Pharmacokinetics of paracetamol and its metabolites in women at delivery and post-partum

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- In adults, paracetamol is almost exclusively metabolized by the hepatic route and excreted into urine, with paracetamol glucuronide (47–62%) and paracetamol sulphate (25–36%) as the main metabolites. Between 8–10% of the paracetamol dose is oxidized by cytochrome P450 (CYP2E1) into 3-hydroxy-paracetamol and the toxic metabolite N-acetyl-p-benzoquinone-imine (NAPQI), while only 1–4% is excreted in urine as unchanged paracetamol.
- Total clearance of paracetamol appears higher at Caesarean delivery compared with healthy female volunteers but it is unknown which pathways are affected.

WHAT THIS STUDY ADDS

- Population pharmacokinetic modelling showed a substantially higher paracetamol clearance in women at delivery compared with a subset of the same women 12 weeks post-partum.
- The increase in total paracetamol clearance at delivery is due to a disproportional increase in glucuronidation clearance and a proportional increase in clearance of unchanged paracetamol and in oxidation clearance.
- Compared with modelling based on metabolite fractions retrieved in urine only, population modelling based on both plasma and urine collections was of added value to gain insight into how different metabolic pathways of paracetamol contribute to changes in total clearance.

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Keywords

acetaminophen, elimination routes, i.v.
paracetamol, population
pharmacokinetics, post-partum,
pregnancy

Received

29 March 2012

Accepted

24 July 2012

Accepted Article Published Online

30 July 2012

AIM

A recent report on intravenous (i.v.) paracetamol pharmacokinetics (PK) showed a higher total clearance in women at delivery compared with non-pregnant women. To describe the paracetamol metabolic and elimination routes involved in this increase in clearance, we performed a population PK analysis in women at delivery and post-partum in which the different pathways were considered.

METHODS

Population PK parameters using non-linear mixed effect modelling were estimated in a two-period PK study in women to whom i.v. paracetamol (2 g loading dose followed by 1 g every 6 h up to 24 h) was administered immediately following Caesarean delivery and in a subgroup of the same women to whom single 2 g i.v. loading dose was administered 10–15 weeks post-partum.

RESULTS

Population PK analysis was performed based on 255 plasma and 71 urine samples collected in 39 women at delivery and in eight of these 39 women 12 weeks post-partum. Total clearance was higher in women at delivery compared with 12th post-partum week (21.1 vs. 11.7 l h⁻¹) due to higher clearances to paracetamol glucuronide (11.6 vs. 4.76 l h⁻¹), to oxidative metabolites (4.95 vs. 2.77 l h⁻¹) and of unchanged paracetamol (1.15 vs. 0.75 l h⁻¹). In contrast, there was no difference in clearance to paracetamol sulphate.

CONCLUSION

The increased total paracetamol clearance at delivery is caused by a disproportional increase in glucuronidation clearance and a proportional increase in clearance of unchanged paracetamol and in oxidation clearance, of which the latter may potentially limit further dose increase in this patient group.

Introduction

Extensive physiological alterations, such as expansion of maternal blood volume with haemodilution and hypoalbuminaemia, increase in blood flow to vital organs, increase in glomerular filtration rate, either inhibition or induction of hepatic iso-enzymes, occur during pregnancy [1–4]. These physiological alterations can result in clinically relevant changes in drug disposition [5–7]. However, since pregnant women are typically excluded from drug development research, knowledge on obstetrical and post-partum clinical pharmacology is generally poorly quantified [8]. Consequently, even pharmacokinetic (PK) data on drugs that are frequently used during pregnancy and the post-partum period, such as paracetamol, are limited [9].

