Enantiomer-specific ketorolac pharmacokinetics in young women, including pregnancy and postpartum period

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ABSTRACT

Racemic ketorolac clearance (CL) is significantly higher at delivery, but S-ketorolac disposition determines the analgesic effects. The aim of this study was to investigate the effect of pregnancy and postpartum period on enantiomer-specific (S and R) intravenous (IV) ketorolac pharmacokinetics (PKs). Data in women shortly following cesarean delivery (n=39) were pooled with data in a subgroup of these women that was reevaluated in the later postpartum period (postpartum group, n=8/39) and with eight healthy female volunteers. All women received single IV bolus of 30 mg ketorolac tromethamine. Five plasma samples were collected at 1, 2, 4, 6, and 8 hours and plasma concentrations were determined using high performance liquid chromatography. Enantiomer-specific PKs were calculated using PKSolver. Unpaired analysis showed that distribution volume at steady state (Vss, L/kg) for S- and R-ketorolac was significantly higher in women shortly following cesarean delivery (n=31) compared to postpartum group (n=8) or to healthy female volunteers (n=8). CL, CL to body weight, and CL to body surface area (CL/BSA) for S- and R-ketorolac were also significantly higher in women following delivery. In addition, S/R-ketorolac CL/BSA ratio was significantly higher at delivery. Paired PK analysis in eight women shortly following delivery and in postpartum group showed the same pattern. Finally, the simultaneous increase in CL and Vss resulted in similar estimates for elimination half-life in both unpaired and paired analysis. In conclusion, pregnancy affects S-, R-, and S/R-ketorolac disposition. This is of clinical relevance since S-ketorolac (analgesia) CL is even more increased compared to R-ketorolac CL, and S/R-ketorolac CL ratio is higher following delivery compared to postpartum period or to healthy female volunteers.

KEY WORDS: Pharmacokinetics; ketorolac; enantiomers; pregnancy; cesarean delivery; postpartum
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INTRODUCTION

Ketorolac is a potent nonsteroidal anti-inflammatory drug. It is a chiral substance consisting of S (–) and R (+) enantiomers. Although these ketorolac enantiomers come in equal portions [1], pharmacological activity, being almost exclusively attributed to S-ketorolac [2-6], makes enantiomer-specific ketorolac pharmacokinetics (PKs) clinically relevant.

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Stereoselectivity has been described for ketorolac binding to plasma albumin as well as for ketorolac metabolism. Stereoselective binding to plasma albumin, which is lower for S- (98.4%) than for R-ketorolac (99.2%) [3], can explain enantiomer-specific PK differences [7,8]. In addition, stereoselective ketorolac metabolism by uridine-diphosphate-glucuronosyltransferase (UGT) 2B7 has been documented as higher for S- than for R-ketorolac [8,9]. As a consequence of those important stereoselective processes, a 4-5 fold higher distribution volume and clearance (CL) as well as twice shorter elimination half-life (2.5 versus 5 hours), have been documented for S- compared to R-ketorolac [10,11]. The S/R-ketorolac area under the curve (% AUC) after intravenous (IV)

administration in adult patients is 0.36, independent of the administered dose [3].

Ketorolac is frequently used as analgesic drug in pregnancy and postpartum period [12-18]. Physiological changes during pregnancy and postpartum period (e.g., changes in total body water, plasma volume, plasma albumin levels, cardiac output, drug-metabolizing enzymes and drug transport, and kidney filtration) have been repeatedly shown to affect PKs of many drugs [19,20]. A higher free drug fraction in pregnancy is suggested to facilitate both the extraction in the liver and primary renal elimination [21]. Furthermore, the increase in *in vivo* phenotypic oxidation (CYP2C8-9) [8,9,22,23] and UGT2B7 activity during pregnancy [8,9], as well as different routes of drug elimination during pregnancy compared to those in the postpartum period and in healthy female volunteers, are also suggested [24].

Despite the frequent and off-label use of ketorolac in pregnancy and postpartum period [12-18], no data on the impact of pregnancy and postpartum period on enantiomer-specific ketorolac PK parameters are available. Therefore, the aim of our study was to investigate the effect of pregnancy and postpartum period on enantiomer-specific ketorolac PK parameters after a single IV ketorolac bolus.

MATERIALS AND METHODS

Ethics and study registration

The study was approved by the Ethics Committee of the University Hospitals, Leuven (internal study number 53048). Written informed consent was obtained from all women. The study was registered at ClinicalTrials.gov (NCT01291472, EudraCT 2011-000367-27).

Patients, ketorolac dosing, sample collection, and sample handling

Enantiomer-specific ketorolac PKs were calculated in women shortly following cesarean delivery (n = 39). A subgroup of these women (n = 8/39) was reevaluated in the later postpartum period. In addition, a cohort of healthy female volunteers was evaluated (n = 8).

An IV bolus of 30 mg ketorolac tromethamine (Taradyl®, Roche, Anderlecht, Belgium), equal to 20.345 mg of pure ketorolac (67%), was administered to all women. For women shortly following cesarean delivery, ketorolac was administered as part of multimodal analgesia at the University Hospitals Leuven, Belgium [24]. Except for the locoregional anesthetics and IV paracetamol administered as part of the multimodal analgesia following cesarean delivery, those women used no other medications for at least 48 hours before and during the study.

