VIEWPOINT

AMERICAN PEDIATRIC SOCIETY

Global Collaboration to Develop New and Existing Drugs for Neonates

Jonathan M. Davis, MD
Department of Pediatrics, Floating Hospital for Children, Tufts Medical Center, Boston, Massachusetts; and Tufts Clinical and Translational Science Institute, Tufts University, Boston, Massachusetts.

Mark A. Turner, MB, PhD, MRCPCH
Institute of Translational Medicine, Department of Women's and Children's Health, University of Liverpool, Liverpool, England.

Corresponding Author: Jonathan M. Davis, MD, Department of Pediatrics, Floating Hospital for Children, Tufts Medical Center, 800 Washington St, Mailbox 44, Boston, MA 02111 (jdavis@tuftsmedicalcenter.org).

Neonates do not have access to medicines that have been adequately tested for dosing, safety, and efficacy.[1] Physicians must use their best judgment to make up for these knowledge gaps, leading to incorrect, and possibly harmful, doses of unnecessary and expensive medications. Some experts even believe that it is difficult or unethical for research to be conducted in neonates.[2] Neither of these beliefs are justified, and it is inappropriate to expose neonates to potential risk without conclusive evidence that the drugs they are receiving are safe and efficacious. Neonates must participate in all stages of drug development in trials that use contemporary methods, because the health care industry has an ethical duty to meet the needs of this population.[3]

Most research of new and existing drugs in neonates has been stimulated in the United States and European Union by governmental initiatives. However, most drugs that have received US Food and Drug Administration (FDA) approval for this population are rarely used.[4] Drug development should be directed to specific therapeutic needs that must be met to improve long-term outcomes (**Box**). These studies will be cost-effective owing to the potential for life-long benefits.

To address these issues, the FDA, Burroughs Wellcome Fund, and Critical Path Institute cosponsored a scientific workshop titled Roadmap for Applying Regulatory Science to Neonates. The goal was to "break down silos" and bring together key stakeholders from multiple disciplines, including regulatory agencies (FDA, European Medicines Agency, and Health Canada), the academic community, industry sources, and charitable foundations to establish a global consortium to facilitate neonatal drug development. The following specific areas were identified and included:

Innovative trial designs (eg, adaptive designs). Innovative designs offer the potential to select doses or assess efficacy most efficiently. Although randomized clinical trials represent the criterion standard, this study design may not always be possible or optimal to evaluate drugs. Because innovative trial designs represent a novel approach in neonates, significant methodological work is required.

Trials that allow for extrapolation. Existing legislation states that a pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the course of the disease and the drug's effects are sufficiently similar in children and adults. This statement implies that the disease and the drug's effects are well understood and have been studied in neonates—an assertion that may not be true for the most relevant neonatal conditions.

Box. Priority Conditions Requiring Study in Newborns

- Neonatal brain injury: prevention and treatment of seizures, asphyxia, stroke, intraventricular hemorrhage, and white matter injury
- Neonatal lung injury: prevention and treatment of bronchopulmonary dysplasia and persistent pulmonary hypertension
- Neonatal gastrointestinal injury: prevention and treatment of necrotizing enterocolitis
- Perinatal infection: prevention and treatment of bacterial and viral infections (early and late onset)
- Retinopathy of prematurity: prevention and treatment
- Neonatal abstinence syndrome: prevention and treatment of withdrawal from in utero exposure to opiates
- Prevention of preterm labor and delivery

Criteria for initiating trials in neonates. Drugs are often studied in neonates when safety has first been established in adults, which can result in significant delays. There are urgent clinical needs that can only be addressed if drugs are studied before adult trials have been completed or if products are developed specifically for neonates.

Pharmacokinetic and pharmacodynamic modeling. Although neonates are distinct from other age groups, these differences are not consistent. Variations in the volume of distribution and clearance may make it impossible to predict the effects of gestational and postnatal age. Well-designed pharmacokinetic studies of appropriate size should be conducted before the initiation of more comprehensive clinical trials.

Clinical outcome measures. Drugs should only be used to positively influence important clinical outcomes, which need to be defined and used consistently. Examples of therapeutic areas hampered by the lack of well-defined clinical outcome measures include bronchopulmonary dysplasia and brain injury.

