

Neonatal Pharmacotherapy: Issues, Concerns and Challenges

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Reviewing the current status of neonatal pharmacotherapy, Goodyear [1] has recently expressed concerns about the restricted progress made in the area.

Notwithstanding the advances in the basic science research that have improved our understanding of use of pharmacological agents in the neonate, neonatal pharmacotherapy remains an area that has not received the attention that it indeed deserves. Today, several drugs are used in the newborn in spite of the lack of specific clinical research in this vulnerable age group. In fact, present day pharmacotherapy in neonates is mainly based on the individual clinical expertise of specialised neonatologists and paediatricians. Around 60 - 70% drugs used in neonates and infants are unlicensed, the so-called "off-label drugs" [2]. These continue to be employed in neonatal drug therapy without the recommended regulatory phases of drug development.

The several issues such as physiology of hematopoietic factors, the pharmacological responses of conditions like patent ductus arteriosus (PDA) and persistent pulmonary hypertension (PPHN) and newer technologies for drug administration, as well as other pharmacological responses in the neonate, though vital in the development of safe and efficacious treatments for neonates, remain unexplored.

Understandably, there is a need to reviews some current issues related to neonatal pharmacotherapy that are of paramount importance for the clinician. In particular, the peculiar pharmacokinetics of drugs during the neonatal period and its clinical implications are important [2].

Let's have some idea about the peculiarities of the neonate in relation to drug therapy. First, in the newborn, the individual response to a drug in terms of efficacy and safety is highly variable. Predicting drug dosing is complex since rapid physiological changes occurring during the perinatal and early postnatal periods affect the pharmacokinetic profile of several drugs.

Secondly, neonatal disorders such as renal and hepatic diseases may also have significant implications for drug pharmacokinetics.

Thirdly, pharmacotherapy in the newborn poses difficulties in accurate drug delivery and, consequent upon that a high risk of adverse drug reactions.

Fourthly, the neonates, especially in NICU, are highly exposed to the risk of medication errors, with potentially serious adverse events.

In other words, the extensive variability in pharmacokinetics and pharmacodynamics because of its fast maturation is a glaring feature of the newborn. This together with the newly-evolving treatment modalities, environmental issues and pharmacogenetics renders clinical pharmacological research in neonates utmost important though cumbersome.

Obviously, all this is challenging too [3]. Why? This is understandable on account of quite a few reasons. First and foremost, the pharmacological trial in neonates are more difficult to perform. Secondly, appropriate dosing is hampered by the rapid physiological changes

occurring at this stage of development, and the selection of proper end-points. Thirdly, biomarkers are complicated by the limited knowledge of the pathophysiology of the specific neonatal diseases. Fourthly, there are many ethical challenges in planning and conducting drug studies in the newborns.

These "pharmacological" challenges add to the ethical challenges that are always present in planning and conducting clinical studies in neonates. These challenges justify that clinical research in neonatology should be evaluated by ad hoc ethical committees with specific expertise.

How to overcome the challenges? Tailored tools and legal initiatives, combined with clever trial design are likely to result in more robust information on neonatal pharmacotherapy. This necessitates collaborative efforts between clinical researchers, sponsors, and regulatory authorities. Additionally, patient representatives and society need to make their contribution.

The regulatory framework for model-based neonatal medicinal development needs to be streamlined and initiated wherever it doesn't exist. In trials, success is assured by the implementation of specific pharmacokinetic assessments as a result of accurate drug dosing achieved with a combination of dose validation, population pharmacokinetics and mathematical models of drug clearance and distribution.

Further, age-specific pharmacodynamics need to be considered via appropriate evaluations of drug efficacy with end-points adapted to the peculiar pathophysiology of diseases in this age group.

Tailoring research tools is urgently needed [4]. Development of dried blood spot techniques and the introduction of micro-dosing and tracer methodology in neonatal drug studies as well as building research networks and clinical research skills for neonates must take precedence and that too on priority. Both techniques can be combined with sparse sampling techniques through population modelling. Building The initiatives to build and integrate knowledge on neonatal pharmacotherapy through dedicated working groups, research networks and clinical research skills can go a long way in meeting the aims and objectives.

All in all, as put forward by O'Hara, *et al.* [5], new innovations in pharmacokinetic research, like population pharmacokinetic modelling, present opportunities to conduct clinical trials in neonates aimed at improving the safety and effectiveness of the drugs in this vulnerable population.

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