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Excretion of Paracetamol in Human Breast Milk

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Summary. Breast milk and plasma levels of paracetamol were monitored in 3 lactating women after ingestion of a single 500 mg dose of paracetamol. The paracetamol concentrations were consistently lower in milk, with a mean milk/plasma AUC ratio of 0.76. This value was in close agreement with the milk/plasma partition ratio of 0.81 found *in vitro,* and could be related to quantitative binding differences between the two fluids. The half-lives of paracetamol in plasma and breast milk were almost identical, with an overall mean of 2.7 h. As less than 0.1% of the maternal dose would be present in 100 ml milk, breast feeding need not be discontinued due to paracetamol treatment in conventional dosage.

Key words: paracetamol, breast milk; plasma, drug excretion in breast milk, protein binding

Antipyretic analgesics are among the drugs liable to be ingested by lactating women. This raises the question whether these drugs are excreted in breast milk to such an extent that the infant will be exposed to significant amounts of them. The present study deals with the excretion of paracetamol in breast milk.

Materials and Methods

Subjects

Three lactating women (24, 29 and 31 years old) were examined. They had decided to cease breast-feeding, but agreed to take a single dose of paracetamol during a day when lactation was maintained by breast pumping. Each woman gave a written consent to participate in the study. None had taken any drugs for the preceding 72 h.

Drug Administration and Sampling of Blood and Breast Milk

Each woman ingested 3.31 mmol (500 mg) paracetamol* (Alvedon®) in the fasting state, at 8 a. m. Concomitant samples of blood and breast milk were obtained before and approximately 2, 4, 6, 8, 10 and 12 h after drug intake. Blood was sampled by vein puncture, and milk by emptying the breasts with a pump. Plasma and milk samples were stored at − 20 °C until analysed for their paracetamol content.

Paracetamol Assay

Plasma or breast milk 1.0 ml was extracted with ethyl acetate 4.0 ml containing 24.2 nmol of the internal standard, N-butyryl-p-amino-phenol. After centrifugation, the organic phase was separated and evaporated to dryness under nitrogen at 40 °C. The residue was dissolved by adding carbon disulphide 100 µl and trifluoroacetic anhydride 50 µl. The sample was Vortex-mixed for 30 s and then heated at 40 °C for 15 min. Plasma and breast milk standards were constructed between 0.33 and 66.16 µmol/l.

The plasma concentrations of paracetamol were determined with a Perkin Elmer Model F11 gas chromatograph. Separations were made at 130 °C on a silanized glass column (2.0 m × 2 mm i. d.) packed with 3% OV-17 on 100–120 mesh Gas Chrom Q.

Due to contamination problems, the breast milk concentrations of paracetamol were analysed by mass fragmentography. An LKB model 2091-051 gas chromatographmass spectrometer with an LKB

* Paracetamol, 1 mmol = 151 mg

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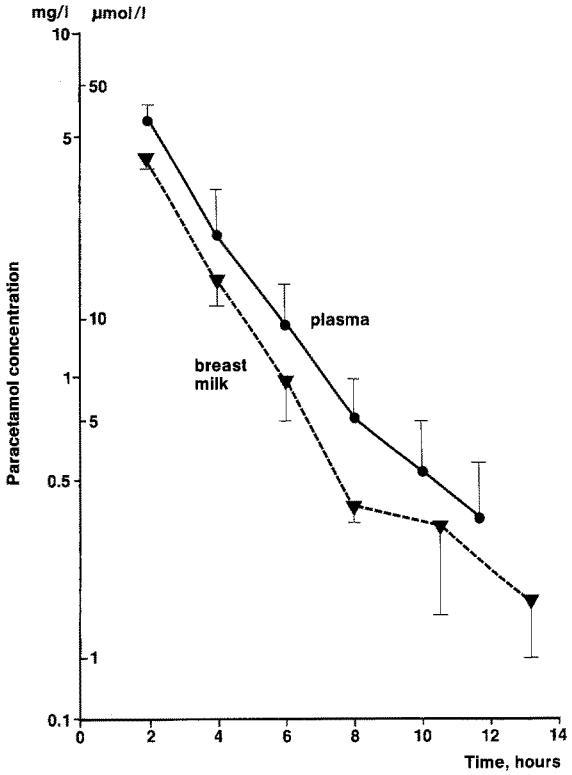

Fig. 1. Mean (± SEM, $n = 3$) concentration of paracetamol in plasma (●) and breast milk (▼) in three lactating women

Table 1. Pharmacokinetic parameters of paracetamol in plasma and breast milk from 3 lactating women after ingestion of paracetamol 3.31 mmol (500 mg)

Subject	Plasma		Breast milk		AUC_{milk}
	$t_{½}$ [h]	AUC [µmol·h·1^{-1}]	$t_{½}$ [h]	AUC [µmol·h·1^{-1}]	AUC_{plasma}
A	2.79	113.0	2.15	92.0	0.81
B	2.44	143.9	2.42	105.0	0.73
C	3.00	200.0	3.35	148.1	0.74
Mean	2.74	152.3	2.64	115.0	0.76
SD	0.28	44.1	0.63	29.3	0.04

Table 2. Binding of paracetamol in plasma and breast milk over a wide concentration range

Plasma		Breast milk	
Paracetamol conc. [µmol/l]	Per cent bound paracetamol	Paracetamol conc. [µmol/l]	Per cent bound paracetamol
7.3	20.3	6.6	2.25
37.7	19.8	34.4	2.37
75.4	20.3	68.8	2.38
375.1	19.1	344.7	3.13
678.1	19.3	687.4	2.64
Mean	19.8	Mean	2.55
SD	0.6	SD	0.35

2091-710 multiple ion detector was used. Separations were made at 150 °C on a silanized glass column (2.1 m × 2 mm i. d.) packed with 1% HI-EFF-8BP on 100–120 mesh Gas Chrom Q. The mass spectrometer was set to monitor m/z 301 (base peak for the acetylated compounds).

Plasma Protein Binding Analyses

Drug-free plasma samples were obtained from 3 clinically healthy, young volunteers. Drug-free breast milk was obtained from Modersmjölkscentralen, Södertälje. The degree of paracetamol binding to proteins in breast milk and plasma was assessed by equilibrium dialysis [1], using ^{3}H-labelled paracetamol (15.1 MBq/µmol, New England Nuclear Corp., Boston, Mass., USA). Breast milk and plasma (0.8 ml) were equilibrated against an equal volume of a buffer [2] containing various concentrations of paracetamol (6.62–662 µmol/l) diluted with labelled drug to suitable activity. The breast milk/plasma partition ratio of paracetamol was studied by the same technique. All dialysis experiments were run in duplicate at each concentration, for 2.5 h at 37 °C.

Calculations

The elimination half-lives of paracetamol in breast milk and in plasma were calculated by regression analysis from concentrations observed 3 h or more after drug intake, as the terminal mono-exponential decay in plasma has been reported to occur after this time [3]. The areas under the time – concentration curves (AUC) were calculated by the trapezoidal rule and were extrapolated to infinity.

Results

The highest concentrations of paracetamol were found within 2 h, both in plasma (mean 37.0 µmol/l; range 30.4–43.7 µmol/l) and in breast milk (27.8 µmol/l; 26.5–29.1 µmol/l).

The mean concentration curves of paracetamol in plasma and milk are shown in Fig. 1, and the individual kinetic data are given in Table 1. It appears that the drug concentrations in breast milk were lower than those in plasma, with a mean milk/plasma AUC ratio of 0.76. The elimination half-lives in plasma and milk were almost identical, with an overall mean of 2.69 h (range 2.15–3.35 h).

The binding of paracetamol to plasma proteins was found to be concentration independent over a wide concentration range (6.62–662 µmol/l), with a mean binding of 19.8% (Table 2). The binding of

paracetamol to breast milk proteins was also concentration independent. The degree of binding was much lower than in plasma, with a mean of 2.55% (Table 2).

The partitioning of paracetamol between plasma and breast milk after equilibration showed a milk/plasma ratio of 0.81.

Discussion

Due to pH differences between plasma and milk, leading to different proportions of unionized and ionized drug [4], agents that are weak bases, e. g. beta blockers [5], may accumulate in breast milk, while weakly acidic drugs may behave in the opposite fashion. Paracetamol is a weak acid with a pK_a of 9–10 [6, 7]. The present finding that paracetamol appeared in lower concentration in breast milk than in plasma is in accordance with this theory. The fact that the binding of paracetamol to plasma proteins was higher than that to breast milk is a further likely factor behind the distribution difference. This is further supported by the similar values for the breast milk/plasma AUC ratio and breast milk/plasma concentration ratio in vitro (0.76 and 0.81, respectively). The possibility of more rapid disappearance of paracetamol from breast milk than from plasma is unlikely, as the half-lives of paracetamol in the two fluids were essentially identical.

The present findings support the view that a breast-fed infant would not risk exposure to effective amounts of paracetamol. Indeed, the maximum exposure, as judged from the current figures, would be paracetamol 2.91 μmol per 100 ml breast milk, i. e. less than 0.1% of the maternal dose. Accordingly, breast-feeding need not be interrupted due to maternal medication with conventional doses of paracetamol.

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References

1. Weder HG, Schildknecht J, Kesselring P (1971) A new equilibrium dialysing system. Am Lab 10: 15–21
2. Ehrnebo M, Agurell S, Boreus LO, Gordon E, Lönrot U (1974) Pentazocine binding to blood cells and plasma proteins. Clin Pharmacol Ther 16: 424–429
3. Rawlins MD, Henderson DB, Hijab AR (1977) Pharmacokinetics of paracetamol (acetaminophen) after intravenous and oral administration. Eur J Clin Pharmacol 11: 283–286
4. Wilson JT, Brown RD, Cherek DR, Dailey JW, Hillman B, Jobe PC, Manno BR, Manno JE, Redetzki HM, Stuart JJ (1980) Drug excretion in human breast milk: Principles, pharmacokinetics and projected consequences. Clin Pharmacokinet 5: 1–66
5. Liedholm H, Melander A, Bitzén P-O, Helm G, Lönnerholm G, Mattiason I, Nilsson B, Wåhlin-Boll E (1981) Accumulation of atenolol and metoprolol in human breast milk. Eur J Clin Pharmacol 20 (in press)
6. Martindale (1978) The extra pharmacopoeia, 27th ed. The Pharmaceutical Press, London, p 201
7. Florey K (1974) Analytical profiles of drug subatances, vol 3. Academic Press, New York London, p 27

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