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Paracetamol metabolism in pregnancy

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Paracetamol disposition was studied in groups of pregnant and non-pregnant women of comparable age. Paracetamol apparent oral clearance was 58% higher and elimination half-life was 28% lower in the pregnant women compared to the control group. The higher clearance in the pregnant women was due to increased activity of the glucuronidation (75% higher) and oxidative (88% higher) pathways of paracetamol metabolism. There was no difference between the two groups in paracetamol sulphation or renal clearance of unchanged drug.

Keywords paracetamol drug metabolism pregnancy glucuronidation

Introduction

It is now apparent that the physiological and biochemical changes occurring during pregnancy may influence drug metabolism (Cummings, 1983; Krauer & Krauer, 1977). However, published studies to date have largely investigated the effect of pregnancy on the elimination of renally cleared drugs and drugs metabolised by the hepatic mixed function oxidase system (Cummings, 1983). There is little information relating to drug conjugation in pregnant women. Paracetamol is metabolised in the liver primarily by conjugation with glucuronic acid and sulphate and thus serves as a useful model drug for simultaneously determining effects on both glucuronide and sulphate conjugation. This communication reports differences in paracetamol disposition parameters for groups of pregnant and non-pregnant women.

Methods

Subjects

Eight women, aged 26–32 years, weight 61–77 kg (mean 68 ± 5 kg), in the third trimester of pregnancy participated in the study. The control group comprised 12 women, weight 54–72 kg (mean 63 ± 7 kg), aged 19–31 years, who participated in previous and concurrent paracetamol metabolism studies performed by this group. All subjects were healthy as determined by medical history, physical examination and standard haematological and biochemical parameters. In addition, all subjects were non-smokers and used no other medications, other than those required for the study, for 1 week before and during the study. The study was approved by the Clinical Investigation and Drug and Therapeutics Advisory Committee and written informed consent was obtained from each subject.

Protocol

After an overnight fast subjects received 2 × 500 mg paracetamol tablets (Panadol) with 150 ml of tap water. Saliva samples were collected prior to and at 0.5, 1, 1.5, 2, 3, 4, 5, 6 and 8 h after drug administration. Urine was collected for 24 h following the paracetamol dose. Subjects were permitted to eat 3 h after the paracetamol dose. Saliva samples were stored at −20° C until assayed but urine samples were analysed within 8 h of collection.

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Analytical procedures

Salivary paracetamol concentrations and the concentrations of unchanged paracetamol and its glucuronide, sulphate, cysteine and mercapturic acid conjugates in urine were determined by high performance liquid chromatographic procedures (Miners *et al.*, 1983, 1984a).

Analysis of results

Area under the paracetamol saliva concentration–time curve (AUC) was calculated by the trapezoidal rule with extrapolation to infinity. Elimination half-life ($t_{½,z}$) was determined from the slope of the terminal portion of the log saliva concentration–time curve by linear least squares regression. Paracetamol apparent oral clearance was calculated as,

$$CL_{po} = D/AUC$$

CL_{po} of a drug that is completely absorbed and hepatically metabolised is equivalent to intrinsic clearance (Wilkinson & Shand, 1975). It should be noted that the use of salivary paracetamol concentrations for the determination of CL_{po} has previously been validated in this laboratory (Miners *et al.*, 1983; Maddern *et al.*, 1985). Partial metabolic and renal clearances of paracetamol were calculated as,

$$CL_m = f_m.CL_{po}$$

where CL_m is the metabolic clearance to the glucuronide (CL_G), sulphate (CL_S) and glutathione-derived (CL_{GSH}, cysteine plus mercapturic acid) conjugates or the renal clearance of unchanged paracetamol (CL_R) and f_m is the fractional recovery of each conjugate or of unchanged paracetamol.

Results are expressed as mean ± s.d. The significance of the difference between study groups for each parameter was determined using the Mann Whitney U-test. The null hypothesis was rejected when $P < 0.05$.

Results

Paracetamol disposition parameters for each of the pregnant and non-pregnant subjects are shown in Table 1. Mean CL_{po} in the pregnant women (27.10 ± 5.73 l h^{-1}) was 58% higher ($P < 0.002$) than in the non-pregnant group (17.12 ± 2.53 l h^{-1}). Mean $t_{½,z}$ was 28% lower ($P < 0.002$) in pregnant women compared to the control group (1.52 ± 0.40 *vs* 2.11 ± 0.27 h). The metabolic clearances to the glucuronide (17.37 ± 4.06 l h^{-1} *vs* 9.95 ± 1.74 l h^{-1}; $P < 0.002$) and to the glutathione-derived conjugates (3.00 ± 0.53 l h^{-1} *vs* 1.60 ± 0.46 l h^{-1}; $P < 0.002$) were 75% and 88% higher respectively in the pregnant women. There was no significant difference between pregnant and non-pregnant women in metabolic clearance to the sulphate (5.57 ± 1.00 l h^{-1} *vs* 4.67 ± 0.68 l h^{-1}) and in renal clearance of unchanged drug (1.18 ± 0.46 l h^{-1} *vs* 0.89 ± 0.27 l h^{-1}).

The recovery of paracetamol and its metabolites in urine in both the non-pregnant (97.2 ± 6.8%) and pregnant (93.9 ± 5.9%) groups was essentially quantitative.

