Medical physiology and drug disposition in special populations: from compound specific observations to physiology based pharmacokinetics

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Abstract: The general pharmacokinetic principles of disposition and elimination of exogenous compounds apply, irrespective of population specific characteristics. However, perinatal characteristics like pregnancy or early infancy warrant a focussed approach because important alterations in physiology (either pregnancy or maturation, age-related changes) affect drug disposition in a clinical relevant way. During pregnancy, there are changes in distribution volume due to changes in body composition, in metabolic activity affecting drug metabolism and in renal elimination (GFR, tubular) capacity. In early neonatal life, maturational changes in drug disposition are most prominent Almost all phase I and phase II metabolic processes display ontogeny in an iso-enzyme specific pattern while renal elimination clearance in early life is low.

The link between pregnancy related changes in medical physiology and changes in drug disposition will be illustrated based on aspects of cefazolin disposition during pregnancy while the complex interaction between maturation, genetic polymorphisms and renal elimination in early life will be illustrated based on tramadol observations in early life. We hereby aim to stress the relevance to link medical physiology with clinical pharmacology through physiology based models in order to improve predictability of clinical pharmacology in these specific populations. Beyond the anecdotal observations, patterns related to medical physiology are unveiled.

Key-Words: physiology based pharmacokinetic model – pregnancy – neonate –drug disposition – developmental physiology

1 Introduction
Safe and effective dosing of drugs requires an understanding of the covariates of drug disposition in the individual patient. The general pharmacokinetic principles of disposition and elimination of exogenous compounds apply, irrespective of population specific or individual characteristics [1,2].

However, perinatal characteristics like pregnancy or early infancy warrant a focussed approach because important alterations in physiology (either pregnancy or maturation, age-related changes) affect drug disposition in a clinical relevant way. Pregnancy as well as developmental aspects in early life result in extensive alterations in pharmacokinetics (PK) with a subsequent extensive inter-individual variability in drug response [1,2].

In general, renal drug clearance is enhanced during pregnancy (i.e. higher glomerular filtration rate, higher active tubular excretion), the basal metabolic activity is also increased likely resulting in increased metabolic drug clearance. Finally, changes in body weight or binding capacity (protein changes) likely will affect the volume of distribution. Similarly, duration of pregnancy, co-morbidity (e.g. pre-eclampsia) or labour itself may further affect variability in drug disposition [1,3].

Early neonatal life is associated with a decreased renal clearance due to immaturity of renal function with subsequent maturation. Metabolic clearance displays iso-enzyme specific ontogeny and thus largely depends on the postmenstrual or postnatal age of the child. Besides age (maturation), the route of drug administration, co-morbidity, concomitant
medication and polymorphisms in drug metabolizing enzymes or transporters also contribute to this inter-individual variability in neonates [2,4]. Throughout this paper, we aim to stress the relevance to link medical physiology with clinical pharmacology through physiology based models in order to improve predictability of clinical pharmacology in these specific populations: beyond anecdotal or compound-specific observations, patterns related to medical physiology explain covariates of clinical pharmacology and have the potential to predict the extent of interindividual variability.

2 Problem Formulation
A drug is prescribed with the intention to obtain a dose-related therapeutic effect, preferably without side-effects. Clinical pharmacology aims to predict these effects based on drug, population and/or patient-specific pharmacokinetics and –dynamics [1-4]. Physiology based pharmacokinetic models can be helpful to reach these aims since there is already a proven track record to extrapolate animal experimental observations to ‘first in man’ studies. This methodology should be further developed to improve the safety of clinical pharmacology in these specific populations [5,6,7]. Focused studies during pregnancy and within the neonatal population should enable us to unveil covariates within these populations [6,7].

To illustrate at least the feasibility in a clinical setting, the link between pregnancy related changes in medical physiology and changes in drug disposition will be illustrated based on aspects of cefazolin (CFZ) disposition during pregnancy [8,9]. To illustrate the feasibility in early human life, the complex phenotypic disposition of tramadol as final result of interactions between maturation, genetic polymorphisms and renal elimination in early life will be illustrated based on tramadol plasma observations in early life [10,11].

3 Problem Solution: an illustrative approach
3.1. Cefazolin disposition in pregnancy
CFZ is a first generation cephalosporin for intravenous administration. This drug has a narrow bactericidal spectrum, mainly covering Gram positive bacteria. CFZ is administered for prophylaxis during a variety of surgical interventions, including interventions during pregnancy [12]. CFZ clearance is almost exclusively renal and consequently depends on glomerular filtration rate (GFR) and renal tubular function. GFR increases approximately 50% in the first trimester of pregnancy and continues to increase up to about 37 weeks GA [1,3]. Data on alterations of renal tubular function during pregnancy are not available. Pregnancy also affects protein binding capacity. CFZ protein binding in human plasma is high but displays important intra- and interindividual variability in adults as Vella Brincat et al. described [13]. This is of clinical relevance, since the unbound CFZ plasma concentration correlates with the unbound tissue concentration and it is the unbound drug that is active against the micro-organisms [13].

To document cefazolin (CFZ) plasma binding and its covariates during pregnancy and compare these observations with already reported observations in non-pregnant adults, maternal CFZ plasma samples were collected during in utero surgery [8]. Plasma (n = 130) samples were collected during 30 interventions. Median unbound CFZ fraction was 0.25 (range 0.14 – 0.41). Correlations between the unbound CFZ fraction and total CFZ plasma concentration (0.46), time after administration (-0.38), albuminaemia (-0.39) and gestational age (-0.19) were significant. Median unbound CFZ fraction was higher during pregnancy when compared to observations in non-pregnant adults (0.25 vs 0.19, p < 0.001). In a multiple regression model, total plasma CFZ concentration and albuminaemia were co-variates of the unbound CFZ fraction ($r^2 = 0.4$) [8]. We therefore concluded that the saturability of CFZ plasma protein binding as described in non-pregnant adults was confirmed during pregnancy, but CFZ free fraction is higher, likely explained by the lower albuminaemia during pregnancy [8,13].

