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Commentary

Pharmacotherapy and the Newborn Infant: Premium Non Noncore

Steven M*

Department of Pediatrics, University of Michigan, Ann Arbor, Michigan, USA

DESCRIPTION

The newborn infant, especially those who are born prematurely, are among the most vulnerable patients in all of medicine. Organs and organ systems are incompletely formed and are still developing, metabolic pathways are also in a state of evolution, and both hepatic and renal functions are relatively inadequate compared to older children or adults. The developing brain and central nervous system may be affected and show evidence of dysfunction years later. Yet, infants in the milieu of the Neonatal Intensive Care Unit (NICU) are exposed to countless pharmaceutical agents of dubious efficacy and potentially dangerous toxicity without a sufficient evidence base to justify their use.

A recent study by Bamat and colleagues looked at medication use in preterm infants with severe bronchopulmonary dysplasia, the most severe long term respiratory morbidity in this population resulting from the combination of ventilator-induced lung injury, oxygen toxicity, and a developmental arrest of alveolarization. They performed a retrospective cohort study to identify the number of cumulative medication exposures and characterize the most frequently used agents. Astoundingly, in 43 hospitals surveyed, encompassing 3,252 patients, a median of 30 cumulative medication exposures per infant was found, with an interquartile range of 17-45. Diuretics, drugs of doubtful efficacy and significant toxicity, were the most frequently prescribed agents [1].

The history of neonatology is replete with examples of good ideas that turned into abject disasters. In 1959, the use of the antimicrobial, chloramphenicol was found to cause the "gray baby syndrome," characterized by severe hypotension, cyanosis, and even death. Some infants developed fatal aplastic anemia [2]. In the 1960's Usher introduced the practice of using sodium bicarbonate therapy to maintain blood pH in preterm infants with respiratory distress syndrome. After some preliminary success, the dose of sodium bicarbonate was increased but led to a significant incidence of intraventricular hemorrhage [3]. The use of intravenous vitamin E in the 1980's produced the "gasping syndrome," resulting from the preservative benzyl alcohol. More than a dozen deaths were attributed to this. Affected infants developed metabolic acidosis which progressed to severe respiratory distress as well as seizures and brain hemorrhages [4]. More recently, the prokinetic agent, cisapride, used to promote gastrointestinal motility, was found to be associated with prolongation of the QTc interval in very preterm infants, leading to serious cardiac arrhythmias and mortality and was withdrawn from the market [5].

This handful of examples demonstrates the severity of unintended consequences in this population. The problem is underscored by the fact that most, pharmaceuticals administered in the NICU are off label (two-thirds to three-quarters), and thus have not undergone adequate testing or gained approval for use by the US Food and Drug Administration. These infants are particularly susceptible to injury because of organ immaturity, especially the brain, and many pharmaceutical agents that are well tolerated in the adult population may have undesirable side effects in the preterm infant; many may not surface for years. Other potential dangers are unknown drug-drug interactions, and drug-nutrient interactions.

While neonatologists are intensivists and deal with a critically ill and unstable patient population and are quick to reach for therapeutic solutions, it would behoove all of us to remember the oath we took at the outset of our careers, "Primum non nocere." First, do no harm.

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Correspondence to: Steven M, Department of Pediatrics, University of Michigan, Ann Arbor, Michigan, USA; Tel: 916369869687; E-mail: smdonnmd@med.umich.edu

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