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Paracetamol metabolites in the neonate following maternal overdose

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1 A case of paracetamol overdose in a 36 week pregnant woman is described. The baby was delivered by Caesarian section 6 h after the overdose. The mother but not the baby was treated with *N*-acetylcysteine and neither suffered liver damage.
2 The plasma paracetamol half-life was prolonged to 10 h in the neonate compared to 2.5 h in the mother and was unaffected by a two volume exchange transfusion.
3 The pattern of urinary metabolites in the neonate was similar to that observed in the mother, but there was a marked delay in the time taken to reach peak plasma concentrations of metabolites. This is consistent with a very slow biotransformation of the drug and may explain the relative resistance of very young children to the hepatotoxicity of paracetamol.
4 There was no evidence of limited or decreasing capacity in sulphate conjugation nor was sulphation the major metabolic pathway.
5 In retrospect both the obstetrical intervention and the exchange transfusion were unnecessary.

Keywords paracetamol maternal overdose neonate pharmacokinetics

Introduction

Poisoning by paracetamol is a major cause of hospital admission. Of enquiries received by the National Poisons Information Service regarding paracetamol overdose 20% of cases involved children 13 years old or less (Meredith *et al.*, 1981). It is generally accepted that young children (less than 10 years old) have a degree of resistance to the hepatotoxic effects of paracetamol (Meredith *et al.*, 1978; Rumack & Peterson, 1978; Peterson & Rumack, 1981), although the basis to this resistance has not been fully established (Peterson & Rumack, 1978). There is thus a therapeutic dilemma when considering the treatment of paracetamol overdosage in the very young. We recently had the opportunity to investigate the metabolism and the pharmacokinetics of paracetamol in a neonate born following a maternal paracetamol overdose.

Case history

Mother

A 25 year old gravida 5 who was 36 weeks pregnant was admitted about 3–4 h after taking approximately 20 g paracetamol and eight cans of Heineken lager. On admission the blood screening tests were positive for amylobarbitone (0.31 mg/l), ethanol (11.8 mg/l) and paracetamol (280 mg/l) with a half-life of 4.5 h. The emergency paracetamol determination was by the method of Glynn & Kendal (1975), and suggested some risk of hepatotoxicity (Prescott *et al.*, 1976). As the mother had previously had two Caesarian sections the decision was taken to deliver this baby similarly. The neonate was delivered 3 h after admission and post partum the mother was treated with *N*-acetylcysteine. Her subsequent clinical course was uneventful.

Baby

The male infant weighed 2.69 kg (normal for 36 weeks gestation) and was not asphyxiated at birth. Using the method of Glynn & Kendal (1975), the paracetamol concentration in cord plasma was 217 mg/l and 1 h post partum the plasma paracetamol was 260 mg/l. At 12 h a two volume exchange transfusion was performed but *N*-acetylcysteine was not given. The clinical course was unremarkable and the baby was discharged on the fortieth day. Subsequently the infant died (a cot death) aged 155 days.

Methods

Plasma and urine samples were stored at −20°C. Paracetamol and its sulphate glucuronide, mercapturic acid and cysteine conjugates in plasma and urine were estimated by high performance liquid chromatography (Adriaenssens & Prescott, 1978).

Results

Neither mother nor baby developed any biochemical evidence of hepatocellular necrosis. The plasma half-life of paracetamol was normal in the mother (2.5 h) but was markedly prolonged in the baby (10 h) (Figure 1). The neonatal exchange transfusion did not alter paracetamol half-life (Figure 1) and therefore is unlikely to have been of any clinical benefit. The glucuronide and sulphate conjugates of paracetamol also disappeared from the blood more slowly in the neonate than in his mother (Figure 2) and peak concentrations in the neonate occurred at between 15 and 30 h after exposure to paracetamol.

The pattern of paracetamol metabolites excreted in the urine was similar in the neonate and mother (Figures 3 and 4, Tables 1 and 2). In both, the predominant metabolite excreted was the glucuronide, and in the neonate a significant proportion was recovered as the cysteine and mercapturic acid conjugates. This indicates the capacity for metabolism of paracetamol in the neonate via cytochrome P-450 to a potentially hepatotoxic metabolite. The mother produced higher proportions of these metabolites than did her baby (Figure 5) but this could have been due to treatment with *N*-acetylcysteine.

