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Weight, pregnancy and oral contraceptives affect intravenous paracetamol clearance in young women

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Abstract. – OBJECTIVES: Because of the extensive variability in paracetamol clearance in young women, published data were pooled with newly collected observations in search of covariates of paracetamol pharmacokinetics (PK) within this specific population.

SUBJECTS AND METHODS: PK estimates and clinical characteristics [pregnant, weight, exposure to oral contraceptives (OC)] in young women following IV loading dose (2 g paracetamol) were pooled, using a non-compartmental linear disposition model in individual time-concentration profiles. Data were reported by median and range. Rank correlation was used to link clearance (l/h) to weight, Mann Whitney U test to compare clearance (l/h.m^{-2}) between subgroups (pregnant, OC exposure). Finally, a multiple regression model with clearance (l/h) in all women and all non-pregnant women was performed.

RESULTS: Based on 73 paracetamol PK estimates, a 8-fold variability in clearance (range 7.1-62.2 l/h) was documented, in part explained by a correlation (r2=0.36) between clearance (l/h) and weight. Clearance (l/h and l/h.m^{-2}) and distribution volume (l) at delivery (n=36) were higher compared to non-pregnant observations. In non-pregnant women, women on OC (n=20) had a higher paracetamol clearance (l/h.m^{-2}) compared to women (n=17) not on OC (p = 0.023). Weight (p = 0.0043) and pregnancy (p = 0.02) were independent variables (r=0.56) of paracetamol clearance (l/h). In non-pregnant women, weight (p = 0.009) and OC exposure (p = 0.03) were independent variables (r=0.51).

CONCLUSIONS: Weight, pregnancy and OC result in higher clearance of IV paracetamol in young women. Besides compound specific relevance, these findings also unveil covariates of drug metabolism in young women.

Key Words:
Paracetamol, Pregnancy, Pharmacokinetics, Oral contraceptives.

Introduction

In the therapeutic concentration range, paracetamol is metabolized by the liver to paracetamol-glucuronide (47-62%) and paracetamol-sulphate (25-36%) as main metabolites, subsequently eliminated by renal route. The sulphation route is rapidly saturable at doses that exceed the therapeutic doses. Only 1-4% is excreted unchanged in urine, and about 8-10% of paracetamol is oxidized to 3-hydroxy-paracetamol (cytochrome p450 (CYP)3A4, 2E1, and 1A2), mainly depending on the paracetamol concentration) and the (hepatic)toxic metabolite N-acetyl-p-benzoquinone-imine (NAPQI)[1,2,3]. Under normal condition of use, NAPQI is rapidly detoxified by glutathione (GSH) and eliminated in the urine after conjugation with cysteine and mercapturic acid.

Paracetamol is perceived to have a good efficacy-to-safety ratio as analgesic in a wide range of patient populations. However, since paracetamol is one of the most commonly used drugs to treat pain or fever, knowledge on the covariates of paracetamol disposition remains crucial to avoid toxicity through unanticipated variability[1-3].

In addition to oral and rectal formulations, several intravenous (IV) formulations became available more recently[1]. Such a formulation en-

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ables the administration of paracetamol when the enteral route cannot (yet) be used and should improve the predictability by the reduction in variability related to absorption. We recently reported on IV paracetamol pharmacokinetics (PK) (2 g, loading dose) at delivery and hereby documented a significant increase in paracetamol clearance compared to healthy female volunteers[3,4]. To further illustrate the pregnancy related changes, a paired PK approach was applied in 8 women initially included at delivery, who underwent a second evaluation 12-18 weeks after delivery. These intra-individual changes were even more pronounced (11.7 at delivery to 6.4 l/h.m^{-2} at 12-18 weeks postpartum)[5]. Compared to these postpartum observations, the higher paracetamol clearance (l/h, + 80%) at delivery related to an increase in clearance to paracetamol glucuronidation (+ 144%), to primary renal paracetamol elimination (+ 53%), but also in clearance to oxidative metabolites (+ 78%)[6].

Intrigued by the extensive variability in paracetamol clearance (2 g loading dose, IV, l/h) both during and outside of pregnancy and despite the use of an IV route, we decided to pool these available data with newly collected observations in search of covariates of paracetamol PK in young women.