An IV bolus of 30 mg ketorolac tromethamine was administered as a single dose in the subgroup that was reevaluated in the postpartum period as well as in healthy female volunteers. Those women also used no other medications for at least 48 hours before and during the study.

To all women, ketorolac was administered as a slow injection over 30 seconds through a peripherally inserted venous cannula in the hand of the patient. Five blood samples (i.e., at 1, 2, 4, 6, and 8 hours post dose) were collected from a second peripheral venous cannula, dedicated only for study purposes. Blood samples were collected in lithium heparinized tubes, centrifuged, and plasma was stored at –20°C until analysis. Plasma concentrations of S- and R-ketorolac were determined using a validated high performance liquid chromatography analysis with UV detection after extraction procedure based on solid-phase extraction [25].

Pharmacokinetics

The main outcome measures were individual enantiomer-specific PK parameters. These were calculated using PKSolver, a program for PK and pharmacodynamic (PD) data analysis in Microsoft Excel [26]. We hereby assumed a noncompartmental model for IV bolus. $AUC_{(0-\infty)}$, mg·h/L, elimination half-life ($t_{1/2}$, h), distribution V_{ss}, distribution V_{ss} corrected for body weight (V_{ss}/BW, L/kg), CL, CL corrected for BW (CL/BW, L/h·kg), and CL corrected for body surface area (CL/BSA, L/h·m^2) were calculated, with BSA calculated by the following formula: BSA (m^2) = 0.024265 body height (cm)$^{0.3964}$ BW (kg)$^{0.5378}$ [27]. To compare changes in CL between enantiomers, the ratio of S/R-ketorolac CL/BSA was also calculated and compared between the cohorts.

Statistics

Data were compared using the Kruskal–Wallis test for unpaired comparisons and the Wilcoxon signed-rank test for paired comparisons, and explored using Spearman's rank correlation coefficient (MedCalc, Mariakerke, Belgium). A $p < 0.05$ was considered statistically significant. Results were reported by median and range.

RESULTS

A total of 47 women and 235 time-concentration profiles were included in this study.

PK estimates for S- and R-ketorolac in three groups

PK estimates in 31 women shortly following cesarean delivery were compared to the observations in eight women in the postpartum period (mean 21st, 17.1-22.6th postpartum week) and in eight healthy female volunteers (Table 1). The observed C_{max} values for S- and R-ketorolac were significantly lower in the women shortly following cesarean delivery compared

TABLE 1. Clinical data and PK estimates for S- and R-ketorolac (IV ketorolac single-dose) following cesarean delivery, in the postpartum period, and in healthy female volunteers

Clinical data and PK estimates	Women shortly following cesarean delivery (n=31)[a]	Postpartum group (n=8)	Healthy female volunteers (n=8)	*p* value
Age (year)	33 (25-44)	31.5 (25-35)	32.5 (28-43)	0.376
BW (kg)	73.20 (40-106)	60.75 (49-87)	62.75 (56-69)	1≠2, 3; 0.035*; 0.004**
BSA (m^2)	1.82 (1.29-2.26)	1.66 (1.48-2.01)	1.69 (1.57-1.82)	1≠2, 3; 0.026*; 0.015**
S-ketorolac PK parameters				
C_{max} (mg/L)	0.42 (0.22-0.63)	0.70 (0.40-1.13)	0.74 (0.61-1.08)	1≠2, 3; <0.001**; <0.001**
$AUC_{(0-\infty)}$ (mg·h/L)	1.56 (0.87-3.00)	2.73 (1.69-4.53)	2.88 (2.22-4.51)	1≠2, 3; <0.001**; <0.001**
$t_{1/2}$ (h)	1.84 (0.98-3.32)	1.88 (1.64-2.87)	2.15 (1.60-3.38)	0.181
V_{ss} (L)	12.79 (5.79-30.39)	7.84 (4.82-15.89)	9.14 (6.07-11.53)	1≠2, 3; 0.011*; 0.002**
V_{ss}/BW (L/kg)	0.18 (0.08-0.43)	0.11 (0.07-0.27)	0.15 (0.10-0.18)	1≠3; 0.037*
CL (L/h)	6.49 (3.39-11.68)	3.73 (2.24-6.02)	3.60 (2.26-4.58)	1≠2, 3; <0.001**; <0.001**
CL/BW (L/h·kg)	0.09 (0.05-0.19)	0.06 (0.04-0.10)	0.06 (0.04-0.07)	1≠2, 3; 0.005**; <0.001**
CL/BSA (L/h·m^2)	3.47 (1.89-6.67)	2.13 (1.40-3.97)	2.06 (1.43-2.62)	1≠2, 3; 0.002**; <0.001**
R-ketorolac PK parameters				
C_{max} (mg/L)	0.90 (0.48-1.16)	1.41 (0.91-2.00)	1.62 (1.36-1.93)	1≠2, 3; 0.001**; <0.001**
$AUC_{(0-\infty)}$ (mg·h/L)	4.76 (2.90-9.30)	7.10 (5.14-11.20)	10.26 (6.56-14.03)	1≠2, 3; 0.002**; <0.001**; 2≠3; 0.046*
$t_{1/2}$ (h)	3.11 (1.58-6.20)	3.23 (2.37-4.80)	3.51 (2.55-7.36)	0.306
V_{ss} (L)	8.96 (5.51-16.34)	5.86 (4.09-8.65)	5.51 (4.40-6.89)	1≠2, 3; 0.001**; <0.001**
V_{ss}/BW (L/kg)	0.12 (0.09-0.23)	0.09 (0.06-0.15)	0.09 (0.07-0.12)	1≠3; 0.001**
CL (L/h)	2.14 (1.09-3.51)	1.43 (0.91-1.98)	0.99 (0.73-1.55)	1≠2, 3; 0.002**; 0.001**; 2≠3; 0.046*
CL/BW (L/h·kg)	0.03 (0.02-0.06)	0.02 (0.02-0.03)	0.02 (0.01-0.02)	1≠2, 3; 0.044*; <0.001**; 2≠3; 0.016*
CL/BSA (L/h·m^2)	1.18 (0.65-1.87)	0.81 (0.57-1.30)	0.59 (0.43-0.89)	1≠2, 3; 0.012*; <0.001**; 2≠3; 0.021*
S/R ratio				
S/R CL/BSA	3.07 (1.91-4.97)	2.73 (2.12-3.05)	3.11 (2.47-4.36)	1≠2; 0.020*

[a]Excluding eight women who were reevaluated again in the later postpartum period, to ensure unpaired analysis. All values were reported as median (minimum-maximum). Kruskal–Wallis U-test was used to compare the data. $p<0.05$ was considered to be statistically significant (*$p<0.05$; **$p<0.01$). IV: Intravenous; BW: Body weight; BSA: Body surface area; PKs: Pharmacokinetics; C_{max}: The maximum or "peak" concentration; AUC: Area under the curve; $t_{1/2}$: Elimination half-life; V_{ss}: Distribution volume at steady state; V_{ss}/BW: Distribution V_{ss} corrected for body weight; CL: Clearance; CL/BW: CL corrected for BW; CL/BSA: CL corrected for BSA

to the postpartum group and healthy female volunteers. As anticipated from the observed C_{max}, the median V_{ss} values for S- and R-ketorolac were significantly higher in the women shortly following cesarean delivery compared to the postpartum group and healthy female volunteers. When corrected for BW, the median V_{ss} values for S- and R-ketorolac were significantly higher in the women shortly following cesarean delivery compared to the healthy female volunteers.

The median CL, CL/BW and CL/BSA values for S- and R-ketorolac were significantly higher in the women shortly following cesarean delivery compared to the postpartum group and healthy female volunteers (Figures 1 and 2).

The ratio of S/R-ketorolac CL/BSA was significantly higher in the women shortly following cesarean delivery compared to the postpartum group (Figure 3).

No difference in the median elimination half-life was documented between the three groups (Table 1).

Paired analysis of PK estimates in women shortly following cesarean delivery and in postpartum period

For the same women (n = 8) the PK estimates observed shortly following cesarean delivery and those obtained in the postpartum period (mean 21st, 17.1-22.6th postpartum week), were compared (Table 2). The observed C_{max} values for S- and R-ketorolac were significantly lower shortly following cesarean delivery compared to the postpartum period.

No differences either in V_{ss} or V_{ss}/BW were found for S-ketorolac while median V_{ss} for R-ketorolac was significantly higher shortly following cesarean delivery compared to the postpartum period of the same women.

The CL and CL/BSA values for S- and R-ketorolac were significantly higher shortly following cesarean delivery compared to the postpartum period of the same women. In addition, for S-ketorolac, the median CL/BW value was also significantly higher shortly following cesarean delivery compared to the postpartum period.

The ratio of S/R-ketorolac CL/BSA was not different between shortly following cesarean delivery and postpartum periods of the same women. No difference in the median elimination half-life was documented between these two physiological states of the same women (Table 2).

DISCUSSION

To the best of our knowledge, this study is the first report on the impact of pregnancy and postpartum period on enantiomer-specific PKs of IV ketorolac. Significant differences in median PK estimates in the women shortly following cesarean

