Excretion of doxepin and *N*-desmethyldoxepin in human milk

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Doxepin and *N*-desmethyldoxepin concentrations in plasma and breast milk from a lactating mother and in plasma from her infant were measured during an 8 week period using high performance liquid chromatography. Plasma concentrations ranged from 35–68 $\mu\text{g l}^{-1}$ for doxepin and 65–131 $\mu\text{g l}^{-1}$ for *N*-desmethyldoxepin. Mean pre-feed milk/plasma ratios were 1.08 and 1.02 for doxepin and *N*-desmethyldoxepin respectively and increased to 1.66 and 1.53 at the post-feed samples. Only *N*-desmethyldoxepin (15 $\mu\text{g l}^{-1}$) was detectable in the infant's plasma sampled after 43 days of maternal therapy.

Keywords doxepin *N*-desmethyldoxepin human milk

Introduction

Doxepin, a tricyclic antidepressant, is one of a number of similar compounds which are commonly used to treat major depressive disorders including those occurring in the postnatal period. In addition to its antidepressant properties, the drug also has some anticholinergic activity. Both doxepin and its *N*-desmethyl metabolite are pharmacologically active. Breast feeding of infants is currently considered to provide the optimal nutrition for the newborn infant and also maximum psychological well-being for both mother and child. In Western societies, the prevalence of breast feeding, particularly in the first 6 months postpartum, has increased markedly over the past 10 years (Wilson *et al.*, 1980). Doxepin, *N*-desmethyldoxepin (pK_a s = 8.96 and 9.75, respectively; Embil & Torosian, 1982) and tricyclic antidepressants in general are all weak bases and as such would be predicted to have milk/plasma (M/P) ratios greater than 1 (Rasmussen, 1973). Thus, the physician wishing to use tricyclic antidepressants to treat postnatal depression in a patient who desires to breast feed her infant is faced with the dilemma of evaluating what effect, if any, such treatment may have on the infant. As we can find no data on the excretion of doxepin in breast milk and little on the excretion of tricyclic antidepressants in general (Rees *et al.*, 1976; Sovner & Orsulak,

1979; Erickson *et al.*, 1979; Bader & Newman, 1980), we have opportunistically documented the levels of both doxepin and its *N*-desmethyl metabolite in human milk and in plasma from a mother and her infant.

Methods

The subject was a lactating 26-year-old housewife (64 kg) diagnosed as having a major depressive disorder. Treatment with oxazepam initiated by the obstetrician was unsuccessful and caused some drowsiness in the infant. On admission to a psychiatric inpatient unit 30 days postpartum she was treated with 150 mg doxepin at night. The acute episode began to resolve after 2 weeks, after which she was discharged and then treated as an outpatient for some 6 months. Blood samples were obtained after 7, 14, 22, 28, 36, 43, 50 and 99 days of treatment at a mean of 18 h after the last dose (s.e. mean = 0.1). On each occasion milk samples were obtained by manual expression at the start (17.2 ± 0.2 h after the last dose) and at the end of the feed (17.7 ± 0.2 h after the last dose). A blood sample was also obtained from the infant 43 days after commencement of maternal doxepin therapy. The patient gave informed consent for the study.

Doxepin and *N*-desmethyldoxepin concentrations in the milk and plasma were analysed by high performance liquid chromatography (h.p.l.c.). An aliquot of biological fluid (1 ml) was placed in a polypropylene tube, 200 ng of amitriptyline was added as internal standard and the sample was alkalinised by the addition of 0.1 ml 1 M NaOH. The sample was extracted with 10 ml hexane containing 1% isoamyl alcohol by shaking for 5 min. After centrifugation, 9 ml of the organic phase was transferred to a clean polypropylene tube and the compounds of interest were back extracted by shaking with 0.2 ml of 0.05 M HCl. After a further centrifugation, the organic phase was aspirated and discarded and 50 µl aliquots of the acidic extract were injected onto the h.p.l.c. column. A µ-Bondapak C₁₈ column (30 cm × 4 mm i.d., Waters Assoc., Aust.) was used with a mobile phase of 40% acetonitrile in an aqueous solution of 0.01% H₃PO₄ and 0.01% NaCl (flow rate = 2 ml min⁻¹). Peaks were detected by their ultraviolet absorbance at 210 nm. Known concentrations of doxepin and *N*-desmethyldoxepin in both milk and plasma were put through the above procedure and test samples were quantified from a plot of peak height ratio (drug/internal standard) vs drug concentration. The intra-assay coefficient of variation for doxepin in plasma and milk was tested at 50 and 200 µg l⁻¹ and ranged from 1.3 to 3.6% (*n* = 5); coefficients of variation for *N*-desmethyldoxepin at similar plasma concentrations ranged from 0.6 to 3.8% (*n* = 5). Inter-assay coefficient of variation, assessed from the slope of the standard curve on different days was 6.2% for doxepin and 8.7% for *N*-desmethyldoxepin in milk (*n* = 4) and 6.2% for

doxepin and 8.4% for *N*-desmethyldoxepin in plasma (*n* = 7).

Results

Concentrations of doxepin and *N*-desmethyldoxepin in plasma and the pre- and post-feed M/P ratios for both drugs at different times after commencement of doxepin therapy are shown in Table 1. Plasma from the infant taken at 43 days, showed no detectable concentration of doxepin (limit of detection = 5 µg l⁻¹) and 15 µg l⁻¹ of the *N*-desmethyl metabolite.

Discussion

Plasma levels of doxepin plus its metabolite had stabilised around the lower end of the suggested therapeutic range of 125–250 µg l⁻¹ (Ward *et al.*, 1982) after 1–2 weeks and did not vary greatly throughout the study. Mean M/P ratio for doxepin was 1.08 before and 1.66 after feeding while mean M/P ratio for *N*-desmethyldoxepin was 1.02 before and 1.53 after feeding. The increase in concentration of both doxepin and *N*-desmethyldoxepin in the milk during feeding is most probably related to the high lipid solubility of these compounds (log hexane: water partition coefficient for doxepin = 4.13; Embil & Torosian, 1982) and the marked 4–5 fold increase in lipid content of milk which occurs during feeding (Hall, 1975). The M/P ratios for doxepin and *N*-desmethyldoxepin are similar to those reported for amitriptyline and nortriptyline (Bader & Newman, 1980) and imipramine and

Table 1 Plasma levels and milk/plasma ratios for doxepin and desmethyldoxepin before and after feeding

Treatment day	Plasma concentration (µg l ⁻¹)		Milk/plasma ratio			
	Doxepin	<i>N</i> -desmethyldoxepin	Doxepin		<i>N</i> -desmethyldoxepin	
			Pre-feed	Post-feed	Pre-feed	Post-feed
7	44	80	1.15	1.38	0.91	1.15
14	41	75	1.32	1.59	1.15	1.37
22	38	103	1.24	2.18	1.02	1.65
28	41	87	1.44	1.80	1.45	1.71
36	68	131	0.51	0.79	0.54	0.85
43	57	98	1.02	1.32	1.00	1.32
50	44	84	0.91	2.39	0.95	2.35
99	35	65	1.06	1.85	1.12	1.80
Mean ± s.e. mean	46 ± 4	90 ± 7	1.08 ± 0.10	1.66 ± 0.18	1.02 ± 0.10	1.53 ± 0.16

desipramine (Sovner & Orsulak, 1979). Published data for dothiepin in two patients (Rees *et al.*, 1976) showed M/P ratios of 1 and 3, respectively.

Assuming an average daily milk consumption of 1.18 l for the infant (Rattigan *et al.*, 1980), and using the mean milk concentrations of 60 and 111 $\mu\text{g l}^{-1}$ of doxepin and *N*-desmethyldoxepin respectively, it can be calculated that the infant received an average of 71 μg doxepin and 131 μg desmethyldoxepin per day. The infant's mean weight during the study was 4 kg and hence he received a daily dose of around 18 $\mu\text{g kg}^{-1} \text{ day}^{-1}$ of doxepin and 33 $\mu\text{g kg}^{-1} \text{ day}^{-1}$ desmethyldoxepin. Thus, the combined doxepin and desmethyldoxepin dose (51 $\mu\text{g kg}^{-1} \text{ day}^{-1}$) for

the infant is approximately 2.2% of the maternal doxepin dose of 2.4 $\text{mg kg}^{-1} \text{ day}^{-1}$. Throughout the study period no untoward effects were noted in the infant who was not sedated, was neurologically intact and achieved motor developmental milestones at the expected rate.

While it is difficult to give general guidelines for the drug treatment of major depression in lactating mothers, the low levels of desmethyldoxepin in the infant's plasma and the lack of untoward effects seen in the present case would suggest that it is unwarranted to categorically recommend that such mothers should discontinue breast feeding. However, in the final analysis, evaluation of the risk-benefit ratio must rest with the individual physician.

References

- Bader, T. F., & Newman, K. (1980). Amitriptyline in human breast milk and the nursing infant's serum. *Am. J. Psychiat.*, **137**, 855-856.
- Embil, K. & Torosian, G. (1982). Solubility and ionisation characteristics of doxepin and desmethyldoxepin. *J. pharm. Sci.*, **71**, 191-192.
- Erickson, S. H., Smith, G. H. & Heidrich, F. (1979). Tricyclics and breast feeding. *Am. J. Psychiat.*, **136**, 1483.
- Hall, B. (1975). Changing composition of human milk and early development of an appetite control. *Lancet*, **i**, 779.
- Rasmussen, F. (1973). The mechanism of drug secretion into milk: In *Concepts in biochemical pharmacology*, Vol 1, eds. Brodie, B. B. & Gillette, J. R., pp. 231-245. New York: Springer-Verlag.
- Rattigan, S., Ghisalberti, A. V. & Hartmann, P. E. (1981). Breast-milk production in Australian women. *Br. J. Nutr.*, **45**, 243-249.
- Rees, J. A., Glass, R. C. & Sporne, G. A. (1976). Serum and breast milk concentrations of dothiepin. *The Practitioner*, **217**, 686.
- Sovner, R., & Orsulak, P. J. (1979). Excretion of imipramine and desipramine in human breast milk. *Am. J. Psychiat.*, **136**, 451-452.
- Ward, N. G., Bloom, V. L., Wilson, L., Raskind, M., & Raisys, V. A. (1982). Doxepin plasma levels and therapeutic response in depression: preliminary findings. *J. clin. Psychopharmac.*, **2**, 126-128.
- Wilson, J. T., Brown, R. D., Cherek, D. R., Dalley, J. W., Hilman, B., Jobe, P. C., Manno, B. R., Manno, J. E., Reclatzki, H. M. & Stewart, J. J. (1980). Drug excretion in human breast milk. Principles, pharmacokinetics and projected consequences. *Clin. Pharmacokin.*, **5**, 1-66.

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