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Invited review

Clinical research in neonates and infants: Challenges and perspectives

Raffaele Coppini[a,*], Sinno H.P. Simons[b], Alessandro Mugelli[a], Karel Allegaert[c,d]

[a] Department of Neuroscience, Drug Research and Child's Health (NeuroFarBa), Division of Pharmacology, University of Florence, Italy
[b] Department of Pediatrics, Division of Neonatology, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands
[c] Intensive Care and Department of Pediatric Surgery, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands
[d] Department of Development and Regeneration, KU Leuven, Belgium

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ABSTRACT

To date, up to 65% of drugs used in neonates and infants are off-label or unlicensed, as they were implemented in clinical care without the usual regulatory phases of pharmacological drug development. Pharmacotherapy in this age group is still mainly based on the individual clinical expertise of specialized pediatricians. Pharmacological trials involving neonates are indeed more difficult to perform: appropriate dosing is hampered by the rapid physiological changes occurring at this stage of development, and the selection of proper end-points and biomarkers is complicated by the limited knowledge of the pathophysiology of the specific diseases of infancy. Moreover, there are many ethical challenges in planning and conducting drug studies in pediatric patients (especially in newborns and infants).

In the current review, we address some challenges and discuss possible perspectives to stimulate scientific and clinical pharmacological research in neonates and infants. We hereby aim to illustrate the add on value of the regulatory framework for model-based neonatal medicinal development currently used in Europe and the United States. We provide several examples of successful recent pharmacological trials performed in neonates and infants. In these examples, success was ensured by the implementation of specific pharmacokinetic assessments, thanks to accurate drug dosing achieved with a combination of dose validation, population pharmacokinetics and mathematical models of drug clearance and distribution; moreover, age-specific pharmacodynamics was considered via appropriate evaluations of drug efficacy with end-points adapted to the peculiar pathophysiology of diseases in this age group. These "pharmacological" challenges add to the ethical challenges that are always present in planning and conducting clinical studies in neonates and infants and support the opinion that clinical research in pediatrics should be evaluated by ad hoc ethical committees with specific expertise.

Contents

1. Neonatal pharmacological research: current understanding

Despite governmental initiatives to stimulate pharmacological research in neonates and infants both in the United States and

* Corresponding author at: Department NeuroFarBa, University of Florence, Viale G. Pieraccini 6, 50139 Florence, Italy.
E-mail address: raffaele.coppini@unifi.it (R. Coppini).

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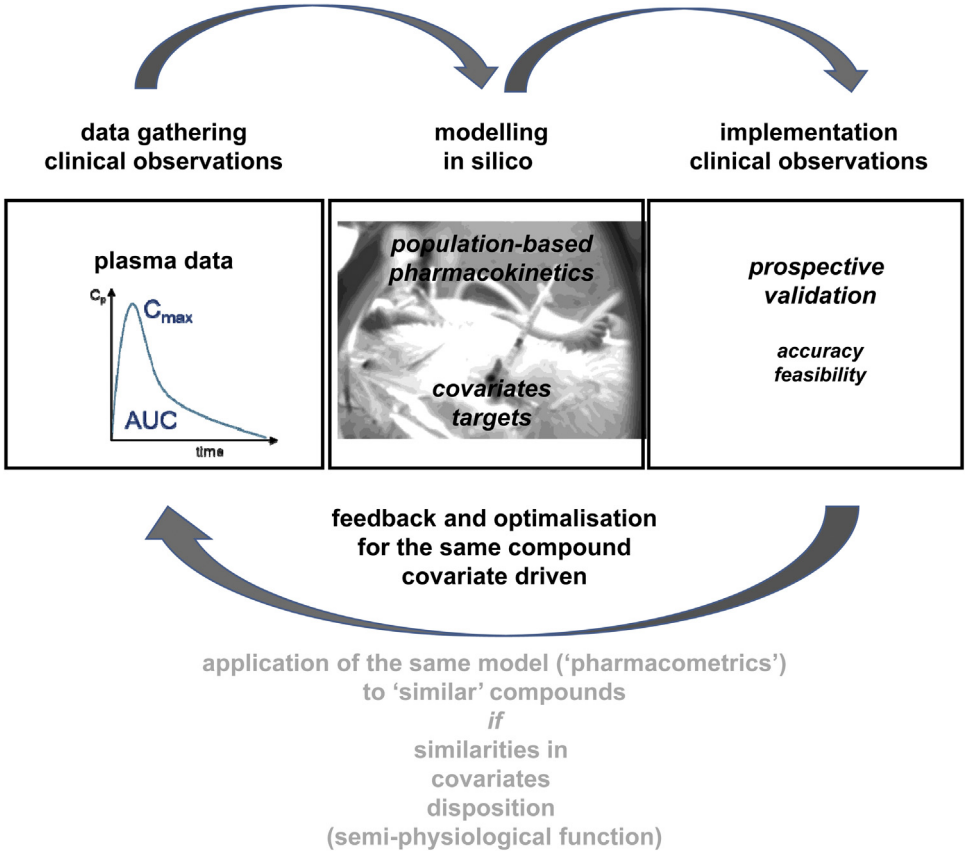

Fig. 1. The currently used regulatory framework is based on specific questions (highlighted in light blue) and results in 3 different types of product development plans (dark blue) for a given compound in neonates.

Europe, the majority of drugs in this pediatric population are still used off-label or unlicensed. In a recent American survey, this mounted up to 65% of the drugs used in Neonatal Intensive Care Units (NICUs) [1]. Similar, in a recent French survey on 8891 prescriptions to 910 NICU neonates, still 5.2% were unlicensed and 59.5% off label. This resulted in exposure to at least one off label or unlicensed drug in 94.8% of these neonates [2]. This is because most of currently used drugs in newborns were implemented in clinical care without the usual regulatory phases of pharmacological drug development. Consequently, neonatal pharmacotherapy is still mainly based on clinical experience, expertise and opinions and is lagging behind when compared to other pediatric subpopulations [3–5].

Because of scientific, regulatory and ethical challenges, trials involving neonates are indeed more difficult to perform. The rapid physiological changes and population specific pathophysiology in the developing neonate affect study design (e.g. dosing, biomarkers, efficacy, endpoints). Protocols and procedures appropriate in adults and older children should not simply be miniaturized to neonates. Lack to consider these issues may in part explain study failures. In a recent survey on 43 drugs studied in neonates between 1998 and 2014 registered in the US Food and Drug Administration databases, 10 drugs were approved based on efficacy data, further supported by pharmacokinetic observations in 4/10 of these drugs [6]. Another 10 drugs were approved based on full (n = 6) or partial (n = 4) extrapolation. Failures were due to inappropriate dose selection (pharmacokinetics) or failure to proof efficacy (maturational pharmacodynamics, biomarkers) [6].

A worldwide collaboration to develop new and existing drugs for neonates has recently been initiated. In a first step, priority conditions required to be studied in this specific population were identified [7]. Besides the conditions, specific areas – including pharmacokinetic modelling – to facilitate neonatal drug development were described [7]. Because of the extensive variability in physiological characteristics within this pediatric subpopulation, we suggest to use a structured approach to generate robust information on neonatal pharmacotherapy (i.e. "pharmacometrics", see below).

In the current review, we want to address some challenges and discuss possible perspectives to stimulate scientific and clinical research. We hereby aim to illustrate the add on value of the regulatory framework for model-based neonatal medicinal development currently used in Europe and the United States (Fig. 1) [8]. Questions on the similarity between neonates and other populations on disease evolution, response to intervention, concentration-response and pharmacodynamic measurement (biomarkers) drive the study decision tree to result in 3 different types of product development programs. The relevance of this decision tree will be illustrated for antibiotics and cardiovascular drugs (Fig. 1).

2. Towards evidence-based antibiotic dosing regimens in neonates: a stepwise approach

When applying the decision tree (Fig. 1) for aminoglycosides, it seems reasonable to postulate similarities (disease evolution, response to intervention and concentration-response) and consequently, to focus on PK (aim for levels similar to other populations) and safety studies. Development of an evidence-based individual dosing regimen by population pharmacokinetic modelling is optimally achieved using a structured approach, based on (*step a*) optimal study design based on data gathering during drug use in clinical practice, (*step b*) development and internal validation of