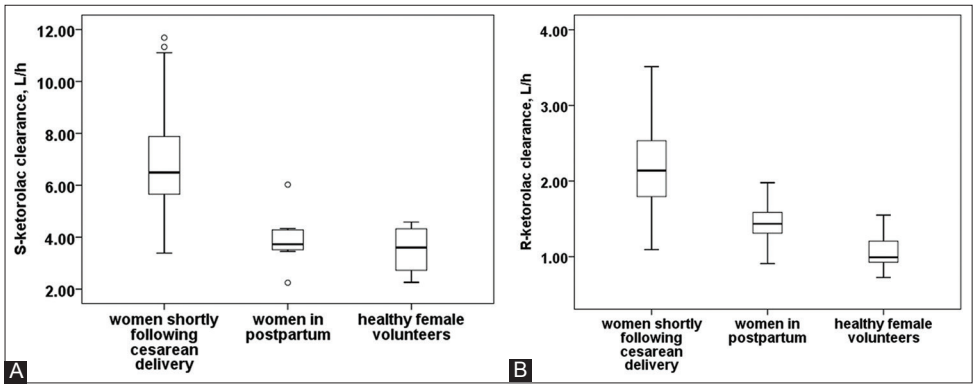

FIGURE 1. Unpaired comparison of (A) S-ketorolac clearance and (B) R-ketorolac clearance (CL) in women shortly following cesarean delivery versus postpartum group versus healthy female volunteers. The median CL values (L/h) for S- and R-ketorolac were significantly higher in the women shortly following cesarean delivery compared to the postpartum group (S-ketorolac +42.5%; R-ketorolac +33.2%) and healthy female volunteers (S-ketorolac +44.5%; R-ketorolac +53.7%).

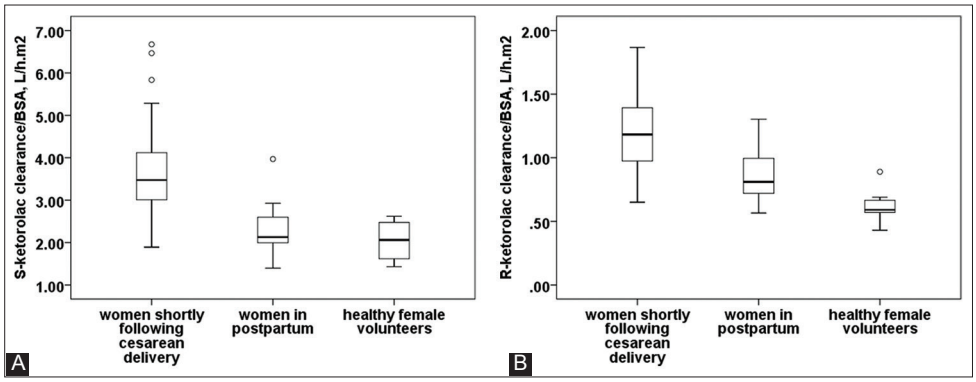

FIGURE 2. Unpaired comparison of (A) S-ketorolac clearance corrected for body surface area (CL/BSA) and (B) R-ketorolac CL/BSA in women shortly following cesarean delivery versus postpartum group versus healthy female volunteers. The median CL/BSA (L/h·m^2) values for S- and R-ketorolac were significantly higher in the women shortly following cesarean delivery compared to the postpartum group (S-ketorolac +38.6%; R-ketorolac +31.4%) and healthy female volunteers (S-ketorolac +40.6%; R-ketorolac +50.0%).

delivery were observed compared to the postpartum group and healthy female volunteers.

As anticipated, higher BW and BSA values were observed in the women shortly following cesarean delivery compared to the postpartum group (Table 1). However, even after taking the body size differences into account, the CL values of S- and R-ketorolac were shown to be higher in the women shortly following cesarean delivery compared to the observations in the postpartum group (mean 21st week) (S-ketorolac: +33.3%, L/h·kg, +38.6%, L/h·m^2; R-ketorolac: +33.3%, L/h·kg, +31.4%, L/h·m^2) and in healthy female volunteers (S-ketorolac: +33.3%, L/h·kg, +40.6%, L/h·m^2; R-ketorolac: +33.3%, L/h·kg, +50.0%, L/h·m^2) (Table 1 and Figure 2).

The ratio of S/R-ketorolac CL/BSA reflects the difference in changes of the enantiomer-specific CLs (S or R). Interestingly, S/R-ketorolac CL/BSA was significantly higher in the women shortly following cesarean delivery compared to the postpartum group (Figure 3). As mentioned earlier, enantiomer-specific PK differences may be explained by stereoselective binding of ketorolac to plasma albumin [7,8]. Lower albumin binding for S- than for R-ketorolac [3], with additional lower protein binding due to pregnancy induced hypoalbuminemia [8,9,28], results in even higher free concentrations of S- compared to R-ketorolac. This, at least in part, may explain the impact of pregnancy on the S/R-ketorolac ratio.

The impact of pregnancy on the S/R-ketorolac ratio is of PD relevance, since this means that S-CL is somewhat more increased compared to R-CL, in women shortly following cesarean delivery. Since the analgesic effect of ketorolac relates exclusively to S-ketorolac, it is reasonable to assume that analgesia will disappear earlier shortly following cesarean delivery compared to the postpartum period.

The additional paired PK analysis in the eight women following cesarean delivery and in their later postpartum period confirmed this pattern. Finally, the simultaneous increase in CL and V_{ss} resulted in similar estimates for elimination half-life in both unpaired and paired analysis.

As for other analgesics, a single dose of ketorolac can be applied, making C_{max} a relevant parameter for determining the therapeutic effect [29]. As anticipated from our results, increased ketorolac V_{ss} in the women shortly following cesarean delivery resulted in C_{max} to be significantly lower compared to the postpartum group (–40.0% for S-ketorolac and

–36.2% for R-ketorolac), as well as compared to the healthy female volunteers (–43.2% for S-ketorolac and –44.4% for R-ketorolac).

The current enantiomer-specific PKs confirm previously reported effect of physiological changes in pregnancy and postpartum period on racemic ketorolac PKs [21,23,30,31]. Distribution volume of racemic ketorolac was 40% and CL was 50% higher in post-cesarean women compared to healthy female volunteers [21]. This was also confirmed by paired analysis which showed distribution volume of racemic ketorolac in post-cesarean women to increase 40-50% and total CL to increase 30-40% compared to those results in 4-5 months postpartum of the same women [21].

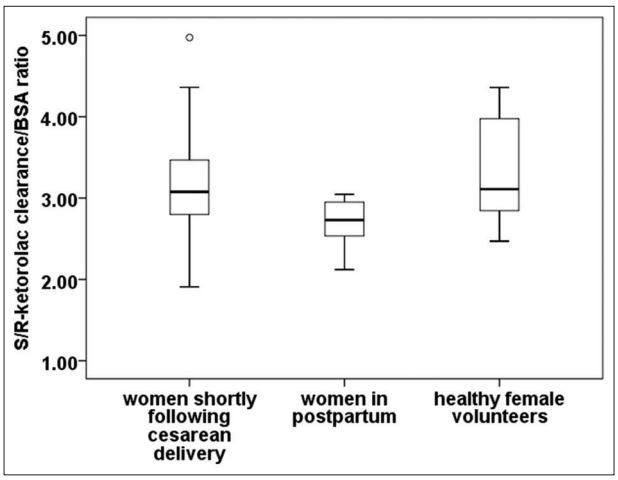

FIGURE 3. Unpaired comparison of the ratio of S and R-ketorolac clearance corrected for body surface area (S/R-ketorolac CL/BSA ratio), in women shortly following cesarean delivery versus postpartum group versus healthy female volunteers. The ratio was significantly higher in the women shortly following cesarean delivery compared to the postpartum group.

Compared to non-pregnant women, pregnant women have lower protein binding as well as a higher fractional volume of body water [8,9,28]. In addition, a 3-7% decrease in plasma protein binding was documented to double distribution volume of ketorolac [32]. Having in mind that ketorolac is also a low-extraction drug [2,32], its hepatic CL [33] is directly proportional to its unbound fraction in plasma [34]. This likely explains the higher CL and distribution volume for racemic ketorolac [30,31] and both ketorolac enantiomers in women shortly following cesarean delivery compared to group in postpartum period and in healthy female volunteers. Proportional change in CL and distribution volume results in no change in ketorolac half-life, as documented in this study.

The same pattern of CL and distribution volume, in which these values are higher for pharmacologically active S- compared to R-ketorolac [10,11], was documented after IV ketorolac administration in children [8,10,11] and after all ketorolac administration routes in non-pregnant women and men [3,35]. These results are also confirmed in each cohort

TABLE 2. Clinical data and PK estimates for S- and R-ketorolac (IV ketorolac single-dose) in the same group of women (n=8) in two different periods

Clinical data and PK estimates	Shortly following cesarean delivery (n=8)	Postpartum period (n=8)	*p* value
BW (kg)	75.50 (60-85)	60.75 (49-87)	0.017*
BSA (m^2)	1.89 (1.65-1.98)	1.66 (1.48-2.01)	0.017*
S-ketorolac PK parameters			
C_{max} (mg/L)	0.41 (0.26-0.60)	0.70 (0.40-1.13)	0.036*
$AUC_{(0-\infty)}$ (mg·h/L)	1.51 (1.32-2.40)	2.73 (1.69-4.53)	0.012*
$t_{1/2}$ (h)	2.18 (1.26-2.58)	1.88 (1.64-2.87)	0.674
V_{ss} (L)	12.22 (8.92-16.86)	7.84 (4.82-15.89)	0.093
V_{ss}/BW (L/kg)	0.18 (0.14-0.22)	0.11 (0.07-0.27)	0.327
CL (L/h)	6.76 (4.24-7.73)	3.73 (2.24-6.02)	0.012*
CL/BW (L/h·kg)	0.09 (0.05-0.11)	0.06 (0.04-0.10)	0.036*
CL/BSA (L/h·m^2)	3.81 (2.14-4.09)	2.13 (1.40-3.97)	0.025*
R-ketorolac PK parameters			
C_{max} (mg/L)	0.87 (0.74-1.08)	1.41 (0.91-2.01)	0.017*
$AUC_{(0-\infty)}$ (mg·h/L)	4.80 (3.20-7.79)	7.10 (5.14-11.20)	0.017*
$t_{1/2}$ (h)	3.39 (1.90-4.89)	3.23 (2.37-4.80)	0.779
V_{ss} (L)	8.42 (6.64-10.41)	5.86 (4.09-8.65)	0.017*
V_{ss}/BW (L/kg)	0.13 (0.10-0.14)	0.09 (0.06-0.15)	0.069
CL (L/h)	2.15 (1.31-3.17)	1.43 (0.91-1.98)	0.017*
CL/BW (L/h·kg)	0.03 (0.02-0.04)	0.02 (0.02-0.03)	0.069
CL/BSA (L/h·m^2)	1.20 (0.66-1.61)	0.81 (0.57-1.30)	0.025*
S/R ratio			
S/R CL/BSA	3.09 (2.28-3.99)	2.73 (2.12-3.05)	0.123

All values were reported as median (minimum-maximum). The Wilcoxon signed-rank test was used to compare the data. $p<0.05$ was considered to be statistically significant (*$p<0.05$). IV: Intravenous; BW: Body weight; BSA: Body surface area; PKs: Pharmacokinetics; C_{max}: The maximum or "peak" concentration; AUC: Area under the curve; $t_{1/2}$: Elimination half-life; V_{ss}: Distribution volume at steady state; V_{ss}/BW: Distribution V_{ss} corrected for body weight; CL: Clearance; CL/BW: CL corrected for BW; CL/BSA: CL corrected for BSA

TABLE 3. Clinical data, IV dose administered, and CL and distribution volume (Vd) estimates for S- and R-ketorolac in different studies

Population	Age, years	BW, kg	IV dose, mg/kg	S-ketorolac		R-ketorolac		References
				CL, mL/min·kg	Vd, L/kg	CL, mL/min·kg	Vd, L/kg	
Children, n=11	1.7-15.6	10.7-67.4	0.5	2.98 L/h	13.2 L	1.5 L/h	8.2 L	Mohammed et al., 2015. [37]
Infants, n=10, n=20	2.2-18 months	NA	0.5, 1	5.1±4.3	0.45±0.33	0.95±0.54	0.27±0.17	Lynn et al., 2011.
Children, n=18	8.1±1.5	31±7	0.5	66.8±13.8 mL/h·kg	0.715±0.415	21.1±4.9 mL/h·kg	0.155±0.034	Hamunen et al., 1999.
Children, n=47	11.7	NA	0.6	6.2±3.3	0.82±0.38	1.4±0.5	0.50±0.34	Kauffman et al., 1999.
Adolescents, n=18	14.2±1.7	54±11	0.5	66.2±17.5 mL/h·kg	0.442±0.305	21.4±5.9 mL/h·kg	0.141±0.030	Hamunen et al., 1999.
Adults, n=18	31.3±7.4	72±12	0.5	57.7±11.0 mL/h·kg	0.282±0.140	22.2±4.3 mL/h·kg	0.129±0.022	Hamunen et al., 1999.
Healthy volunteers	45	74	10	0.020 L/h·kg	0.062	0.019 L/h·kg	0.066	Brocks and Jamali, 1992.
Healthy adults, n=9	NA	NA	10 mg	0.660±0.114	0.140±0.021	0.280±0.059	0.109±0.016	Mroszczak et al., 1996.

Age and BW values were reported as mean, mean±SD, or min-max range; CL and Vd values were reported as mean or mean±SD. IV: Intravenous; SD: Standard deviation; CL: Clearance; Vd: Distribution volume; BW: Body weight; NA: Not available

of the current study (Table 3). S-ketorolac CL [6,33] and distribution volume [11] are also shown to be age-dependent (i.e., higher in children compared to adults). The age range in our study was limited to young adulthood (25-44 years).

This study certainly has some limitations. First, due to the vulnerability of the postpartum period, the sample size of those women was limited. Nevertheless, we were still able to perform reliable paired analysis. Second, according to some authors, the analysis of only 8-hour time course might cause an underestimation of the true half-life [2]. However, the 8-hour time interval in our study was initially based on the clinical practice of post cesarean delivery ketorolac administration (q8h) in our hospital [31]. In addition, this study showed the 8-hour interval to represent a minimum of 2 half-life values for R-ketorolac and a minimum of 3-4 half-life values for S-ketorolac in all cohorts that were evaluated.

The fact that only one of the ketorolac enantiomers has analgesic effects makes enantiomer-specific PKs of clinical relevance and illustrates the need to explore the enantiomer-specific PK/PD relation. In addition, taking into account other factors that can influence the PDs, we suggest reconsidering the current dosing regimens. This means that, due to PK changes during pregnancy, extrapolation of dosing regimens from the results obtained in adult women should be performed with caution. Accordingly, because of the higher distribution volume, an initial loading dose is suggested in women following delivery, to achieve therapeutic plasma concentrations. Furthermore, the BW-adjusted maintenance doses of ketorolac could be higher in women following delivery compared to postpartum and non-pregnant/non-postpartum women, and could be applied with higher intermittent dosing or more frequent administration.

Documented PK differences and quite extensive enantiomer-specific ketorolac PK variability among young women illustrate the relevance to perform PK studies in different states of adult women's life and confirm our earlier observations on IV paracetamol [36]. For definitive physiological state-specific dosing recommendations in women, we encourage future repeated dosing PK studies in this specific population.

CONCLUSION

Pregnancy affects S-, R-, and S/R-ketorolac disposition. This is of clinical relevance, since S-ketorolac (analgesia) CL is higher in women shortly following cesarean delivery compared to postpartum group and healthy female volunteers, and this increase is even higher for S-CL compared to R-CL (S/R CL ratio).