Subjects and Methods

Clinical Characteristics and Study Related Aspects

For this analysis, datasets of 4 studies in young women from 2 different research groups were pooled. In all included studies, the same dose (2 g IV paracetamol) was administered, and plasma samples collected 1, 2, 4 and 6 h after the initiation of administration were considered for the individual PK calculations. The administration of 2 g IV paracetamol reflects the practice to administer a loading dose, aiming to result in more effective analgesia[1-4].

Cohort 1: Following study registration (EudraCT 2010-020164-37) and approval by the Ethics Committee of the University Hospitals Leuven, women who were scheduled to undergo a (semi)elective Caesarean delivery were recruited for this study after written, informed consent[4,6]. The administration of IV paracetamol started with a loading dose of 2 g over 15 minutes shortly after delivery of the newborn. Body weight and height were recorded just before the Caesarean delivery was performed, and the body surface are (BSA) was calculated based on these data.

Blood samples from a dedicated peripheral IV catheter were collected 1, 2, 4 and 6 h after loading dose administration. These samples were centrifuged and plasma was stored at -20°C until high performance liquid chromatography (HPLC) analysis was performed[7]. 36 paracetamol-time profiles following delivery were available for the current analysis. For additional information on the specific clinical setting and the multimodal analgesia applied in these women, we refer to the original papers[4,6].

Cohort 2: A subgroup of 8 women initially included at delivery were recruited for a second PK study with the same dose (2 g IV paracetamol) 10-15 weeks after delivery[5]. In addition, 7/8 of these women were re-evaluated a third time one year after delivery. Body weight and height were recorded just before the study drug was administered, BSA was calculated based on these data. In addition, the use of oral contraceptives (OC) was registered (4/8 at the second study, 2/7 at the third study of whom one during both PK studies).

Cohort 3: An additional, unrelated group of 8 healthy female volunteers, not taking OC were also recruited. Body weight and height were recorded just before the study drug was administered, BSA was calculated based on these data. A single dose of 2 g of IV paracetamol was administered over 15 minutes and venous samples were collected (1, 2, 4 and 6 h). The studies in cohort 2 and 3 were performed at the Centre for Clinical Pharmacology, University Hospitals Leuven following approval of these study protocols by the Ethics Committee, based on amendments of the initial study protocol on IV paracetamol disposition at delivery. For both cohorts, blood samples were centrifuged an plasma samples were stored at –20°C until the same high performance liquid chromatography (HPLC) analysis was performed to quantify paracetamol concentrations[7].

Cohort 4: Gregoire et al[3] published on the PK of IV paracetamol during repeated administration in 26 young healthy volunteers, including 14 young women[3]. As part of the study protocol, these women were on OC during the study. Plasma samples collected 1, 2, 4 and 6 h after the first dose (2 g IV paracetamol) were extracted from the original datasets (study report pro-

vided by Bristol Myers Squibb, Braine l'Alleud, Belgium) to calculate individual PK using the same method as described below. Samples were analysed using reversed phase HPLC with uv detection. Additional details on this study can be retrieved in the original publication[3].

Pharmacokinetics

A non-compartmental linear disposition model was used for the analysis of paracetamol time-concentration profiles[5]. The peak and trough plasma concentrations (C_{max}, 1h and C_{min}, 6h mg/l) were obtained directly from the individual experimental data. The terminal elimination rate constant (k_e, h^{-1}) was determined by log-linear regression analyses of the final data points (at least 3) and calculation of the corresponding slope ($-k_e/2.303$). The area under the plasma concentration-time profile (AUC, mg/l.h) from 0 to 6 hours (AUC_{0-6}) was calculated by using the linear trapezoidal method. The AUC from 6 hours to infinity ($AUC_{6-\infty}$) was determined by dividing the final plasma concentration by k_e, and the AUC from 0 hours to infinity ($AUC_{0-\infty}$) was the sum of AUC_{0-6} and $AUC_{6-\infty}$. The total plasma clearance (CL, l/h) was determined by Dose/$AUC_{0-\infty}$ and the volume of distribution (Vd, l) by CL/k_e. Finally, Cl and Vd were also calculated by BSA (l/h.m^{-2}) and weight (l/kg) respectively.

