Abstract: During pregnancy, changes in renal elimination, body composition and metabolic activity occur. Since these important alterations in physiology also affect drug disposition, pregnancy warrants a focused approach. Despite these differences, even commonly administered drugs have not undergone pharmacokinetic evaluation in pregnant women or at delivery. This is also true for analgesics routinely administered by anesthesiologists during pregnancy or at delivery, like intravenous (IV) paracetamol or ketorolac.

We report on our observations on IV paracetamol and ketorolac disposition following cesarean delivery to illustrate the feasibility of such focused studies and the impact of pregnancy on drug disposition. The clinical relevance of these observations are subsequently discussed, and some future research directions are suggested.

Key words: Pregnancy; delivery; paracetamol; ketorolac; clinical pharmacology; drug metabolism.

INTRODUCTION

Clinical pharmacology aims at predicting drug-related effects based on drug, population and patient specific pharmacokinetics (PK, concentration-time), and -dynamics (PD, concentration-effect): drug dosing needs to be based on the physiological characteristics of the individual patient (1). Similar to other special populations like infants or geriatric patients, pregnancy, labor and the postpartum warrant a focused approach (1-5).

Renal clearance is enhanced during pregnancy and the increased metabolism, as reflected by raised oxygen consumption or cardiac output, often results in increased metabolic drug clearance (phase I and phase II), although alterations are in part isoenzyme specific. Rarely, iso-enzyme specific activity (e.g. CYP1A2 and CYP2C19) is decreased during pregnancy through an estrogen-mediated inhibition (3-5). Finally, body weight increases during pregnancy, and binding capacity is also altered due to changes in plasma protein concentrations. These changes affect drug distribution. The duration of pregnancy (i.e. gestational age), co-morbidities (e.g. pre-eclampsia, HELLP [hemolysis, elevated liver enzymes, and low platelets]), and labor further affects PK variability (3-5). These PK alterations can subsequently affect the variability in the observed drug response (PD) (1, 3-5).

As earlier discussed in this journal, PK and PD-driven drug description aims at optimizing drug dosing as to obtain ideal duration and intensity of effect (1). In anesthesia practice, the therapeutic window is – in general – narrow and versatile. Rapid adjustments and rapid reversal of drug effects are mandatory. Despite the pregnancy-related changes in PK, and despite the clinical importance of having accurate PK and PD models during pregnancy and at delivery, most of the drugs administered by anesthesiologists have not been thoroughly evaluated in this specific population. This is also true for commonly administered analgesic medications such as intravenous (IV) paracetamol or ketorolac. We will first report on our observations on IV paracetamol (6-9) and ketorolac disposition (9-11) following caesarean delivery to illustrate the feasibility of such studies. The clinical relevance of these observations will subsequently be discussed, and some future research directions will be suggested.

For methodological aspects, issues about ethics and study registration related topics, we refer...
to the original publications (6-11). We also took the option to report clearance data by l/h.m² only to compensate for the pregnancy related changes in body weight or size. In doing so, we might in part underestimate the overall phenotypic changes, in so far as it involves a correction for the increase in body weight throughout pregnancy.

**Paracetamol Disposition**

Paracetamol is metabolized by the liver and excreted in the urine, with paracetamol-glucuronide (47-62%) and paracetamol-sulphate (25-36%) as main metabolites. Eight to ten percent of paracetamol is oxidized (CYP2E1) to 3-hydroxy-paracetamol and the toxic metabolite N-acetyl-p-benzoquinone-imine (NAPQI). Only 1-4% is excreted unchanged in the urine (12). However – until recently – data on IV paracetamol pharmacokinetics at delivery were absent. In a first step, loading dose pharmacokinetics (2 g IV paracetamol, n = 28) immediately following caesarean delivery were described. Pharmacokinetics were calculated based on plasma samples collected 1, 2, 4 and 6 h after loading dose administration (6).

