The impact of pregnancy on the pharmacokinetics of non-opioid analgesics

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Abstract: 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. Consequently, pregnancy warrants a focussed approach in clinical pharmacology, since these important alterations in physiology (e.g. renal, hepatic, metabolism, body composition) affect drug disposition. Despite these differences, even commonly administered drugs like non-opioids have not been evaluated on their pharmacokinetics during pregnancy. We report on our observations on paracetamol and ketorolac disposition following caesarean delivery to illustrate the feasibility and relevance of such focussed studies.

Key-Words: pregnancy – pharmacokinetics – paracetamol – ketorolac – multimodal analgesia

1. multimodal analgesia at delivery

A drug is administered 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 (PK, concentration-time) and -dynamics (PD, concentration-effect). Pregnancy, labour and postpartum warrant a focussed approach [1,2,3]. Renal clearance is enhanced during pregnancy (i.e. higher glomerular filtration rate, higher active tubular excretion), the metabolic activity (e.g. oxygen consumption, cardiac output) is also increased often resulting in increased metabolic drug clearance (phase I and phase II), although alterations are in part iso-enzyme specific. Rarely, iso-enzyme specific activity (e.g. CYP1A2 and CYP2C19) is decreased during pregnancy through oestrogen mediated inhibition [2,3]. Finally, changes in body weight or binding capacity (protein changes, pH shifts) affect drug distribution. Duration of pregnancy (gestational age), co-morbidity (e.g. pre-eclampsia) or labour itself further modulate the variability in pharmacokinetics [1,2,3].

These PK alterations can subsequently affect the variability in the observed drug response, including the level of analgesia. The inter-individual variability in drug response is further affected by between individual differences in PD covariates. When applied to post caesarean pain management, the presence of labour but also aspects related to individual thermal pain thresholds, personality characteristics or the duration of surgery further modulate the inter-individual variability in pain reported and analgesics administered post caesarean [4,5].

Multimodal analgesia following caesarean should focus on effective pain relief so that the mother can mobilise early, but she also has the added responsibility of needing to care for her newborn [3,4]. There is no single ‘magic bullet’ for postoperative pain management following caesarean. The options are extensive and are at least in part driven by availability, preferences, experience, resource limitations and costs. Most methods rely on opioids, supplemented with nerve blocks, adjunctive techniques, and anti-inflammatory analgesics, including intravenous (iv) paracetamol or ketorolac [3,4,5].

Despite the fact that both compounds are routinely used as part of multimodal analgesia, there are no PK observations to suggest dosing regimens. Commonly, dosing is similar to other postoperative analgesia indications, without taking the impact of pregnancy on the clinical pharmacology of these compounds into account.
account. In a stepwise approach to improve multimodal analgesia after caesarean, we aim to describe iv paracetamol and iv ketorolac PK.

### 2 iv paracetamol PK at delivery

Pregnancy and postpartum affect drug disposition, but data on iv paracetamol loading dose pharmacokinetics at delivery have not been reported. We aimed to describe loading dose pharmacokinetics of intravenous paracetamol following surgical delivery and to compare these postpartum observations with similar observations as reported in young female volunteers [5,6].

Shortly following caesarean section, women received a loading dose (2 g) of IV paracetamol and 4 (1,2,4 and 6 h) plasma samples were collected. Individual pharmacokinetics were calculated assuming a linear one compartment model with instantaneous input, first order output and compared with similar observations (2 g IV loading dose, same time points) reported in 14 young female volunteers [6,7]. Observations were reported by median and range, compared by Mann-Whitney U test. Observations were available in 42 cases, 28 following caesarean section. Median paracetamol plasma concentrations after 1, 2, 4 and 6 hours following operative delivery were 22.5, 15.25, 7.9, and 3.9 mg/l. In healthy volunteers, median concentrations were 31.5, 21.3, 10.9, and 5 mg/l respectively (all at least p<0.01). Median clearance (15.5 vs 20.3 l/h, p<0.01) and distribution volume (43.7 vs 58.3 L, p<0.001) were significantly higher post caesarean section. Even after correction for body surface area, this increase (9.6 vs 10.9 l/h.m$^2$) remained significant (p<0.05) (figure 1).

**Fig 1:** paracetamol clearance (l/h) in healthy volunteers or at delivery

Following caesarean delivery, paracetamol clearance (+35%) and distribution volume (+30%) are increased compared to healthy adult volunteers. Finally, the between individual variability in paracetamol clearance is significantly higher at delivery (4-fold instead of 2-fold), suggesting that there are other covariates besides weight changes involved at delivery. To further explore this, we evaluated the impact of gestational age at delivery on the individual clearance estimates. In a scatter diagraph, it seems that there is an overall higher clearance throughout pregnancy, with a subsequent reduction at term age. (figure 2)

**Fig. 2:** scatter diagram: individual clearance (l/h.m$^2$) on gestational age (weeks).

### 3 iv ketorolac PK at delivery

Ketorolac tromethamine is administered by iv route as part of a multimodal analgesia protocol after cesarean [5], but data on ketorolac pharmacokinetics (PK) at delivery are absent. The aim was to estimate ketorolac PK post-cesarean and compare these values with estimates in non-pregnant adult volunteers [8]. Women who underwent a cesarean section and received an iv dose of 30 mg ketorolac shortly after delivery of the newborn, were included in this open-label PK study. Blood samples were collected 1, 2, 4, 6 and 8 hours after ketorolac administration. Racemic ketorolac was quantified by HPLC with UV detection and PK were calculated assuming a linear one compartment model with instantaneous input and first order output [7]. The distribution volume (Vd, l and l/kg) and concentration at t = 0 (Cmax0) were calculated. The slope of the
curve was used to calculate time constant $K$, elimination half life, and clearance [7].

Individual PK estimates were calculated in 39 cases (12 delivered preterm, < 37 weeks). Median weight at delivery was 73.2 (range 40-106) kg. Median distribution volume was 0.23 (range 0.16-0.42) l/kg, elimination half life 2.41 (1.26-4.75 h), clearance 5.2 (2.25-15.60) l/h and 0.069 (0.027-0.163) l/kg/h respectively. There were no significant differences in PK estimates between term and preterm cases (0.23 vs 0.22 l/kg, 2.40 vs 2.38 h, 5.22 vs 4.95 l/h, 0.068 vs 0.069 l/kg/h). When compared to data as published in healthy non-pregnant adults, clearance (0.069 vs 0.018-0.033 l/kg/h) seems to be higher (2 fold) at delivery compared to the non-pregnant setting [8].

4. Discussion and conclusions

Clinical pharmacology aims to predict effects based on drug, population and/or patient-specific pharmacokinetics (PK, concentration-time) and -dynamics (PD, concentration-effect) [1,2,3]. Understanding this dose-exposure and dose-response relationship remains a major challenge for clinicians to optimize safety and efficacy when drugs are administer. This is even more pronounced in specific populations like pregnant women. In the present case studies, we illustrated the impact of pregnancy on paracetamol and ketorolac pharmacokinetics. Although subsequent extrapolation of these PK observations to PD needs extensive prospective evaluation, these findings do suggest that higher doses (either shorter time interval between consecutive doses or higher doses) should be considered.

Besides generating data on the clinical pharmacology of intravenous paracetamol in postpartum, the present findings are also of clinical relevance. The administration of 5 g (2g loading dose, followed by 1g every 6 h) resulted in healthy adult volunteers in paracetamol through levels of 4-6 mg/L [9]. Extrapolating the impact of increased paracetamol clearance after caesarean delivery, a similar through level will already be reached after 4 instead of 6 h (Figure 3) [5,6]. Paracetamol plasma concentration time points in healthy volunteers (+) and post caesarean (x) are provided. Assuming a linear one compartment model with instantaneous input and first order output, a trend line has been added for both cohorts. [X-axis = time (hours); Y-axis = paracetamol plasma concentration (mg/l)]

![Fig. 3: paracetamol plasma concentration-time observations in healthy volunteers (+) or post caesarean (x) cases.](image)

Although the relation between plasma paracetamol concentration and the level of analgesia has not yet been fully described, McNicol et al. recently reported on a systematic review on single dose intravenous paracetamol or propacetamol for prevention or treatment of postoperative pain [10]. Intravenous paracetamol (1 g) provides around 4 h of effective (pain relief, opioid sparing) analgesia with a subsequent decrease in effectiveness to 6 h. Similarly, an intraoperative loading dose of two grams compared to one gram in a minor hand surgery model provided better analgesia (VAS score) in a minor hand surgery and in a molar surgery model in the first 24 h after the intervention [5,9]. These reports strongly suggest a link between median or through paracetamol plasma concentrations and the level of analgesia. Consequently, it might be considered to further decrease the time interval between consecutive doses (at present guidelines q6h) or increase the dose (at present 1 g) in the immediate postpartum to mimic the time-concentration profile aimed for in the non-pregnant adult.

A similar extrapolation can be made for ketorolac. Assuming that there is a given
threshold concentration of plasma ketorolac that results in reoccurrence of pain, the higher clearance during pregnancy will result in a faster reappearance of pain.

At least, we claim that this report illustrates the need for integrated PK/PD studies in the field of peripartal analgesia. Similar to the currently used general pattern of pediatric investigation plan (PIP) design, PK data are needed before we can consider PD differences when PK differences are anticipated [11,12]. As discussed earlier, PK changes related to pregnancy are anticipated and have been documented for paracetamol and ketorolac. Consequently, the description of iv loading dose paracetamol and ketorolac pharmacokinetics is only a first, but necessary piece, to improve peripartal pain management.

Referring to the recently published survey on drugs administered for pain, nausea or pruritus after caesarean delivery, we encourage caregivers to consider similar efforts for other compounds, since it is unlikely that the impact of pregnancy on PK is limited to these non-opioid analgesics [13]. We encourage caregivers to perform similar within-pregnancy studies for other drugs administered in this population because of absence of PK data. Exploration of the links between the physiological changes and the changes in vivo observations should facilitate and guide further research and also clinical management of these specific populations, similar to other special populations like pediatrics [12,14].

References: