International Journal of Obstetric Anesthesia (2012) **21**, 334–338
0959-289X/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijoa.2012.06.001

ELSEVIER
www.obstetanesthesia.com

ORIGINAL ARTICLE

Pharmacokinetics of intravenous ketorolac following caesarean delivery

A. Kulo,[a] M. van de Velde,[b] K. van Calsteren,[c] A. Smits,[d] J. de Hoon,[a] R. Verbesselt,[a] J. Deprest,[c] K. Allegaert[d]
[a] *Center for Clinical Pharmacology,* [b] *Anesthesiology,* [c] *Obstetrics and Gynaecology,* [d] *Neonatal Intensive Care Unit, University Hospital, Leuven, Belgium*

ABSTRACT
Background: Drug disposition is altered by pregnancy and the peripartum period but data on intravenous ketorolac pharmacokinetics following caesarean delivery have not been previously reported.
Methods: At the end of caesarean delivery, women received an intravenous bolus of ketorolac tromethamine 30 mg (immediate postpartum, Group IP). Plasma samples were collected at 1, 2, 4, 6 and 8 h. A similar pharmacokinetic study was repeated in a subgroup of these women 4–5 months after delivery (late postpartum, Group LP) and in a group of unrelated, healthy non-pregnant female volunteers (controls, Group C). A non-compartmental linear disposition model was applied to analyse individual ketorolac time–concentration profiles. Results at delivery were compared with controls using unpaired or paired statistics as appropriate. Covariates of pharmacokinetic estimates at delivery were examined.
Results: Thirty-nine women were studied at caesarean delivery, of whom eight were re-evaluated 4–5 months later. In addition, eight volunteers were studied. Clearance in Group IP was higher compared to Groups LP and C (2.11 vs. 1.43 and 1.07 L/h·m^2 respectively, $P < 0.05$). Volume of distribution was also increased in Group IP compared to Groups LP and C (0.24 vs. 0.16 and 0.17 L/kg respectively, $P < 0.05$). No significant covariates of pharmacokinetic estimates, including gestational age, preterm vs. term, twin vs. singleton and maternal co-morbidity, were seen in Group IP.
Conclusions: Ketorolac clearance and distribution volume are significantly increased following caesarean delivery. These data provide pharmacokinetic estimates on which to base studies on post caesarean analgesia.
© 2012 Elsevier Ltd. All rights reserved.

Keywords: Pharmacokinetics; Pregnancy; Postpartum; Ketorolac; Caesarean delivery; Postoperative pain

Introduction

Although many compounds and techniques are available for postoperative pain management, effective analgesia remains a clinical challenge.[1] Women who undergo caesarean delivery have particular requirements, notably related to the specific risk of thromboembolic events, which may be exacerbated by immobility, the need for minimal sedation to permit mother-child interaction and promotion of breastfeeding.[2–4] Preventive analgesia using non-opioid drugs is accepted as one of the strategies to improve postoperative pain control,[1–3,5–8] with paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) frequently administered as part of multimodal analgesia. The transfer of paracetamol and NSAIDs to the newborn through breastfeeding is very low and considered to be safe by the American Academy of Pediatrics (AAP) while reducing opioid exposure to the mother and newborn.[4,9]

Despite the use of non-opioid analgesics and evidence from meta-analysis in support of a relation between plasma concentration and level of analgesia, pharmacokinetic observations at delivery and postpartum are almost completely absent.[1–3,6–8] Clinical pharmacology aims to predict effects based on drug, population- or patient-specific pharmacokinetics (PK, concentration–time) and pharmacodynamics (PD, concentration-effect, in the current setting: level of analgesia). PK estimates are a starting point to improve analgesia following caesarean delivery.[10]

We recently quantified intravenous (i.v.) paracetamol clearance immediately following caesarean delivery.[11] Median clearance and distribution volume were significantly higher in women undergoing caesarean delivery when compared to healthy female volunteers. Even after correction for body surface area, paracetamol clearance remained higher in women undergoing caesarean

Accepted June 2012
Correspondence to: Karel Allegaert, Center for Clinical Pharmacology, University Hospital, Herestraat, Leuven, Belgium.
E-mail address: karel.allegaert@uzleuven.be

delivery. In that study, paracetamol was started shortly after delivery, and combined with bilateral transversus abdominis plane (TAP) blocks and i.v. ketorolac at the end of surgery. The aim of the current study was to quantify i.v. ketorolac pharmacokinetics in women immediately following caesarean delivery, and to compare these findings with both observations in a subset of the same women some months after delivery; and an additional group of non-pregnant young female volunteers.