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DECLARATION OF INTERESTS

The authors declare no conflict of interests.

REFERENCES

[1] Cohen MN, Christians U, Henthorn T, Vu Tran Z, Moll V, Zuk J, et al. Pharmacokinetics of single-dose intravenous ketorolac in infants aged 2-11 months. Anesth Analg 2011;112(3):655-60. http://dx.doi.org/10.1213/ANE.0b013e3182075d04.

[2] Brocks DR, Jamali F. Clinical pharmacokinetics of ketorolac

tromethamine. Clin Pharmacokinet 1992;23(6):415-27. http://dx.doi.org/10.2165/00003088-199223060-00003.
[3] Mroszczak E, Combs D, Chaplin M, Tsina I, Tarnowski T, Rocha C, et al. Chiral kinetics and dynamics of ketorolac. J Clin Pharmacol 1996;36(6):521-39. http://dx.doi.org/10.1002/j.1552-4604.1996.tb05042.x.
[4] Guzmán A, Yuste F, Toscano RA, Young JM, Van Horn AR, Muchowski JM. Absolute configuration of (-)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-alpha]pyrrole-1-carboxylic acid, the active enantiomer of ketorolac. J Med Chem 1986;29(4):589-91. http://dx.doi.org/10.1021/jm00154a027.
[5] Jamali F. Pharmacokinetics of enantiomers of chiral non-steroidal anti-inflammatory drugs. Eur J Drug Metab Pharmacokinet 1988;13(1):1-9. http://dx.doi.org/10.1007/BF03189920.
[6] Jung D, Mroszczak E, Bynum L. Pharmacokinetics of ketorolac tromethamine in humans after intravenous, intramuscular and oral administration. Eur J Clin Pharmacol 1988;35(4):423-5. http://dx.doi.org/10.1007/BF00561376.
[7] Lapicque F, Muller N, Payan E, Dubois N, Netter P. Protein binding and stereoselectivity of nonsteroidal anti-inflammatory drugs. Clin Pharmacokinet 1993;25(2):115-23. http://dx.doi.org/10.2165/00003088-199325020-00004.
[8] Kauffman RE, Lieh-Lai MW, Uy HG, Aravind MK. Enantiomer-selective pharmacokinetics and metabolism of ketorolac in children. Clin Pharmacol Ther 1999;65(4):382-8. http://dx.doi.org/10.1016/S0009-9236(99)70131-1.
[9] Feghali MN, Mattison DR. Clinical therapeutics in pregnancy. J Biomed Biotechnol 2011;2011:783528. http://dx.doi.org/10.1155/2011/783528.
[10] Lynn AM, Bradford H, Kantor ED, Andrew M, Vicini P, Anderson GD. Ketorolac tromethamine: Stereo-specific pharmacokinetics and single-dose use in postoperative infants aged 2-6 months. Paediatr Anaesth 2011;21(3):325-34. http://dx.doi.org/10.1111/j.1460-9592.2010.03484.x.
[11] Hamunen K, Maunuksela EL, Sarvela J, Bullingham RE, Olkkola KT. Stereoselective pharmacokinetics of ketorolac in children, adolescents and adults. Acta Anaesthesiol Scand 1999;43(10):1041-6. http://dx.doi.org/10.1034/j.1399-6576.1999.431012.x.
[12] Wu CL, Raja SN. Treatment of acute postoperative pain. Lancet 2011;377(9784):2215-25. http://dx.doi.org/10.1016/S0140-6736(11)60245-6.
[13] McDonnell NJ, Keating ML, Muchatuta NA, Pavy TJ, Paech MJ. Analgesia after caesarean delivery. Anaesth Intensive Care 2009;37(4):539-51.
[14] Pan PH. Post cesarean delivery pain management: Multimodal approach. Int J Obstet Anesth 2006;15(3):185-8. http://dx.doi.org/10.1016/j.ijoa.2006.04.004.
[15] White PF, Raeder J, Kehlet H. Ketorolac: Its role as part of a multimodal analgesic regimen. Anesth Analg 2012;114(2):250-4. http://dx.doi.org/10.1213/ANE.0b013e31823cd524.
[16] Pavy TJ, Paech MJ, Evans SF. The effect of intravenous ketorolac on opioid requirement and pain after cesarean delivery. Anesth Analg 2001;92(4):1010-4. http://dx.doi.org/10.1097/00000539-200104000-00038.
[17] Dahl V, Hagen IE, Sveen AM, Norseng H, Koss KS, Steen T. High-dose diclofenac for postoperative analgesia after elective caesarean section in regional anaesthesia. Int J Obstet Anesth 2002;11(2):91-4. http://dx.doi.org/10.1054/ijoa.2001.0931.
[18] De Oliveira GS Jr, Agarwal D, Benzon HT. Perioperative single dose ketorolac to prevent postoperative pain: A meta-analysis of randomized trials. Anesth Analg 2012;114(2):424-33. http://dx.doi.org/10.1213/ANE.0b013e3182334d68.
[19] Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 2009;48(3):143-57. http://dx.doi.org/10.2165/00003088-200948030-00001.