To study cefazolin pharmacokinetics in maternal plasma and during pregnancy, newly collected time-concentrations profiles and reported studies investigating cefazolin disposition were pooled [9]. Based on 187 plasma samples were...
collected in pregnancies (17–40 weeks gestational age, GA), cefazolin clearance and distribution estimates were 7.44 L/h and 12.04 L respectively, about twice higher compared to the non-pregnant setting [9]. However, a GA-dependent trend was not observed although there is a progressive increase in renal function (GFR) throughout pregnancy and a progressive reduction in albumin plasma binding capacity throughout pregnancy. These *in vivo* observations suggest that the increase in GFR is compensated by a similar increase in tubular resorption activity during pregnancy.

### 3.2. Tramadol disposition in early life

In the evaluation of age-dependent maturational processes, co-variables should be based on general physiological principles, like age, size, co-morbidity or genetic polymorphisms [2,4,6,7]. Phenotypic variation in metabolism of exogenous compounds is based on constitutional, environmental and genetic factors, but in early life mainly reflects ontogeny, i.e. age-dependent maturation [2,4]. This results in overall low metabolic clearance but extensive interindividual variability during infancy [4]. Almost all metabolic processes display ontogeny in an iso-enzyme specific pattern. Total CYP content in the foetal liver equals about 30 to 60 % of adult values but iso-enzyme specific ontogeny precludes the generalisation of a simple single developmental pattern and makes iso-enzyme specific assessment necessary [2,4]. Since we intend to illustrate the complex interplay between ontogeny, pharmacogenetics and renal elimination clearance based on *in vivo* observations on tramadol disposition during infancy and its pharmacodynamic relevant metabolite, O-demethyl tramadol (M1) is generated through CYP2D6 activity, we focus on this specific iso-enzyme [2,10,11]. *In vitro* observations on CYP2D6 iso-enzyme specific ontogeny have been published [2,10,11]. CYP2D6 ontogeny was assessed based on dextromethorphan O-demethylase activity, quantitative Western blotting to identify CYP2D6 developmental expression patterns and immunodetectable levels of CYP2D6 protein. CYP2D6 expression in liver samples from neonates less than 7 days postnatal life was higher than that observed in fetal samples from first and second trimester of pregnancy, but not significantly higher than samples collected in the third trimester of pregnancy. In contrast, expression in postnatal samples greater than 7 days of age was substantially higher than that for any earlier age category. When combined with proportional changes in liver size, these observations can be used for predictions in physiology based pharmacokinetic models [5,6,7,10,11]. *In vivo* observations on CYP2D6 ontogeny in infancy have been described based on ontogeny of dextromethorphan O- and N-demethylation metabolism. Besides age and size, polymorphisms further contribute to the interindividual variability in metabolic drug elimination since the CYP2D6 iso-enzyme is highly polymorphic with more than 75 allelic variants identified [10,11].

Based on 1 275 tramadol time-concentration profiles in 57 neonates, 33 children and 32 adults, 50 % of adult clearance was reached at 44 weeks postmenstrual age, with a maturational half life in tramadol clearance of 3.6 weeks, resulting in about 90 % of adult tramadol clearance capacity at 100 weeks PMA, equal to a postnatal age of 1 year in a full term born [11]. Clearance to M1 formation does not only depend on postmenstrual age, but also on the individual CYP2D6 activity score (CYP2D6 polymorphisms). Phenotypic time-concentration profiles will depend on maturation of both M1 synthesis (age, ontogeny) and subsequent renal elimination clearance (GFR maturation and its covariates like ibuprofen exposure) [2,14,15].

### 4 Discussion and conclusion

Understanding the dose-exposure relationship and the subsequent dose-response relationship in humans remains a major challenge for clinicians to optimize safety and efficacy when drugs are administer [1-7]. This is even more pronounced in specific populations like pregnant women or neonates [1-4]. Using a pooled dataset on CFZ disposition during pregnancy, we illustrated the complex interaction of pregnancy related changes in GFR, tubular activity and plasma protein binding, resulting in an increased CFZ
clearance capacity, irrespective of the GA (17-40 weeks) at inclusion [8,9]. Similarly, using a pooled tramadol disposition dataset, we illustrated that the phenotypic final result of a given time-concentration profile of both the parent compound depends on maturational trends in drug metabolism (CYP2D6 ontogeny and polymorphisms) and subsequent maturation of renal elimination capacity (GFR)(figures 2-5) [10,11,14,15].

In addition to the compound specific clinical implications of these observations, it is important to stress that the description of pregnancy of maturation related processes is applicable beyond the compound-specific use by pattern recognition and subsequent prediction [1-7].

Physiologically-based pharmacokinetic (PBPK) modeling allows predictions of the absorption, distribution, metabolism and elimination (ADME) processes, based on detailed knowledge about the physiological processes that affect the pharmacokinetics of a drug [5]. By evaluating the pharmacokinetic data of specific compounds during pregnancy or in early life and using a descriptive physiology-based approach, we can start to predict the effect of either pregnancy or early life for a large number of clinically used drugs. However, because of the limitations, more clinical in vivo studies are needed to fully elucidate the pharmacokinetics of drugs and to further validate physiology-based pharmacokinetic models in these specific populations [4-7]. At least, we aimed to illustrate the potential impact of medical physiology in specific human populations to improved clinical pharmacology in some vulnerable, underserved populations.

References: