Model-Informed drug development and precision dosing in neonates, infants and toddlers (MONI)

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Model-informed drug development is a valuable tool for data analysis, dose optimization, and decision-making in paediatric scenarios [1]. Clinical studies, particularly in neonates, infants, and toddlers, are limited by small sample sizes, restricted blood volumes, and ethical constraints [2,3]. Consequently, first-in-child dose can be defined based on prior information from adults or older children using allometric and maturation functions to extrapolate clearance (CL) across age subgroups [4], a key aspect to characterize dose-exposure-response and establish drug dose. Therefore, dose selection relies on the accuracy and precision of CL prediction.
This project aims to validate the a priori guidance of paediatric decision tables for CL extrapolation across age subgroups and drug characteristics, while integrating study design scenarios to improve the accuracy and precision of CL estimation.
Data were retrospectively obtained from data-sharing platforms (Project ID-0011384), including paediatric patients aged 0-2 years receiving intravenous and/or oral administration of drugs subject to phase I metabolism, transporter activity, and hepatic or renal excretion. A theoretical paediatric model will be developed from an established adult model, incorporating scaling functions (linear or fixed exponent) and maturation functions, depending on the drug's pharmacokinetic properties and the paediatric age range, guided by the decision tables [4]. In parallel, a nonlinear mixed-effect model will be implemented in NONMEM® (data-based model). CL estimation (data-based model) and prediction (theoretical model) will be compared in terms of bias and precision (relative standard and absolute errors) to assess the decision table performance.
Four paediatric pharmacokinetic datasets are currently available: gentamicin (n=207, 20 days – 23 months), busulfan (n=64; 3 months – 12 years), mebendazole (n=295; 1-16 years), and topiramate (1-24 months). Additional datasets will be incorporated as they become available to enhance the robustness and generalizability of the analysis. One preliminary data-based model for gentamicin consists of a two-compartment model with exponential inter-individual variability and combined residual unexplained variability.
Preliminary conclusions: It is expected to provide insights into selecting the optimal first-in-child dose for the youngest paediatric patients while addressing the challenges inherent in paediatric clinical trials.

Literature:

[1] F. Bellanti, et al., *Eur. J. Clin. Pharmacol.* 2011, 67 (Suppl. 1), 75–86.
[2] D. Karres, et al., *Br. J. Pharmacol.* 2025, 182 (3), 484–494.
[3] Y. Zou, J. Nedelman, M. O. Karlsson, et al., *Clin. Pharmacokinet.* 2025, 64, 1357–1365.
[4] A. van Rongen, et al., *Expert Opin. Drug Metab. Toxicol.* 2022, 18 (2), 99–113.

Short CV:

My name is Ana Rodríguez-Báez, and I am a Postdoctoral Researcher in Pharmacometrics working on a collaborative project between the University of Bonn and the Federal Institute for Drugs and Medical Devices (BfArM). My research focuses on the application of modelling and simulation approaches to optimize pharmacokinetic parameter estimation in first-in-children studies, as well as to support study design in the youngest paediatric patients. I have a background in pharmacy, and throughout my career, I have developed expertise in population pharmacokinetics and physiologically based pharmacokinetic modelling in special populations, including critically ill adults and paediatric patients. What I find most interesting in pharmacometrics is how models can bridge the gap between preclinical and clinical applications, ultimately contributing to more efficient and evidence-based therapeutic strategies. I am very curious about how this works, and I enjoy learning from others in the field and sharing ideas about current challenges and new approaches.