Statistical Analysis

Data were reported by median and range. Rank correlation was used to describe the link between clearance and weight. Clinical characteristics and individual pharmacokinetic estimates between women at delivery or not pregnant women were compared (Mann Whitney U test). Similarly, clinical characteristics and individual pharmacokinetic estimates in non-pregnant women either or not exposed to OC were compared. Finally, a multiple regression model with clearance (l/h) as dependent variable in all women and all non-pregnant women was performed (MedCalc®, Mariakerke, Belgium). A *p*-value < 0.05 was considered to be significant.

Results

Clinical characteristics and pharmacokinetic estimates were based on 73 paracetamol PK profiles and are provided in Table I. Observations on differences in clearance (l/h.m^{-2}) between the different groups (not pregnant, not OC exposed *vs*. not pregnant, OC exposed *vs*. at delivery) are illustrated in Figure 1. An extensive between individual variability in clearance (7.1-62.2 l/h, 8 fold) was observed, only marginally less pronounced after corrected for BSA (4.7-28 l/h.m^{-2}, 6 fold). This is also reflected by the significant correlation (r = 0.6, 95% CI 0.43-0.73, $p < 0.0001$) between clearance (l/h) and body weight (Figure 2).

Both clearance (l/h and l/h.m^{-2}) and distribution volume (l) at delivery were significantly higher when compared to estimates in all non-pregnant women, and remained significantly different when only compared to non-pregnant either on OC or not on OC (all at least $p < 0.05$). When observations were limited to non-pregnant women (n = 37), women on OC (n = 20, based on 14 observations of the Gregoire et al[3] cohort and 6/15 observations of cohort 2) had a significantly higher paracetamol clearance (l/h.m^2)

Table I. Clinical characteristics and pharmacokinetic estimates based on 73 pharmacokinetic profiles in young women. Data were provided by median and range (OC = oral contraceptives).

	All cases (n=73)	At delivery (n=36)	Not pregnant (n=37)	
			on OC (n=20)	not on OC (n=17)
Weight (kg)	71 (49.2-110)	78 (57-110)	59 (49-88)	65.3 (52.2-78)
Body surface area (m^2)	1.82 (1.48-2.35)	1.93 (1.54-2.35)	1.7 (1.48-2.0)	1.78 (1.51-1.95)
C_{max}, 1h (mg/l)	29.1 (7.9-75.7)	22.9 (7.9-32.3)	31.7 (23.3-72.2)	34.4 (28.5-75.8)
C_{min}, 6 h (mg/l)	5.7 (0.6-15)	3.9 (0.6-9.4)	6.1 (2.5-12.6)	8.2 (2.06-15)
Slope (h^{-1})	0.36 (0.15-0.55)	0.38 (0.2-0.55)	0.36 (0.3-0.37)	0.27 (0.15-0.47)
$AUC_{0-\infty}$ (mg/l.h)	120 (32.2-281.3)	102.1 (32.2-169.1)	129.6 (75.7-214.3)	157 (79.9-281.3)
Elimination halflife (h)	1.95 (1.26-4.75)	1.83 (1.26-3.47)	1.9 (1.38-3.11)	2.55 (1.47-4.75)
Clearance (l/h)	16.6 (7.1-62.2)	19.6 (11.8-62.2)	15.4 (9.3-26.4)	12.7 (7.1-25.0)
Clearance (l/h.m^{-2})	9.4 (4.7-28)	10.46 (7-28)	9.0 (5.0-13.3)	6.9 (4.7-14.1)
Distribution volume (l)	49.2 (24.7-155)	56 (36.8-155)	45.9 (25.4-66)	46.8 (24.7-64.4)
Distribution volume (L/kg)	0.72 (0.29-1.99)	0.69 (0.5-1.99)	0.76 (0.29-1.20)	0.74 (0.36-1.05)

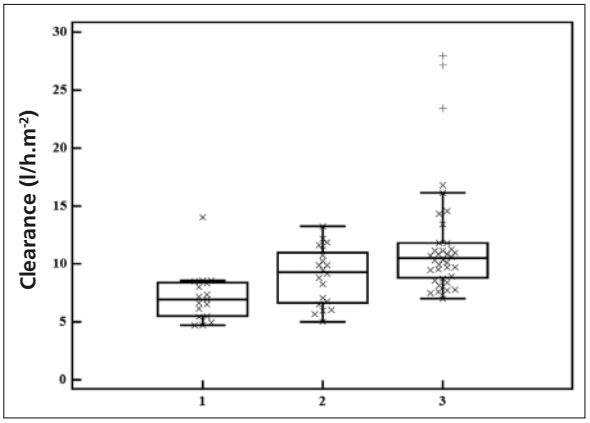

Figure 1. Paracetamol clearance (l/h.m^{-2}, box plots and individual estimates) in 3 subgroups of young women (not pregnant, no oral contraceptives = 1, not pregnant, on oral contraceptives = 2, pregnant = 3).

compared to women not on OC (n = 17, 9/15 observations of cohort 2, 8 observations of cohort 3) (p = 0.023) (Figure 1). In a multiple regression model with all 73 observations, weight (p = 0.0043) and pregnancy (p = 0.02) were two independent variables (multiple correlation coefficient = 0.56) of paracetamol clearance (l/h). When observations were limited to non-pregnant women, weight (p = 0.009) and OC exposure (p = 0.03) were two independent variables (multiple correlation coefficient = 0.51).

Discussion

Clinical pharmacology aims to predict pharmacokinetics and -dynamics (PK, PD) to improve the effect/side-effect balance in every individual patient. Consequently, exploration of the impact of clinical characteristics on the between individual PK in a specific subpopulation like during pregnancy or in young women remains of relevance[8,9]. Based on 73 PK estimates (2 g IV loading dose) in young women, a 8-fold range in paracetamol clearance (median 16.6, range 7.1-62.2 l/h) was observed. Weight was an important covariate of this variability (r^2 = 0.36, Figure 2) together with pregnancy (multiple correlation coefficient = 0.56). OC exposure in non-pregnant women (multiple correlation coefficient = 0.51) further explained this variability.

In essence, the current observations on covariates of paracetamol clearance confirm earlier reports on the impact of weight, pregnancy and OC exposure on paracetamol disposition. The available literature on the impact of weight, pregnancy and OC exposure has been summarized in Table II[4-6,10-18]. The strength of the current study is the use of an IV route and the study size, since based on 73 PK profiles. An IV route avoids the additional variability related to absorption (e.g. delayed gastric emptying during pregnancy), although Rayburn et al[12] documented that – using a paired design in 6 women – paracetamol absorption was not different in late pregnancy compared to early postpartum (36 weeks gestational age *vs.* 6 weeks postpartum). Modeling also suggested[19] that compared to oral administration, IV paracetamol dosing reduces first pass hepatic exposure, minimizing the likelihood of saturating the glucuronidation and sulfation pathways and decreasing hepatotoxic oxidation activity[19]. The study size (n=73) enabled the simultaneous analysis of weight, pregnancy and OC exposure on paracetamol clearance and explained about 50% of the variability in clearance.

The current observations are of compound specific relevance, both for the level of analgesia and the safety. The higher paracetamol clearance, the more likely will this result into faster disappearance of the analgesic effect, since there is a link between the median paracetamol plasma concentration and the level of analgesia[1,2]. Moreover, the higher overall paracetamol clearance is likely explained by higher glucuronidation and higher oxidation activity as suggested following both oral and IV administration[6,14,17,18]. The higher oxidation activity results in higher production of the hepatotoxic NAPQI (N-acetyl-p-benzoquinone imine), normally removed by combination with glutathione to cysteine and

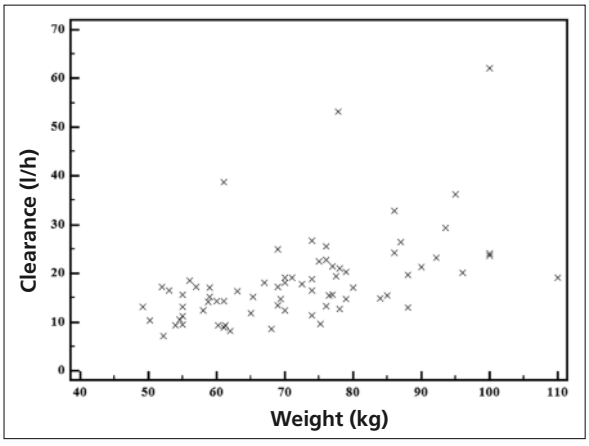

Figure 2. Paracetamol clearance (l/h) on weight (kg), based on 73 pharmacokinetic profiles.

Table II. Literature on the impact of weight, pregnancy and oral contraceptives on paracetamol pharmacokinetics and metabolism.