Methods

The study was a prospective, single-centre, open-label study of the PK of i.v. ketorolac administration in pregnant women after caesarean delivery. Following approval by the Ethics Committee of the University Hospitals Leuven (EudraCT 2011-00367-27) and study registration (www.clinicaltrials.gov, NCT01291472), women scheduled to undergo caesarean delivery were enrolled after providing written, informed consent.

Local multimodal analgesic practice includes the administration of a 30 mg i.v. bolus of ketorolac (ketorolac tromethamine, equal to 20.345 mg of ketorolac, Taradyl®, Roche, Anderlecht, Belgium) at the end of surgery. This dose is repeated after 8 and 16 h and is subsequently changed to oral ibuprofen administration.[11] Clinical characteristics including weight, body surface area, (BSA), gestational age at delivery, twin pregnancy and pregnancy related medical conditions were collected shortly before delivery (immediate postpartum, Group IP). Blood samples were collected via a dedicated peripheral i.v. cannula at 1, 2, 4, 6 and 8 h after the first ketorolac administration.

To enable comparison of PK collected at delivery with non-pregnant women, a subset of eight women who were studied at delivery were re-evaluated 4–5 months after delivery (late postpartum, group LP). In addition, eight other unrelated, non-pregnant healthy female volunteers were also recruited (controls, Group C). The same methodological approach (ketorolac 30 mg i.v. bolus and blood sampling 1, 2, 4, 6 and 8 h after administration) was applied to all subjects.

Racemic ketorolac concentration in plasma was measured by high-performance liquid chromatography after solid-phase column extraction, according to the method described by Zhao Wang et al. with some modifications made to the solid-phase extraction column (Bond Elut C2 100 mg, 1 mL volume, Agilent Technologies, Eindhoven, Netherlands) and the extraction procedure.[12] The lower limit of quantification was 0.025 μg/mL, being the lowest concentration of the standard curve with a coefficient of variation <20%. Coefficients of variation for intra- and inter-day precision and accuracy were all <15%.

A non-compartmental linear disposition model was applied to analyse the individual ketorolac time-concentration profiles. Maximal and minimal ketorolac plasma concentrations were obtained directly from experimental data in each case. The terminal elimination rate constant (k_e) was determined by log-linear regression analyses of at least three of the final data points and calculation of the corresponding slope ($-k_e$/2.303). The apparent elimination half-life of the log-linear phase ($t_{½}$) was calculated (0.693/k_e), as was the area under the plasma concentration–time profile (AUC) from 0 to 8 h ($AUC_{0–8}$) using the linear trapezoidal method. The AUC from 8 h to infinity ($AUC_{8–\infty}$) was determined by dividing the final plasma concentration by k_e, and the AUC from 0 h to infinity ($AUC_{0–\infty}$) was the sum of $AUC_{0–8}$ and $AUC_{8–\infty}$. Total plasma clearance (CL) was determined by Dose/$AUC_{0–\infty}$ and the distribution volume (Vd) by CL/k_e. Clearance was reported as clearance (CL, L/h), clearance/body weight (L/h·kg) and clearance/BSA (L/h·m^2). Similarly, total distribution volume (L) and distribution volume/body weight (L/kg) were calculated.

Statistical analysis

Clinical characteristics and individual PK estimates were reported by mean ±SD when normal distribution had been confirmed by Kolmogorov–Smirnov test, otherwise by median [range] or incidence. Covariates of individual PK estimates at delivery were explored (Rank correlation, Mann–Whitney U test). Results collected at delivery were compared with either late postpartum (4–5 months after delivery, paired, Wilcoxon test) or with healthy unrelated volunteers (unpaired, Mann–Whitney U test) statistics respectively. A P value <0.05 was considered statistically significant.

Results

In total, 55 PK studies were performed: 39 at delivery (Group IP). Eight of these patients were re-evaluated postpartum at 20.3 ±2.2 weeks (Group LP). Of these eight patients, four were still breastfeeding. Eight additional PK studies were performed in another group of healthy, non-pregnant female volunteers (Group C). Clinical characteristics and individual PK estimates at delivery and in healthy volunteers are presented in Table 1 and for paired observations in Table 2.

Variability in PK estimates between the 39 observations at delivery was explored. There was no significant correlation between gestational age and any PK estimates. There was, however, a significant correlation ($r = 0.38$, 95% CI 0.07–0.62) between BSA and clearance (L/h) but this was not present when clearance (L/h·m^2) was corrected for BSA. There was no significant difference in mean PK estimates between preterm and term deliveries, twin and singleton pregnancies or women with or without associated maternal medical conditions.

Download English Version:

https://daneshyari.com/en/article/2757888

Download Persian Version:

https://daneshyari.com/article/2757888

Daneshyari.com