Discussion

Young children are generally considered to be

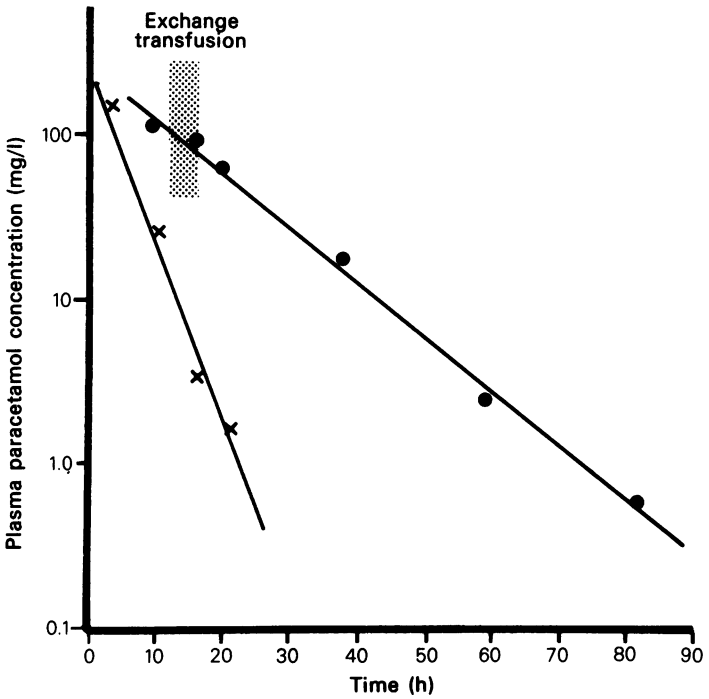

Figure 1 Decline in plasma paracetamol with time in the mother (x) and neonate (●). The neonatal exchange transfusion did not affect the neonatal plasma paracetamol half-life ($t_{1/2}$ = 10h). Maternal plasma paracetamol half-life ($t_{1/2}$ = 2.5h).

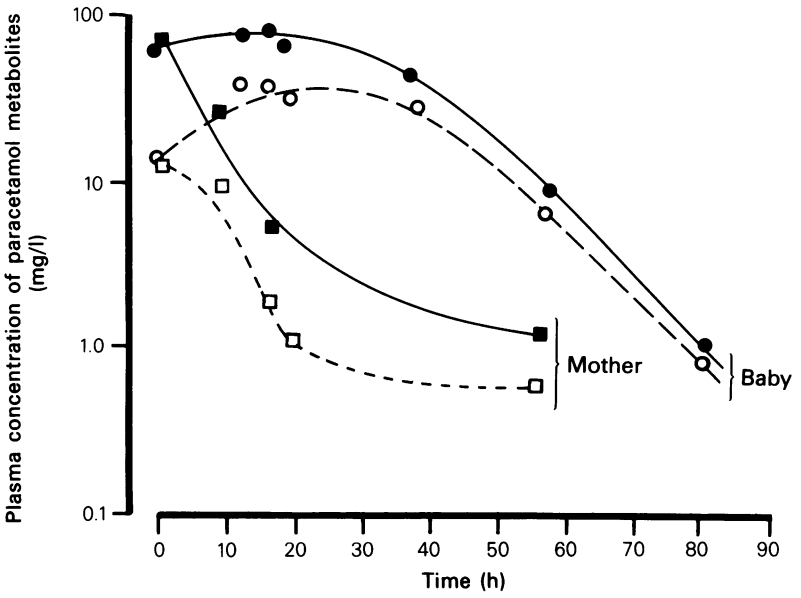

Figure 2 Decline in plasma paracetamol glucuronide (-) and plasma paracetamol sulphate (- -) with time in mother (■) and neonate (●) (expressed as paracetamol equivalents).

resistant to the hepatotoxic effects of paracetamol (Meredith *et al.*, 1978; Rumack & Peterson, 1978; Peterson & Rumack, 1981) but the mechanism is not understood, and very little is known of the sensitivity of neonates to the drug.

In adults the decision to treat a patient poisoned with paracetamol depends on the plasma paracetamol concentration and *N*-acetylcysteine is usually given when this is above the treatment line (Prestcott *et al.*, 1979). The prognosis is also related to the paracetamol half-life and if greater than 4 h this usually predicts hepatotoxicity. In this case neither mother nor baby developed hepatocellular necrosis although the half-life of paracetamol in the neonate was greatly prolonged to 10 h (Figure 1). Therefore criteria of toxicity in adults do not seem to apply to neonates. This is hardly surprising since drug metabolism is greatly

