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Estradiol and Weight Are Covariates of Paracetamol Clearance in Young Women

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Key Words
Paracetamol · Estradiol · Covariates · Pregnancy · Oral contraceptives · Glucuronidation

Abstract
Aim: Paracetamol clearance differs between pregnant and non-pregnant women and between women with or without specific oral contraceptives (OCs). However, an association between female sex hormones and paracetamol clearance has never been explored. ***Methods:*** In total, 49 women at delivery, 8 female control subjects without OC use, historical data of 14 women taking OCs, and 15 postpartum observations with and without OCs were pooled to explore covariates of paracetamol clearance. All received a single intravenous 2-gram paracetamol dose, and blood samples were collected up to 6 h after dosing. High-performance liquid chromatography was used to quantify paracetamol. The area under the curve to time infinity ($AUC_{0-\infty}$) was determined and clearance ($l/h \cdot m^2$) was calculated by dose/$AUC_{0-\infty}$. In addition, estradiol and progesterone were quantified by ELISA with electro-chemiluminescence. ***Results:*** Median paracetamol clearance at delivery was significantly higher when compared to postpartum or non-pregnant women (11.9 vs. 6.42 and 8.4 $l/h \cdot m^2$, at least $p < 0.05$), while an association between paracetamol clearance and estradiol was observed ($R = 0.494$, $p < 0.0001$). In non-pregnant subjects, there was no impact of OC exposure on paracetamol clearance. Multiple regression revealed a linear association ($R_{adj} = 0.41$, $p < 0.001$) between paracetamol clearance and weight ($p = 0.0462$) and estradiol ($p < 0.0001$). ***Conclusion:*** Estradiol and weight in part explain the variation in paracetamol clearance in young women.

Introduction

Paracetamol (acetaminophen) is the most commonly used analgesic and antipyretic drug, and is the first choice compound for the symptomatic treatment of pain or fever. 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 oxidation (<10%) to result in toxic metabolites (N-acetyl-p-benzoquinone) [1]. Due to its safety profile, paracetamol is commonly used during pregnancy, after caesarean delivery or in postpartum. However, physiological changes during pregnancy (e.g. increased plasma volume and body weight, increased metabolic rate and enhanced renal drug transport processes) and their subsequent normalisation in postpartum influence paracetamol disposition and

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metabolism [2]. These peripartum alterations may relate to changes in female sex hormones.

The claim on the link between female sex hormones and drug metabolism is supported by in vivo and in vitro studies in rodents and humans. Rat studies performed in the early 70s revealed influences of sex hormones on drug enzyme activities [3]. Transgenic UDP glucuronosyltransferase (UGT) 1 mice described the influence of circulating hormonal factors on UGT 1A gene expression, which is involved in paracetamol glucuronidation [4]. More recently, Chen et al. [5] demonstrated that estradiol upregulates UGT 1A4 expression in vitro by documenting increased lamotrigine glucuronidation in a transfected liver cell model. This is in line with in vivo observations in humans, since compound-specific studies (e.g. lamotrigine, propofol and paracetamol, all undergoing glucuronidation) show raised metabolic drug clearance during pregnancy [6–8].

Based on these in vivo observations on compounds primarily eliminated via glucuronidation [9–11], and on the earlier mentioned in vitro observations [3–5], it seems reasonable that estradiol-induced enhanced glucuronidation in part explains the increased paracetamol clearance during pregnancy. Moreover, oral contraceptive (OC) steroids also cause an increased drug metabolism of lamotrigine, via induction of the glucuronosyltransferase [12], as well as a rise in metabolic clearance of paracetamol via induced glucuronidation and oxidative pathways [13, 14]. Consequently, we aimed to explore covariates – including female sex hormones – of paracetamol clearance in a further extended cohort of women undergoing elective caesarean delivery compared to postpartum women (intra-individual) or those exposed or not to OCs (inter-individual) [14, 15].

