

## Improving Drug Formulations for Neonates: Making a Big Difference in Our Smallest Patients

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Safe treatment with any drug depends on understanding how that drug is metabolized, cleared, and interacts with its primary target. For each of these factors, newborns can differ markedly from older children and adults.<sup>1-3</sup> For this reason, extrapolating safety and efficacy of a drug in critically ill newborns based on data collected in older children and adults can be inaccurate. Although progress has been made in meeting the challenge of defining the safety and efficacy of drugs by encouraging involvement of critically ill newborns in therapeutic drug trials, additional important considerations that directly affect safe drug administration in neonates have often been overlooked or underemphasized. These include unsafe administration of drugs to newborns related to: (1) administering small volumes of drugs to newborns that cannot be accurately measured because they have been manufactured and tested at fixed concentrations designed to meet the needs of adults; (2) untoward effects of extemporaneous formulations on the bioavailability, stability, and chemical properties of drugs; and (3) unexpected drug-drug interactions that occur because of drug combinations that may be used uniquely in neonatal intensive care.

Continued discussion among the multiple stakeholders who can best help to address unmet therapeutic needs in the neonatal intensive care unit, and that includes the voice of those who care for sick newborns, has been effective in defining problems and mapping out potential solutions. To this end, the Institute for Pediatric Innovation convened a group at Children's National Medical Center in Washington, DC, on December 7, 2011, that included experts in drug development and formulation, pediatric clinical pharmacology, regulatory process, public health, health economics, ethics, and neonatal intensive care. Their day-long agenda of the symposium entitled "Opportunities and Challenges in Developing Drug Formulations for Neonatal Intensive Care" was aimed at updating the progress, evolving needs, challenges, and opportunities related to optimizing drug formulations for use in the critically ill newborn.

In preparation for this meeting and with the intention of providing a starting point to focus on specific unmet needs, a simple 13-question online survey was conducted. Two questions in the survey were related to the number of sick newborns the respondents cared for in 1 month and how long the respondents had been practicing. The remaining questions related to how frequently the respondents believed suboptimally formulated drugs are given to newborns, to identify the drugs most in need of being reformulated, to the general category of deficiency in existing formulations, and to the general impression of outcomes related to having to

give inappropriately formulated drugs. Respondents to the survey typically cared for >25 critically ill newborns per month, and >70% had been involved with providing neonatal intensive care for >10 years. Greater than 80% of respondents indicated that poor formulation of a drug was occasionally associated with an untoward effect (eg, prolonged hospitalization, complication of an existing condition, or cause of a new condition), and nearly 40% believed that lack of a properly formulated parenteral drug occasionally contributes to death. This survey suggested that although certain commonly used agents such as caffeine, gentamicin, and ampicillin have been optimally formulated, there were also commonly used drugs whose formulation needed to be improved. Topping this list of drugs were fentanyl, phenobarbital, morphine, hydrocortisone, insulin, and enoxaparin.

By its design, the survey results were not intended to establish a list of drugs for which formulation or reformulation work should begin. Rather, the brief survey helped to focus a group of experts on general themes that could be addressed with rigor and with a commitment that would result in meaningful change. Several recommendations aimed at improving safe administration of drugs to critically ill newborns emerged over the course of this discussion. First, based on the drugs identified in the informal survey, it seems that there is substantial need for either formulating or reformulating several drugs that have been used for decades in the neonatal intensive care unit. Participants agreed that a more rigorous, data-driven assessment is required to confirm this opinion and focus the need. Even with a more rigorous quantification of the need, it seems unlikely that the resources required to succeed in improving formulations of drugs that are currently being used in critically ill newborns will come from manufacturers of branded drug products. During the past decade, manufacturers of new drugs have been obligated under regulations (the Pediatric Research Equity Acts) to study

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these new agents in children. This obligation may, in part, be contributing to the view that needs related to these newer agents have been met. However, it is important to recognize that in many cases the opportunity for encouraging this study under these regulatory obligations will present for only a brief period of time as the new drug finishes clinical development and appears on the market. Furthermore, as outlined in the recent Institute of Medicine report concerning the Pediatric Research Equity Acts and the Best Pharmaceuticals for Children Act, neonates were not included in many of the studies. Currently, it seems the greatest immediate needs are to formulate old drugs that have long since lost patent exclusivity. For this reason, it is unlikely that manufacturers will be incentivized to do work to address this need. Therefore, the path forward is likely to depend on collaboration between key stakeholders, including physicians, academicians, manufacturers, and public health interest specialists, who will need to lead in framing the challenge and in identifying a process for bringing appropriate drug formulation development and regulatory expertise together to address the challenge. This path is not well worn, and it is clear that it will be challenging. Given the small potential market for these products and changes on the horizon for how products will be reimbursed, a clear and feasible path for ensuring sustained supply of these new formulations needs to be defined. Although manufacturers probably will not lead this effort, engaging these stakeholders early in the process will be critical to defining product opportunities carefully and developing formulations that can be acquired by commercial entities. In engaging these entities, consideration should be given to the potential for a Food and Drug Administration–approved formulation being priced at a premium compared with the standard active ingredient that must be rendered into correct dosage and delivery form by a hospital pharmacy. Commercial viability of such a formulation may depend on an analysis of the impact of the new formulation on mitigating the risk of medication error and on the economic value of this risk mitigation. In addition, novel formulations may provide opportunities for proprietary protection or exclusivity, making such drugs more attractive to commercial vendors.

A second theme identified over the course of this meeting is the need to organize research aimed at developing novel formulations for the critically ill neonate. The impact of this work, perhaps initially driven by work done with newly developed drugs, could prove to be the single most important advance in developing safer formulations for older drugs. This work may include applying well-established methods for formulating drugs into absorbable films or drug patches. This approach needs to consider, at all stages from conception through to testing, the uniqueness of the neonate's physiology, especially with an eye toward how this physiology may be leveraged to offer innovative approaches such as transmucosal or transdermal drug administration. For more traditional parenteral drug administration, it will be important to conduct studies with formulations that account for the adherence of active drug ingredient to pumps, catheters, and other means of delivery, as this adherence, sometimes consid-

ered irrelevant to doses used in older children and adults, could result in loss of a substantial proportion of doses prescribed for newborns.

Delivering care to the severely ill is nearly always complicated by the need to administer multiple drugs. Caring for the critically ill newborn is no exception. Given differences between adult and newborn hepatic and renal function, it can be difficult to extrapolate the potential for drug-drug interactions, even when experience in adults and older children has established this potential. Further complicated by considerations of chemical compatibility of the multiple drugs that are often administered through the same vascular catheter, a third theme of addressing the safe administration of drugs to newborns is related to defining the potential for physicochemical as well as pharmacologic drug interactions. In this regard, optimal development of formulations to be used in the critically ill newborn must be attentive to the drug combinations that are frequent and might be unique in this population and that consider the value of alternate routes of administration to avoid potentially unsafe interactions.

Finally, as work proceeds in improving formulations of old and new drugs to meet the needs of critically ill newborns, it will be important to recognize the heterogeneity of this population. Newborns receiving critical care have a variety of underlying conditions, including organ immaturity, acute infectious disease, congenital disease, and postoperative complications. Furthermore, as advances are made in delivery of intensive care, it seems likely that new conditions will arise and, it is hoped, some will become less important. Each of these underlying conditions can present a unique set of challenges. Although the most efficient means of meeting the needs of this heterogeneous group of patients would be to identify singular approaches to meet multiple unmet needs, it may be that in certain circumstances it will require an approach that is unique to a small group of newborns.

As the therapeutic drug armamentarium has continued to expand, those caring for critically ill newborns have been remarkably innovative and successful in meeting the challenges posed by the lack of, and sometimes incomplete, information about the efficacy and safety of drugs in the neonate. Involving newborns in clinical trials that aim to provide critical information and guide clinicians based on evidence-based medicine is a major step forward. However, the ultimate impact of this information on improving care depends on parallel advances in the formulation of drugs, both old and new, that consider the uniqueness of critically ill newborns. Addressing this challenge holds the promise of not only meeting a medical need that is likely to continue to increase but also making a big difference in the health of our smallest patients. ■

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## Appendix

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