Hindawi Publishing Corporation
Journal of Biomedicine and Biotechnology
Volume 2012, Article ID 437639, 5 pages
doi:10.1155/2012/437639

Research Article

The Impact of Caesarean Delivery on Paracetamol and Ketorolac Pharmacokinetics: A Paired Analysis

Aida Kulo,[1] Kristel van Calsteren,[2] Rene Verbesselt,[1] Anne Smits,[3] Roland Devlieger,[2] Jan de Hoon,[1] and Karel Allegaert[3]

[1] *Center for Clinical Pharmacology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium*
[2] *Obstetrics and Gynaecology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium*
[3] *Neonatal Intensive Care Unit, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium*

Correspondence should be addressed to Karel Allegaert, karel.allegaert@uzleuven.be

Received 9 February 2012; Revised 20 March 2012; Accepted 21 March 2012

Academic Editor: Ali Khraibi

Pharmacokinetics is a first, but essential step to improve population-tailored postoperative analgesia, also after Caesarean delivery. We therefore aimed to quantify the impact of caesarean delivery on the pharmacokinetics of intravenous (iv) paracetamol (2 g, single dose) and iv ketorolac tromethamine (30 mg, single dose) in 2 cohorts eachof 8 women at caesarean delivery and to compare these findings with postpartum to quantify intrapatient changes. We documented a higher median paracetamol clearance at delivery when compared to 10–15 weeks postpartum (11.7 to 6.4 L/h·m^2, $P < 0.01$), even after correction for weight-related changes. Similar conclusions were drawn for ketorolac: median clearance was higher at delivery with a subsequent decrease (2.03 to 1.43 L/h·m^2, $P < 0.05$) in postpartum (17–23 weeks). These differences likely reflect pregnancy- and caesarean-delivery-related changes in drug disposition. Moreover, postpartum paracetamol clearance was significantly lower when compared to estimates published in healthy young volunteers (6.4 versus 9.6 L/h·m^2), while this was not the case for ketorolac (1.43 versus 1.48 L/h·m^2). This suggests that postpartum is another specific status in young women that merits focused, compound-specific pharmacokinetic evaluation.

1. Introduction

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 compound, population, and patient-specific pharmacokinetics (PK, concentration time) and pharmacodynamics (PD, concentration effect). As recently reviewed in this journal, pregnancy and postpartum warrant a focused approach due to the physiological changes throughout pregnancy [1]. First, there are obvious changes in body weight and body surface area that already result in differences in concentration time profiles when fixed doses are applied. In addition to these size-related changes, protein-binding capacity (e.g., decrease albumin, pH shifts) may affect drug plasma protein binding [1–4]. Renal clearance is enhanced during pregnancy (i.e., higher glomerular filtration rate, higher active renal tubular transport). Finally, metabolic activity (e.g., oxygen consumption, cardiac output) is also increased often resulting in increased metabolic drug clearance (phase I and phase II oxidative metabolism), although alterations are in part enzyme-specific. Rarely, enzyme specific activity (e.g., CYP1A2 and CYP2C19) is decreased during pregnancy [1–4]. Observations on the postpartum involution of these changes back to prepregnant values are very limited [1–4].

The options for post-caesarean pharmacological pain management are extensive and in part driven by availability, preferences, experience, and costs. Most strategies for post-caesarean analgesia rely on opioids, supplemented with nerve blocks, adjunctive techniques, and anti-inflammatory analgesics, including intravenous (iv) paracetamol (acetaminophen) or iv ketorolac tromethamine [5]. Despite the fact that these compounds are commonly administered as part of multimodal analgesia, PK observations at delivery and in postpartum are almost completely absent. We aimed to describe iv paracetamol and iv ketorolac PK

in women immediately following caesarean delivery and compared these findings with postpartum, using a paired study design to quantify intrapatient changes.

