Clinical pharmacology in neonates: limited in their size, extensive in their interindividual variability

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Abstract: The general principles of disposition and elimination of exogenous compounds apply in neonates, but their specific characteristics warrant a focussed approach. Maturational changes in drug disposition occur throughout childhood, but are most prominent in early life. Elimination clearance is mainly through metabolic or renal elimination clearance. Almost all phase I and phase II metabolic processes display ontogeny in a iso-enzyme specific pattern while renal elimination clearance in early life is low and almost completely depends on glomerular filtration. Interindividual variation in phenotypic clearance is based on constitutional, environmental and genetics factors. Despite the overall low clearance, interindividual variability is already extensive and can be explained by covariates like age, co-administration of drugs, growth restriction, disease characteristics.

Key-Words: ontogeny – interindividual variability – newborn – maturation – developmental pharmacology

1 Introduction
Although the general principles of disposition of exogenous compounds apply in neonates, their characteristics warrant a tailored approach. History provides us with evidence on the deleterious effects of chloramphenicol (gray baby syndrome), benzyl alcohol (gasping syndrome) or dexamethasone (cerebral palsy) in neonates to warrant this specific focussed interest [1,2].

Children display maturation in the disposition of exogenous compounds, most prominent in early life. There are age-dependent changes in body composition, almost all phase I and phase II metabolic processes mature while renal drug clearance in early life is low and almost completely depends on glomerular filtration rate (GFR). These changes all affect pharmacokinetics (concentration-time, PK) [1,2].

Phenotypic variation in metabolism of exogenous compounds is based on constitutional, environmental and genetic factors, but in early life mainly reflects ontogeny, resulting in overall low clearance but already extensive interindividual variability within this population [1,2].

In the current paper, we would like to focus on developmental aspects of metabolic and renal clearance based on probe specific observations with focus on the covariates of drug disposition involved.

2 Problem Formulation
Covariates of interindividual variability have to be based on general biological principles (e.g. weight, age, disease characteristics, co-medications). Besides covariates, there is also a need for specific methods to study maturational aspects of drug clearance in neonates. With conventional approaches, a model is defined for each individual, based on the concentration-time profiles available hereby using the best fitting model (type of compartment). Such a compartment model is based on the diffusion characteristics of the drug and the route of administration. Kinetic variables can be estimated based on these individual concentration-time profiles and can subsequently be described and compared using statistical approaches. There are important prerequisites to use such an individual approach [1,2,6].

The number of observations in one individual should be sufficient enough to calculate kinetics and a stringent sampling strategy should be used to limit variability. In addition, within subject variability should be limited since estimated PK parameters are subsequently used a measured variables, resulting in limited accuracy to explore variability while variability is the most relevant question in neonates. We therefore need models, based on a limited number of samples in every single individual infant.

In a population approach, the entire population is modelled. Therefore, there is no need to have sufficient data in every individual to define a predictive model and analysis after random sampling is feasible. Population
pharmacokinetics provides a tool to learn more on what we want to know, i.e. with data on the degree and sources of variation. In a non-linear mixed effects modelling (NONMEM) approach, all data are fitted together with the individual covariates, using non linear regression [6].

2 Problem Solution
Focused studies within the neonatal population should enable us to unveil covariates within this population. The usefulness of population pharmacokinetics to unveil covariates of drug disposition in neonates can be illustrated. Renal elimination clearance in early life is low while interindividual variability is extensive. Renal clearance almost completely reflects GFR capacity [3]. Interindividual variability in renal clearance capacity in neonates is illustrated based on observations on amikacin and vancomycin [4,5]. The interindividual variability in phase I (cytochrome p-450 (CYP) 2D6, CYP3A4, esterase) and phase II (glucuronidation) metabolism will be illustrated based on tramadol, paracetamol and propofol observations.

2.1 covariates of renal drug clearance
Aminoglycoside clearance reflects GFR and is a validated tool to study GFR maturation [1,2,3]. Based on the characteristics of vancomycin, it is to be anticipated that maturation of vancomycin clearance displays a similar trend. Interindividual variability in amikacin or vancomycin clearance therefore reflects the interindividual variability in GFR maturation. The interindividual variability in drug clearance for both amikacin and vancomycin within the neonatal population was about 10-fold [4,5,6].

