NEONATAL PHYSIOLOGY REFLECTS NEONATAL PHARMACOLOGY

Karel ALLEGAERT\textsuperscript{1}, Jan DE HOON\textsuperscript{2}, Liesbeth THEWISSEN\textsuperscript{1}, Maissa RAYYAN\textsuperscript{1}, Gunnar NAULAERS\textsuperscript{1}

Neonatal Intensive Care Unit\textsuperscript{1} and Center for Clinical Pharmacology\textsuperscript{2}
University Hospitals Leuven, Herestraat 49, 3000 Leuven, BELGIUM
e-mail: karel.allegaert@uz.kuleuven.ac.be

Abstract: Drug dosing in infants should be based on their physiological characteristics and the pharmacokinetic and –dynamic parameters of the compound. Since maturational physiological changes are most prominent in infancy, variability is the key feature of clinical pharmacology in infancy: developmental physiology reflects developmental pharmacology.

This is illustrated by the link between renal physiology and renal drug clearance and between hepatic physiology and hepatic drug metabolism for some specific compounds. However, because the slope of these maturational processes differs, integration of these routes is needed to estimate phenotypic in vivo observations of infancy. In addition to the integration of in vivo observations to validate mechanistic (observations to estimates) or physiology based pharmacokinetic (PBPK, developmental physiology to estimates) models, an comparative approach between both approaches in search for discrepancies between both may provide information on ‘missing’ links in maturational physiology or clinical pharmacology (e.g. ontogeny renal or hepatic drug transporters).

Key-Words: developmental pharmacology, maturation, infant, developmental physiology, newborn, renal clearance, hepatic metabolism

1. introduction
Drug dosing during infancy should be based on the physiological characteristics of this population and the pharmacokinetic and –dynamic parameters of the compound. When we consider these physiological changes and the subsequent between individual variability in characteristics, we have to be aware that maturational changes are most prominent in infancy \cite{1,2}. Energy requirements will increase dramatically since total energy requirements is the sum of energy expenditure and energy deposition for growth. Energy demands for growth constitute about 40% in the newborn, are still 35% of the energy requirement during the next 2 months, with a subsequent decrease to 17.5% between 3 and 6 months of life and a further reduction to one-third of that during the next 6 months to result in about 3% at the end of infancy \cite{3}.

In essence, all above mentioned indicators (growth, weight, energy requirements) reflect a very dynamic biological system where maturation is the most crucial feature and both the within as well as the between individual variability in estimates are the key issues. From a clinical pharmacology perspective, the consequence of such a dynamic system is that this results in extensive inter- and intra-individual variability in drug disposition (concentration-time relation, pharmacokinetics, PK) and drug effects (concentration-effect relation, pharmacodynamics, PD) in early life\cite{1,2,4}. This phenotypic variability is further aggravated by interfering pathological processes (e.g. growth restriction, sepsis, associated cardiopathy) or treatment modalities (e.g. co-medication, extracorporeal membrane oxygenation, surgical intervention). Consequently, there is an need to focus on covariates of variability in this population \cite{4,5}. Disposition of drugs in early infancy differs substantially from children or adults as a result of physiology-related maturation in absorption, distribution and subsequent elimination, either through metabolic elimination or through primary renal elimination (ADME, pharmacokinetics) \cite{1,2,6}. The objective of this review is to discuss how maturational
physiology affects the ontogeny of renal and hepatic elimination routes. Because the slope of these maturational elimination processes is different, it is of relevance to integrate both routes to understand phenotypic in vivo observations of infancy: there is no such thing as an isolated neonatal liver or an isolated neonatal kidney. These maturational processes are further affected by other, non-ontogeny related, covariates [1-6]. Finally, the newborn is not just a small child: the importance of a given route of elimination as documented in adults or children is not necessary of similar magnitude during infancy, while minor or irrelevant pathways for adult clearance may turn out to be the most relevant elimination pathway in infants [1-6].

2. Neonatal renal drug elimination

Most drugs or their metabolites are excreted from the body through renal elimination. The renal elimination capacity is reflected by diuresis, glomerular filtration (GFR) and renal tubular activities (both reabsorption and secretion) [7]. This renal elimination capacity in neonates displays extensive variability and in part depends on maturation (e.g. postnatal, postmenstrual age, birth weight), disease characteristics (e.g. peripartal asphyxia, renal congenital disease), genetic polymorphisms, co-medication (e.g. ibuprofen, indomethacin) or growth restriction [7-12]. The main drivers of the maturation of the renal elimination capacity are age (gestational or postmenstrual age, nephrogenesis and renal tubular growth) and the impressive hemodynamic changes in cardiac output and regional perfusion after birth (postnatal age) [1,7]. The haemodynamic alterations at birth relate to the disappearance of the placental circulation with its low resistance, high blood flow in fetal life and redistribution and are further modulated by disease characteristics (e.g. peripartal asphyxia) or co-medication (e.g. ibuprofen, indomethacin) [7-12].

