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The excretion of dothiepin and its primary metabolites in breast milk

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1 The excretion of dothiepin, nordothiepin, dothiepin-S-oxide and nordothiepin-S-oxide into breast milk was studied in eight women. Exposure to drug was measured in five of their infants, and possible drug-related effects were assessed in all eight infants.

2 Using pre-feed milk samples mean (± s.e. mean) milk:plasma (M:P) ratios were 0.78 ± 0.12, 0.85 ± 0.16, 1.18 ± 0.29 and 1.86 ± 0.29 for dothiepin, nordothiepin, dothiepin-S-oxide and nordothiepin-S-oxide, respectively. In post-feed milk samples, the mean M:P ratio for dothiepin (1.59 ± 0.32) was significantly greater ($P < 0.05$) but M:P ratios for the metabolites were similar.

3 Mean total calculated infant daily doses, (in dothiepin equivalents and as a percent of the maternal dose) were 0.58% for dothiepin, 0.23% for nordothiepin, 2.47% for dothiepin-S-oxide, and 1.17% for nordothiepin-S-oxide.

4 Plasma samples were obtained from five infants. In one, both dothiepin and nordothiepin were below their minimum quantifiable levels (2 $\mu g\ l^{-1}$) while in four others both dothiepin-S-oxide and nordothiepin-S-oxide were below their minimum quantifiable levels (10 $\mu g\ l^{-1}$). No adverse effects were found in any of the eight infants.

5 Use of dothiepin by depressed mothers is unlikely to be a significant hazard to their breast-feeding infants.

Keywords dothiepin nordothiepin dothiepin-S-oxide nordothiepin-S-oxide milk relative maternal dose

Introduction

Tricyclic antidepressants such as amitriptyline and dothiepin are not only widely used in the treatment of major depressive illness (Lancaster & Gonzalez, 1989) but also are often recommended for postnatal depression (George, 1987; Oates, 1986). The question of excretion in breast milk and safety in lactation is therefore relevant. The potential risks to the suckling neonate from exposure to this group of drugs are central nervous system disturbances including sedation, and antimuscarinic side effects such as decreased motility of the urinary tract or gut. With one exception (Matheson *et al.*, 1985), central nervous system sedation has not been reported to be a significant problem (Bader & Newman, 1980; Erickson *et al.*, 1979; Kemp *et al.*, 1985; Sovner & Ursulak, 1979) while antimuscarinic effects have not been reported. However, the excretion of tricyclic antidepressants into breast milk has not been studied extensively (Atkinson *et al.*, 1988). In all, excretion in milk has been studied in only three patients taking amitriptyline (Bader & Newman, 1980; Brixen-Rasmussen *et al.*, 1982; Pittard & O'Neal, 1986), one taking desipramine (Stancer & Reed, 1986), two taking doxepin (Kemp *et al.*, 1985; Matheson *et al.*, 1985), two taking dothiepin (Rees *et al.*, 1976), one taking imipramine (Sovner & Ursulak, 1979) and one taking nortriptyline (Matheson & Skjaeraasen, 1988). Generally, milk:plasma ratios between 0.7 and 3.7 were found in these studies, with infants receiving about 1% of the maternal daily dose. In Australia, dothiepin has some 22% of the anti-depressant market share (Drug Utilization Sub Committee, Pharmaceutical Benefits Advisory Committee, 1990) and is often preferred to amitriptyline in depressed patients because of its generally lower incidence of side effects (Lancaster &

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Table 1 Maternal dothiepin dose, sample time and concentrations of dothiepin and its metabolites in plasma

Subject number	*Dose (mg kg^{-1} day^{-1})*	*Duration of therapy*	*Blood sample (h after dose)*	*Plasma concentration (μg l^{-1})*			
				Dothiepin	*Nordothiepin*	*Dothiepin-S-oxide*	*Nordothiepin-S-oxide*
1	0.38	7 days	13.8	11	3	58	18
2	0.95	2 days	13.2	12	3	224	50
3	1.5	5 years	5.0	138	18	682	96
4	1.61	18 days	15.4	18	20	95	48
5	1.67	26 days	2.8	62	28	244	102
6	3.13	> 5 years	13.8	151	55	204	73
7	3.46	0.8 years	9.2	170	68	554	192
8	4.5	1.5 years	15.8	62	27	475	173

Gonzalez, 1989). In the present study, the concentrations of dothiepin and its primary metabolites in milk have been measured to provide a detailed assessment of the exposure risk of breast fed infants whose mothers are treated with dothiepin during the postnatal period.