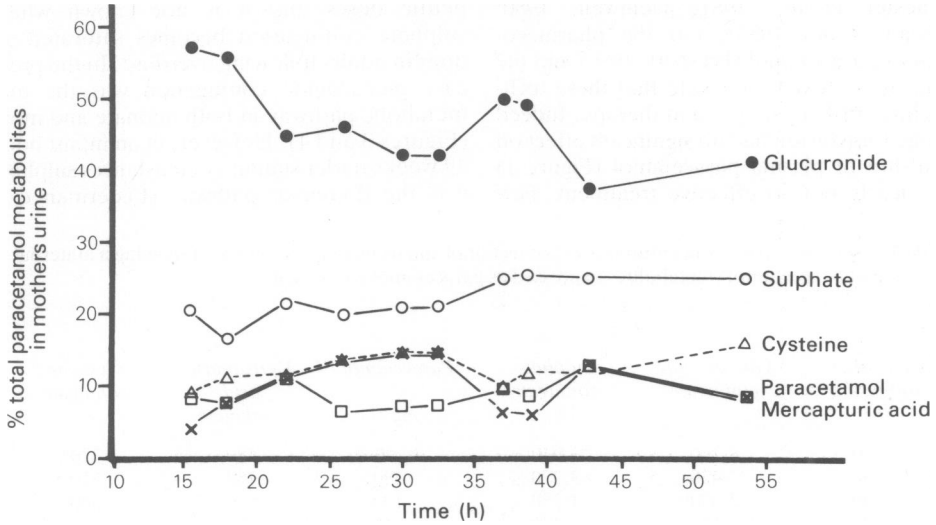

Figure 3 Changes in the proportional urinary excretion of paracetamol (□) and its glucuronide (●), sulphate (○), mercapturate (x), and cysteine (△) conjugates in maternal urine with time after an overdose of paracetamol (metabolites expressed as paracetamol equivalents).

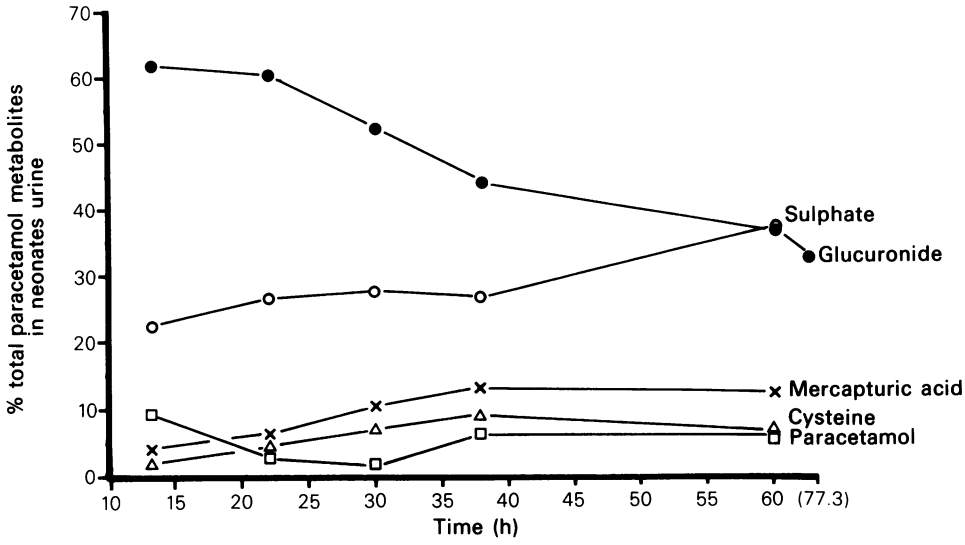

Figure 4 Changes in the proportional urinary excretion of paracetamol (□) and its glucuronide (●), sulphate (○), mercapturate (x) and cysteine (△) conjugate in neonatal urine with time after a maternal overdose of paracetamol (metabolites expressed as paracetamol equivalents).

depressed in foetal liver (Rollins *et al.*, 1979), and the metabolic activation of paracetamol is a prerequisite for hepatotoxicity (Mitchell *et al.*, 1974). Although there is much individual variation in susceptibility to the hepatotoxicity of paracetamol, in retrospect neither mother nor baby were at great risk of serious toxicity and delivery and exchange transfusion were almost certainly unnecessary.

The role of extracorporeal treatment of paracetamol overdose has been discussed (Winchester *et al.*, 1981; Helliwell, 1980; Lederman *et al.*, 1983), but the pharmacokinetics of paracetamol (Prescott, 1980) and the mechanism of toxicity indicate that these techniques have little or no place in therapy. Indeed exchange transfusion had no significant effect on the half-life of plasma paracetamol (Figure 1) and is clearly not an effective treatment. Few cases of hepatotoxicity from paracetamol overdose have been reported in the very young (Meredith *et al.*, 1978; Arena *et al.*, 1978; Nogen & Bremmer, 1978; Weber & Cutz, 1980; Peterson & Rumick, 1981; Greene *et al.*, 1983) and this may be due in part to age related effects on paracetamol metabolism (Peterson & Rumack, 1981; Miller *et al.*, 1977; Alam *et al.*, 1977). The neonate and young child are said to be more dependent on sulphate than glucuronide conjugation of paracetamol at therapeutic doses and it is not known whether sulphate conjugation becomes saturated as it does in adults following overdose. In the present case glucuronide conjugation was the major metabolic pathway in both neonate and mother (Figures 3 and 4). However, in an infant born at 29 weeks under similar circumstances sulphation was the dominant pathway (Lederman *et al.*,

Table 1 Neonatal urine concentrations of paracetamol and its metabolites *vs* time following a maternal overdose of paracetamol (metabolites expressed as paracetamol equivalents).

Baby

Time after admission (h)	*Glucuronide conjugate*	*Sulphate conjugate*	*Paracetamol (mg/l)*	*Mercapturic acid conjugate*	*Cysteine conjugate*
13.20	8,360	3,040	1,240	580	320
22.00	7,420	3,270	380	750	510
30.00	2,600	1,350	100	510	360
38.00	290	170	40	90	60
60.15	60	60	10	20	10
67.45	10	20	—	—	—

Table 2 Maternal urine concentrations of paracetamol and its metabolites *vs* time following a maternal overdose of paracetamol (metabolites expressed as paracetamol equivalents).

Mother

Time after admission (h)	*Glucuronide conjugate*	*Sulphate conjugate*	*Paracetamol (mg/l)*	*Mercapturic acid conjugate*	*Cysteine conjugate*
15.25	710	260	110	60	100
18.30	290	90	40	40	60
22.00	40	20	10	10	10
26.00	70	30	10	20	20
30.00	60	30	10	20	20
32.50	60	30	10	20	20
37.00	160	80	30	20	30
38.30	170	90	30	20	40
43.00	30	20	10	10	10
54.00	50	30	10	10	20

1983). In this context the prior use by the mother of amylobarbitone and her high alcohol intake may well have resulted in induction of the neonatal UDP glucuronyl transferase.

Production of the cysteine and mercapturic acid conjugates of paracetamol is of major toxicological significance (Mitchell *et al.*, 1973, 1978). These conjugates are derived from the glutathione conjugate of the hepatotoxic metabolite of paracetamol and therefore indirectly reflect its production. Foetal liver cells can oxidize paracetamol to its toxic liver metabolite (Rollins *et al.*, 1979), although activity is much decreased compared to adult liver microsomes. Our data confirm that neonates also produce this potentially hepatotoxic metabolite, but the decreased ratio of cysteine + mercapturic acid to sulphate + glucuronide conjugates observed (Figure 5) suggests a relatively lower activity of this variant of cytochrome P-450 in the neonate. Although this may explain the resistance to paracetamol-induced hepatotoxicity seen in neonates the probable mechanism is a reduced rate of formation of the toxic products. In this context it is notable that the peak excretion of the mercapturic and cysteine conjugates was delayed for 20–30 h (Figure 3, Table 2), a pattern seen in adults only when the paracetamol poisoning has resulted in severe liver damage (Prescott, 1980). It cannot however be assumed that a similar mechanism of protection applies to older children. The finding of cysteine and mercapturic acid conjugates in the urine suggests that young children with paracetamol overdose should be treated with *N*-acetylcysteine (Peterson & Rumack, 1981), though further work is necessary to define criteria for this. It is also important that the methods used for emergency plasma paracetamol measurements are specific. In the present case the emergency method (Glynn & Kendal, 1975), gave a maternal plasma level of 280 mg/l at 3 to 4 h after overdose with a half life of 4.5 h. This is a level at which treatment is recommended (Prescott *et al.*, 1976). However, subsequent measurement of the free paracetamol by h.p.l.c.

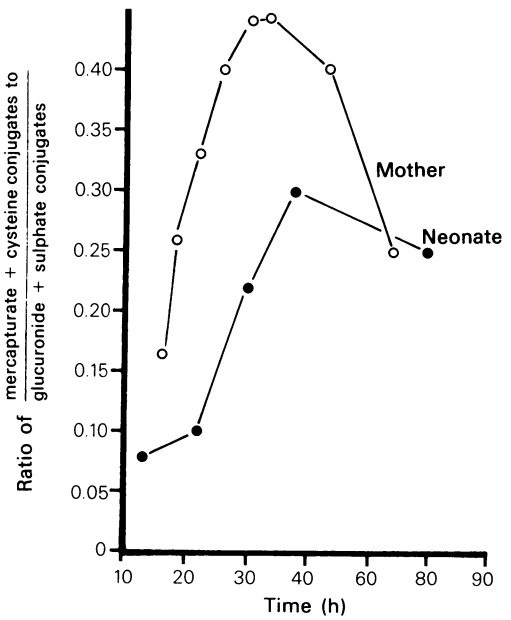

Figure 5 Urinary ratio of mercapturate + cysteine conjugates of paracetamol to the glucuronide + sulphate conjugates of paracetamol against time (expressed as paracetamol equivalents).

(Adriaenssens & Prescott, 1978) gave a level of 205 mg/l with a half-life of 2.5 h. At this level treatment of the mother with *N*-acetylcysteine would not have been necessary.

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