2. Methods

2.1. Ethics and Recruitment. Following approval of the study protocols by the Ethics Committee of the University Hospitals Leuven (EudraCT 2010, 020164-37 and 2011, 000367-27 resp.), women scheduled for (semi) elective caesarean delivery were recruited after providing written, informed consent in either the iv paracetamol (EudraCT 2010, 020164-37), or—more recently—the iv ketorolac (EudraCT 2011, 000367-27) pharmacokinetic study.

For both studies, 8 of the women included at delivery were invited to return for a second pharmacokinetic study with the same dose of the same compound 10–15 weeks (for iv paracetamol) or 17–23 weeks (for iv ketorolac) after delivery ("postpartum") to quantify intraindividual pharmacokinetic differences between "*at delivery*" and "*postpartum*" in a paired approach (intraindividual variability).

2.2. Clinical Setting. Anaesthesia for caesarean delivery in our institution is provided based on combined spinal-epidural (CSE) anaesthesia with hyperbaric bupivacaine 7.5 mg and sufentanil 2.5 μg. For the postoperative analgesia following caesarean delivery, a multimodal analgesic approach is applied and includes the use of iv paracetamol and iv ketorolac [6].

Shortly after delivery of the newborn, paracetamol 2 g (Perfusalgan, Bristol Myers Squibb, Braine-l'Alleud, Belgium or Paracetamol Fresenius, Fresenius Kabi, Schelle, Belgium) is given intravenously over 15 minutes as a loading dose, followed by 1 g of iv paracetamol every 6 h for the first 24 h. Immediately following closure of the skin, bilateral transversus abdominis plane (TAP) blocks are provided with 0.375% ropivacaine 20 mL per side, and iv bolus of ketorolac (30 mg ketorolac tromethamine, equal to 20.345 mg of ketorolac, Taradyl, Roche, Anderlecht, Belgium) is given every 8 h for 24 h [6]. After this first 24 h time interval, treatment is continued by oral paracetamol and ibuprofen.

2.3. Clinical Characteristics, Sample Collection, and Analysis. Clinical characteristics [weight and body surface area, (BSA)] were collected shortly before caesarean delivery or immediately before the postpartum PK study was performed. In postpartum women, breastfeeding was registered. The duration of administration of iv paracetamol (2 g, loading dose) was recorded, but was aimed to be 15–20 minutes. Blood samples from a dedicated peripheral iv catheter were collected at 1, 2, 4, and 6 h after loading dose administration. Plasma samples were centrifuged and stored at −20°C until high-performance liquid chromatography (HPLC) analysis was performed [7]. Similarly, blood samples from a dedicated peripheral iv catheter were collected at 1, 2, 4, 6, and 8 h after the first ketorolac bolus administration. Racemic ketorolac was quantified by HPLC with UV detection [8].

The methodological approach applied (dose, sampling times, storage, and analysis) following caesarean delivery was repeated 10–15 weeks postpartum for women included in the iv paracetamol study, and 17–23 weeks for the iv ketorolac cohort.

2.4. Pharmacokinetics. A noncompartmental linear disposition model was used for the analysis of paracetamol and ketorolac time-concentration profiles. The peak and trough plasma concentrations (C_{max} and C_{trough}) were obtained directly from the individual experimental data. The terminal elimination rate constant (k_e) was determined by log-linear regression analyses of the final data points (at least 3) and calculation of the corresponding slope ($-k_e/2.303$). The apparent elimination half-life of the log-linear phase ($t_{1/2}$) was calculated as $0.693/k_e$. The area under the plasma concentration-time profile (AUC) from 0 to 6 hours (AUC_{0-6}) was calculated by using the linear trapezoidal method. The AUC from 6 hours to infinity ($AUC_{6-\infty}$) was determined by dividing the final plasma concentration by k_e, and the AUC from 0 hours to infinity ($AUC_{0-\infty}$) was the sum of AUC_{0-6} and $AUC_{6-\infty}$. The total plasma clearance (CL) was determined by dose/$AUC_{0-\infty}$ and the volume of distribution (V_d) by CL/k_e.