Discussion

This study has demonstrated that paracetamol apparent oral clearance was 58% higher in pregnant women compared to a group of non-pregnant women of comparable age. The higher clearance in the pregnant women was due to enhanced glucuronide conjugation and oxidation (clearance to the glutathione-derived conjugates). Paracetamol sulphation and renal clearance of unchanged drug were not altered by pregnancy. Although the degree of variability in paracetamol apparent oral clearance was similar in non-pregnant (1.62 fold range) and pregnant women (1.84 fold range), the variability in paracetamol half-life was greater in the pregnant subjects (2.47 fold *vs* 1.60 fold range). The latter observation suggests greater variability in distribution volume in pregnant women.

There are data to suggest that the half-life of paracetamol is not altered in women during labour (Nimmo *et al.*, 1975). Most of our subjects were studied early in the third trimester (weeks 31–33), although it is interesting to note that the two subjects studied during week 38 had the lowest paracetamol clearances and longest half-lives. Whether physiological changes occur in labour which are likely to alter drug disposition compared to other stages of pregnancy is unknown. Urinary excretion data have been reported (Galinsky & Levy, 1984) for a single subject administered paracetamol on the last day of pregnancy and 38 days after parturition. The major finding in this subject was that the urinary glucuronide to sulphate ratio was higher during pregnancy than postpartum. This is consistent with our observations, although at the time it was thought to reflect decreased paracetamol sulphation as has been shown to occur in pregnant rats (Lin & Levy, 1983). While there appear to be major differences between rats and humans in terms of effects of pregnancy on the formation of individual metabolites, the absolute

Table 1 Paracetamol disposition parameters in pregnant and non-pregnant women

Group/subject	CL_{po} ($l\,h^{-1}$)	$t_{1/2,z}$ (h)	CL_G[1] ($l\,h^{-1}$)	CL_S ($l\,h^{-1}$)	CL_{GSH} ($l\,h^{-1}$)	CL_R ($l\,h^{-1}$)
Pregnant						
1 (38)[2]	20.11	1.95	12.83	4.34	2.43	0.51
2 (38)	21.64	1.96	13.11	4.75	2.70	1.09
3 (33)	23.49	1.78	13.95	5.68	2.82	1.04
4 (33)	25.32	1.67	16.76	5.01	2.76	0.79
5 (31)	26.99	1.38	17.61	5.29	2.83	1.38
6 (31)	29.79	1.37	18.79	6.58	3.20	1.22
7 (31)	32.38	1.29	22.47	5.46	3.09	1.36
8 (33)	37.10	0.79	23.41	7.42	4.19	2.08
Mean	27.10	1.52	17.37	5.57	3.00	1.18
± s.d.	± 5.73	± 0.40	± 0.46	± 1.00	± 0.53	± 4.06
Non-pregnant						
1	12.93	2.88	6.30	4.58	1.27	0.78
2	14.36	2.24	8.86	3.80	1.06	0.64
3	14.94	2.17	8.45	4.37	1.31	0.81
4	15.25	2.09	8.88	4.44	1.39	0.55
5	16.47	2.04	11.10	3.56	1.14	0.67
6	16.92	2.15	9.90	4.83	1.53	0.66
7	17.20	1.96	9.13	5.30	1.52	1.24
8	17.54	2.01	10.35	4.84	1.56	0.79
9	18.46	2.05	10.35	5.47	1.63	1.01
10	19.47	2.08	11.66	3.91	2.69	1.21
11	20.82	1.91	12.36	5.48	1.99	0.99
12	21.02	1.80	12.06	5.47	2.12	1.37
Mean	17.12	2.11	9.95	4.67	1.60	0.89
± s.d.	± 2.53	± 0.27	± 1.74	± 0.68	± 0.46	± 0.27

[1]CL_G, clearance to glucuronide; CL_S, clearance to sulphate; CL_{GSH}, clearance to glutathione-derived conjugates (cysteine + mercapturic acid); CL_R, renal clearance of unchanged paracetamol.
[2]Figure in parenthesis indicates number of weeks gestation.

plasma clearance of a 15 mg kg^{-1} dose of paracetamol has been shown (Lin & Levy, 1983) to be higher in pregnant rats than in control female animals. However, this difference was not apparent in rats administered a 300 mg kg^{-1} dose of the drug. The dose of paracetamol administered to our subjects was in the range 13–16 mg kg^{-1} for the pregnant women and 14–19 mg kg^{-1} for control females.

Available evidence suggests that hormonal factors play an important role in the regulation of glucuronidation in humans. Sex-related differences have been demonstrated for paracetamol glucuronidation (Miners *et al.*, 1983) while the clearances of clofibric acid (Miners *et al.*, 1984b) and temazepam (Stoehr *et al.*, 1984) as well as paracetamol glucuronidation (Miners *et al.*, 1983) are known to be enhanced in oral contraceptive steroid users. Apart from the present paper, there is also evidence (Tomson *et al.*, 1979) to suggest that oxazepam clearance is increased in pregnant women. However, with the limited data available it cannot be assumed that glucuronidation will invariably be induced in pregnancy, particularly given the variability of the effect (induction, inhibition or no change) of pregnancy on the elimination of drugs undergoing oxidative metabolism (Cummings, 1983).

Paracetamol is the recommended antipyretic/analgesic agent for use in pregnancy (Rao & Arulappu, 1981). In view of the more rapid elimination of paracetamol in pregnant women, further study is warranted to determine whether the dosage requirement for effective analgesia is different in this group.

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