Methods

Materials

Reference samples of dothiepin, dothiepin-S-oxide, nordothiepin and nordothiepin-S-oxide were obtained from The Boots Company Australia (Sydney, Australia) Pty Ltd. Solvents for h.p.l.c. analyses were purchased from Millipore-Waters Ltd (Sydney, Australia) and all other chemicals were of analytical reagent grade.

Subjects

Eight breast-feeding women were enrolled in the study. The women ranged in age between 28 and 40 years with body weights ranging from 50–79 kg. Dothiepin was prescribed for continued treatment of major depressive illness (n = 4) or for post-natal depression (n = 4) in doses ranging from 25–225 mg day^{-1}. The duration of dothiepin therapy is shown in Table 1. The ages of their infants at the time of study were 5, 0.5, 0.25, 6.7, 2.5, 0.13, 12.5 and 0.25 months for subjects 1 to 8, respectively. The design of the study was approved by the King Edward Memorial Hospital Ethics Committee and all subjects gave written informed consent to their participation. Several of the subjects were taking concomitant medications, none of which interfered in the assay procedure. Milk samples (10–20 ml) were collected both immediately before and after infant feeding using a manual breast pump. A single blood sample was taken from each mother either immediately before or after the feed, and, in five cases, a single blood sample was obtained from the infant at the same time.

Assay of dothiepin and its metabolites by h.p.l.c.

For estimation of dothiepin and nordothiepin in plasma, 1 ml of plasma was mixed with 0.2 ml 1 M NaOH and 85 ng *N*-desmethyldoxepin (internal standard) and extracted with 10 ml hexane containing 1% v/v isoamyl alcohol. After centrifugation, 9 ml of the organic phase was removed to a clean tube and extracted with 0.2 ml 0.05 M HCl. Aliquots (0.08 ml) of the HCl extract were injected onto the h.p.l.c. The assay used a μ-Bondapak Phenyl column (30 cm × 4 mm i.d.; Millipore Waters Ltd, Sydney, Australia) with a solvent of 35% v/v CH_3CN in 0.01% v/v H_3PO_4 and 0.01% w/v NaCl. The flow rate was 1.8 ml min^{-1} with detection by u.v. absorption at 230 nm. Results were interpolated from a standard curve constructed for each batch of unknown samples. The coefficients of variation for the assay of dothiepin at 5, 25 and 250 μg l^{-1} were 3.2%, 4.9% and 1.3%, respectively (n = 5) and for the assay of nordothiepin at 5, 25 and 250 μg l^{-1} they were 1.9%, 1.2% and 1.7%, respectively (n = 5).

For estimation of dothiepin and nordothiepin in milk, known amounts of the two drugs were added to 1 ml aliquots of milk from the patient to give final concentrations of 0, 50, 100 and 250 μg l^{-1}. The samples were then extracted and chromatographed as described above for plasma. A plot of peak height ratio (y-axis; drug:internal standard) *vs* added drug concentration (x-axis) was constructed and the unknown initial concentrations of dothiepin and nordothiepin in each milk sample were obtained from the positive y-axis intercepts. The coefficients of variation for the assay of dothiepin at 5, 25 and 250 μg l^{-1} were 5.3%, 4.4% and 3.1%, respectively (n = 5) and for nordothiepin at 5, 25 and 250 μg l^{-1} were 4.5%, 1.4% and 1.6%, respectively (n = 5).

