Neonatal Clinical Pharmacology: A Rapidly Maturing Discipline

The clinical outcome of preterm and term neonates can be significantly improved with the use of safe and effective medicines appropriately investigated in this fragile neonatal population. However, even in 2017, health care professionals involved in neonatal care are routinely prescribing drug formulations, and applying dosing regimens, that initially have been developed for use in adults. Furthermore, the medicines these professionals are using were developed with adult pathophysiology in mind, and are based on adult indications [1, 2]. The overall aim of administering a specific drug to a patient is to reach effective treatment for a given disease while avoiding disproportional side-effects. Clinical pharmacology aims to predict drug-specific (side-)effects based on its pharmacokinetics and pharmacodynamics. Pharmacokinetics (PK, absorption, distribution and elimination, through either metabolism or primary renal elimination, ADME) hereby estimates the relationship between a drug concentration at a specific site (e.g. plasma, cerebrospinal fluid) and time after its administration ("what the body does to the drug"). Pharmacodynamics (PD) aims at both the effects and side-effects of a given drug ("what the drug does to the body"). PK and PD display extensive variability with population specific characteristics because of the fast maturational changes in early infancy, while side effects may be more difficult to unveil.

In this thematic issue on neonatal clinical pharmacology, we have the ambition to provide the readership with a roadmap outlining the multidisciplinary input and expertise needed to improve the current situation. In essence, this roadmap can be viewed as a call to develop a tailored drug (right pathway and target) that needs to be evaluated in the neonatal population using the correct dose, and focussing on the relevant endpoints [1, 2].

This issue starts with a general introduction on the overall theme and provides specific neonatal aspects with a review on maturational PK [3], a paper on formulations and excipients [4], and specific issues to consider when applying therapeutic drug monitoring in this extremely young population [5]. Obviously, pharmacological research in neonates can only be performed within the regulatory framework, and is stimulated through multidisciplinary efforts [e.g. international neonatal consortium (INC), and neonatal ILSI Health and Environmental Sciences Institute (HESI) initiative] supported by these regulatory agencies [6].

A second part of this issue provides reflections on how the pediatric study decision tree [Figure 1] as applied by the authorities can be used for neonatal drug development [7]. We hereby first present different aspects for 3 types of compounds (beta-lactam antibiotics, acetaminophen (paracetamol), inotropic agents), and how the PK and PD data of these compounds can be translated into age-appropriate dosing regimens [8-10]. In a second step, the same pediatric study decision tree is applied to discuss short and long-term aspects of analgosedatives in neonates [11,12].

In the final part of this issue, we aimed to provide the readership with different research approaches (in vivo and in vitro models, turn already existing knowledge or drugs into new information or indications, develop new PK and PD tools) that can be applied to make progress in neonatal drug development. First, research in juvenile animal models may provide us with the tools to explore mechanisms or targets of the human equivalent disease. This is illustrated by the juvenile rabbit bronchopulmonary dysplasia (BPD) model to assess short term respiratory outcome and the juvenile rat model to explore the impact of repetitive painful procedures on the long term development of the nociceptive system [13,14]. The in vitro model development approach is illustrated by the renal tubular cell model since this model has the potential to explore drug-drug interactions or drug toxicity in an in vitro setting [15]. Second, we can use already available data to build knowledge, or explore the relevance of existing drugs or routes of administration to treat specific neonatal diseases. This is illustrated by the use of clinical data routinely collected during clinical care to assess PK/PD of doxapram [16] or novelities on aerosolized surfactant to enable its use as a vehicle [17]. Along the same line, the allopurinol review describes the rationale and drug development plan as an add-on treatment modality to treat perinatal asphyxia [18]. Finally, we should integrate and translate available knowledge and develop new PK and PD tools tailored to neonatal research. The feasibility and relevance to integrate neonatal patho-physiology in physiology based PK models is discussed [19]. Similarly, the experience with (non)-invasive monitoring tools to document hemodynamic and cerebral PD effects of propofol or inotropic agents in neonates is presented [20]. The final paper of this special issue is an outstanding illustration of the experience gained during a full product development plan for recombinant human Insulin Growth Factor-1 (IGF-1) as a possible therapy to promote growth and maturation, and reduce morbidities in extremely preterm infants. The paper covers translation of animal experimental findings to the conduct of clinical studies and collection of safety and outcome data [21].

We hope that this special issue on neonatal clinical pharmacology will not only provide you with state-of-the-art scientific knowledge in a myriad of areas related to this important discipline but also will stimulate collaboration between the relevant stakeholders such as health care professionals in neonatal care, their patients and their parents, academic researchers, regulatory scientists, and pharmaceutical companies to keep this discipline growing. The take home message of this volume is that to improve the safe and effective use of medicines in the most vulnerable patients we are caring for is collaboration between all involved in the care of these newborn infants.

**Keywords:** Clinical pharmacology, newborn, pharmacokinetics, pharmacodynamics.

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Fig. (1). Pediatric study decision tree applied to drug development plans relevant to neonates.

REFERENCES


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