

Passage of paracetamol into breast milk and its subsequent metabolism by the neonate

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1 Paracetamol was administered to nursing mothers. The drug passed rapidly into milk and the milk:plasma concentration ratio was approximately unity.

2 The estimated maximum dose to the neonate was 1.85% of the weight-adjusted maternal oral dose of paracetamol 1.0 g. Recovery of paracetamol was greater from the breast from which samples were taken frequently than from the breast which was sampled only once.

3 Paracetamol, its glucuronide, sulphate, cysteine and mercapturate conjugates were found in the urine of the neonates although only the parent drug was detected in breast milk.

4 The neonates excreted significantly greater proportions of unchanged paracetamol ($P < 0.01$) and significantly lesser proportions of paracetamol sulphate ($P < 0.001$) than did healthy volunteers aged 11–80 years who received a therapeutic dose of paracetamol.

5 The findings are compatible with a deficiency of sulphate conjugation by the neonate.

Keywords paracetamol neonate metabolism breast milk biotransformation

Introduction

Paracetamol is widely used as a post-partum analgesic in nursing mothers (Passmore *et al.*, 1984; Matheson, 1985). It is believed to present no risk to the suckling infant since less than 0.25% of a maternal single dose is estimated to reach the child (Berlin *et al.*, 1980; Bitzen *et al.*, 1981). As many drug metabolic reactions are deficient in the newborn (Rane & Wilson, 1983), ingestion of seemingly small quantities of drug may assume importance. Levy *et al.* (1975) and Miller *et al.* (1976) found that neonates had limited capacity to conjugate paracetamol with glucuronic acid but that sulphate conjugation was well developed.

Methods

Subjects

The following were studied:

(a) Four volunteer nursing mothers (a,b,c,d)

aged 26–37 years and 2–8 months post-partum, breast-fed their babies in the Clinical Pharmacology Unit, Royal United Hospital, Bath. Each mother then received paracetamol 1.0 g as a single dose by mouth. Blood and milk samples were taken concurrently every 30 min for 3.0–3.5 h thereafter, the milk being taken from the same breast each time by means of an electrically-driven breast pump which extracted all the available milk. No samples were taken from the other breast until the end of the study when all available milk was extracted from it also.

(b) Paired milk and blood samples were obtained from nine nursing mothers aged 20–38 years, 2–10 days after delivery; each had received paracetamol (1.0–2.0 g) in the preceding 12 h for post-partum pain.

(c) Six infants (2–6 days old) of five mothers aged 28–30 years (E,F,G,H,I) (one with twins) who took paracetamol for post-partum pain, were studied. The infants received paracetamol

via the breast milk and neither the dose administered to the mother nor the timing of the feed after dosing was influenced by the requirements of the study in any way. The mothers received paracetamol (1.0–2.0 g) 2.0–4.0 h before breast feeding; immediately after each infant had suckled, a 'Coloplast' baby urine collector was applied to it and urine was collected for 1.0–3.5 h (Table 1).

(d) Forty-nine healthy male and female volunteers aged 11–80 years, comprising hospital and university staff and fit elderly patients contacted from general practitioner lists, received paracetamol 0.5 g or 1.0 g as a single oral dose. Paracetamol and metabolites were assayed in urine collected over the next 8 h.

All the studies were approved by the ethics committee of the Bath Health District.

Samples

The pH and volume of each milk sample were measured immediately upon collection and milk, plasma and urine samples were stored at -20°C prior to analysis.

Analyses

Paracetamol (P) and its glucuronide (PG), sulphate (PS), cysteine (PC), and mercapturic acid (PM) metabolites were assayed by high performance liquid chromatography using a modification of the method of Adriaenssens & Prescott (1978). The values for each metabolite were converted to the equivalent weight of paracetamol from which it was derived by correction for molecular weight. All values were then expressed as a percentage of the total recovery.

Standard metabolites were the gift of Dr R. Andrews, Sterling Winthrop R & D, Newcastle. The calibration curves were linear over the range $0.2\text{--}30\text{ mg l}^{-1}$ (paracetamol), and $0.5\text{--}50\text{ mg l}^{-1}$ (metabolites). The coefficients of variation at 0.5 mg l^{-1} were 6% (paracetamol) and 8% (metabolites).

Calculations

The areas under the concentration-time curves were calculated by the trapezoidal rule to the last datum point.

Results

(a) Figure 1 shows milk and plasma concentration-time profiles in the volunteers who took paracetamol 1.0 g by mouth (Subjects, a). Following its ingestion by the mother, paracetamol rapidly entered milk and the milk concentration exceeded that in plasma in each volunteer. The mean area (\pm s.e. mean) under the milk concentration-time curve was $21.10 \pm 4.63\text{ mg l}^{-1}\text{ h}$ and that for plasma was $13.08 \pm 2.75\text{ mg l}^{-1}\text{ h}$.