For estimation of dothiepin-S-oxide and nordothiepin-S-oxide in plasma, a 0.5 ml aliquot of plasma was mixed with 0.2 ml 0.1M sodium tetraborate (adjusted to pH 10 with 5M NaOH) and 2 μg cocaine hydrochloride (internal standard) and extracted with 10 ml diethylether. After centrifugation, 9 ml of the organic phase was transferred to a pointed tube and extracted with 0.2 ml 0.1M HCl. The diethylether was aspirated to waste and the aqueous phase was evaporated to approximately 0.1 ml in a 50° C water bath under a stream of N_2. The volume was made up to approximately 0.2 ml with distilled water. Aliquots (0.025 ml) of the HCl extract were injected onto the h.p.l.c. The assay used a Waters Associates, μ-Bondapak Phenyl column (30 cm × 4 mm i.d.; Millipore Waters Ltd, Sydney, Australia) with a solvent of 18% v/v CH_3CN in 0.01% v/v H_3PO_4 and 0.01% w/v NaCl. The flow rate was 1.5 ml min^{-1} with detection by u.v. absorption at 210 nm. Results were interpolated from a standard curve constructed for each batch of unknown samples. The coefficients of variation for the assay of

Table 2 Sample times and concentrations of dothiepin and its metabolites in milk

Subject number	*Milk sample (h after dose)*		*Milk concentration[a] (μg l⁻¹)*			
	Pre-feed	*Post-feed*	*Dothiepin*	*Nordothiepin*	*Dothiepin-S-oxide*	*Nordothiepin-S-oxide*
1	14.2	14.6	8:26	3:10	68:65	30:27
2	16.2	16.9	16:20	5:5	254:244	134:120
3	3.4	4.2	81:62	13:13	544:520	120:124
4	15.0	15.4	5:21	4:11	94:102	64:84
5	2.9	3.9	33:52	11:18	175:193	102:111
6	11.8	13.3	110:128	56:56	468:456	246:200
7	7.5	8.2	207:475	45:73	610:536	258:232
8	14.5	15.0	52:150	31:49	617:714	367:400

[a]Data as pre-feed : post-feed concentrations.

dothiepin-S-oxide at 50 and 500 μg l^{-1} were 1.3% and 2.5% ($n = 5$), respectively and for nordothiepin-S-oxide at 50 and 500 μg l^{-1} were 1.0% and 2.5%, respectively ($n = 5$).

For estimation of dothiepin-S-oxide and nordothiepin-S-oxide in milk, known amounts of the two drugs were added to 0.5 ml aliquots of milk from the patient to give final concentrations of 0, 100, 250 and 500 μg l^{-1}. The samples were then extracted and chromatographed as described above for plasma. A plot of peak height ratio (y-axis; drug:internal standard) *vs* added drug concentration (x-axis) was constructed and the unknown initial concentrations of dothiepin-S-oxide and nordothiepin-S-oxide in each milk sample were obtained from the positive y-axis intercepts. The coefficients of variation for the assay of dothiepin-S-oxide at 50 and 600 μg l^{-1} were 3.6% and 2.6% ($n = 5$), respectively and for nordothiepin-S-oxide at 50 and 600 μg l^{-1} were 4.4% and 2.1%, respectively ($n = 5$).

The minimum quantifiable levels (5 × baseline noise) were 2 μg l^{-1} for dothiepin and nordothiepin and 5 μg l^{-1} for dothiepin-S-oxide and nordothiepin-S-oxide in both plasma and milk.

Measurement of octanol:buffer pH 7.4 partition coefficients

Dothiepin and nordothiepin (1 mg l^{-1}) or dothiepin-S-oxide and nordothiepin-S-oxide (100 μg l^{-1}) were dissolved in 2 ml in Sorensen's phosphate buffer (20 mM, pH 7.4) and equilibrated with an equal volume of purified water-saturated octan-1-ol by gentle shaking. The drug concentration in the aqueous phase (before and after equilibration) was measured by h.p.l.c. as described above. Partition coefficients were expressed as log P values.

Calculation of dosage

The absolute infant doses of dothiepin and its metabolites were calculated by taking the mean of the pre- and post-feed milk concentrations and converting it to mg kg^{-1} day^{-1} (Bennett, 1988). Relative doses of dothiepin and its metabolites received by the infant were calculated as the absolute infant dose × 100, divided by the maternal dose, where both infant and maternal doses were expressed as mg dothiepin equivalents kg^{-1} day^{-1}.

Data analysis

Data are summarized as mean ± s.e.mean. Mean pre- and post-feed milk:plasma ratios were compared by a paired *t*-test.

Results

The maternal daily doses of dothiepin and plasma concentrations of dothiepin, dothiepin-S-oxide, nordothiepin and nordothiepin-S-oxide are summarized in Table 1. The concentrations are in a similar range to mean steady-state plasma concentrations of dothiepin (68 μg l^{-1}), dothiepin-S-oxide (410 μg l^{-1}), nordothiepin (38 μg l^{-1}) and nordothiepin-S-oxide (135 μg l^{-1}) measured in 29 non-lactating patients receiving therapeutic doses (75–300 mg day^{-1}) of dothiepin (Ilett *et al.*, 1991). The concentrations of dothiepin and its metabolites in both pre- and post-feed milk samples are shown in Table 2 and the pre- and post-feed milk:plasma (M:P) ratios in Figure 1. Mean pre-feed M:P ratios were less than post-feed values for both dothiepin (0.78 ± 0.12 and 1.59 ± 0.32, respectively) and nordothiepin (0.85 ± 0.16 and 1.36 ± 0.33, respectively), although the difference was statistically significant ($t = 3.0$, $P < 0.02$) only for dothiepin. Mean pre- and post-feed M:P ratios for dothiepin-S-oxide (1.18 ± 0.17 and 1.20 ± 0.17, respectively) and nordothiepin-S-oxide (1.86 ± 0.29 and 1.79 ± 0.22, respectively) were similar. Log $P_{octanol:buffer}$ values for dothiepin, nordothiepin, dothiepin-S-oxide and nordothiepin-S-oxide were 2.8, 1.68, 0.54 and −0.74, respectively.

Infant daily doses of dothiepin and its metabolites are shown in Table 3. Mean daily infant doses (in dothiepin equivalents and as percent of the maternal intake) were 0.58% for dothiepin, 0.23% for nordothiepin, 2.47% for dothiepin-S-oxide and 1.17% for nordothiepin-S-oxide. Because of the small blood samples (0.5 – 0.8 ml) available from the infants, we could only look for dothiepin and nordothiepin or for dothiepin-S-oxide and nordothiepin-S-oxide. In infant 1, concentrations of both dothiepin and nordothiepin were below minimum quantifiable level (2 μg l^{-1}) while in infants 2, 3, 7 and 8, both dothiepin-S-oxide and nordothiepin-S-oxide were below their minimum quantifiable level (10 μg l^{-1}; 0.5 ml plasma). No adverse drug-related side effects were found in any of the eight infants.

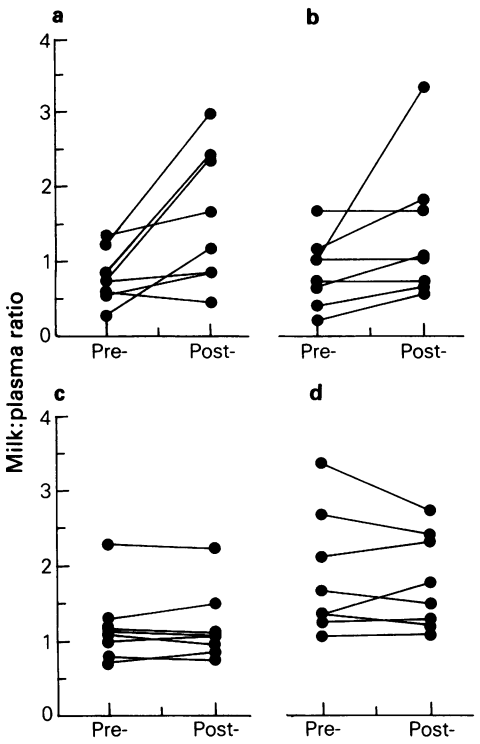

Figure 1 Pre- and post-feed milk:plasma ratios for dothiepin (panel a), nordothiepin (panel b), dothiepin-S-oxide (panel c) and nordothiepin-S-oxide (panel d). Paired ratios for each of the eight subjects are joined by solid lines.