In adults, the centrally acting analgesic and antipyretic agent paracetamol is almost exclusively metabolized by the hepatic route. While only 1–4% [10] of the dose is excreted in urine as unchanged paracetamol, the majority of the dose is excreted as paracetamol glucuronide [11, 12] (47–62%) [13] and paracetamol sulphate [14, 15] (25–36%) [13]. A smaller part (8–10%) is oxidized by cytochrome P450 (CYP2E1) to 3-hydroxy-paracetamol and the toxic metabolite N-acetyl-p-benzoquinone-imine (NAPQI) [13]. The latter is in its turn conjugated by glutathione into urinary excreted non-toxic thiol metabolites (cysteine, mercapturate, methylthioparacetamol and methanesulfinylparacetamol) [16]. Toxicity occurs when glutathione is depleted resulting in conjugation of NAPQI with hepatocellular proteins leading to centrilobular liver necrosis.

Intravenous (i.v.) paracetamol is frequently used as an analgesic in the immediate post-operative period, which includes women after Caesarean delivery [17]. While its maximum recommended daily dose is 4 g [18], the use of an i.v. loading dose of 2 g, followed by 1 g every 6 h up to 24 h, has been confirmed as safe and well tolerated in healthy volunteers [19]. Being safe and effective in non-pregnant subjects [20–22], the use of this i.v. loading dose of 2 g paracetamol is an accepted practice for immediate post-Caesarean delivery pain relief [23].

Previous reports on the PK of paracetamol showed a substantially higher total clearance of paracetamol during pregnancy and at delivery compared with non-pregnant women [24, 25]. However, in view of potential toxicity of oxidative paracetamol metabolites, it is important to know to what extent the different paracetamol metabolic and elimination routes are involved in this increase in total paracetamol clearance at delivery. So far, only a small study reported on different paracetamol metabolic and elimination routes after a single oral dose of paracetamol (1 g) in eight women in the third trimester of pregnancy compared with 12 non-pregnant female controls [24]. More specifically, there is no information on the pharmacokinetics of paracetamol in women after delivery.

In the present paper, we aimed to develop a population PK model of i.v. paracetamol based on both plasma and urine collections, with specific focus on the different routes of paracetamol elimination in women at delivery and post-partum. Therefore, we performed a two period PK study in women to whom i.v. paracetamol (2 g loading dose followed by 1 g every 6 h up to 24 h) was administered immediately following Caesarean delivery (first study period), while in a subgroup of these women, another single i.v. paracetamol 2 g loading dose was administered 10–15 weeks post-partum (second study period).

Methods

Study population and design

This was an open label, two period PK study conducted from August 2010 to March 2011 (EudraCT Number 2010-020164-37). The study documents (study protocol, informed consent) were reviewed and approved by the local Ethics Committee of the University Hospitals Leuven before the start of the study. This study followed ICH GCP (Good Clinical Practice), GLP (Good Laboratory Practice) and local regulations.

Written informed consent of each woman was obtained before study initiation. The administration of i.v. paracetamol (vial containing 1000 mg in 100 ml infusion solution, Perfusalgan®, Bristol Myers Squibb Braine l'Alleud, Belgium) is part of routine multimodal analgesia following Caesarean delivery in our hospital [25]. Consequently, patient consent was limited to the collection of additional blood samples, urine collection and the inclusion in a database (demographic and clinical characteristics).

Pregnant women scheduled for (semi)urgent Caesarean delivery and immediate post-operative i.v. paracetamol pain relief were considered for this study. Women with known paracetamol intolerance or who were already receiving paracetamol in the period of 48 h prior to study were not included.

In the first study period, an initial i.v. 2 g loading dose of paracetamol (two vials) was administered to the patient by the attending anaesthesiologist within 5 min following delivery of the newborn. Subsequent 1 g maintenance doses were administered by the nurse at 6 h intervals. Paracetamol was administered either as 20 min (loading dose) or 10 min (maintenance dose) infusion, through a peripherally inserted venous catheter.

During the second study period, a subgroup of eight women from the first study period were admitted again for a single i.v. 2 g loading dose administration and 6 h follow up, scheduled 10–15 weeks after delivery of the newborn. For the duration of the first study period, the subjects were hospitalized in the maternity ward and for the second study period at the Centre for Clinical Pharmacology, University Hospitals Leuven, Leuven, Belgium.

Blood and urine sample collection and bioanalytical methods

During the first study period, seven blood samples (2 ml per sample) were collected per subject. The first three samples were collected at 1, 2 and 4 h after initiation of the 2 g loading dose while the next four samples were collected just before the next maintenance dose (i.e. at 6, 12, 18 and 24 h). Blood samples, drawn through a second, peripherally inserted venous catheter dedicated for blood sampling only, were collected into plastic lithium heparin tubes, immediately centrifuged and stored at -20°C until analysis. Urine was collected through a bladder catheter. Before the first dose, the urine collection bag was emptied and a blank urine sample was collected in order to exclude the possibility of paracetamol being present in urine. Second and third urine samples were collected from 0–6 and 6–24 h urine collections respectively, after the total volume of each of those was measured. After collection, urine samples were immediately stored at -20°C until analysis.

In the second study period, a 2 g loading dose was administered to the subjects after they had voided. Four blood samples at predetermined time points (1, 2, 4 and 6 h after initiation of dosing) and one urine sample (extracted from 0–6 h urine collection) were collected following the same principles described for the first study period.

Plasma and urine concentrations of unchanged paracetamol and its metabolites paracetamol glucuronide and paracetamol sulphate were determined by high performance liquid chromatography (HPLC) according to a previously validated and reported method [26, 27]. The lower limit of quantification for paracetamol and its metabolites in plasma was 0.08 mg l^{-1} and in urine 1 mg l^{-1} . Coefficients of variation for intra- and inter-day precision and accuracy were all below 15% [26, 27].

Data analysis

The amounts of unchanged paracetamol, paracetamol glucuronide and paracetamol sulphate excreted in urine were calculated by urinary concentration (mg l^{-1}) multiplied by urine volume, and subsequently converted to mg paracetamol equivalents using a molecular weight of $151.2\text{ mg mmol}^{-1}$ for paracetamol, $328.3\text{ mg mmol}^{-1}$ for paracetamol glucuronide and $230.2\text{ mg mmol}^{-1}$ for paracetamol sulphate.

Data analysis was performed using non-linear mixed effect modelling (NONMEM, GloboMax LLC, Hanover, MD, version VI) by use of the first order conditional estimation (Method 1) with η - ϵ interaction and ADVAN6 TOL5. S-plus (Insightful software, Seattle, WA, USA, version 6.2) was used to visualize the data. Model building was performed in four different steps: (i) selection of the structural model (one, two or three compartment model), (ii) choice of a statistical sub-model, (iii) covariate analysis and (iv) model evaluation. Discrimination between different models was made

Figure 1

Schematic representation of the pharmacokinetic model of paracetamol and its metabolites in plasma (circles) and urine (squares). Abbreviations: P, paracetamol; PG, paracetamol glucuronide; PS, paracetamol sulphate; PU, paracetamol-unchanged; V_1 , volume of the central compartment of paracetamol; V_2 , volume of the peripheral compartment of paracetamol; V_3 , volume of paracetamol-glucuronide compartment; V_4 , volume of paracetamol sulphate compartment; Q , inter-compartmental clearance between central and peripheral compartment of paracetamol; CL_{PO} , clearance to oxidative paracetamol metabolites; k , elimination coefficients; rectangle compartments 5, 6, 7, urine compartments for paracetamol glucuronide, paracetamol sulphate and paracetamol unchanged, respectively.

by comparison of the objective function. We conducted a likelihood ratio test for $\alpha = 0.05$ significance to discriminate between nested models with one parameter difference between models. This corresponded to a reduction of 3.84 units in the objective function (χ^2 , $P < 0.05$). In addition, goodness of fit plots including observations vs. individual predictions, observations vs. population predictions, conditional weighted residuals vs. time and conditional weighted residuals vs. population predictions were used for diagnostic purposes. Furthermore, the confidence interval (CI) of the parameter estimates, the correlation matrix and visual improvement of the individual plots were used to evaluate the model.

Population values were estimated for the volume of the central compartment (V_1), inter-compartmental clearance between central and peripheral volume (Q), peripheral volume (V_2), clearance to paracetamol glucuronide ($CL_{PG} = V_1 \times k_{13}$), clearance to paracetamol sulphate ($CL_{PS} = V_1 \times k_{14}$), clearance of unchanged paracetamol ($CL_{PU} = V_1 \times k_{17}$) and clearance attributable to pathways other than these measured in urine, the oxidative metabolites (CL_{PO}) (Figure 1).

The metabolite volumes of distribution of paracetamol glucuronide and paracetamol sulphate (V_3 and V_4) could not be identified using the current study design and were fixed to 18% of the central distribution volume of paracetamol in plasma [28]. Using this approach, both the elimination rate of paracetamol glucuronide (k_{35}) and paracetamol sulphate (k_{46}) from plasma to urine could be identified. The model could however be simplified by assuming that k_{35} equals k_{46} and by subsequent estimation of both k_{35} and k_{46} as a fraction (multiplication factor, MF) of the rate of elimination of unchanged paracetamol (k_{17}), as the objective function of this simplified model decreased by 40.74 points. Saturation of different pathways (e.g. Michaelis Menten kinetics) was explored by checking goodness of fit plots.

The uncertainty in the population parameters was estimated by determining the asymptotic standard error from the covariance step in NONMEM, and was expressed as CV%. Individual estimates of the PK parameters were assumed to follow a log-normal distribution. Therefore, an exponential distribution model was used to account for inter-individual variability. The residual errors were described with a proportional error model as an additive or combined proportional and additive model were not superior.

Covariate analysis

The covariates body weight, body height, body surface area, age, gestational age (GA), being at delivery or post-partum, being in labour on admission, term/pre-term delivery, twin pregnancy, maternal morbidity (pre-eclampsia, diabetes mellitus, either type 1 or gestational) and urine rate (ml h^{-1}) were each plotted against the individual *post hoc* parameter estimates and the weighted residuals to visualize potential relationships. Based on these plots, covariates were tested for their influence in different functions. Starting from the basic model without covariates, the covariate model was first built up using forward inclusion. The contribution of each covariate was

confirmed by stepwise backward deletion. In the final model, all covariates associated with a significant decrease in objective function after elimination were maintained. The choice of the model was further evaluated as described under Data analysis.

Model validation

The internal validity of the population PK model was assessed by the bootstrap re-sampling method (repeated random sampling to produce another dataset of the same size but with a different combination of individuals) with stratification, taking into account the number of individuals at delivery and post-partum. Parameters obtained with the bootstrap replicates (250 times) were compared with the estimates obtained from the original dataset.

Simulations

With the developed PK model, simulations were performed in NONMEM to illustrate what amounts of paracetamol and its metabolites would appear in urine over time intervals of 3 h urine collection. Simulations were performed for both women at delivery and women 12 weeks post-partum and upon both a single i.v. loading dose of 2 g and four doses of 1 g paracetamol every 6 h.

Results

Subjects

Forty-one pregnant women were enrolled during the first (at delivery) study period. Two women were excluded, one woman due to withdrawal of consent before sampling and one due to failed collection of both plasma and urine samples (early post-operative bleeding needing re-intervention). Table 1 summarizes the clinical characteristics of the 39 women whose plasma and/or urine observations were included in the population PK analysis. Eight

Table 1

Clinical characteristics of the study population

Clinical characteristics	All subjects At delivery (<i>n</i> = 39)	Paired subset of subjects	
		At delivery (<i>n</i> = 8)	Post-partum (<i>n</i> = 8)
Age (years)	31.1 (5.28)	32.13 (3.87)	32.13 (3.87)
Gestational age at delivery (weeks)	35.9 (4.09)	35.75 (4.53)	–
<37 weeks at inclusion	13	3	–
37–41 weeks at inclusion	26	5	–
Post-partum (weeks)	–	–	12.39 (1.72)
Body weight (kg)	79.37 (13.0)	77.3 (11.0)	68.83 (11.7)
Body surface area (m^2)	1.92 (0.19)	1.90 (0.17)	1.79 (0.17)
Twin pregnancies	10	3	3
Pre-term twin pregnancy	8	2	2
Maternal pregnancy related disease	5	0	0
Pre-eclampsia	3	0	0
Diabetes mellitus	2	0	0

Data are reported by mean (SD) or by absolute numbers.

Figure 2

Observed paracetamol plasma concentrations (A and B) and amounts of paracetamol and metabolites excreted in urine (C and D) with arrows indicating the administration of a dose of paracetamol in the specified amount. A and B show observed paracetamol plasma concentrations (filled circles) vs. time in women at delivery (A) and in women in 12th post-partum week (B). C and D show observed amounts of paracetamol glucuronide in urine at collection time minus 1 h (open circles), paracetamol sulphate in urine at collection time (open triangles) and unchanged paracetamol in urine at collection time plus 1 h (dashes). The thick line around the x-axis represents the collection times for urine (0–6 h and 6–24 h).

of 39 women were enrolled again between their 10.7th and 15th (mean 12.4th) post-partum week for the second part of the study (single i.v. 2 g loading dose paracetamol). Table 1 shows that these eight women had similar clinical characteristics compared with the 39 subjects at delivery.

All women were non-smokers and used no other medications for at least 48 h before and during the study, except for the locoregional anaesthetics and i.v. ketorolac administered as part of the multimodal analgesia after Caesarean delivery [25].

Population PK of paracetamol

The population PK parameters of paracetamol were estimated on the basis of both plasma and urine observations;

223 plasma concentration–time points and 63 urine samples were collected in the first study period and 32 plasma concentration–time points and eight urine samples in the second study period. Figure 2 shows the observed paracetamol concentration–time points in plasma and observed paracetamol amounts in urine in women at delivery and in 12th post-partum week. This figure shows that in women after delivery both paracetamol plasma concentrations 1 h after the loading dose (23.1 vs. 54.2 mg l⁻¹) and paracetamol trough concentrations in plasma (4.1 vs. 7.2 mg l⁻¹) were lower than those in women after delivery. Concerning excreted amounts of paracetamol and its metabolites in urine over the first 6 h, differences between women at delivery and post-partum seem

Table 2

Parameter estimates of the final population PK model for paracetamol and its metabolites in women at delivery and post-partum, where differences in parameters between the groups were estimated as a fraction of the parameter at delivery, and the stability of the parameters using the bootstrap validation

Parameter	Mean (CV %) at delivery	Mean (CV %) post-partum	Bootstrap (CV %)
Fixed effects			
CL _{PG} (l h ⁻¹)	11.6 (4.3)	11.6 × 0.41 (15.5) = 4.75	11.6 (9.1) and 0.43 (18.5)
CL _{PS} (l h ⁻¹)	3.42 (5.9)		3.41 (8.2)
CL _{PU} (l h ⁻¹) (singleton)	1.15 (6.3)	1.15 × 0.65 (12.1) = 0.75	1.16 (6.7) and 0.66 (14.6)
CL _{PU} (l h ⁻¹) (twin)	0.86 (8.8)	0.86 × 0.65 (12.1) = 0.56	0.86 (8.8) and 0.66 (14.6)
CL _{PO} (l h ⁻¹)	4.95 (2.1)	4.95 × 0.56 (33.2) = 2.77	4.85 (18.5) and 0.51 (45.1)
V ₁ (l)	50.2 (3.1)	50.2 × 0.33 (17.4) = 16.5	48.9 (14.8) and 0.34 (17.9)
V ₂ (l)	17.9 (23.1)		18.6 (19.2)
Q (l h ⁻¹)	10.1 (2.2)		11.0 (30.1)
MF	9.73 (12.1)		9.78 (27.5)
Inter-individual variability			
ω ² (CL _{PG})	0.12 (32.4)		0.11 (30.2)
ω ² (CL _{PU})	0.02 (66.9)		0.02 (89.8)
ω ² (V ₁)	0.14 (39.1)		0.15 (57.3)
Residual error			
σ ² (P plasma)	0.09 (9.5)		0.09 (13.6)
σ ² (PG urine)	0.11 (27.9)		0.11 (26.3)
σ ² (PS urine)	0.08 (17.8)		0.08 (20.8)
σ ² (P urine)	0.13 (41.8)		0.12 (18.4)
Performance measures			
-2LL	2982.78		2946.22 (4.9)