Materials and Methods

Ethics and Recruitment

The study protocol was reviewed and approved by the Ethics Committee of University Hospitals Leuven, Belgium (S52366, EUDRACT 2010-020164-37). A total of 49 women scheduled for caesarean delivery were included after written informed consent was obtained; 8 of these women initially included at delivery returned for a 2nd paracetamol pharmacokinetic study (n = 8), using the same loading dose at 10–15 weeks postpartum, and for a 3rd visit (n = 7) approximately 1 year after delivery. We hereby aimed to quantify intra-individual pharmacokinetic changes in paracetamol clearance at delivery and in early and late postpartum. Finally, 8 non-pregnant female control subjects between the ages of 27 and 37 years, not taking OCs, were enrolled (table 1).

Supplementary Data

In addition, raw data from another 14 non-pregnant control subjects between the ages of 19 and 32 years, all on OCs, were available. These data were reported by Gregoire et al. [16], independently from our data. We hereby aimed to quantify inter-individual pharmacokinetic differences between women at delivery and non-pregnant women, either exposed or not to OCs.

Dosing, Sampling, Assay and Female Hormones

Blood samples from 49 patients at delivery were collected in 4.5-ml lithium heparin tubes, through a peripherally inserted venous catheter, according to the following schedule: 1, 2, 4 and 6 h after intravenous administration of a 2-gram paracetamol loading dose over 15 min. Observations in 5/49 patients at delivery had to be excluded from this analysis since the number of blood samples (n <3) available for individual pharmacokinetic calculations was insufficient. After each sample collection, the peripherally inserted venous catheter dedicated for blood sampling only was flushed with heparin (2 U/ml) to prevent blood clotting and obstruction of the catheter. Immediately following collection, blood samples were centrifuged at 2,500 rpm for 10 min. Subsequently, plasma was transferred to 3.6-ml polypropylene cryotubes (Nunc CryoTubes®), labelled and stored at –20°C until high-performance liquid chromatography analysis was performed, as described earlier [17].

A subgroup of 8/44 women initially recruited at delivery received a second 2-gram paracetamol loading dose during a 2nd visit, 10–15 weeks postpartum, of whom 7/8 came back after approximately 1 year for a 3rd visit, following the same procedure: i.e. blood samples were collected at 1, 2, 4 and 6 h after initiation of a 2-gram paracetamol loading dose, and handled as described before. In addition, 8 female controls using no OCs were also enrolled, to whom a 2-gram paracetamol loading dose was administered, and blood samples were collected, handled and stored as described for postpartum women. Finally, and as mentioned earlier, raw data of similar observations (a single 2-gram intravenous paracetamol loading dose, with observations at 1, 2, 4 and 6 h) in 14 healthy female volunteers were provided by Gregoire et al. [16].

Estradiol and progesterone levels were determined for each (recurrent) patient (44 patients at delivery, 8 cases at 15 weeks and 7 cases at approx. 1 year postpartum, as well as 8 female controls with no OCs) via ELISA with electro-chemiluminescence (MODULAR® ANALYTICS E-170; Roche/Hitachi) by the clinical laboratory of University Hospitals Leuven. Estradiol and progesterone observations in the cohort of Gregoire et al. [16] were not available, but all these women were on OCs.

Pharmacokinetics and Statistics

A non-compartmental approach was used to calculate the paracetamol pharmacokinetic estimates. After determining the paracetamol plasma concentration, the elimination rate constant (k_e) was calculated for every individual data set. Subsequently, terminal elimination half-life was derived and the area under the curve to time infinity ($AUC_{0-\infty}$) was determined, as published earlier [18]. The total plasma clearance (CL) was calculated by dose/$AUC_{0-\infty}$ and the volume of distribution by CL/k_e. Paracetamol clearance ($l/h \cdot m^2$) was corrected for body surface area (BSA), a suitable surrogate for body dimensions. The BSA was calculated making use of the Haycock formula ($BSA = 0.024265 \times weight^{0.5378} \times height^{0.3964}$), previously used [18], and was also applied on the data set of Gregoire et al. [16].

Clinical characteristics and individual pharmacokinetic estimates were reported by median and range. Inter-individual data were compared using Kruskal-Wallis analysis, while Friedman and

Table 1. Clinical characteristics, estradiol and progesterone levels, and pharmacokinetic estimates in the different cohorts

	Women at delivery	Early postpartum	Late postpartum	Female control subjects	Data set of Gregoire et al. [16]
Number of profiles	49 (44 for analysis)	8	7	8	14
Status	at delivery	15 weeks postpartum	±1 year postpartum	non-pregnant women	non-pregnant women
Length, cm	168.0 (150.0–182.0)	167.5 (154.0–177.0)	162.0 (154.0–177.0)	166.3 (162.0–174.3)	165.0 (160.0–174.0)
Weight, kg	78.0 (57.0–110.0)	69.0 (52.2–88.0)	62.0 (50.2–87.0)	67.2 (54.6–74.0)	55.5 (49.2–76.0)
BSA, m^2	1.95 (1.58–2.35)	1.83 (1.51–2.01)	1.73 (1.48–1.99)	1.78 (1.58–1.86)	1.59 (1.49–1.89)
OC use	not applicable	4/8	2/7	0/8	14/14
Sex hormones determined, n	44	8	7	8	0
Estradiol, pg/ml	4,210 (350–19,245)	75 (55–160)	50 (25–216)	53 (29–257)	not available
Progesterone, ng/ml	83.0 (14.0–412.0)	1.0 (0.5–2.0)	0.4 (0.2–0.7)	0.7 (0.4–10.6)	not available
Clearance, $l/h \cdot m^2$	11.9 (7.1–31.9)	6.42 (5.36–7.82)	7.13 (4.97–13.25)	8.4 (6.2–14.1)	9.9 (6.0–13.7)
Distribution volume, l	64.6 (42.0–176.2)	35.76 (30.1–58.99)	46.94 (36.86–65.98)	47.2 (35.8–56.0)	46.7 (38.8–59.5)
Distribution volume, l/kg	0.77 (0.56–2.22)	0.59 (0.35–0.84)	0.75 (0.6–1.05)	0.76 (0.59–0.81)	0.78 (0.67–0.92)
Elimination half-life, h	1.82 (1.23–4.14)	2.34 (1.36–3.58)	2.61 (1.73–4.73)	2.26 (1.47–2.88)	1.91 (1.56–3.11)

Mann-Whitney U analysis were used to analyse intra-individual observations. Pearson's correlation coefficient was determined as a measure of statistical dependence between two parameters. Simple linear regression and Mann-Whitney U analysis were used prior to generating a statistical generalized linear model. Finally, a multiple regression analysis was performed, making use of Statistica® 8, to determine the association between paracetamol clearance and female sex hormones. Statistical analysis and graphical representation (mean ± SEM) were performed using MedCalc® 12.5 and Prism® 5.01, respectively. Clinical characteristics were tabulated per patient group, with median and range.

Results

Paracetamol concentrations in 325 samples were available to calculate 81 paracetamol pharmacokinetic profiles. Clinical characteristics, estradiol (pg/ml) and progesterone (ng/ml) levels, and pharmacokinetic estimates in the different cohorts are provided in table 1.

Effect of Pregnancy and OC Use on Paracetamol Clearance

Inter-individual differences in paracetamol clearance among pregnant women and healthy female controls, either OC exposed or not [16], are shown in figure 1 and table 1. Even after correction for BSA, a significantly higher median paracetamol clearance was observed in pregnant women (11.9 $l/h \cdot m^2$) compared to healthy female controls without OCs (8.4 $l/h \cdot m^2$, $p < 0.05$), as well as to the historical data set published by Gregoire et al. [16] (9.9 $l/h \cdot m^2$, $p < 0.01$). An effect of OC use on paracetamol clearance in non-pregnant women could not be established.

Intra-individual differences in paracetamol clearance at delivery and at 15 weeks and approximately 1 year postpartum are illustrated in figure 2. There was a significant higher median paracetamol clearance in women at delivery (11.8 $l/h \cdot m^2$) compared to women 10–15 weeks (6.42 $l/h \cdot m^2$) and approximately 1 year postpartum (7.13 $l/h \cdot m^2$, both $p < 0.05$). A difference in paracetamol clearance between both postpartum measurements (15 weeks vs. 1 year postpartum) or between women exposed or not exposed to OCs in postpartum could not be observed.

Effect of Gestational Age on Paracetamol Clearance during Pregnancy

Differences in paracetamol clearance in women delivering at term (≥37 weeks, n = 18) or preterm (<37 weeks,

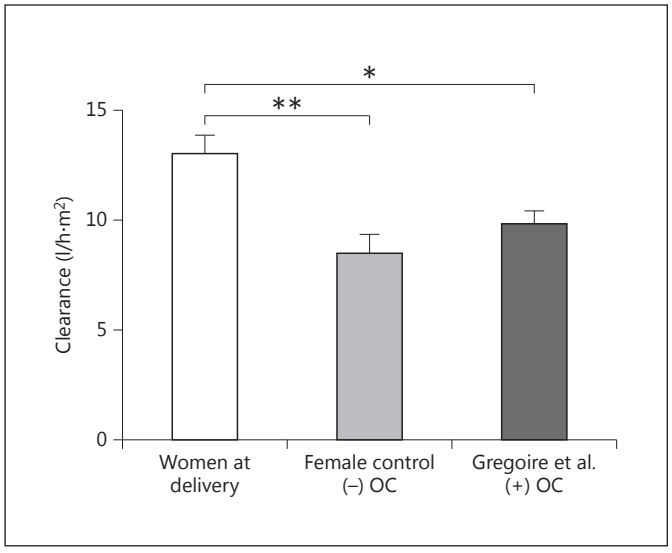

Fig. 1. Inter-individual comparison of paracetamol clearance in pregnant vs. non-pregnant women. Bar graph provides mean ± SEM of paracetamol clearance in women at delivery (n = 44), female control subjects not taking OCs (n = 8) and non-pregnant women with OC use (n = 14, historical data from Gregoire et al. [16]). * $p < 0.05$; ** $p < 0.01$.

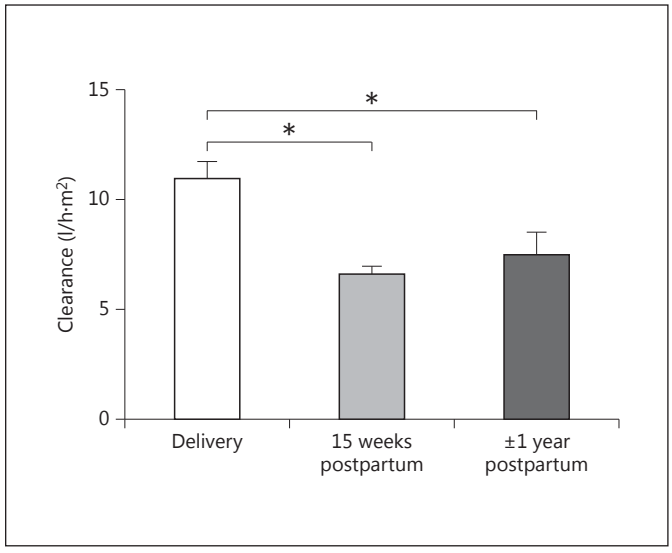

Fig. 2. Intra-individual changes of paracetamol clearance in women at delivery or in postpartum. Bar graph provides mean ± SEM of paracetamol clearance in women at delivery (n = 8) and women 15 weeks (n = 8) and ±1 year postpartum (n = 7), both with and without OC use. * $p < 0.05$.

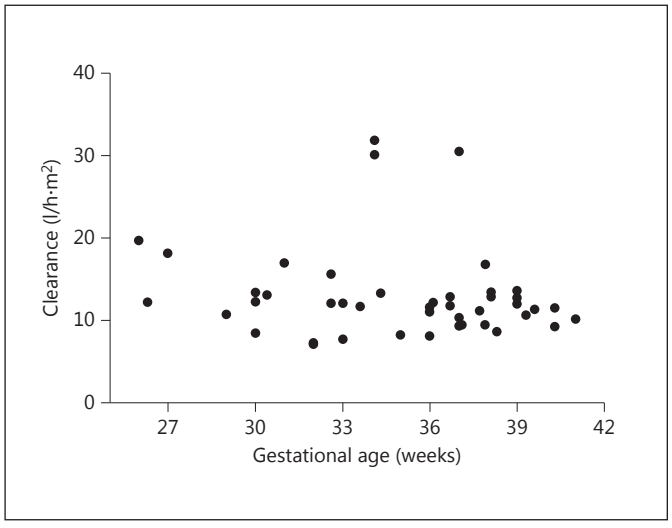

Fig. 3. Spearman's correlation between gestational age and paracetamol clearance.

n = 26) were not documented (p = 0.452). Similarly, Spearman's correlation revealed no significant correlation between gestational age and paracetamol clearance (R = –0.179, p = 0.244; fig. 3).

Effect of Female Sex Hormones on Paracetamol Clearance

As paracetamol clearance was significantly higher in pregnant women compared to non-pregnant and postpartum women (see above), as well as estradiol and progesterone levels, a correlation analysis was performed to quantify the degree to which paracetamol clearance relates to both estradiol and progesterone concentrations. Spearman's analysis revealed a correlation between paracetamol clearance and estradiol (R = 0.494, $p < 0.0001$), as well as between paracetamol clearance and progesterone (R = 0.474, p = 0.0001).

Generalized Linear Model

Based on significant values in simple linear regression and Mann-Whitney U analysis, body weight, BSA, and estradiol and progesterone concentrations were used in a generalized linear model to examine the relationship between these independent variables and paracetamol clearance. Multiple linear regression revealed a linear association ($p < 0.001$) between paracetamol clearance and the independent variables body weight (p = 0.0462) and estradiol levels ($p < 0.0001$), as shown in figure 4. Clearance $(l/h \cdot m^2) = 0.8609 + 0.1248 \cdot x + 0.0003 \cdot y$, $R^2_{adj} = 0.41$, where x = body weight (kg) and y = estradiol (pg/ml).

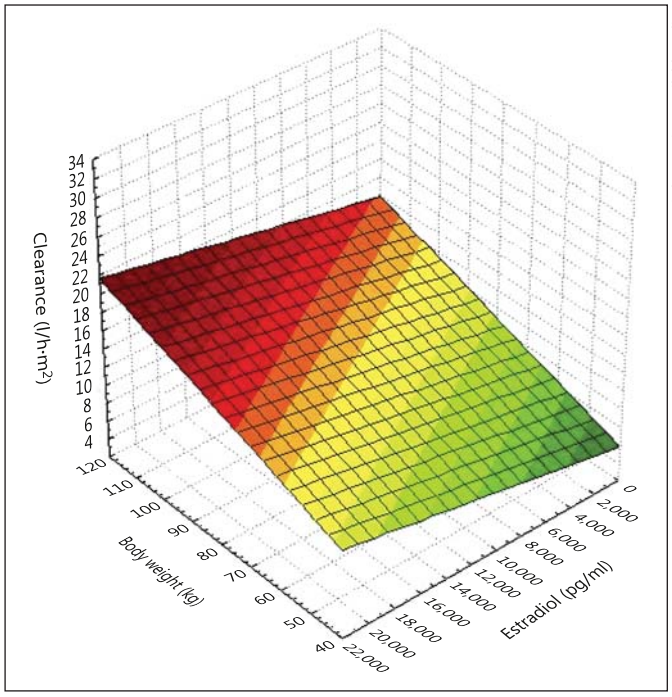

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Fig. 4. 3D surface plot of paracetamol clearance against plasma estradiol concentration and body weight. Clearance ($l/h \cdot m^2$) = $0.8609 + 0.1248 \cdot x + 0.0003 \cdot y$, where x = body weight (kg) and y = estradiol (pg/ml).