Discussion

In the present study, we were able to make only a single point observation of M:P drug distribution for each of eight patients. While multiple sampling within a dose interval is sometimes recommended (Neville *et al.*, 1984), it is not necessary for dothiepin since the half-lives of dothiepin (14–24 h), dothiepin-S-oxide (23–26 h), nordothiepin (35–46 h) and nordothiepin-S-oxide (24–36 h) are relatively long (Lancaster & Gonzales, 1989). In our study, the three primary metabolites of dothiepin were measured since they are known to have pharmacological activity (Fulton *et al.*, 1982) and since the sulphoxides are present in plasma at concentrations which are 3.5–6 fold greater than those of dothiepin and nordothiepin (Ilett *et al.*, 1991). In three different *in vitro* systems, dothiepin and nordothiepin had similar potency while the S-oxide metabolites were 1–2 orders of magnitude less potent (Fulton *et al.*, 1982).

Our data show clearly that dothiepin, nordothiepin and their sulphoxide metabolites are excreted in breast milk and that mean total daily infant exposure amounts to some 4.4% of the maternal dothiepin dosage. This can be compared with calculated infant doses of 3.3% for amitriptyline alone (Bader & Newman, 1980), 1.9% (mean data) for amitriptyline plus nortriptyline (Bennett, 1988), 1% for despiramine alone (Stancer & Reed, 1986), 2.2% for doxepin plus desmethyldoxepin (Kemp *et al.*, 1985), 0.3% (mean data) for imipramine plus desipramine (Bennett, 1988) and 2.3% for nortriptyline alone (Matheson & Skjaerssen, 1988). Nevertheless, considering the *in vitro* potencies of dothiepin and its metabolites as well as their concentrations in milk, it seems likely that only dothiepin and nordothiepin would contribute significantly to any pharmacological effects in the nursing infant. The low log P values for the two sulphoxide metabolites suggest that their absorption by the infant is likely to be low. Given that the mean daily infant exposures for dothiepin and nordothiepin were 0.58 and 0.23% of the daily maternal dothiepin intake respectively, drug-related effects in the infants are unlikely. Indeed, none of the infants in the study showed any signs of toxicity. Moreover, neither a parent drug nor its metabolites were detected in the infant's plasma, despite a significant intake particularly of the S-oxide metabolites.

M:P ratios for dothiepin and its metabolites were of similar magnitude. Dothiepin concentrations in milk increased significantly from the pre- to the post-feed sample, presumably as a result of the increase in milk lipid content which occurs during feeding (Wilson *et al.*, 1980). M:P ratios for nordothiepin and the two sulphoxide metabolites did not change significantly between the pre- and post-feed samples. These data are in agreement with the order of log $P_{octanol\text{-}buffer}$ values which was dothiepin > nordothiepin > dothiepin-S-oxide > nordothiepin-S-oxide. It is of interest to note that doxepin and its desmethyl metabolite also show a marked increase (approximately 50%) in M:P ratios between pre- and post-feed samples (Kemp *et al.*, 1985). In addition, Matheson & Skjaeraasen (1988)

Table 3 Calculated[a] infant daily intake of dothiepin and its metabolites

Infant number	*Calculated daily dose (as % of maternal dose)*			
	Dothiepin	*Nordothiepin*	*Dothiepin-S-oxide*	*Nordothiepin-S-oxide*
1	0.67	0.27	2.50	1.12
2	0.29	0.53	3.37	1.99
3	0.72	0.14	5.05	1.21
4	0.12	0.07	0.86	0.68
5	0.38	0.14	1.29	0.95
6	0.57	0.28	2.21	1.06
7	1.48	0.27	2.36	1.06
8	0.38	0.14	2.10	1.27
Mean ± s.e. mean	0.58 ± 0.15	0.23 ± 0.05	2.47 ± 0.46	1.17 ± 0.13

[a]Infant daily intake (mg dothiepin equivalents kg^{-1} day^{-1}) as percent of maternal dothiepin dose (mg kg^{-1} day^{-1}).

found a 100% increase between pre- and post-feed M:P ratios for nortriptyline.

In summary, our study has shown that exposure of the breast fed neonate to pharmacologically active tricyclic antidepressant equivalents, as a consequence of maternal dothiepin use, was small and did not result in toxicity in the infant. These findings support a low risk-benefit ratio for the use of dothiepin in breast feeding mothers with major depressive illness. Nevertheless, one should always be cognisant of the remote possibility of concentration-independent adverse effects in the infant.

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