Pharmacokinetics of routinely administered compounds during pregnancy reflect pregnancy related physiological changes

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Abstract: The general pharmacokinetic principles of disposition and elimination of exogenous compounds apply, irrespective of population specific characteristics. However, pregnancy and delivery warrant a focussed approach because important alterations in physiology (e.g. renal, hepatic, metabolism, body composition) 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. The link between pregnancy related changes in medical physiology and changes in drug disposition will be illustrated based on aspects of cefazolin and paracetamol disposition during pregnancy and after delivery. Beyond these anecdotal observations, patterns related to medical physiology are unveiled.

Key-Words: pregnancy – drug disposition – medical physiology – paracetamol – cefazolin

1. Introduction

The general pharmacokinetic principles of disposition and elimination of exogenous compounds apply, irrespective of population specific or individual characteristics [1,2]. However, characteristics like pregnancy or postpartum warrant a focussed approach because important alterations in physiology affect drug disposition in a clinical relevant way. Pregnancy results in extensive alterations in pharmacokinetics (PK, concentration-time profile) 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 (phase I and phase II processes), although the alterations are in part iso-enzyme specific. Rarely, enzymatic activity (CYP1A2 and CYP2C19) can be suppressed during pregnancy through oestrogen mediated inhibitory activity [1]. Finally, changes in body weight or binding capacity (protein changes, pH) 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 [1-4]. Throughout this paper, we aim to stress the relevance to link general medical physiology with clinical pharmacology through physiology based models in order to improve predictability of clinical pharmacology during pregnancy [1-4]: 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 and the subsequent prediction of the concentration-effect profile.

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 [5,6]. 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 this specific population [1-6]. Focused studies during pregnancy should enable us to unveil covariates and the patterns within this population [1-6]. 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 both aspects of intravenous cefazolin (CFZ) disposition [7,8] and intravenous paracetamol disposition during pregnancy.

3. 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 [7,8]. 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 [1,2]. 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 [9]. 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.

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 [7,8]. 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 covariates 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].

To study cefazolin pharmacokinetics in maternal plasma and during pregnancy, newly collected time-concentrations profiles and reported studies investigating cefazolin disposition were pooled [7]. 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. 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. Paracetamol disposition in pregnancy

Paracetamol, N-acetyl-p-aminophenol, is a readily available antipyretic and analgesic agent. It is the most often prescribed drug for treatment of mild to moderate pain or fever and can be administered by oral, rectal but also by intravenous route. In adults, paracetamol is almost exclusively eliminated by renal way after conjugation with either glucuronic acid to paracetamol-glucuronide (APAP-G, 47-62%) or with sulfate to paracetamol sulfate (APAP-S, 25-36%) resulting in a APAP-G/APAP-S ratio of about 2. Only limited amounts are excreted in the urine as free paracetamol or are metabolized through oxidation to N-acetyl-p-benzoquinone-
Imine (NAPQI) and into 3-hydroxy-APAP by the cytochrome p 450 enzyme system. If not depleted, glutathione conjugates with the hepatotoxic metabolite NAPQI resulting in cysteine and mercapturic acid metabolite. Uridinediphosphate-glucuronosyltransferases (UGT’s) are part of a superfamily of enzymes that catalyse the addition of a glycosyl group from a nucleotide sugar to a small molecule enhancing renal elimination of this molecule. Paracetamol is mainly metabolized by UGT-1A6 and to a much lesser extent by UGT-1A1 and UGT-1A9 [10]. As part of an ongoing project, we would like to report on the impact of pregnancy on loading dose (2 g iv) pharmacokinetics of iv paracetamol when compared to (i) observations as reported in literature (healthy adult volunteers, 2 g iv) and (ii) a subgroup of former pregnant women to whom a similar loading dose was administered immediately following caesarean and after 10 weeks postpartum (paired analysis).