For the ketorolac samples, a similar approach was applied, but the area under the plasma concentration-time profile (AUC) from 0 to 8 hours (AUC_{0-8}) and the AUC from 8 h to infinity ($AUC_{8-\infty}$) were determined. The differences in time interval relate to the clinical dosing regimen currently applied.

2.5. Statistics. Clinical characteristics and individual pharmacokinetic estimates were reported by median and range. Results collected at delivery and in postpartum were compared using paired statistics (Wilcoxon, MedCalc, Mariakerke, Belgium).

3. Results

The clinical characteristics and individual pharmacokinetic estimates for the iv paracetamol study are provided in Table 1. For the iv ketorolac study, the same dataset is provided in Table 2. Respectively, 6/8 and 3/8 women were breastfeeding at the time of the postpartum PK study.

For both compounds, there is a significant decrease (at least, $P < 0.05$) in median clearance (22.19 to 11.31 L/h and 11.7 to 6.4 L/h·m^2 for iv paracetamol and 3.80 to 2.53 L/h and 2.03 to 1.43 L/h·m^2 for iv ketorolac) when observations in postpartum were compared with observations collected at delivery, even after correction for BSA-related changes.

Figure 1 illustrates the intraindividual changes in paracetamol clearance (L/h·m^2) (80% increase at delivery, decrease in 8/8 cases postpartum). Figure 2 illustrates the intraindividual changes in ketorolac clearance (L/h·m^2) (40% increase at delivery, decrease in 7/8 cases postpartum). Both figures provide paired individual estimates with intraindividual trend lines, mean, and standard deviation.

Table 1: Clinical characteristics and pharmacokinetic estimates for intravenous paracetamol (single dose, 2 g) in 8 women as collected at delivery and in postpartum (10–15 weeks after delivery). Data provided by median and range.

	At delivery	Postpartum	P value
Body weight (kg)	78.5 (61–92.2)	69 (52.2–88)	$P = 0.0078$
Body surface area, BSA (m^2)	1.96 (1.65–2.06)	1.83 (1.51–2.01)	$P = 0.0078$
Clearance (L/h)	22.19 (13.08–27.32)	11.31 (8.06–15.72)	$P = 0.0078$
Clearance (L/h·kg)	0.29 (0.2–0.32)	0.17 (0.15–0.2)	$P = 0.0078$
Clearance/BSA (L/h·m^2)	11.7 (7.7–13.3)	6.4 (5.3–7.8)	$P = 0.0078$
Distribution volume (L)	61.7 (43.5–75)	35.7 (29.5–59.3)	$P = 0.0234$
Distribution volume (L/kg)	0.77 (0.7–0.87)	0.59 (0.35–0.85)	n.s.
Elimination half-life (h)	1.9 (1.8–2.5)	2.3 (1.4–3.6)	n.s.

Table 2: Clinical characteristics and pharmacokinetic estimates for intravenous ketorolac (single dose, 30 mg) in 8 women as collected at delivery and in postpartum (17–23 weeks after delivery). Data provided by median and range.

	At delivery	Postpartum	P value
Body weight (kg)	75.5 (60–85)	60.8 (48.8–87.2)	$P = 0.0156$
Body surface area, BSA (m^2)	1.89 (1.65–1.98)	1.69 (1.48–2.01)	$P = 0.0156$
Clearance (L/h)	3.8 (2.68–4.50)	2.53 (1.4–3.02)	$P = 0.0078$
Clearance (L/h·kg)	0.05 (0.03–0.07)	0.04 (0.02–0.06)	$P = 0.0469$
Clearance/BSA (L/h·m^2)	2.03 (1.35–2.66)	1.43 (0.88–1.83)	$P = 0.0391$
Distribution volume (L)	14.6 (10.8–27.7)	10.88 (6.94–14.01)	$P = 0.0156$
Distribution volume (L/kg)	0.19 (0.15–0.38)	0.16 (0.11–0.24)	$P = 0.0391$
Elimination half-life (h)	3.08 (1.85–4.79)	2.84 (2.28–5.11)	n.s.