When compared to observations in 14 unrelated healthy female volunteers, there was a significantly higher median clearance at delivery (10.9 vs. 9.6 l/h.m²) (Fig. 1a). To further illustrate this, a paired clinical research approach was applied in 8 women initially included at delivery, who underwent a second evaluation 12-18 weeks after delivery and a third evaluation 1 year after delivery (Fig. 1b) (9). On all 3 occasions, an IV loading dose of 2 g of paracetamol was administered, and plasma samples were collected up to 6 hours afterwards. The intra-individual changes were even more pronounced (11.7 at delivery vs. 6.4 l/h.m2 at 12-18 weeks postpartum and 7.04 l/h.m2 one year postpartum, P at least < 0.05 as compared to at delivery) (6).

The between-subject variability in paracetamol clearance is significantly higher at delivery (4-fold instead of 2-fold) (Fig. 1a), suggesting that there are other covariates besides weight changes involved within this population. In an attempt to further explore the covariates of paracetamol disposition at delivery, we were only able to document a modest impact of preterm delivery: women who delivered preterm had a significantly higher median paracetamol clearance when compared to term delivery (12.55 vs. 10.03 l/h.m2, P < 0.05) following a single IV paracetamol loading dose administration (7) (Fig. 1c).

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**Fig. 1.** — a. Paracetamol clearance at delivery compared to 14 unrelated, healthy volunteers following administration of 2 g IV paracetamol (10.9 vs. 9.6 l/h.m2, p < 0.05) (6). Data are presented as ‘Box and Whiskers’ plots, reflecting median, 25th to 75th percentile range and outliers. b. Paracetamol clearance at delivery in 8 patients who were re-evaluated 10-15 weeks and 12 months postpartum. All data were collected following the administration of 2 g IV paracetamol (11.7 vs. 6.4 vs. 7.04 l/h.m2) (6, 9). Data are presented as ‘Box and Whiskers’ plots, reflecting median, 25th to 75th percentile range and outliers. c. The impact of gestational age at caesarean delivery on paracetamol clearance (7). Median clearance following preterm delivery was significantly higher (12.55 vs. 10.03 l/h.m², P < 0.05) compared to term delivery. Data are presented as ‘Box and Whiskers’ plots, reflecting median, 25th to 75th percentile range and outliers.
To unveil the changes in elimination routes at delivery and in postpartum, we collected plasma and urine during repeated IV paracetamol administration and introduced these data in a population pharmacokinetic model (8). It was thereby illustrated that – compared to the postpartum observations in the subgroup of women initially included at delivery – the increase in total paracetamol clearance (11.7 to 21.12 l/h) related to an increased clearance to paracetamol glucuronidation (4.75 to 11.6 l/h), primary renal paracetamol elimination (0.75 to 1.15 l/h) and oxidative metabolites (2.77 to 4.95 l/h), without any change in sulphation (3.42 l/h) (8). In Figure 2, proportional changes (% of total elimination) at delivery or in postpartum are provided. It is thereby illustrated that the overall increase in paracetamol clearance is due to a higher than proportional increase in glucuronidation, a proportional increase in oxidation, a subproportional increase in primary renal elimination while sulphation remains at the same absolute metabolic clearance, resulting in a proportional decrease at delivery compared to postpartum (8).

**KETOROLAC DISPOSITION**

Ketorolac is mainly eliminated by primary renal elimination (55-60%), but also undergoes phase I [oxidation, cytochrome P450 (CYP)2C8-9 related oxidation to p-hydroxy-ketorolac, 12-22%] and phase II [glucuronidation, likely uridine diphosphate glucuronosyltransferase (UGT)2B7, 21-24%] metabolism (13, 14). Similar to the paracetamol project, we first aimed at describing IV ketorolac pharmacokinetics (30 mg ketorolac tromethamine) immediately following caesarean delivery and to compare these findings with late postpartum or volunteers (9, 10). Pharmacokinetics were calculated based on plasma samples collected 1, 2, 4, 6 and 8 h after a loading dose administration. Based on 39 women who were studied at caesarean delivery, of whom 8 were re-evaluated 4 months after delivery, and 8 volunteers, clearance at delivery was higher compared to postpartum or volunteers (2.11 vs. 1.43 vs. 1.07 l/h.m², P < 0.05) (Fig. 3) (10).

To explore the alterations that explain this higher clearance, urinary ketorolac metabolites collected at delivery were compared to postpartum (paired, n = 8) after an IV bolus administration of 30 mg ketorolac tromethamine (11). The mean ketorolac-glucuronide portion at delivery was lower (5 to 21%, p = 0.002), the mean total urinary ketorolac portion was lower (62 to 73%, p = 0.015), while the portion retrieved as p-hydroxy-ketorolac was significantly higher at delivery compared to postpartum (38 to 28%, p = 0.031). The differences in urine metabolites suggest that the increased ketorolac clearance at delivery is in part explained...
by increased metabolic clearance to p-hydroxyketorolac, reflecting increased oxidation activity, similar to the above-mentioned observations on the impact of pregnancy on paracetamol metabolism (11).

**DISCUSSION : ON THE CLINICAL RELEVANCE AND FUTURE RESEARCH DIRECTIONS**

Understanding the dose-exposure and dose-response relationship remains a major challenge for clinicians to optimize safety and efficacy when drugs are administered. This is even more pronounced in specific populations like pregnant women or at delivery. In the present case studies, we illustrate the impact of pregnancy on paracetamol and ketorolac pharmacokinetics (6-11). Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) decrease opioid consumption with the aim to reduce opioid-related side effects. Preventive analgesia using non-opioid analgesic strategies is one of the pathways to improve postoperative pain while minimizing opioid-related side effects, for both the mother and the newborn (15, 16).

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 the prevention or treatment of postoperative pain (17). Intravenous paracetamol (1 g) provides approximately 4 h of effective (pain relief, opioid sparing) analgesia with a subsequent decrease in effectiveness to 6 h. Similarly, an intra-operative loading dose of two grams compared to one gram following minor hand or third molar surgery respectively provides better analgesia (VAS score) during the first 24 h after the intervention (12, 17). These reports strongly suggest a link between paracetamol plasma concentrations and the level of analgesia. Based on the pharmacokinetics observed at delivery, it might be considered to decrease the time interval between consecutive paracetamol doses (at present guidelines q6h) or increase the dose (at present 1 g) during the immediate postpartum to mimic the time-concentration profile aimed for in the non-pregnant adult. However, increasing paracetamol dosing also results in higher oxidative metabolism (Fig. 2) during pregnancy. Consequently, in order to avoid hepatotoxicity, we suggest that it may be more reasonable to anticipate a shorter, and less persistent analgesic effect of paracetamol in pregnant women due to the higher clearance, than increasing the dose (12). A similar extrapolation can be made for ketorolac. Assuming that there is a given low threshold concentration of plasma ketorolac where pain reappears, the higher clearance during pregnancy will result in a faster reappearance of pain. A decrease in the interval between consecutive administrations (at present, q8h) can be considered to maintain the ketorolac level above this threshold (13, 14).

At present, we only have a limited number of pharmacokinetic observations in a population that is genetically relatively homogeneous. Further research is still needed to confirm the current findings and unveil biomarkers of the inter-individual variability in paracetamol metabolism in young women (3-5). Similarly, ketorolac observations were only analyzed based on racemic mixtures of the R and S-enantiomers. There are observations on enantiomer specific PK and metabolism (13, 14). Our team described phenotypic modifications, not necessarily limited to delivery or pregnancy themselves, but also describing the potential impact a surgical intervention, of an anesthetic technique and/or of the administered co-medications. Anyhow, the phenotypic pharmacokinetic changes will likely affect the phenotypic pharmacodynamic effects.

The subsequent ‘translation’ of PK to PD (‘level of analgesia’) is the next step of such a research project. The relationship between paracetamol or ketorolac plasma concentrations and analgesia has not been fully described, while the severity of post cesarean pain also relates to pharmacodynamic covariates such as the presence of pre-cesarean labor, duration of surgery, and individual pain thresholds (15, 16). At least, we claim that this report illustrates the need for integrated PK/PD studies in the field of peripartal analgesia : PK data are needed before we can consider PD differences when PK differences are anticipated. Referring to the recently published survey on drugs administered for pain, nausea or pruritus after cesarean 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 non-opioid analgesics (18).

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