The mean milk:plasma concentration ratio for 21 paired samples in the four volunteers was 1.24 ± 0.12 ; this value refers to mature milk. Seven milk samples (at least one from each mother) were assayed for metabolites of paracetamol but none was detected, the limit of detectability being $< 100\text{ ng ml}^{-1}$.

Figure 2 shows that both the concentration of paracetamol in milk and the milk volumes were higher in the breast that was expressed every 30 min for 3.0–3.5 h, compared with the breast that was sampled only once at the end of the collection period.

Table 1 Recovery of paracetamol and its metabolites in the urine of breast-fed neonates

Mother	Dose (g)	Dose-feed interval (h)	Urine collection time (h)	Paracetamol and metabolites in urine of neonate (μg)
E	1	3.5	3.0	85.2
F	1	3.2	3.5	59.8
G(1)*	1	2.0	2.5	27.6
G(2)*	1	2.0	1.0	486.6
H	2	4.0	3.0	822.2
I	2	4.0	3.5	921.9

Urine collections commenced immediately after feeding had been completed. Paracetamol recovered includes all metabolites corrected for molecular weight. * Indicates twin babies; the infant G(2) produced 10.5 ml urine compared to 0.6 ml by his sister.

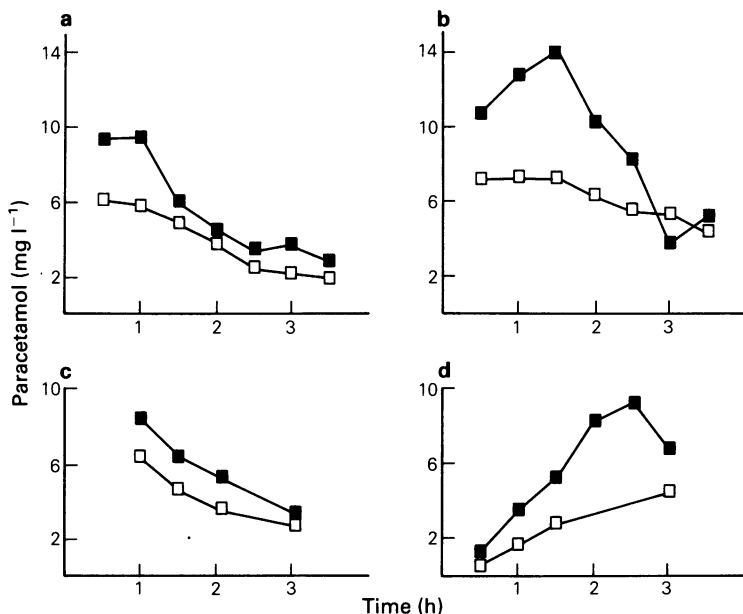


Figure 1 Milk (■) and plasma (□) concentrations of paracetamol in four volunteers after administration of paracetamol 1.0 g by mouth.

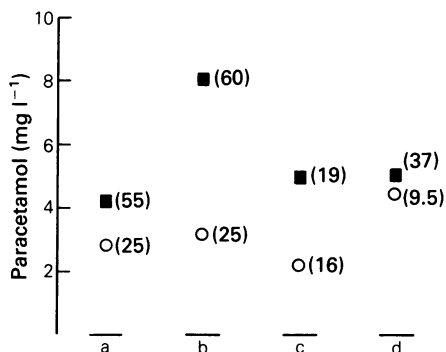


Figure 2 Paracetamol concentration in milk taken from breasts emptied at 30 min intervals (■) and after single expression at 3.0–3.5 h (○) in volunteers a, b, c and d. The figures in brackets give the volume of milk obtained (ml).

(b) The mean milk:plasma ratio for paracetamol in the samples obtained from nine mothers who took the drug for therapeutic purposes (Subjects, b) was 0.95 ± 0.16 ; this value refers to colostrum and transitional milk and was not significantly different from that obtained in mature milk (Subjects, a).

(c) Table 1 shows that the total amount of paracetamol and its metabolites excreted by the neonates in their urine (Subjects, c) ranged from

27.6–921.9 μg (mean \pm s.e. mean, $400.6 \pm 164.5 \mu\text{g}$); the large variation reflects differences in urine volume, collection time, dose received and the interval from dose to feed. The recovery of paracetamol and its metabolites in these infants is presented in Table 2. All the babies excreted paracetamol, PG and PS, but PC or PM were not found in every urine. The major metabolite was PG, followed in decreasing proportion by paracetamol, PC + PM, and PS. Since no metabolites were detected in milk, it was assumed that these products were synthesised by the neonates.

(d) A summary of the percentages of paracetamol and its metabolites recovered from the urine of healthy volunteers (Subjects, d) also appears in Table 2. The neonates excreted a significantly greater proportion of paracetamol ($P < 0.01$) and a significantly lesser proportion of PS ($P < 0.001$) than did the volunteers. Full details of the findings in the volunteers will be reported elsewhere.