Author	Route, number of cases	Clinical characteristics	Results
Weight			
Abernethy et al[10]	IV, single dose, 650 mg 22 women, 17 men	Volunteers 14/22 and 7/17 were obese	Clearance increase with weight and therefore is much higher in obese volunteers and in men
Pregnancy			
Kulo et al[4]	IV, single dose, 2000 mg 28 cases	Immediately after caesarean delivery preterm and term cases	Clearance is significantly higher at delivery, also after correction for weight ($l/h.m^{-2}$)
Kulo et al[5]	IV, single dose, 2000 mg 8 cases	Paired design, at delivery and 10-15 weeks postpartum	Clearance ($l/h.m^{-2}$) is significantly higher at delivery
Beaulac-Baillargeon et al[11]	Oral, single dose, 650 mg case report	Before and in 1st, 2nd and 3rd trimester of the pregnancy, in the same patient	Increased clearance, throughout pregnancy (5.25 to 9.83, 8.42 and 9.67 $ml/min.kg^{-1}$ respectively)
Rayburn et al[12]	Oral, single dose, 1000 mg 6 cases	Paired design 36 weeks of pregnancy vs 6 weeks postpartum	CL/F significantly higher during pregnancy (42%) no changes in absorption
Beaulac-Baillargeon et al[13]	Oral, single dose, 650 mg 18 cases	Unpaired design, 8 pregnant women (first trimester of pregnancy) and 10 controls	CL/F significantly higher during pregnancy weight increase in part explained these differences
Miners et al[14]	Oral, single dose, 1000 mg 20 women	Unpaired design, 12 non-pregnant women 8 women in 3rd trimester of pregnancy	CL/F significantly higher during pregnancy (+58%, l/h) increase in glucuronidation (75%) and oxidation (88%)
Kulo et al[6]	IV, repeated dose 2000 mg loading dose, 1 g q6h	39 observations at delivery, pooled with 8 observations in postpartum (plasma+urine)	Clearance significantly higher at delivery (+80%), due to increased glucuronidation (+144%), renal elimination (+53%) and oxidation (+78%), not sulphation
Oral contraceptives/ oestrogens			
Scavone et al[15]	IV, single bolus, 650 mg 12/18 either or not exposed to estrogens	"Matched" for weight and age, 12 exposed median age 45 year, median weight 60-64 kg	Clearance 4.61 vs. 4.26 $ml/kg.min^{-1}$ (NS)
Abernethy et al[16]	IV, single bolus, 650 mg 8/8, low dose estrogen OC (< 50 µg)	8 OC exposed, matched to 8 non OC exposed age range 23 to 32 year, median weight 55-58 kg	Clearance 5.81 vs. 4.12 $ml/kg.min^{-1}$ ($p < 0.005$)
Mitchell et al[17]	Oral, single, 1500 mg 7/7, low dose estrogen OC (< 50 µg)	7 OC exposed, matched to 7 not OC exposed age range 21 to 34 year, weight not reported	Clearance 470 vs. 287 ml/min, due to increased glucuronidation and oxidation, not sulphation
Miners et al[18]	Oral, single, 1000 mg 8/8, different "Combination" OC	16 females, of whom 8 OC exposed median age 22 year, median weight 61.7 kg	Clearance 6.88 vs. 4.61 $ml/kg.min^{-1}$, due to increased glucuronidation (77%) and oxidation (36%)

mercapturic acid conjugates. Consequently, the higher phenotypic NAPQI production potential results in either earlier or more pronounced depletion of glutathione reserves[1-3,6].

Besides compound specific relevance, the current observations also illustrate patterns of *in vivo* phenotypic drug metabolism (e.g. glucuronidation, oxidation, sulphation) and the impact covariates

(e.g. weight, pregnancy, OC exposure) on the phenotypic drug metabolism in young women[8,9,20-23]. The increased glucuronidation activity during pregnancy is not limited to paracetamol, but has also been described for other compounds like e.g. propofol or lamotrigine[20,22]. Similarly, the impact of OC exposure on anti-epileptics or benzodiazepines has been quantified[23].

Pregnant women are usually not part of the traditional drug development program, but pregnancy is associated with major biological and physiological changes that alter PK. *In silico* prediction of PK behaviour during pregnancy can provide a valuable aid to dose adjustment in pregnant women, but *in vivo* observations are needed to validate such pregnancy physiologically-based pharmacokinetic (p-PBPK) models. The same holds true for OC exposure[8,9].

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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