Values in parentheses are CV, coefficient of variation of the parameter values. -2LL, objective function; CL_{PG}, clearance to paracetamol-glucuronide; CL_{PO}, clearance to paracetamol-oxidative metabolites; CL_{PS}, clearance to paracetamol-sulphate; CL_{PU}, clearance of paracetamol-unchanged for twin or singleton; MF, multiplication factor for k_{35} and k_{46} compared with k_{17} ; P, paracetamol; PG, paracetamol glucuronide; PS, paracetamol sulphate; Q, inter-compartmental clearance between central and peripheral volume; V₁, central volume; V₂, peripheral volume; σ², proportional intra-individual variance; ω², interindividual variance, the square root of the exponential variance of η minus 1 which is the percentage of interindividual variability in the parameters.

hard to identify from this figure due to variability in the two groups.

The PK data analysis showed that the concentrations of paracetamol and its metabolites in plasma and urine were adequately described by a model considering the different metabolic and elimination routes as depicted in Figure 1, while large and significant differences in PK parameters between women at delivery and women post-partum were found. The systematic covariate analysis showed that the most significant covariate was being at delivery compared with post-partum for the parameter clearance to paracetamol glucuronide. Addition of this covariate resulted in a population value for clearance to paracetamol glucuronide of 11.6 vs. 4.76 l h⁻¹ (multiplication factor for post-partum status (FCL_{PG}) of 0.41) in women at delivery vs. women post-partum, respectively (decrease in objective function from 3099.317 to 3056.078, $P < 0.001$) (Table 2). The addition of the covariate at delivery on V₁ was then identified as the most significant covariate, thereby further improving the model (objective function decreased from 3056.078 to 3002.583, $P < 0.001$) with values of 50.2 vs. 16.5 l for women at delivery vs. women in 12th post-partum week. This covariate being at delivery also had a significant effect on clearance to oxidative metabolites (4.95 vs. 2.77 l h⁻¹, FCL_{PO} 0.56) and clearance of unchanged paracetamol (1.15 vs. 0.75 l h⁻¹, FCL_{PU} 0.65) ($P < 0.05$) (Table 2). Furthermore, it was

found that clearance of unchanged paracetamol was related to singleton or twin pregnancies (1.15 vs. 0.86 l h⁻¹ at delivery and 0.75 vs. 0.56 l h⁻¹ post-partum, in singleton and twin pregnancy, respectively), with a decrease in objective function of 6.23 points. None of the other tested covariates [body weight, body height, body surface area, age, GA, being in labour on admission, term/preterm delivery, twin pregnancy, maternal morbidity (pre-eclampsia, diabetes mellitus, either type 1 or gestational) or urine rate] proved significant for any of the PK parameters of the model, although there was a trend towards an influence of GA on glucuronidation clearance (decrease in objective function of 3.99, $P < 0.05$, failure in the validation step). Absence of significant effects of body weight or body surface area itself on paracetamol elimination PK parameters suggests that the differences in paracetamol elimination at delivery compared with post-partum are not a matter of size but of pregnancy related increases in both metabolic clearance (higher clearance to paracetamol glucuronide and to oxidative metabolites) and primary renal elimination activity (higher clearance of unchanged paracetamol). The absence of the identification of other significant covariates also demonstrated that clearance to paracetamol sulphate was not influenced by the covariate at delivery or post-partum.

In Table 2, the PK parameter estimates including the values on inter-individual and residual variability of the

Figure 3

Diagnostic plots for the final PK model for (A) women at delivery and (B) women in 12th post-partum week including observations vs. individual predictions (left) and observations vs. population predictions (right) for paracetamol concentrations (circles) in plasma (first and third row) and amounts of paracetamol glucuronide (circles), paracetamol-sulphate (triangles) and unchanged paracetamol (squares) in urine (second and fourth row), with $x = y$ line.

final PK model, and the stability of these parameters using bootstrap validation are presented. In this table, PK parameters are presented for both women at delivery and women post-partum.

In Figure 3A and B, diagnostic plots are provided for women at delivery and women post-partum separately to allow for evaluation of the final model for both plasma paracetamol and urine paracetamol and metabolites data in both groups.

Figure 4 illustrates the difference between women at delivery and women 12 weeks post-partum in total paracetamol clearance (21.1 vs. 11.7 l h⁻¹) as well as in its different components (i.e. clearance to paracetamol glucuronide, clearance to paracetamol sulphate, clearance of unchanged paracetamol and clearance to oxidative paracetamol metabolites) as also presented in Table 2.

Figure 5 shows model based simulations of paracetamol and its metabolites per 3 h sampling interval in urine in women at delivery and women in the 12th week post-partum upon both a single i.v. loading dose of 2 g and four doses of 1 g paracetamol every 6 h. The figure shows differences in excretion of paracetamol metabolites over time between the two groups, as well as different time windows needed for the metabolites to reach steady-state in their metabolite ratios.

Discussion

The current study is the first to explore the population PK of i.v. paracetamol in women at delivery and in a subgroup of these women post-partum, with specific emphasis on

Figure 3

Continued

the quantification of the different metabolic and elimination clearance values of paracetamol during repeated administration. The results of this population PK analysis on the basis of both plasma and urine collections confirmed the previously reported higher total clearance in women at delivery compared with women in the 12th post-partum week [25]. In the current study, this higher total clearance was found to result from a 2.4-fold higher clearance to paracetamol glucuronide, 1.8-fold higher clearance to oxidative metabolites and 1.5-fold higher clearance of unchanged paracetamol. In contrast, the absolute value for clearance to paracetamol sulphate was similar whether at delivery or post-partum (Table 2, Figure 4).

However, when expressed as a fraction of total paracetamol clearance (Figure 4), clearance to paracetamol glucuronide was higher at delivery compared with post-partum at the cost of a lower fraction for clearance to

paracetamol sulphate and a similar fraction for clearance of unchanged paracetamol. While for clearance to potentially hepatotoxic oxidative metabolites the fraction of total paracetamol clearance was also similar between women at delivery and post-partum, the higher absolute value for clearance to those metabolites could imply that their higher amounts are produced at delivery. However, because we were not able to estimate the volume of distribution of these metabolites nor were we able to measure the concentration of these metabolites in plasma, little can be said about the potential implications of these results in terms of toxicity of paracetamol in women at delivery.

In this study, lower paracetamol plasma concentrations were measured 1 h after administration of the loading dose in women at delivery compared with women in their 12th post-partum week (Figure 2), which resulted in the estimation of an increased volume of distribution. A potential physiological explanation for this result is the increased

Figure 4

Total paracetamol clearance in women at delivery and women in 12th post-partum week divided by clearance to paracetamol glucuronide (CL_{PG}, grey), clearance to paracetamol sulphate (CL_{PS}, striped), clearance of unchanged paracetamol (CL_{PU}, white) and clearance to paracetamol oxidative metabolites (CL_{PO}, dark grey).

water content within the body that is associated with pregnancy, which may result in a larger distribution volume in particular for hydrophilic drugs [29] but also for intermediate lipophilic drugs such as paracetamol. However, to estimate V_1 properly, which may be of interest for the direct effect or primary pain relief, blood samples that are taken directly after dosing are required. As our primary interest was to study how individual pathways of paracetamol metabolism and elimination are affected by pregnancy, only limited efforts were put into obtaining samples for estimation of V_1 . As such, a study with more samples in the initial distribution phase is required to estimate exactly the initial volume of distribution of paracetamol in women at delivery.

As a result of both the more rapid clearance and the increase in volume of distribution in women at delivery that were identified from plasma and urine observations in this study, a more frequent dosing regimen or a higher maintenance dose for women at delivery may be suggested. It is noted, however, that also a higher clearance to potentially hepatotoxic oxidative metabolites was found in women at delivery, which may limit a higher paracetamol dose in this specific subpopulation at this point.

By investigating covariates that may affect paracetamol disposition within pregnant women, no significant relationships were found, except for twin pregnancies which compared with singleton pregnancies were shown to have lower clearance of unchanged paracetamol (1.15 vs. 0.86 l h⁻¹ at delivery and 0.75 vs. 0.56 l h⁻¹ post-partum in singleton and twin pregnancy, respectively). This can potentially be explained knowing that eight out of 10 analyzed twin pregnancies were pre-term and that there was a trend

towards a higher clearance to paracetamol glucuronide at the cost of lower clearance of unchanged paracetamol in pre-term compared with term deliveries. This is, however, of minor clinical relevance since total paracetamol clearance was not significantly different between singleton and twin pregnancies in this repeated dose study.

This model based on simultaneous collection and analysis of both plasma and urine observations allowed for a full analysis of different paracetamol pathways which could not have been obtained using metabolite fractions measured in urine only. As an illustration, despite the higher total clearance documented at delivery, a lower fraction of the paracetamol dose was retrieved in the first 6 h urine collection at delivery compared with post-partum (36.95 to 47.62%). This delayed appearance in urine may be explained by pregnancy related differences in distribution volume or renal clearance of the paracetamol metabolites, which may not have been captured on the basis of urine collections alone. Additionally, model based simulation of amounts of paracetamol metabolites in urine showed that different time windows are needed for the metabolites to reach steady-state (Figure 5). This figure also suggests that for proper estimation of the different metabolic and elimination pathways, urine should be collected over a prolonged time window.

This study has several limitations. As mentioned, oxidative paracetamol metabolites (mercapturic acid and cysteine conjugates) derived from NAPQI formation, could not directly be measured in plasma or urine and were estimated instead, based on the difference between total paracetamol clearance and clearance to paracetamol glucuronide, to paracetamol sulphate and to unchanged paracetamol. However, we assume that those constraints are compensated for by the paired study design, by repeated dose administration, and by the fact that advanced data techniques were used to derive a population PK model for paracetamol and available metabolites, based on both plasma and urine observations (Figure 3). Furthermore, only a relatively limited number of women included at delivery were re-evaluated in their post-partum period and in those women measurements were only performed up to 6 h after one loading dose. This was mainly due to logistic reasons since co-admission of the infant to facilitate breastfeeding made a full 24 h PK study, even in a limited group of women, not feasible in our hands. Despite these issues, we think that our results are valid as these data were analyzed together with data collected at delivery.

From this study, we conclude that being at delivery is a significant covariate leading to an increase in total paracetamol clearance. This increase is a result of a disproportional increase in glucuronidation clearance and a proportional increase in clearance of unchanged paracetamol and in oxidation clearance, of which the latter may potentially limit further dose increase in this patient group.

Figure 5

Model based simulation of paracetamol glucuronide (transparent bars), paracetamol sulphate (striped bars) and unchanged paracetamol (grey bars) amounts per 3 h sampling interval in urine, in women at delivery (left panels) and women in 12th week post-partum (right panels) upon a single iv loading dose of 2 g (upper panels, A) and four doses of 1 g paracetamol every 6 h (lower panels, B).

Competing Interests

There are no conflicts of interests to declare.

The clinical research of Karel Allegaert is supported by the Fund for Scientific Research, Flanders (Belgium) (F.W.O. Vlaanderen) by a Fundamental Clinical Investigatorship (1800209 N) and a research grant (1506409N), and of Aida Kulo by a JoinEU-SEE scholarship (2009–2010). This work (partim) has been awarded the best poster presentation at the 10th European Association for Clinical Pharmacology and Therapeutics congress held in Budapest, in June 2011.

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