3. Neonatal hepatic drug elimination

Similar to renal elimination capacity, the phenotypic variation in hepatic elimination relates to constitutional, disease related and genetic factors [13]. In infancy, the main driver is ontogeny, i.e. age-dependent activity. Obviously, drug metabolizing enzymes play a critical role in the extent of drug biotransformation and ontogeny of hepatic drug metabolizing enzymes can significantly alter drug clearance throughout infancy. Drug metabolism mechanisms can be classified into phase I and II reactions, the former involving structural alteration of the drug molecule, and the latter consisting of conjugation with another often more water-soluble moiety.

Krumbiegel et al. explored simultaneously in vivo ontogeny of phase I (cytochrome) as well as phase II (glucuronidation) processes by a modified non-distressing 15N-methacetin test [14]. While postmenstrual age turned out to be the most relevant covariate of phenotypic cytochrome activity, postnatal age – independent of the postmenstrual age – was the most important covariate of glucuronidation activity [14]. Similarly, but based on in vivo tramadol metabolism data, we were able to document that tramadol (M) clearance to O-demethyl tramadol (M1) depends on both postmenstrual age and cytochrome p450 (CYP)2D6 polymorphisms (CYP2D6 activity score) [13,15]. With increasing postmenstrual age and with increasing CYP2D6 activity score, there is a progressive decrease in log M/M1 observations, reflecting increased phenotypic drug metabolism [13,15]. In contrast, glucuronidation activity mainly depends on postnatal age but the impact of this covariate on drug clearance mainly depends on the presence of other routes of elimination in the absence of glucuronidation capacity [1,2,13,15].

4. Discussion and conclusions

When we aim to integrate this knowledge on developmental hepatic physiology into developmental pharmacology, it is anticipated that the same covariates (postmenstrual age, postnatal age, polymorphisms) will affect hepatic drug metabolism. However, the infant is not just a small child: the importance of a given route of elimination as documented in adults or children is not necessary of similar
magnitude during infancy, while minor or irrelevant pathways for adult clearance may turn out to be the most relevant elimination pathway in infants. This is reflected in the contrasting maturational clearance in paracetamol compared to propofol. In the absence of glucuronidation, paracetamol is mainly eliminated through sulphation or primary renal elimination. Consequently, postnatal age does not contribute to the overall clearance: size and postmenstrual age explain the variability in clearance. In contrast, propofol as lipophylic compound has to undergo glucuronidation with only a minor CYP2B6 mediated oxidation pathway. Consequently, the impact of postnatal age (dichotomous, 10 days) on propofol clearance within the neonatal age range is of the same magnitude as the postmenstrual age related clearance capacity in the term neonate [16].

The main routes of clearance of drugs and its metabolites are the hepatobiliary system, kidneys and lungs. Primary elimination clearance is mainly through renal elimination while metabolic clearance is mainly through hepatic metabolism. However, we have to take into account that the maturational slope of elimination routes (either hepatic or renal) is not similar [4,5]. As illustrated for tramadol and morphine, the concentration-time profiles of the metabolites (M1 or morphine-3 and morphine-6 glucuronide respectively) do not only depend on the metabolite clearance to these metabolites, but also on the subsequent renal elimination clearance of these metabolites. For both compounds, this results in higher metabolite plasma concentrations since the renal elimination is even more immature compared to the metabolic clearance. We would like to raise awareness for the relevance of ‘rich data sets’ that contain both clinical characteristics and concentration-time profiles: the description of a compound specific pattern is beyond compound specific relevance. The maturational patterns described and the impact of different covariates can subsequently be applied to predict in vivo time-concentration profiles for compounds that undergo similar routes of elimination. Through improved predictability, mechanism based models can help to improve clinical care and feasibility of clinical studies in neonates [4,5,17,18,19]. Such a ‘bottom-up’ approach – from observations to predictions – is somewhat in contrast with the concept of integration of developmental physiology into pharmacokinetic models through physiologically based pharmacokinetic (PBPK) modelling – from predictions to observations [17-19].

Discrepancies may serve as indicators for ‘missing’ links in our knowledge on maturational anatomy or physiology (e.g. drug receptor activity, receptor expression) and in this way may also shape or guide fundamental research in the field of developmental physiology [17-19]. In this way, PBPK models do not only hold the promise (top-down) to be helpful in the clinical design similar to mechanistic models, but may also serve as indicators to perform developmental anatomy/physiology research projects as ‘confirmatory’ instead of ‘exploratory’. Improved knowledge on developmental pharmacology does not only serve the individual clinician and the patient, but can also improve focused research on aspects of developmental biology that are difficult to explore like the above mentioned hepatic or renal transporter ontogeny.

References:


