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Excretion of Dipyrone Metabolites in Human Breast Milk

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Summary. Breast milk and plasma levels of dipyrone metabolites in 8 mothers given a single oral dose of the drug were determined by HPLC. Four metabolites were demonstrated by the analytical method: 4-methylaminoantipyrine (MAA), 4-aminoantipyrine (AA), 4-formylaminoantipyrine (FAA) and 4-acetylaminoantipyrine (AAA). A good correlation was found between the plasma and milk concentrations of the metabolites. The mean (±SD) milk to plasma concentration ratios were: MAA = 1.37 ± 0.28, AA = 1.15 ± 0.40, FAA = 1.03 ± 0.09, AAA = 0.97 ± 0.24. The disposition pattern of the dipyrone metabolites in milk was studied in two mothers. None of the metabolites was detectable 48 h after drug administration.

Key words: dipyrone; metabolites, excretion in milk

Simple analgesic and antipyretic drugs are frequently used post partum, so it is of interest to determine whether they are excreted in breast milk. In many countries dipyrone (noramidopyrine methane sulphonate) has been one of the most commonly used analgesics for more than 60 years. After its oral administration absorption is preceded by hydrolysis to 4-methyl-aminoantipyrine (MAA), which is further metabolized by the liver to 4-aminoantipyrine (AA), 4-formylaminoantipyrine (FAA) and 4-acetylaminoantipyrine (AAA) (1-2). There do not appear to be published data on the excretion of dipyrone metabolites into human milk. The relationship between plasma and milk concentrations and the excretion into milk of dipyrone metabolites in mothers treated with dipyrone have now been investigated.

Material and Methods

Clinical Procedure

Eight lactating women, who received dipyrone for pain, gave their informed consent to participation in the study. Their age ranged between 23 to 34 years. Six of the subjects were 3 days and 2 subjects (No's. 3 and 8) were five days post partum. A single oral dose of dipyrone 1.0 g was given in 20% syrup. No other drugs were administered in the preceding 48 hours. Simultaneous samples of blood and milk were obtained at some time between 2.2 to 5.5 h after drug intake (Table 1). From two mothers (No's. 9 and 10), who were 3 and 5 days post partum, milk samples were obtained before the administration of a single dose (1.0 g, 20% syrup), and at each feeding time for the following three days. Breast milk samples (approximately 8 ml) were collected by manual expression and were stored at −20 °C like the plasma sample.

Drug Analysis

Dipyrone metabolites in plasma and milk were determined by an HPLC method allowing simultaneous determination of the four metabolites [3]. For analysis of milk samples, calibration curves were established in pooled blank breast milk, and for analysis of plasma samples pooled blank human plasma was used to prepare standard curves. The minimum detectable level was 0.1 μg/ml.

Kinetic Analysis

For Subjects 9 and 10, milk concentrations of the dipyrone metabolites were plotted semilogarithmi-

Table 1. Concentration of dipyrone metabolites in maternal plasma and breast milk following oral administration of 1.0 g dipyrone

Subject	Hours after dose	Dipyrone metabolites concentration (μg/ml)											
		MAA			AA			FAA			AAA		
		P	M	M/P	P	M	M/P	P	M	M/P	P	M	M/P
1	2.2	6.4	8.2	1.28	0.8	1.0	1.25	0.8	0.8	1.00	0.4	0.6	1.50
2	2.3	14.2	17.5	1.23	8.6	13.1	1.52	2.0	2.5	1.25	5.3	5.4	1.02
3	2.5	11.6	13.0	1.12	4.9	7.3	1.49	0.9	0.9	1.00	6.1	6.2	1.02
4	3.0	8.7	14.1	1.62	0.5	0.3	0.60	0.6	0.6	1.00	4.8	4.9	1.02
5	3.0	3.2	5.9	1.84	0.7	1.2	1.71	0.6	0.6	1.00	2.7	2.2	0.81
6	3.5	6.8	10.1	1.49	0.9	0.9	1.00	0.9	0.9	1.00	3.9	3.0	0.77
7	4.0	8.8	12.3	1.40	1.9	1.5	0.79	1.5	1.6	1.07	6.3	5.5	0.87
8	5.5	9.1	8.8	0.97	8.0	6.7	0.84	1.6	1.5	0.94	5.7	4.4	0.77
Mean				1.37			1.15			1.03			0.97
±SD				0.28			0.40			0.09			0.24

P = plasma; M = breast milk; M/P = ratio of milk to plasma concentrations

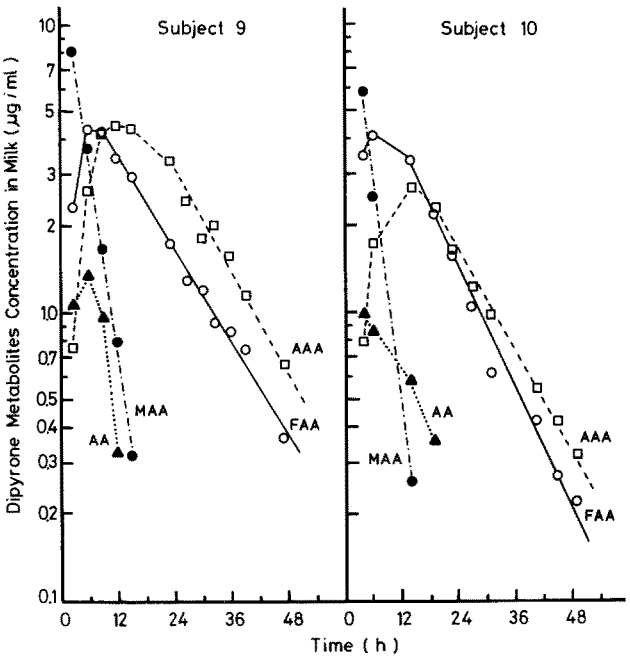

Fig. 1. Concentration-time curves of the dipyrone metabolites in breast milk from two mothers following 1.0 g dipyrone p.o.

cally against time. The elimination rate constant, (K_{el}) was determined by least squares nonlinear regression analysis [4], assuming a first-order one compartment model. The area under the milk concentration-time curve ($AUC_{0\rightarrow\infty}$) was determined by the trapezoidal rule.

Results

Plasma and milk concentrations of the dipyrone metabolites in the 8 subjects at different times following the administration of 1 g dipyrone are presented in Table 1. All four dipyrone metabolites were detected in plasma and milk samples taken from 2.2–5.5 h after drug administration.

A good correlation was found between the maternal plasma and breast milk concentrations for the four metabolites: MAA ($r=0.89$, $p<0.0005$), AA ($r=0.93$, $p<0.0005$), FAA ($r=0.98$, $p<0.0005$) and AAA ($r=0.96$, $p<0.0005$). Milk concentrations of MAA were consistently higher than the plasma concentrations, giving a mean (±SD) milk/plasma ratio (M/P) of 1.37 ± 0.28. The AA concentration in milk was higher than in plasma in four of the cases, lower in two and the same in one, giving a mean M/P ratio of 1.15 ± 0.40. For the two other metabolites similar concentrations were detected in milk and plasma; for FAA the mean M/P ratio was 1.03 ± 0.09, and for AAA it was 0.97 ± 0.24.

The concentration-time profiles of dipyrone metabolites in milk in two mothers are shown in Fig. 1. None of the dipyrone metabolites was detected after 48 hours. The half life of elimination ($t_{½}$) for AA was 3.1 h and 1.8 h for subjects 9 and 10, respectively. The elimination kinetics for the other metabolites were similar in the two subjects, with $t_{½}$ values of 2.7 and 2.3 h for MAA, 11.2 and 9.5 h for FAA, and 10.7 and 11.0 h for AAA.

The area under the milk concentration time curve ($AUC_{0\dagger0\infty}$, $\mu g \cdot ml^{-1} \cdot h$) was 58.3 and 58.2 for MAA, 12.4 and 21.1 for AA, 116.5 and 123.7 for FAA and 223.5 and 110.6 for AAA.

A blood sample from the infant of mother no. 10 was taken for other reasons 40 h after she took the drug. It was impossible to detect even traces of any of the dipyrone metabolites in an aliquot of the sample.

Discussion

Drug excretion in breast milk and factors affecting it have been extensively reviewed [5–7].

The ratio between the drug concentration in maternal milk and in plasma is commonly used to indicate the extent of drug transfer into milk. The present finding that two of the dipyrone metabolites, MAA and AA, were found in a higher concentration in breast milk than in plasma agrees with the physicochemical properties of those compounds.

The milk concentration-time observations from two mothers allowed comparison of the pharmacokinetic parameters of dipyrone metabolites in breast milk with previously determined values for plasma in healthy volunteers. The individual differences observed are explained by acetylation polymorphism [2].

Analgesics-antipyretics, frequently in compound forms, are the drugs most likely to be taken by nursing mothers.

Information on the disposition of the analgesic drugs in milk, gathered from rather limited series of lactating mothers, has recently been summarized by Findlay [6]. The elimination of salicylate from milk appears to be slower than from plasma, therefore an infant can acquire salicylate from the mother up to 24 h after she has taken aspirin. Information concerning the milk to plasma concentration ratio (M/P) of salicylate and the fraction of the dose that will appear in milk is inconclusive [8–10]. For paracetamol, in three mothers given single doses, the drug concentration in milk paralleled that in plasma [11]. It was estimated that 1% of the maternal dose appeared in milk as the parent drug. Information on the excretion of aspirin and paracetamol metabolites in milk is lacking.

On the rather generous assumptions of a maternal dose of 1.0 g dipyrone every six hours, and that 1000 ml milk are consumed daily by the infant, and using the equation $C_{ss} = \frac{AUC_{0 \rightarrow \infty}}{\text{dose interval}}$ [12], an estimate can be made of the amount of drug excreted in milk. In the two mothers examined, the calculated disposition of specific metabolites ranged between 0.1 and 0.9% of the dose taken.

Whether exposure to dipyrone or to other analgesics in milk can have an immunological effect, either as sensitization or producing tolerance remains to be studied. Finally, if nursing commences more than 48 h following dipyrone intake (e.g. for post episiotomy pain), no metabolites will be found in the milk.

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References

1. Volz M, Kellner HM (1980) Kinetics and metabolism of pyrazolones (propyphenazone, aminopyrine and dipyrone). Br J Clin Pharmacol 10: 299S–308S
2. Levy M, Flusser D, Zylber-Katz E, Granit L (1984) Plasma kinetics of dipyrone metabolites in rapid and slow acetylators. Eur J Clin Pharmacol 27: 453–458
3. Zylber-Katz E, Granit L, Drayer DE, Levy M (1984) Simultaneous determination of dipyrone metabolites in plasma by high-performance liquid chromatography. J Chromatogr 305: 477–484
4. Nichols A, Peck CC (1981) General weighed least squares nonlinear regression program. USUHS, version 1.0
5. Wilson JT, Brown RD, Cherek DR, Dailey JW, Hilman B, Jobe PC, Manno BR, Manno JE, Redetzki HM, Stewart JJ (1980) Drug excretion in human breast milk: principles, pharmacokinetics and projected consequences. Clin Pharmacokinet 5: 1–66
6. Findlay JWA (1983) The distribution of some commonly used drugs in human breast milk. Drug Metab Rev 14 [4]: 653–684
7. Chaplin S, Sanders GL, Smith JM (1982) Drug excretion in human breast milk. Adv Drug React Ac Pois Rev 1: 255–287
8. Berlin CM, Pascuzzi MJ, Yaffe SJ (1980) Excretion of salicylate in human milk. Clin Pharmacol Ther 27: 245
9. Levy G (1978) Clinical pharmacokinetics of aspirin. Pediatrics 62: 867–872
10. Findlay JWA De Angelis RL, Kearney MF, Welch RM, Findlay JM (1981) Analgesic drugs in breast milk and plasma. Clin Pharmacol Ther 29: 625–633
11. Bitzen PO, Gustafsson B, Jostell MG, Melander A, Wahlin-Boll E (1981) Excretion of paracetamol in human breast milk. Eur J Clin Pharmacol 20: 123–125
12. Gibaldi M, Perrier D (1975) Pharmacokinetics. Marcel Dekker, New York, p 104

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