Biomarkers. The selection of biomarkers is important for clinical practice and drug development. Biomarkers must first be validated and qualified with interobserver and intraobserver reproducibility, as well as mechanistic approaches, before clinical trials. Biomarkers should be able to help identify the highest-risk neonates, significantly reduce the number of neonates needed for studies, and be associated with short- and long-term outcomes.

Copyright 2015 American Medical Association. All rights reserved.

Downloaded From: http://archpedi.jamanetwork.com/ on 08/19/2015

So what should be done? First, families must be included in all aspects of neonatal research, similar to the successful model adopted by the Medicines for Children Research Network in the United Kingdom.[5] Next, discussions should focus on study design, with an emphasis on obtaining high-quality data (including cost effectiveness).[3,6] It is essential to develop networks of reusable research infrastructure and master protocols, which are parallel goals of the FDA and the National Institutes of Health–sponsored Clinical Translational Science Award program. It is important to highlight programmatic thinking and "team science" to fill key knowledge gaps. This method requires training young investigators in regulatory science because regulatory scrutiny is not an arbitrary imposition but rather the quality assurance our patients deserve. Essential markers of career development should include contributions to the common good, including involvement in commercial trials.[6,7] Most important, there are urgent needs for adequate allocation of resources by the private and public sectors to conduct the significant number of clinical trials that are necessary.

There are great opportunities to develop global neonatal research consortia and networks, primarily owing to enhanced communication and collaboration between regulators from the United States, European Union, Canada, Australia, and Japan (Latin American countries and China are also showing interest). If regulators could agree on protocol designs and outcome measures, clinical trials could be conducted in multiple countries simultaneously, which would enhance access to neonates and significantly reduce product approval timelines and development costs. Essential infrastructure is being developed through the American Academy of Pediatrics, the European Network of Paediatric Research at the European Medicines Agency, the Clinical Translational Science Award program, and industry sources. The National Institute for Health Research Clinical Research Network in the United Kingdom has invested heavily in study sites that are performance managed and operated according to standardized confidentiality agreements, site agreements, and budgets. This investment has led to a 10-fold increase in the number of studies being conducted, with more than 80% of studies sponsored by industry recruiting on time and within budget.[4]

There are unique opportunities to enhance drug development in neonates in the United States and abroad. Good research is possible and best practice exists that can be standardized and disseminated. Only through coordinated efforts of all key stakeholders can we leverage these opportunities and meet the challenges in this vulnerable population.

ARTICLE INFORMATION

Published Online: August 10, 2015. doi:10.1001/jamapediatrics.2015.1640.

Conflict of Interest Disclosures: Dr Davis reports working for the US Food and Drug Administration. Dr Turner reports having consultancy agreements between his university and Chiesi, Shire plc, and Janssen Pharmaceutica for his advice relating to drug development, but he does not receive any additional compensation for this work.

REFERENCES

1. McCune SK, Mulugeta YA. Regulatory science needs for neonates: a call for neonatal community collaboration and innovation. *Front Pediatr*. 2014;2:135-137.

2. Davis JM, Connor EM, Wood AJ. The need for rigorous evidence on medication use in preterm infants: is it time for a neonatal rule? *JAMA*. 2012;308(14):1435-1436.

3. Turner MA. Neonatal drug development. *Early Hum Dev*. 2011;87(11):763-768.

4. Laughon MM, Avant D, Tripathi N, et al. Drug labeling and exposure in neonates. *JAMA Pediatr*. 2014;168(2):130-136.

5. Rose AC, Van't Hoff W, Beresford MW, Tansey SP. NIHR Medicines for Children Research Network: improving children's health through clinical research. *Expert Rev Clin Pharmacol*. 2013;6(5):581-587.

6. Connor EM, Smoyer WE, Davis JM, et al. Meeting the demand for pediatric clinical trials. *Sci Transl Med*. 2014;6(227):227fs11.

7. Davis JM, Smoyer WE, Connor EM, et al. Sponsors meet scientists to speed pediatric medicines development. *Sci Transl Med*. 2015;7(279):279fs11.

Copyright 2015 American Medical Association. All rights reserved.

Downloaded From: http://archpedi.jamanetwork.com/ on 08/19/2015