Loading dose administration (2 g iv) pharmacokinetics of iv paracetamol in non-pregnant adult patient have been documented (1). The goal of this study was to document paracetamol disposition after loading dose (2 g iv) administration in pregnant women. Pregnant women who underwent a cesarean section, received an initial 2 g loading dose of iv paracetamol were included in this open-label, loading dose PK study. Blood samples were collected at predetermined time points (at 1, 2, 4 and 6 hours after the loading dose). Serum concentrations of paracetamol were determined by high-performance liquid chromatography with UV detection [11]. A one-compartmental linear (zero order input, first order elimination) pharmacokinetic model was used. Data on gestational age (GA), body weight (BW) and body surface area (BSA) at delivery were collected and reported as median and range. 128 plasma paracetamol time-concentration points were collected in 35 women [median (range) GA 36.7 (27-41) weeks, BW 80.4 (61-110) kg, BSA 1.92 (1.65-2.35)]. Median (range) C_{max} was 23.12 (7.92-32.32) mg.L^{-1}, median C_{trough} was 3.96 (0.55-9.37) mg.L^{-1}). Consequently, distribution volume was 86.26 L, clearance was 31.54 L.h^{-1} and elimination half life was 1.9 h. When compared to data as published in literature in healthy non-pregnant adults, both distribution volume (86.26 vs 65.4 L) and clearance (31.54 vs 15.9 L.h^{-1}) seem to be higher at delivery compared to the non-pregnant setting. We therefore concluded that An iv 2 g loading dose of paracetamol immediately following cesarean section results in relatively lower initial peak concentrations due to a higher distribution volume and even lower paracetamol concentrations afterwards because of higher clearance in pregnancy compared to non-pregnant healthy adults.

As a second part of this pharmacokinetic (PK) study on 2 g intravenous (iv) loading dose paracetamol in pregnant women, intra-subject (pregnant vs non-pregnant state) PK differences were investigated. Following informed consent, a subgroup of 6 pregnant women who underwent a cesarean section and received a 2 g loading dose of iv paracetamol were admitted again for the same loading dose administration scheduled for at least 10 weeks after the pregnancy. At both visits, blood samples were collected at the same predetermined time points (1, 2, 4 and 6 hours after drug administration). A one-compartmental linear PK model in a naïve pooled approach was used. Paired data were compared using nonparametric Wilcoxon signed-rank test. Clinical data were reported as median (range).

48 plasma concentration-time points were collected in 6 women. Median (range) age was 32 (27-37), gestational age 38 (33-39) weeks, postpartum week 11.2 (10.7-15). When observations in pregnancy were compared to non-pregnant state, median (range) C_{max} [23.06 (13.88-32.32) vs 64.5 (38.49-75.75) mg.L^{-1}] were significantly lower during pregnancy (p=0.0312) while no difference was observed in C_{trough} [4.08 (2.88-8.17) vs 5.73 (2.66-11.88) mg.L^{-1}, p=0.0625]. Naïve pooled paracetamol half-lives were 1.99 vs 2.13 h, clearances 28.73 vs 21.20 L.h^{-1} and distribution volumes 82.34 vs 65.26 L in pregnant vs non-pregnant state respectively. Following an iv paracetamol loading dose, pharmacokinetic intra-individual differences between pregnant and non-pregnant state were in line with differences observed between pregnant women and healthy.
volunteers. These pharmacokinetic estimates might be of pharmacodynamic relevance. We aim to further explain the differences in clearance observed based on 24h urine collections to quantify the impact of pregnancy on the phenotypic glucuronidation, sulfation and primary renal elimination capacity during pregnancy using earlier reported analytical techniques [10].

4. Discussion and conclusion

Understanding the dose-exposure and dose-response relationship remains a major challenge for clinicians to optimize safety and efficacy when drugs are administer [1-6]. This is even more pronounced in specific populations like pregnant women. Using a pooled dataset on CFZ disposition during pregnancy, we illustrated the 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) [7,8]. Paracetamol clearance is significantly higher during pregnancy based on inter-population and paired analyses.

In addition to the compound specific clinical implications of these observations, it is important to stress that the description of pregnancy related processes is applicable beyond the compound-specific use by pattern recognition and subsequent prediction [1-3]. 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 [3]. 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 specific populations, like pregnant women.

References