OPINION

Clinical Trials in Neonates: A Therapeutic Imperative

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The lack of study of medications in pediatric patients has been recognized since the 1960s, when Shirkey described children as "therapeutic orphans."[1] In 1968, only 25% of approved drugs included adequate pediatric prescribing information on the label. This did not begin to improve until the 1990s, with the 1997 US Food and Drug Administration (FDA) Modernization Act, the Best Pharmaceuticals for Children Acts, and the Pediatric Research Equity Acts. By 2009, more than 300 labeling changes improved pediatric prescribing information, but newborns were seldom included.

Recent laws intended to increase the study of drugs for pediatric patients and improve pediatric labeling have not benefited newborns as much as other pediatric patients. In fact, of the 159 label changes associated with market exclusivity implemented by May 2009, only 11 (7%) pertained to neonates.[2] Of the 321 label changes developed through the combination of the acts listed above, only 15 (4.7%) involved prescribing information related to neonates.[3] This would not be expected for drugs developed for diseases that do not occur in newborns, but many of the Written Requests issued by the US Food and Drug Administration (FDA) did not ask for neonatal studies for diseases that are seen in this population. As Janet Woodcock from the FDA pointed out in congressional testimony on 8 May 2001, "Once pediatric exclusivity is granted for the studies conducted in older pediatric age groups, there is not an adequate incentive to conduct additional studies in the younger age groups. This has left some age groups, especially neonates, unstudied, even though the need for the drug in those age groups is great."[4]

A search of the ClinicalTrials.gov website in June 2009 illustrated the deficiency in studies of this vulnerable pediatric population. Of 39,731 ongoing and completed studies conducted in the United States, 9,842 involve pediatric patients from birth to 17 years of age. Of these pediatric studies, 69% (6,788) involve medications, but only 6% (418) of these drug studies involve newborns. Many disorders that are frequent in adults, such as pain, congestive heart failure, seizures, hypertension, hypotension, bronchospasm, and chronic lung disease, also occur in neonates and require treatment. Yet many older drugs used to treat adults are not labeled for the same disorder in the newborn, usually because of limited study—for example, morphine, dopamine, dobutamine, albuterol, rifampin, and many others. Because of developmental differences, weight-based scaling of doses from older infants and children to neonates is often not appropriate, and thorough study is needed.

Inadequate study of medications leaves the sick newborn at significant therapeutic risk for inappropriate dosages. New drugs are introduced into neonatal intensive care units annually without adequate basic studies of maturational changes in clearance or drug distribution, as well as fundamental issues such as clinical effectiveness and the impact of excipients on neonates. History shows how unwise this can be; examples include "gasping syndrome" and death in many newborns from inability to clear benzyl alcohol preservative, mostly from large volumes of saline flush solution; lethal cardiovascular collapse from excessive doses of chloramphenicol, which requires glucuronidation for clearance; and kernicterus from sulfisoxazole displacement of bilirubin from albumin.

Recommended dosages for newborns that have been extrapolated from older children or adults may lead to over- or underdosing or to unique, unanticipated adverse effects, as were discovered in early studies following the 1997 FDA Modernization Act and summarized in a 2001 report to Congress.[5] A recent study of neonatal pharmacokinetics of fluconazole found that the dosages recommended in drug handbooks for neonates of less than 30 weeks' gestation at birth and less than 14 days of age were therapeutically inadequate.[6] Building a population pharmacokinetic model with samples from 55 newborns at 23 to 42 weeks' gestation who were being treated with fluconazole, the dose to reach a therapeutic area under the curve (AUC) was found to be sixfold higher than the currently recommended dose.[6] Thus, inadequate clinical response

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to fluconazole in preterm newborns with systemic candidiasis using the earlier dosing recommendations could easily be the result of inadequate dosing.

The study of drugs in newborns is complicated, and this should not be underestimated. Clinical end points cannot rely on verbal report or patient cooperation with testing. Parents are often reluctant to allow their newborns to participate in studies, especially when direct benefit is limited. The total blood volume in a 0.5-kg patient may be as low as 3 tablespoons, or 45 ml, which means that only a total of 1.5 ml (3 ml/kg) will be allowed by many institutional review boards for samples to be used for investigation. To identify a suitably homogeneous population for study, the investigator must choose between equal stages of development based on an assessment of gestational age at birth or equal weight ranges that may be found in infants at widely different stages of development. Anderson and Holford recommend using postmenstrual age in describing maturational differences in neonatal drug elimination.[7] They show that accounting for the multiple factors known to alter the dose–exposure relationship in infants can predict developmental changes in neonatal drug clearance. Differences in end-organ responsiveness, however, may require exposures in newborns that are different from those of older children and adults.

Ethics of clinical trials in newborns presents another challenge. Studies cannot be conducted in healthy newborn volunteers because they cannot give their own consent. The Office of Human Research Protections specifies that clinical trials in vulnerable populations, such as newborns, may not involve more than a minor increase over minimal risk without approval from the US Department of Health and Human Services. Risk has been normalized to that of a child's risk encountered in normal daily life. Yet drug studies are needed to guide treatment of infants who are much sicker than this, such as those being treated with multiple infusions of cardiotonic drugs or supported for days on a heart–lung machine.

Despite these challenges, clinical studies of drugs in newborns are feasible using innovative and creative approaches, even in the context of their regular clinical care. In the example of fluconazole, the pharmacokinetics was determined during clinical treatment or prophylaxis for *Candida* infections. Of the 357 plasma samples collected, 39% were scavenged from plasma left over from tests obtained as part of patient clinical care. This reduced the number of study-specified samples and improved the pharmacokinetic model. Monte Carlo simulation of the population pharmacokinetic model allowed for estimation of variability in AUC for a given dose that could be expected over the range of neonates studied. Coupled with the knowledge of a target AUC for effectiveness from adult treatment with fluconazole, an effective dose–exposure target could be determined. The use of population pharmacokinetic analysis coupled with Monte Carlo simulation is essential for successfully applying pharmacokinetics in very-low-birth-weight premature newborns to determine effective doses.

Not all clinical trials in newborns incorporate fundamental principles of neonatal clinical pharmacology. Such studies in sick newborns can be costly, dangerous, and unethical. Dexamethasone was widely used to treat newborns to facilitate weaning from ventilator support or to prevent chronic lung disease during the 1980s and 1990s in dosages extrapolated from older patients.[8] As discussed by Ward and Lugo, Yeh and colleagues showed that dexamethasone treatment in preterm newborns started within 12 hours after birth and slowly tapered over 6 weeks could reduce chronic lung disease, but it also impaired neurological function and growth measured several years after birth.[8] When data from 14 patients on neonatal clearance of dexamethasone were finally published, the clearance in neonates of <28 weeks' gestation was significantly lower than that in older newborns. Lower dosages chosen empirically have been used to treat preterm newborns with chronic lung disease without causing impaired neurological development.[9] Numerous articles have criticized the treatment of newborns with dexamethasone, yet its pharmacokinetics has not been studied to determine the appropriate dose–exposure relationship, which is critical to assess whether safe and effective dosing can be achieved. The situation with dexamethasone may be analogous to that of chloramphenicol, which caused the lethal "gray baby syndrome" (characterized by abdominal distension and cardiovascular collapse) when dosages were administered that exceeded clearance and the drug accumulated. The drug is a potent, broad-spectrum antibiotic that later became a mainstay of pediatric treatment of *Haemophilus influenzae* meningitis when the dose was lowered and concentrations carefully monitored. Understanding the correct dose, the target concentration or AUC range, and the maturation of the pathways of clearance is pivotal to safe and effective treatment of newborns.

Despite the increase in pediatric studies after 1997, newborns remain therapeutic orphans, omitted from FDA Written Requests, sponsors' drug development plans, and many National Institutes of Health research initiatives. Out of physicians' desperation to treat critically ill neonates in the neonatal intensive care unit, newborns are exposed to numerous drugs that have not been studied in adequate numbers of infants at similar stages of development. Until neonatal studies of medications become a priority for drug developers, drug regulators, and government research agencies, sick neonates will continue to be at risk for overdosing, underdosing, and unanticipated adverse effects during treatment with inadequately studied drugs. Solving this problem is a shared responsibility not only of drug developers, regulators, and government funders, but also of practicing clinicians, who should not use a drug in the absence of data indicating that it will probably achieve its therapeutic goal. Otherwise, our clinical care is not different from conducting thousands of studies with an $N = 1$. Our most vulnerable pediatric population deserves better care than this—care that we have the capability to provide, if we make it a priority.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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Can We Afford It?: Ethical Consideration of Expensive Drug Treatment for Neonates and Infants

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When considering expensive drug treatment for neonates and infants, how should we decide what we can and cannot afford? Accountably allocating health-care resources can be achieved using a framework that reflects the values a society considers so reflective of the collective will that they have been formally entrenched in law. The values and procedural mechanisms entrenched in the Canadian Charter of Rights and Freedoms are particularly helpful for those faced with these difficult spending decisions.

When considering expensive drug treatment for neonates and infants, how should we decide what we can and cannot afford? Is it possible to develop a process for addressing this multifaceted question that satisfies a societal commitment to justice, perspectives on what constitutes a meaningful quality of life, and the limits of cost-effectiveness analysis? Although the high cost of treatment such as nitric oxide for neonates is not a new issue, the question of whether we can afford it or, bluntly stated, whether the outcome will be worth the monetary cost, has become one that many seem to feel almost duty-bound to explore.[1–3] There is a rich literature debating the prognoses tied to birth weight, gestational age, and specific diseases or congenital abnormalities, as well as the ethical significance of quality-of-life indicators and the extent to which these should be factored into spending decisions.[1] What is missing is a framework for working with societal values and accepted evidence on which to make funding decisions regarding costly drug treatments for neonates and infants. This article proposes values and processes entrenched in the Canadian Charter of Rights and Freedoms as an ethical framework for making decisions involving the funding of such treatments.

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Ability vs. willingness to pay

In the current climate of economic uncertainty, people along every stage of the treatment continuum must be able to defend their spending requests and authorizations. Although the specific professional responsibilities of members of regulatory bodies, clinical pharmacologists in academia, and neonatologists, as well as those working in industry, vary, the fundamental values appealed to when considering where a society should spend public dollars should be consistent. How we balance competing values at the heart of difficult affordability decisions in many ways defines the societies in which we live and whom we aspire to be.

The extent to which something is considered affordable is generally measured by its cost in relation to the amount the purchaser is able to pay, virtually devoid of ethical considerations. However, in most circumstances in which expensive neonatal drug treatments are being considered, the question of whether we think we can afford a drug is more a reflection of our opinion as to whether the potential good is worth the cost than it is an absolute price tag relative to the size of a budget. Affordability thus turns more on what decision makers are willing to pay than on what they are able to pay. This definitional shift from ability to pay to willingness to pay (no matter how able) highlights the need to consider the values that should be reflected in our spending decisions.