Discussion

In addition to a weight-related association, the current pooled analysis documented a significant positive association between paracetamol clearance ($l/h \cdot m^2$) and estradiol levels, indicating a higher paracetamol clearance with increasing estradiol levels (fig. 4). These results were obtained by making use of inter- and intra-individual observations in pregnant women, female control subjects (with or without OC use) and women 15 weeks and approximately 1 year postpartum.

The significant correlation between paracetamol clearance and estradiol was to a certain extent expected. This is because pharmacokinetic studies of lamotrigine, propofol and benzodiazepines all showed increased glucuronidation-related clearance of these compounds in women during pregnancy and following caesarean delivery [6, 8, 19, 20]. Similarly to these drugs, the main route of paracetamol elimination is also through glucuronidation. It is likely that the current data are of relevance as an illustration of estradiol and weight-driven drug clearance in young women, but are also important for the clinical pharmacology of paracetamol itself.

The possible link between estradiol and glucuronidation is of relevance to improve prediction of drug disposition in pregnancy for any drug that undergoes glucuronidation such as lamotrigine, propofol, benzodiazepines or paracetamol. Wegner et al. [21] showed that lamotrigine plasma levels are reduced by >50% during OC use with an increase in lamotrigine levels during the pill-free week, with maximum levels 54% higher than baseline (range 29–129%). Lamotrigine is primarily eliminated via glucuronidation [22]. In this context, Chen et al. [5] already presented a potential mechanism contributing to the enhanced elimination of lamotrigine during pregnancy, probably mediated by both the oestrogen receptor α and the specificity protein-1 binding site, making use of estradiol receptor α-transfected HepG2 cells. Buchanan et al. [23] suggested that female sex hormones are a major contributing factor in the glucuronidation-related increase in propofol clearance. Stoehr et al. [20] suggested an accelerated metabolism of conjugated benzodiazepines, such as temazepam and lorazepam, in women taking low-dose oestrogen OCs. Finally, Miners et al. [13] investigated the effect of OC use on the individual metabolic pathways for paracetamol, and revealed an enhanced glucuronidation in women using OCs compared to female control subjects. In essence, our study confirms the link between estradiol and phenotypic glucuronidation activity, but to a further extent, in a pooled study based on 81 pharmacokinetic profiles, collected during pregnancy, in postpartum and in healthy female volunteers (exposed or not to OCs) and following intravenous administration, avoiding absorption-related interferences.

Besides improved prediction of glucuronidation activity throughout pregnancy and in postpartum, there are also some paracetamol-specific consequences. As a strong link between paracetamol concentration and analgesia is suggested [24], the higher paracetamol clearance in women during pregnancy results in lower paracetamol plasma levels. As a result, less analgesia should be anticipated when conventional doses are administered. Physicians should be aware that the analgesic effect of paracetamol will be shorter in pregnant women or in any setting of raised estradiol levels. However, before higher paracetamol doses are considered to compensate for this, we would like to refer to the recently published evidence that the higher paracetamol clearance during pregnancy is due to a disproportional increase in glucuronidation clearance and a proportional increase in clearance of unchanged paracetamol and in oxidation clearance [7]. It is likely that the latter limits further dose increase in this patient group.

In line with other recent publications in this journal on, for example, the comparison of droperidol, metoclo-

pramide, tropisetron or ondansetron to prevent postoperative nausea and vomiting following gynaecological operations or chemotherapy during pregnancy [25, 26], we hereby re-illustrate the need to further explore population-specific pharmacokinetics and dynamics of commonly used drugs in young women and during pregnancy,

In conclusion, weight and estradiol predict to a certain extent the variation in paracetamol clearance. The estradiol link probably relates to raised glucuronidation activity and may be of relevance for any drug that undergoes glucuronidation. Because of the higher clearance, the analgesic effect will be shorter in a setting of higher estradiol levels.

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