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EDITORIAL

Newborns still lack drug data to guide therapy

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In the US the lack of paediatric studies of medications was recognized within five years of the 1962 passage of legislation requiring new drugs to be shown to be both safe and effective for approval [1, 2]. Despite encouragement in the US by the Food and Drug Administration (FDA) and the American Academy of Paediatrics (AAP) for studies that would provide evidence of safety and efficacy in paediatric patients comparable to that in adults, 80% of approved medications in the US continued to lack adequate paediatric prescribing information through 1999 [3]. In 1997, Congress established an incentive approach to stimulate paediatric studies of new drugs that were not yet approved, called the FDA Modernization Act of 1997 (FDAMA) [4]. FDAMA extended market exclusivity by six months in return for completion of studies specified by the FDA in a formal Written Request. After renewal of FDAMA as the Best Pharmaceuticals for Children Act (BPCA) in 2002 [5], Congress passed the Paediatric Research Equity Act in 2003 requiring studies of new drugs in paediatric patients if the indication in the proposed label was likely to lead to treatment of paediatric patients [6]. These two legislative efforts in the US increased the study and labelling of drugs for paediatric patients more than any previous programmes. A comparable regulation in Europe was also increasing the study of drugs in paediatric patients [7]. By 2016, more than 600 drugs in the US contained new or revised paediatric labels. With the first review of the US studies, newborns were identified as not being adequately represented [8].

In 2015, Laughon *et al*. analysed the drugs studied in newborns to achieve exclusivity from 1997 to 2010 and the frequency of treatment with these drugs among 446 335 neonates in 290 neonatal intensive care units (NICU) [9]. Among the drugs responsible for 406 paediatric label changes during this time, only 28 (7%) enrolled neonates. Of these 28 drugs, 13 were never used in the NICU and 8 were used in less than 0.014% of neonates. Of the 406 paediatric label changes, only 7 (<2%) included drugs frequently used to treat sick newborns. Despite the progress in paediatric studies of drugs in the US since the passage of FDAMA in 1997, sick newborns continue to receive most of their drug treatment off-label and without the evidence provided for adults and older children [10].

The reasons for the limited number of studies of relevant drugs in neonates is complicated, in part because all paediatric studies are problematic. Participation of children in clinical trials for which they cannot consent raises ethical and social issues [11]. Parents often state that they don't want their child for be a 'guinea pig' by participating in a study. Parents fail to recognize that every off-label treatment without collection of data constitutes a poorly designed study that provides no new data for the treatment of their child or for the population of sick paediatric patients who will come after their child. In addition, most off-label treatment does not receive the scrutiny and oversight that accompanies a carefully designed and monitored clinical trial. It is only after conducting carefully designed studies of older medications that we have learned that the recommended dose of midazolam for children with congenital heart disease was too high [12], and treatment of rheumatoid arthritis in young children with etodolac required a dose that was almost twice that used to treat adults [12]. Caffeine therapy for apnea of prematurity has been shown to improve the rate of survival without neurodevelopmental disability at 18 to 21 months in very low birth weight neonates [13]. A recent study [14] aimed to assess the therapeutic outcomes of caffeine therapy in preterm neonates, evaluating onset of early and late therapy. It found that early therapy is associated with a reduced incidence of bronchopulmonary dysplasia. Studies like this can demonstrate approaches that can subsequently reduce the burden of morbidities in preterm infants. However, in a study assessing developmental outcome at five years of age, neonatal caffeine therapy was no longer associated with a significantly improved rate of survival without disability in children with very low birth weights [15]. This indicates that as the infant gets older, the impact of neonatal interventions can be less.

To address the paucity of studies in neonates, the Critical Path Institute organized the International Neonatal Consortium [16]. Its first task was the development of a comprehensive white paper describing how to study drugs in neonates [17]. This document can provide the data needed to develop a regulatory guidance about neonatal pharmacology and how to address the challenges of studies in newborns based on the diverse input of parents, clinical pharmacologists, sponsors, regulators, ethicists and pharmacometricians.

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Clinical trials in paediatric patients and newborns are hard. Few paediatricians and even fewer neonatologists are trained in clinical pharmacology as well as how to conduct clinical research. This leads to few research sites with personnel trained to conduct paediatric clinical trials that are rigorous enough to meet the requirements of Good Clinical Practice. Many ethics boards (EBs) have limited paediatric experience, much less personnel who are knowledgeable in neonatology. This is exemplified by the varying attitudes among EBs about acceptable levels of risk. For vulnerable populations, such as paediatric patients, it is usually considered acceptable to expose them to minimal risk which is indexed to the risk encountered in normal everyday life. Most EB chairpersons would classify a blood draw as a minimal risk while others consider it a minor increase over minimal risk [18].

The need for paediatric studies persists and new efforts to increase the study of drugs in neonates and to improve the efficiency of these studies are underway. We can look to a future when neonatal drug therapy has the same solid data base that is provided for treatment of older children and adults.

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