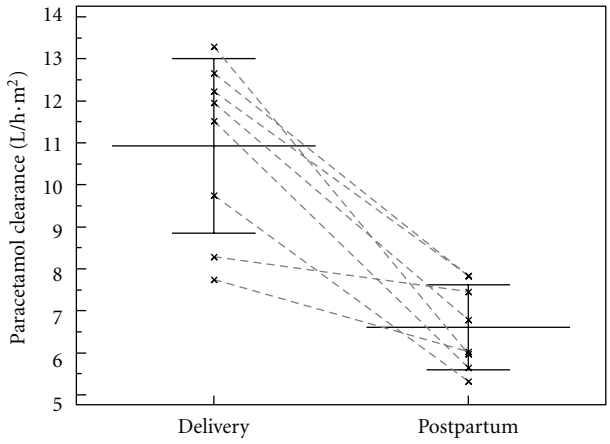

Figure 1: Paired intraindividual estimates for intravenous paracetamol clearance at delivery or in postpartum (L/h·m^2) and mean with standard deviation for both time intervals.

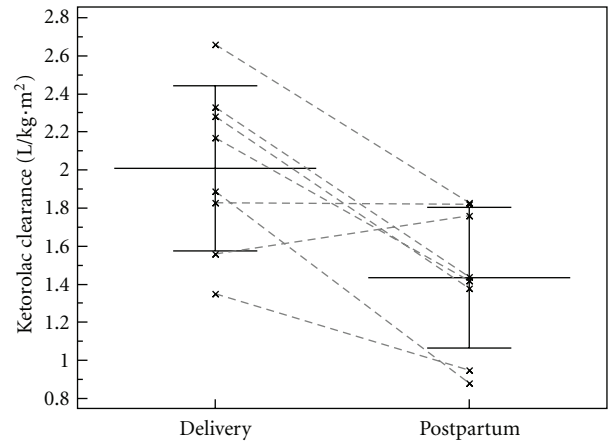

Figure 2: Paired individual estimates for intravenous ketorolac clearance at delivery or in postpartum (L/h·m^2) and mean with standard deviation for both time intervals.

4. Discussion

Knowledge on population-specific dose exposure to predict population-specific dose response relationship remains a clinical challenge [1–4]. In the current paper, we quantified the impact of post-caesarean delivery compared to postpartum for both iv paracetamol and ketorolac PK, using an intraindividual approach.

We recently reported on the impact of pregnancy on iv paracetamol loading dose PK and compared—using an unpaired approach—observations at delivery in 28 women (median clearance 10.9 L/h·m^2) with similar observations (single iv loading dose, 2 g paracetamol) in 14 healthy female volunteers (median clearance 9.6 L/h·m^2) as published by Gregoire et al. [6, 9]. Using a paired approach in 8 women at delivery and in postpartum in the current paper, we confirm the higher paracetamol clearance at delivery when compared to 10–15 weeks postpartum (11.7 to 6.4 L/h·m^2). The same conclusions can be drawn for the ketorolac observations: when compared with data as published in the literature

in 13 healthy male volunteers (1.48 L/h·m^2, single-dose iv ketorolac tromethamine 30 mg), median ketorolac clearance was higher at delivery with a subsequent decrease (2.03 to 1.43 L/h·m^2) in postpartum [10].

In healthy adults, paracetamol is almost exclusively eliminated by conjugation into either paracetamol glucuronide (47–62%) or paracetamol sulphate (25–36%), while limited amounts (1–4%) are excreted in the urine as unchanged paracetamol or undergo (<10%) oxidation to result in toxic metabolites (N-acetyl-p-benzoquinone, NAPQI) [9, 11]. Paracetamol glucuronidation occurs mainly through uridine 5′-diphosphate glucuronosyltransferase (UGT) 1A6 and to a much lesser extent by UGT-1A1 and UGT-1A9, oxidation by cytochrome P450 (CYP) CYP2E1 and CYP2A1 [11]. Following oral paracetamol administration in pregnant women, paracetamol clearance was 58% higher, secondary to a 75% increase in glucuronidation activity of UGT1A6 and UGT1A1 with unaltered sulphation activity [12].

Similarly, ketorolac also mainly undergoes glucuronidation (72–77%, likely UGT2B7) with limited cytochrome P450 (CYP) 2C-related (para-hydroxy-ketorolac) metabolic clearance. We are unaware of any data of ketorolac metabolism during pregnancy [13, 14]. Based on *in vivo* alterations in oxazepam clearance, it is generally believed that the *in vivo* UGT2B7 activity is also increased during pregnancy [1]. For both compounds evaluated, changes in oxidation (CYP2E1, CYP2A1, CYP2C) or in protein binding (ketorolac is highly albumin bound) may further contribute to the phenotypic increase in clearance observed at caesarean delivery in addition to the increase in glucuronidation.

Besides pregnancy itself, the disposition of analgesics in our study may be further affected by procedure-related issues like the extent of the surgical trauma, fluid shifts, or comedication. In a dental pain model, Jamali and Kunz-Dober documented that ibuprofen disposition was affected by the presence of surgical stress [15]. Although these authors mainly related these differences to altered gastric emptying and absorption, we would like to stress that also our observations are phenotypic estimates and may have been modulated by other covariates, including surgical stress, in addition to the pregnant status.

The subsequent extrapolation of population-specific PK to effective post-caesarean analgesia (PD) is not a simple extrapolation of these PK differences. However, the phenotypic PK estimates serve to develop population-tailored dosing guidelines, that subsequently need prospective validation and are a first, but essential step towards improved analgesia [5, 10, 11, 13]. We hereby have to take into account that PD may also be altered due to pregnancy or delivery. When applied to analgesia after caesarean delivery, not only labour prior to the caesarean delivery and patient characteristics (individual thermal pain thresholds, personality characteristics) but also duration of surgery affect pain reporting and analgesic needs after caesarean delivery [6].

Our observations also provide some preliminary *in vivo* observations on the alterations in PK in postpartum [1]. Paracetamol clearance 10–15 weeks after delivery decreased to 6.4 L/h·m^2. This is significantly lower (9.6 L/h·m^2) when compared to observations in healthy female volunteers of Gregoire et al. [9]. Median ketorolac clearance 17–23 weeks after delivery decreased to 1.43 L/h·m^2, similar to median ketorolac clearance reported in 13 healthy male volunteers (1.48 L/h·m^2) [10]. Although limited to paracetamol because of absence of ketorolac PK in healthy nonpregnant female volunteers, the paracetamol observations suggest that women during the postpartum period should also be considered as another specific subpopulation: it seems that paracetamol clearance in postpartum initially decreases to values even lower than healthy female volunteers. Exploration of the links between the physiological changes and the pharmacokinetic *in vivo* changes should guide further research, similar to the methodology of physiologically based pharmacokinetic modeling for other special populations like pediatrics [3, 16, 17].

Conflict of Interests

None of the authors has any other conflict of interests related to this paper.

Acknowledgments

A. Kulo was supported by a JoinEU-SEE scholarship (2009-2010), K. Allegaert by the Fund for Scientific Research, Flanders (Belgium) (FWO Vlaanderen) by a Fundamental Clinical Investigatorship (1800209N) and a research Grant (1506409N).

References

[1] M. N. Feghali and D. R. Mattison, "Clinical therapeutics during pregnancy," *Journal of Biomedicine and Biotechnology*, vol. 2011, Article ID 783528, 13 pages, 2011.

[2] G. D. Anderson, "Pregnancy-induced changes in pharmacokinetics: a mechanistic-based approach," *Clinical Pharmacokinetics*, vol. 44, no. 10, pp. 989–1008, 2005.

[3] S. Pilari, C. Preuße, and W. Huisinga, "Gestational influences on the pharmacokinetics of gestagenic drugs: a combined *in silico, in vitro* and *in vivo* analysis," *European Journal of Pharmaceutical Sciences*, vol. 42, no. 4, pp. 318–331, 2011.

