substantial improvements in survival directly linked to high study participation. The same should be required for the neonatal population. This task should be easier in neonatology because the number of preterm infants born each year far exceeds the number of children diagnosed with cancer.

These challenges are not insurmountable. For example, pharmacokinetic studies requiring multiple blood samples by repeated phlebotomy are inappropriate for preterm infants, yet detailed population pharmacokinetics can be defined in scavenged blood remaining after analysis of clinical samples.[7] This approach could be generalized to many other drugs used in neonates. Multiple organizations could facilitate this process and could benefit by rapid approvals by a single institutional review board (for multisite clinical trials) as well as standardized contract language, protocol templates, and consent forms. Sites in the United States, Canada, and Europe could be included so significant input on trial design can be received from all regulatory agencies and rapid approvals obtained (if appropriate) following the completion of the trial. If a drug lacks sufficient safety or efficacy data, it should no longer be administered outside of clinical trials.

The National Institutes of Health needs to enhance research efforts for maternal and child health, especially in view of the current emphasis on fetal and neonatal origins of adult diseases. All research proposals involving pregnant women or newborn infants should be evaluated at the National Institute of Child Health and Human Development regardless of where the grant proposal is submitted, with uniform review guidelines developed. Appropriate recommendations from the recent Institute of Medicine report[8] should be followed, which has already begun with the recent Congressional reauthorization of the BPCA requiring a greater focus on neonatal drug development at the FDA. The BPCA prioritization program at the National Institute of Child Health and Human Development should be expanded to facilitate the immediate performance of many of these studies. Public and private insurance companies should reimburse treatment costs for infants participating in clinical trials because optimizing treatment guidelines and developing new therapeutics should improve outcome, reduce costs, and benefit all stakeholders (including insurance companies). The March of Dimes and other philanthropic organizations should support studies that generate best treatment practices to improve outcomes for this vulnerable population.

Regulatory agencies should have access to input from neonatologists and pediatric pharmacologists during all stages of drug development. Trials should be designed to ensure that data are generated on the safety of single and multiple agents as well as short- and longer-term outcome measures (using extrapolation when feasible). The FDA should facilitate meeting requests with companies, investigators, or both, who are engaged in neonatal research and use their existing authority to require industry to perform neonatal studies after phase 2 studies demonstrating safety are completed in older children or adults. Most importantly, promising new agents and off-patent drugs should be a priority of the FDA Orphan Drug Program to facilitate potentially high-effect and high-reward neonatal studies.

Efforts to engage industry leaders in research involving newborns are needed. Industry must accept the need to conduct studies of new and existing agents in the neonatal intensive care unit and develop appropriate formulations for infants and children. Neonatologists should work collaboratively with industry earlier in the drug development process so that simple study designs with easily achievable and validated end points can be achieved. The BPCA exclusivity provision could be extended to 9 months for preterm infants to generate further financial and regulatory incentives for this population. Because liability concerns have discouraged many companies from newborn studies, safe harbors need to be created for approved clinical trials involving newborns. This radical new approach is needed by the academic community, the National Institutes of Health, the FDA, and society to improve outcomes for the smallest, most vulnerable, and perhaps most complex patients.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Davis reported being compensated for performing medical malpractice reviews; grants paid to Tufts Medical Center from the National Institutes of Health to support research efforts; and receiving honoraria when giving lectures. Dr Connor reported serving on the board of directors for GenVec; serving on the board of directors as interim CEO for ReveraGen; serving as a consultant to Sarepta Therapeutics (formerly AVI), Prosensa, New Enterprise Associates, and Cytonet; being employed as a part-time chief medical officer for 3V Biosciences; receiving or having grants pending from the National Institutes of Health, the National Institute of Child Health and Human Development, and the Department of Defense; owning stock and stock options in GenVec and stock options in 3V Biosciences; and receiving travel reimbursement from foundations in Duchenne muscular dystrophy. Dr Wood reported serving on the board of directors for Oxigene Pharma and Symphony Evolution; serving as a consultant to Lexicon Pharmaceuticals, RRD International, the University of Florida, Northwestern University, and various international reinsurance companies; receiving lecture fees from Vanderbilt University, Cornell University, the University of Pennsylvania, and Pew Charitable Trust; holding a patent for the treatment of abdominal aortic aneurysm; and being a partner and investor in Symphony Capital.
Additional Contributions: We acknowledge the thoughtful feedback and input provided by William Smoyer, MD, Robert Ward, MD, and Danny Benjamin, MD.

REFERENCES

1. Institute of Medicine of the National Academies. Preterm birth: causes, consequences, and prevention. http://www.iom.edu/Reports/2006/Preterm-Birth-Causes-Consequences-and-Prevention.aspx. Accessibility verified September 14, 2012.
2. Kumar P, Walker JK, Hurt KM, et al. Medication use in the neonatal intensive care unit. *J Pediatr*. 2008;152(3):412-415.
3. Moore TJ, Weiss SR, Kaplan S, Blaisdell CJ. Reported adverse drug events in infants and children under 2 years of age. *Pediatrics*. 2002;110(5):e53-e58.
4. US Food and Drug Administration. New pediatric labeling information database. http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase. Accessibility verified September 14, 2012.
5. US Government Accountability Office. Pediatric research: products studied under two related laws, but improved tracking needed by FDA. http://www.gao.gov/assets/320/319073.pdf. Accessibility verified September 14, 2012.
6. Schmidt B, Anderson PJ, Doyle LW, et al; Caffeine for Apnea of Prematurity (CAP) Trial Investigators. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA*. 2012;307(3):275-282.
7. Cohen-Wolkowiez M, Ouellet D, Smith PB, et al. Population pharmacokinetics of metronidazole evaluated using scavenged samples from preterm infants. *Antimicrob Agents Chemother*. 2012;56(4):1828-1837.
8. Institute of Medicine of the National Academies. Safe and effective medicines for children: pediatric studies conducted under BPCA and PREA. http://www.iom.edu/Reports/2012/Safe-and-Effective-Medicines-for-Children.aspx. Accessibility verified September 14, 2012.