Discussion

The factors that govern drug passage into breast milk are likely to be those that influence drug transfer elsewhere in the body. The physical characteristics of paracetamol suggest that the drug should diffuse readily into milk for it has a

Table 2 Percentage recovery of paracetamol and its metabolites in the urine of neonates and of healthy volunteers aged 11–80 years

	P	PG	PS	PC+PM
<i>Neonates</i>				
(n = 6)				
Mean	24.9	54.1	9.9	11.1
s.e. mean	6.6	6.0	1.9	3.2
Range	9.5–46.9	32.8–71.3	5.0–18.3	0–20.5
<i>Healthy volunteers</i>				
(n = 49)				
Mean	5.2	52.1	35.1	7.4
s.e. mean	0.7	1.4	1.5	0.5

Healthy volunteers took paracetamol 0.5 g (n = 2) or 1 g (n = 47) by mouth; urine was collected for 8 h. Neonates received paracetamol indirectly via the breast milk.

pKa of 9.5, is largely unionised at physiological pH and binding to plasma proteins is low. Our data show that paracetamol passes rapidly into milk and the milk:plasma concentration ratio is approximately unity. Other workers have made similar findings (Berlin *et al.*, 1980; Bitzen *et al.*, 1981; Findlay *et al.*, 1981).

The amount of paracetamol received by the suckling infant in a feed may be calculated as a percentage of the weight-adjusted maternal dose received in this study or as a percentage of the lowest recommended infant single dose. In order to do so it is assumed that:

- the milk intake is 150 ml kg⁻¹ day⁻¹, as at peak lactation,
- the infant suckles five times a day,
- the maternal weight is 60 kg and
- the lowest recommended single infant dose is 60 mg (British National Formulary, 1986)

In the volunteer mothers (Methods, Subjects, a) the mean maximum concentration of paracetamol in milk was 10.3 ± 1.3 mg l⁻¹ and the average concentration was 6.1 ± 0.8 mg l⁻¹. On this basis, an infant suckling once at the time of peak milk paracetamol concentration would receive 1.85% (or on average 1.1%) of the weight-adjusted maternal single dose. Similarly, an infant which suckles once at the peak paracetamol concentration would receive 0.52% of the lowest recommended infant single dose. Clearly these estimates may not be taken to apply when paracetamol is used in repeated doses and there are no literature data on which to base an estimate of the exposure of the infant to paracetamol under such conditions.

The biotransformation of paracetamol in the adult is well established and the major metabolites are PG and PS (Prescott, 1980). A small proportion of the drug (<10%) is oxidised by the mixed function oxidase system to a reactive intermediate(s) which conjugates with hepatic glutathione and appears in the urine as paracetamol cysteine (PC) and paracetamol mercapturic acid (PM) (Mitchell *et al.*, 1973, 1974; Davis *et al.*, 1976; Howie *et al.*, 1977; Slattery & Levy, 1979). Any oxidised metabolite that does not combine with glutathione is a potential cause of cell damage. In our study of six infants who received paracetamol in breast milk, the parent drug, PG and PS were detectable in the urine of them all and PC and/or PM in 5. This finding contrasts with that of Berlin *et al.* (1980) who, also using an high performance liquid chromatographic method of analysis, failed to detect paracetamol or metabolites in the urine of nursing infants. We found that the infants excreted a significantly higher proportion of unchanged paracetamol but a lower proportion of PS than did 49 healthy volunteers who took a single oral dose of paracetamol (Table 2). Levy *et al.* (1975) who gave paracetamol 12 mg kg⁻¹ by mouth to neonates and Miller *et al.* (1976) who gave 10 mg kg⁻¹ found that higher percentages of the dose were excreted as sulphate than as glucuronide. These studies employed both a larger dose of paracetamol and a longer period of urine collection than did the work we report; neither study gave data on PC or PM. Our findings thus differ from those previously reported and are compatible with a deficiency of sulphate conjugation by the neonate, although immaturity of

renal function may also contribute to the differences in the recoveries of paracetamol and of its metabolites between neonates and older subjects.

Despite the increased excretion of the parent drug, no significant increase was noted in the products of cytochrome P-450 oxidation (PC+PM) suggesting that there may be lower concentrations or lower activities of the mixed function oxidase system or glutathione transferase in neonates than in older subjects. Therefore, in infants, either the formation of the reactive metabolite or its detoxication may be incompletely developed.

There was a significant increase in the amount of paracetamol (and milk) excreted from the

frequently sampled breast compared with that recovered from the breast that was sampled only once. This suggests that the quantity of paracetamol received in milk is dependent on milk flow and is a variable that should be taken into account in the design and interpretation of studies of drug passage into breast milk.

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