[4] A. Zajicek and G. P. Giacoia, "Obstetric clinical pharmacology: coming of age," *Clinical Pharmacology and Therapeutics*, vol. 81, no. 4, pp. 481–482, 2007.

[5] N. J. McDonnell, M. L. Keating, N. A. Muchatuta, T. J. G. Pavy, and M. J. Paech, "Analgesia after caesarean delivery," *Anaesthesia and Intensive Care*, vol. 37, no. 4, pp. 539–551, 2009.

[6] A. Kulo, M. van de Velde, J. de Hoon et al., "Pharmacokinetics of a loading dose of intravenous paracetamol post caesarean delivery," *International Journal of Obstetric Anaesthesia*, vol. 21, no. 2, pp. 125–128, 2012.

[7] K. Allegaert, B. J. Anderson, G. Naulaers et al., "Intravenous paracetamol (propacetamol) pharmacokinetics in term and preterm neonates," *European Journal of Clinical Pharmacology*, vol. 60, no. 3, pp. 191–197, 2004.

[8] Z. Wang, R. M. Dsida, and M. J. Avram, "Determination of ketorolac in human plasma by reversed-phase high-performance liquid chromatography using solid-phase extraction and ultraviolet detection," *Journal of Chromatography B*, vol. 755, no. 1-2, pp. 383–386, 2001.

[9] N. Gregoire, L. Hovsepian, V. Gualano, E. Evene, G. Dufour, and A. Gendron, "Safety and pharmacokinetics of paracetamol following intravenous administration of 5 g during the first 24 h with a 2-g starting dose," *Clinical Pharmacology and Therapeutics*, vol. 81, no. 3, pp. 401–405, 2007.

[10] P. Lucker, R. Bullingham, L. Hooftman, J. Lloyd, and E. Mroszczak, "Tolerability, central effects and pharmacokinetics of intravenous ketorolac tromethamine in volunteers," *International Journal of Clinical Pharmacology and Therapeutics*, vol. 32, no. 8, pp. 409–414, 1994.

[11] J. S. Jahr and V. K. Lee, "Intravenous acetaminophen," *Anesthesiology Clinics*, vol. 28, no. 4, pp. 619–645, 2010.

[12] J. O. Miners, R. A. Robson, and D. J. Birkett, "Paracetamol metabolism in pregnancy," *British Journal of Clinical Pharmacology*, vol. 22, no. 3, pp. 359–362, 1986.

[13] D. R. Brocks and F. Jamali, "Clinical pharmacokinetics of ketorolac tromethamine," *Clinical Pharmacokinetics*, vol. 23, no. 6, pp. 415–427, 1992.

[14] K. M. Knights, L. K. Winner, D. J. Elliot, K. Bowalgaha, and J. O. Miners, "Aldosterone glucuronidation by human liver and kidney microsomes and recombinant UDP-glucuronosyltransferases: inhibition by NSAIDs," *British Journal of Clinical Pharmacology*, vol. 68, no. 3, pp. 402–412, 2009.

[15] F. Jamali and C. M. Kunz-Dober, "Pain-mediated altered absorption and metabolism of ibuprofen: an explanation for decreased serum enantiomer concentration after dental surgery," *British Journal of Clinical Pharmacology*, vol. 47, no. 4, pp. 391–396, 1999.

[16] F. Khalil and S. S. Läer, "Physiologically based pharmacokinetic modeling: methodology, applications, and limitations with a focus on its role in pediatric drug development," *Journal of Biomedicine and Biotechnology*, vol. 2011, Article ID 907461, 13 pages, 2011.

[17] K. Allegaert, A. Smits, and J. van den Anker, "Physiologically-based pharmacokinetic modeling in pediatric drug development: a clinician's request for a more integrated approach," *Journal of Biomedicine and Biotechnology*, vol. 2012, Article ID 103763, 3 pages, 2012.