

Developmental Pharmacology – Special Issues During Childhood and Adolescence

Clinical pharmacology aims to quantify drug-specific (side)-effects based on pharmacokinetics (PK) and pharmacodynamics (PD). PK (absorption, distribution, metabolism and excretion, **ADME**) hereby wants to describe the drug concentration over time (*'what the body does to the drug'*) in a specific compartment, like plasma, cerebrospinal fluid or subcutaneous tissues. PD describes the link between drug concentrations and (side)-effects over time (*'what the drug does to the body'*). Besides mean estimates, clinical pharmacology hereby also aims to predict and explain the extent of variability, and this is where pediatric clinical pharmacology has its specific characteristics since between and intra-patient variability is the key characteristic of children. This is because growth and development differences occur throughout the pediatric age span. These differences profoundly alter the PK and PD of drugs in children [1, 2].

Weight gain, growth and maturation hereby display collinearity, but these trends are neither linear nor uniform when applied to distribution or clearance. Consequently, the key question of neonatal and pediatric pharmacotherapy is how to aim for a moving target, with an integrated appreciation on both developmental PK (ADME) and PD (effects and safety) [2, 3]: *preterms are not just small neonates, neonates are not just small children, and children are not small adults.*

Similar to adults, the treatment of children with effective and safe medicines is crucial to improve their outcome and protect their quality of life. A rational approach to determine a safe and effective dose in an individual child necessitates understanding the PK and PD properties of a specific medicine, in combination with the clinical characteristics of a single, specific child. Modelling and simulation is one way to circumvent several difficulties in developing medicinal products in children. It allows the quantitative use of sparse sampling, characterization and prediction of PK and PD, extrapolation from adults to children, interpolation between pediatric age subsets, optimal use of scientific literature

and in vitro/preclinical data [2, 4]. Compound specific pharmacological studies and basic developmental physiology studies describe these developmental changes and its impact on the PK/PD of drugs. Findings on specific compounds are subsequently translated to semi-physiological models that support drug PK prediction in pediatric patient cohorts [5]. However, these models need further improvement by integrating knowledge on non-maturational covariates to result in dynamic system pharmacology models [6].

The regulatory framework for pediatric medicine development in Europe hereby provides a framework on how to address pediatric drug development [4]. Authorities usually consider information regarding: (i) how similar is disease progression between adults and children, (ii) how similar is the response to intervention between these populations, and (iii) which valid and relevant PD measurements (biomarkers, outcome variables) are available to decide on the type of product development program. If it is reasonable to assume that there is a similar concentration-response in children (similar disease progression, similar response to intervention) compared to data in adults, only PK and safety studies are needed. If one does not anticipate such a similar concentration-response relationship, PK, efficacy and safety trials are needed.

Finally, besides fine tuning of drug development to pediatrics through developmental pharmacology, we should be aware that the pattern of ongoing drug evaluation studies in children almost exclusively reflects drugs initially developed for indications in adults that are subsequently considered to be adapted for the same neonatal or paediatric (e.g. infectious diseases, pain, oncology) indications [7]. However, it is obvious that pediatric product development cannot only simply copy product development from adults, but should also be driven by pediatric pathophysiology and diseases.

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Conflict of Interest

There are no conflicts of interest relevant to this paper. An annual updated version of his public declaration of interest can be retrieved on the EMA website (www.ema.europa.eu/docs/en_GB/document_library/contacts/kallegaert_DI.pdf).

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