[20] Messing K, Mager Stellman J. Sex, gender and women's occupational health: The importance of considering mechanism. Environ Res 2006;101(2):149-62. http://dx.doi.org/10.1016/j.envres.2005.03.015.
[21] Kulo A, van de Velde M, van Calsteren K, Smits A, de Hoon J, Verbesselt R, et al. Pharmacokinetics of intravenous ketorolac following caesarean delivery. Int J Obstet Anesth 2012;21(4):334-8. http://dx.doi.org/10.1016/j.ijoa.2012.06.001.
[22] Hebert MF. Impact of pregnancy on pharmacokinetics of medications. J Popul Ther Clin Pharmacol 2013;20(3):350-7.
[23] Kulo A, Hendrickx S, de Hoon J, Mulabegovic N, van Calsteren K, Verbesselt R, et al. The impact of pregnancy on urinary ketorolac metabolites after single intravenous bolus. Eur J Drug Metab Pharmacokinet 2013;38(1):1-4. http://dx.doi.org/10.1007/s13318-012-0108-7.
[24] Allegaert K, Kulo A, Verbesselt R, Hopchet L, Deprest J, de Hoon J, et al. The pharmacokinetics of a high intravenous dose of paracetamol after caesarean delivery: The effect of gestational age. Eur J Anaesthesiol 2012;29(10):484-8. http://dx.doi.org/10.1097/EJA.0b013e32835543a0.
[25] Kulo A, Mulabegovic N, Loga-Zec S, Allegaert K, de Hoon J, Verbesselt R. Determination of racemic ketorolac, ketorolac enantiomers and their metabolites in human plasma and urine by LC–UV, applied in clinical study during and after pregnancy. Chromatographia 2014;77(11):803-12. http://dx.doi.org/10.1007/s10337-014-2670-4.
[26] Zhang Y, Huo M, Zhou J, Xie S. PKSolver: An add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. Comput Methods Programs Biomed 2010;99(3):306-14. http://dx.doi.org/10.1016/j.cmpb.2010.01.007.
[27] Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: A height-weight formula validated in infants, children, and adults. J Pediatr 1978;93(1):62-6. http://dx.doi.org/10.1016/S0022-3476(78)80601-5.
[28] Allegaert K, Van Mieghem T, Verbesselt R, Vanhole C, Devlieger R, Cossey V, et al. Cefazolin plasma protein binding saturability during pregnancy. Methods Find Exp Clin Pharmacol 2009;31(1):25-8. http://dx.doi.org/10.1358/mf.2009.31.1.1346611.
[29] Koren G. Sex dependent pharmacokinetics and bioequivalence – Time for a change. J Popul Ther Clin Pharmacol 2013;20(3):e358-61.
[30] Allegaert K, van Calsteren K, Hendrickx S, Kelchtermans J, Smits A, Kulo A, et al. Paracetamol and ketorolac pharmacokinetics and metabolism at delivery and during postpartum. Acta Anaesthesiol Belg 2012;63(3):121-5.
[31] Kulo A, van Calsteren K, Verbesselt R, Smits A, Devlieger R, de Hoon J, et al. The impact of Caesarean delivery on paracetamol and ketorolac pharmacokinetics: A paired analysis. J Biomed Biotechnol 2012;2012:437639. http://dx.doi.org/10.1155/2012/437639.
[32] Gravenstein D, Suri A, Derendorf HC, Koska AJ. Influence of plasma expansion on plasma protein binding of ketorolac. J Clin Anesth 1998;10(6):464-8. http://dx.doi.org/10.1016/S0952-8180(98)00064-6.
[33] Mroszczak EJ, Lee FW, Combs D, Sarnquist FH, Huang BL, Wu AT, et al. Ketorolac tromethamine absorption, distribution, metabolism, excretion, and pharmacokinetics in animals and humans. Drug Metab Dispos 1987;15(5):618-26.
[34] Olkkola KT, Maunuksela EL. The pharmacokinetics of postoperative intravenous ketorolac tromethamine in children. Br J Clin Pharmacol 1991;31(2):182-4. http://dx.doi.org/10.1111/j.1365-2125.1991.tb05510.x.
[35] Hayball PJ, Wrobel J, Tamblyn JG, Nation RL. The pharmacokinetics of ketorolac enantiomers following intramuscular administration of the racemate. Br J Clin Pharmacol 1994;37(1):75-8. http://dx.doi.org/10.1111/j.1365-2125.1994.tb04243.x.
[36] Kulo A, Peeters MY, Allegaert K, Smits A, de Hoon J, Verbesselt R, et al. Pharmacokinetics of paracetamol and its metabolites in women at delivery and post-partum. Br J Clin Pharmacol 2013;75(3):850-60. http://dx.doi.org/10.1111/j.1365-2125.2012.04402.x.
[37] Mohammed BS, Engelhardt T, Hawwa AF, Cameron GA, McLay JS. The enantioselective population pharmacokinetics of intravenous ketorolac in children using a stereoselective assay suitable for microanalysis. J Pharm Pharmacol 2015;67(9):1179-87. http://dx.doi.org/10.1111/jphp.12418.