Using population pharmacokinetic methods, the impact of covariates as contributors of this extensive interindividual variability in amikacin or vancomycin disposition in preterm neonates has been evaluated. Based on these observations, we were able to show that besides age and weight, co-administration of non-selective cyclo-oxygenase inhibitors or growth restriction had an independent impact of renal drug elimination capacity, while prenatal lung maturation, ventilatory settings or co-administration of inotropics had no additional impact on renal drug clearance.

2.2. covariates of drug metabolic clearance
Tramadol (M) hydrochloride is a 4-phenyl-piperidine analogue of codeine. O-demethyl tramadol (M1) is produced by O-demethylation of M by CYP2D6. The other metabolite (N-demethyl tramadol, M2) is produced after N-demethylation, mainly by CYP3A4. Tramadol disposition can therefore be used as a probe drug to simultaneously assess CYP3A4 and CYP2D6 ontogeny. Based on the collected observations, we were able to document that both age and CYP2D6 genetic polymorphisms are already of relevance from early life onwards, while disease severity had no independent impact on tramadol metabolism in neonates [7].

Besides CYP iso-enzyme specific ontogeny, other phase I enzymes like esterases might also display ontogeny. We are unaware of any in vitro assessment of esterase ontogeny, but propacetamol hydrolysis can serve as in vivo probe drug to assess esterase activity since propacetamol as pro-drug is hydrolysed to paracetamol. The individual standardized predicted hydrolysis half-life in pooled population pharmacokinetic study in neonates, toddlers and children was used to assess potential age-dependent maturation of esterase during childhood. It was hereby documented that there was no age-dependent effect on hydrolysis half-life, strongly suggesting that esterase is already mature at birth [8]. Compared to phase I iso-enzymes, data on iso-enzyme specific phenotypic activity of uridine diphosphate glucuronosyltransferase (UGT) and its covariates in neonates are limited. In vivo observations on morphine, paracetamol (acetaminophen) and propofol disposition throughout childhood confirm the overall low glucuronidation activity in neonates observed in in vitro studies [9]. In addition to the phenotypic low glucuronidation activity, in vivo observations of bilirubin (UGT1A1), morphine (UGT2B7), paracetamol (UGT1A6) and propofol (UGT1A9) glucuronidation in neonates display extensive interindividual variability, only in part explained by postmenstrual and postnatal age. Covariates like disease state characteristics (decreased morphine metabolism during therapeutic head cooling), genetic polymorphisms (UGT1A1 genetic variants and differences in bilirubin metabolism) or environmental factors (increased urinary excretion of paracetamol-glucuronide by repeated administration of paracetamol) further contribute to this variability [9].

2.3 general discussion
Important alterations in hepatic metabolism occur in early life. Besides PMA and PNA, polymorphisms also can have a documented impact on the phenotypic metabolic clearance capacity observed. Similarly, renal elimination capacity displays extensive interindividual variability, in part linked with age, size or co-treatment with ibuprofen. Consecutive studies performed to improve predictability of renal clearance capacity in late fetal and neonatal life were described. These studies enabled us to develop more effective and safe dosing regimes for different drugs (analgesics, sedatives) administered to neonates. Similarly, the documentation of the contribution of various covariates of aminoglycoside clearance resulted in clinical relevant interventions: the implementation of a more adapted...
GA-dependent dose regimen, the additional time interval (6 hours) when ibuprofen is co-administered and the introduction of a paediatric vial.

In addition to the overt clinical implications of these observations, it is important to stress that the collected compound-specific maturational processes have an applicability beyond the drug-specific use by pattern recognition and subsequent prediction. Since age only in part explains the interindividual variability observed, concerted efforts should be developed to simultaneously assess the impact of age, environmental factors, comorbidity and polymorphisms in this specific population. The documentation of the maturational processes in drug metabolism or clearance based on ‘probe’ studies of can be extrapolated to other drugs already prescribed or only considered to be used in neonates by introducing these observations in ‘in silico’, ‘generic physiologically based pharmacokinetic’ or ‘mixed effects’ models [1,2,6].

4 Conclusion
A focused approach to unveil covariates of the interindivudual range is needed and warranted to improve our knowledge on drug disposition in early life.

References: