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Transfer of the antidepressant mirtazapine into breast milk

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What is already known about this subject

- There is presently only a single case report on mirtazapine transfer into breast milk and its effects in the breast-fed infant.

What this study adds

- Most importantly, we have provided quantitative data on the absolute and relative infant doses of mirtazapine and its active metabolite.
- We have also documented a lack of overt adverse effects in the breast-fed infants and low or absent plasma concentrations of mirtazapine in a subset of these infants.
- Hence we now know that breast-fed infants are unlikely to be adversely affected when their mothers need to take mirtazapine.

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Aims
To investigate the transfer of mirtazapine and desmethylmirtazapine into milk and to calculate dose to the infant via milk.

Methods
Plasma and milk samples were obtained from eight breast-feeding women who were taking a median dose of 38 mg mirtazapine per day. Milk/plasma ratio (M/P) and infant doses were estimated by standard methods. The infants were examined clinically and in four infants blood was taken for analysis.

Results
Mean (95% confidence interval) relative infant doses for mirtazapine and desmethylmirtazapine (n = 8) were 1.5% (0.8, 2.2) and 0.4% (0.2, 0.6) respectively. The mean M/P (area under curve n = 4, single or paired samples n = 3) was 1.1 (0.7,1.5) for mirtazapine and 0.6 (0.5, 0.7) for desmethylmirtazapine. No adverse effects were seen. Mirtazapine was detected (1.5 μg l^{-1}) in only one of four infants tested.

Conclusion
We suggest that mirtazapine use by lactating women is safe for the breast-fed infant. Nevertheless, each decision to breast feed should always be made on the basis of an individual risk/benefit analysis.

Introduction

Because of the 10–15% prevalence of depression in the postnatal period, antidepressants are one of the most frequently used drugs in lactation [1]. Children of depressed mothers may exhibit behavioural problems and delayed language development [2–5]. In women with moderate and severe depressive disorders, it is accepted that drug treatment during pregnancy and in the postnatal period has significant benefits for both mother and infant. Mirtazapine is classified as a noradrenergic and specific serotonergic antidepressant which also has effects at histamine receptors [6]. Its efficacy is similar to that of tricyclic and the selective serotonin reuptake inhibitor antidepressants [7]. It can be used as first-line treatment [8] and, because of its action on histamine, H_1 receptors may be preferred in some patients with postnatal depression, when night-time sedation is required. It is marketed as the racemate and both enantiomers are presumed to contribute to the antidepressant activity [9, 10].

The only published information on the transfer of mirtazapine into milk is a single case report [11]. In the present study we have assessed infant dose via milk, and the safety of breast feeding. Desmethylmirtazapine, formed by CYP3A4, was also included because it has steady-state plasma concentrations that are about 33% of those of mirtazapine, and a similar but less active (5- to 10-fold lower) pharmacological profile [10].

Materials and methods

Patients

Eight breast-feeding women who were being treated with mirtazapine for perinatal and/or postnatal depression were recruited and gave written informed consent.

Study protocol and data collection

The study protocol was approved by the Ethics Committee of the Women's and Children's Health Service, Subiaco, Australia. The women were studied at steady state. Milk samples (6 ml by hand expression or electric pump) were collected each time the infant was fed (3–4 hourly) and unless otherwise specified were an equal mixture of fore- and hind-milk. In four of the studies, several paired fore- and hind-milk samples were also collected in the post-absorption phase to investigate the effect of milk fat content on drug transfer. Creamatocrit was measured as previously described [12]. Plasma samples (5 ml heparinized) were also taken from seven of the women, who agreed to blood sampling. Three gave five to eight samples over the dose interval, while the remainder gave only one or two samples. Infant health and well-being were investigated by inquiry of the mother and/or the referring physician and body weight was assessed by reference to standard growth charts [13]. The infants (except no. 3 who was unavailable) were also given a full clinical examination, including a Denver development assessment [14]. A venous blood sample (0.5–2 ml, heparinized) for drug assay was also taken from four infants.

Materials

Authentic *rac*-mitrazapine and *rac*-desmethylmirtazapine were obtained from Organon Australia Pty Ltd (Lane Cove, Australia) and pethidine was from Mayne Pharma Ltd (Melbourne, Australia). All other solvents and chemicals were of analytical grade.

Analysis of *rac*-mirtazapine and *rac*-desmethylmirtazapine was by high-performance liquid chromatography (HPLC). Pethidine (270 ng, internal standard) was added to 1-ml aliquots of plasma, alkalinized with 0.1 ml M NaOH and extracted into 10 ml diethylether. After centrifugation, the organic phase (9 ml) was back-extracted into 0.2 ml 0.05 M HCl and aliquots of the acid phase injected onto the HPLC. Milk samples were extracted similarly except that the 'method of addition' [15] was used. The HPLC system consisted of a RP Select B column (250 × 4.6 mm; Merck KGaA, Darmstadt, Germany), a mobile phase of 20% v/v acetonitrile in 45 mM NaH_2PO_4 (pH 3) pumped at 1.5 ml min^{-1} and detection at 210 nm. Retention times for desmethylmirtazapine, mirtazapine and pethidine were 6.2, 8 and 12.2 min, respectively. Both intra- and interday relative standard deviations (RSD; $n = 5$) for mirtazapine (25 and 350 μg l^{-1}) and desmethylmirtazapine (9 and 300 μg l^{-1}) in plasma were <5.4% and <3% and in milk were <8.9% and <9.3%, respectively. The limit of detection for both analytes in milk and plasma was 1 μg l^{-1} for a 1-ml sample.

Data analysis

Where complete milk and plasma concentration–time data over a dose interval were available ($n = 3$), areas under the respective concentration–time curves ($AUC_{0-24\,h}$) were calculated [16] and the milk to plasma ratio (M/P_{AUC}) was then calculated from these data [15]. The average drug concentration in milk or plasma was calculated as $C_{av} = (AUC_{0-24\,h})/\tau$, where τ = the dose interval. In patients where one or two plasma concentration measurements were available ($n = 4$), $C_{single/dual}$ in plasma was taken as the single, or average of two measurements made on the study day and $M/P_{single/dual}$ was calculated relative to the respective milk $C_{av.}$ Absolute and relative infant doses were calculated as previously described [17]. In graphing the milk concentration–time

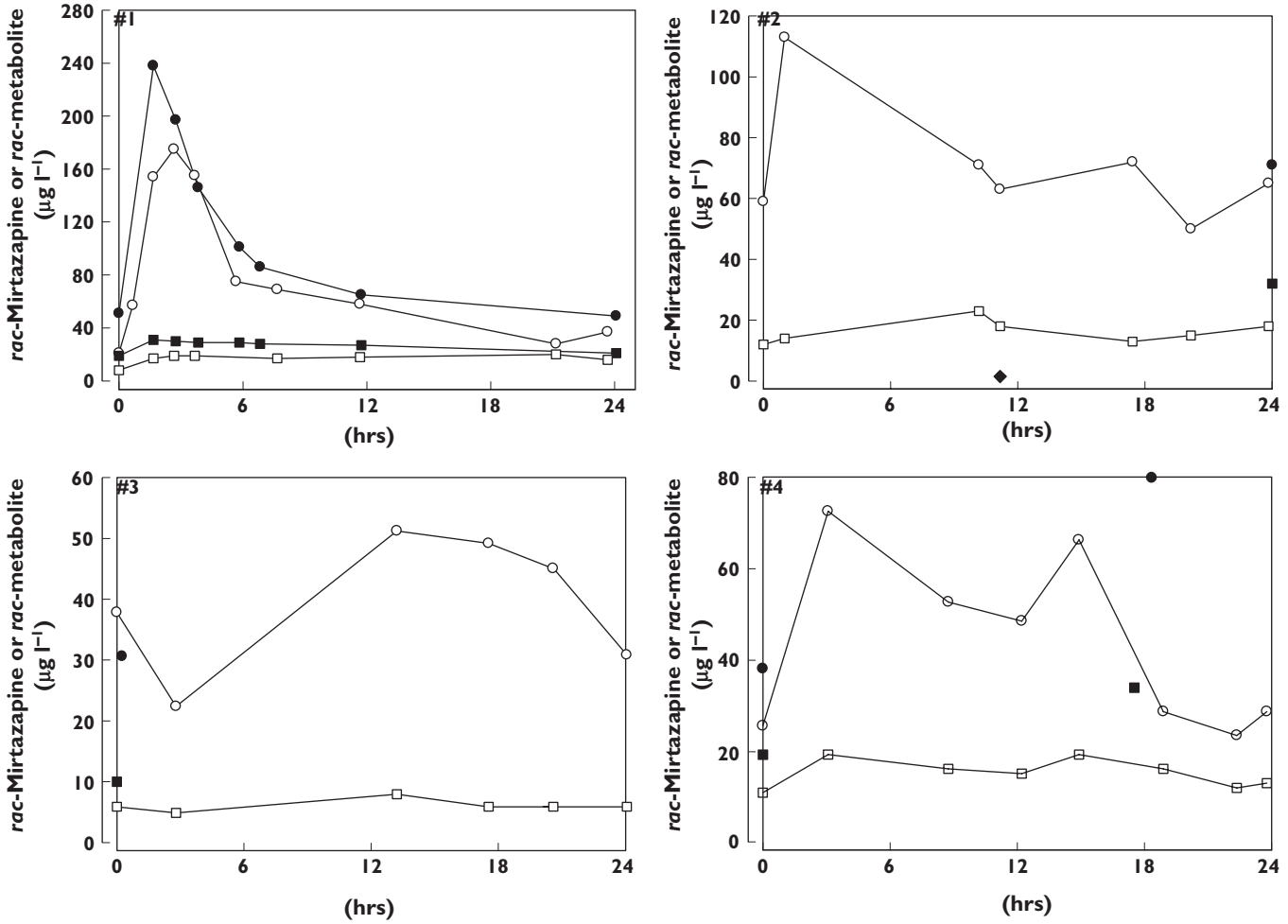

Figure 1
Milk and plasma concentration–time profiles for *rac*-mirtazapine (○, milk, ●, plasma) and *rac*-desmethylmirtazapine (□, milk, ■, plasma) in patients 1 to 8. The symbol (◆) in the graph for patient 2 indicates the plasma concentration of mirtazapine measured in her infant

data (Figure 1) and estimating $AUC_{milk,}$ the concentration values for paired fore- and hind-milk samples were averaged and plotted/analysed against the average of their sampling times. Data have been summarized as mean [95% confidence interval (CI), or range] or median (range, or 25th and 75th percentiles) and differences between means examined by Student's *t*-test or a paired *t*-test (SigmaStat Ver 3.1; SPSS Inc., Chicago, IL, USA).

Results

The mothers had a mean age of 35 years (range 32–36 years), a mean body weight of 77 kg (range 58–97 kg) and all were taking a single daily dose of mirtazapine (median 38 mg; range 30–120 mg). Therapy had commenced a median of 32 days (range 6–129 days) prior to the study. Concomitant drug therapy was oxazepam, inhaled fluticasone and salbutamol in patient 1, inhaled fluticasone and salbutamol in patient 4 and escitalopram (20 mg kg^{-1} day^{-1}) in patient 6. The infants were two females and six males with a mean age of 6.3 months (range 1.5–13 months) and a mean weight of 7.4 kg (range 5.5–10.5 kg) on the study day. Five of the infants had achieved weight for age within 25th to 75th percentiles and the remaining three were within the 10th and 25th percentiles at the time of study. Of the three infants below the 25th percentile, one was small for gestational age at birth and the other two had correspondingly low birth weights. Nevertheless, the paediatric assessment done on seven infants revealed no adverse findings and the mean Denver developmental age was 101% (95% CI 92, 110) of the actual age. No adverse drug-related effects were reported for any infant.

Milk and plasma concentration–time profiles for the

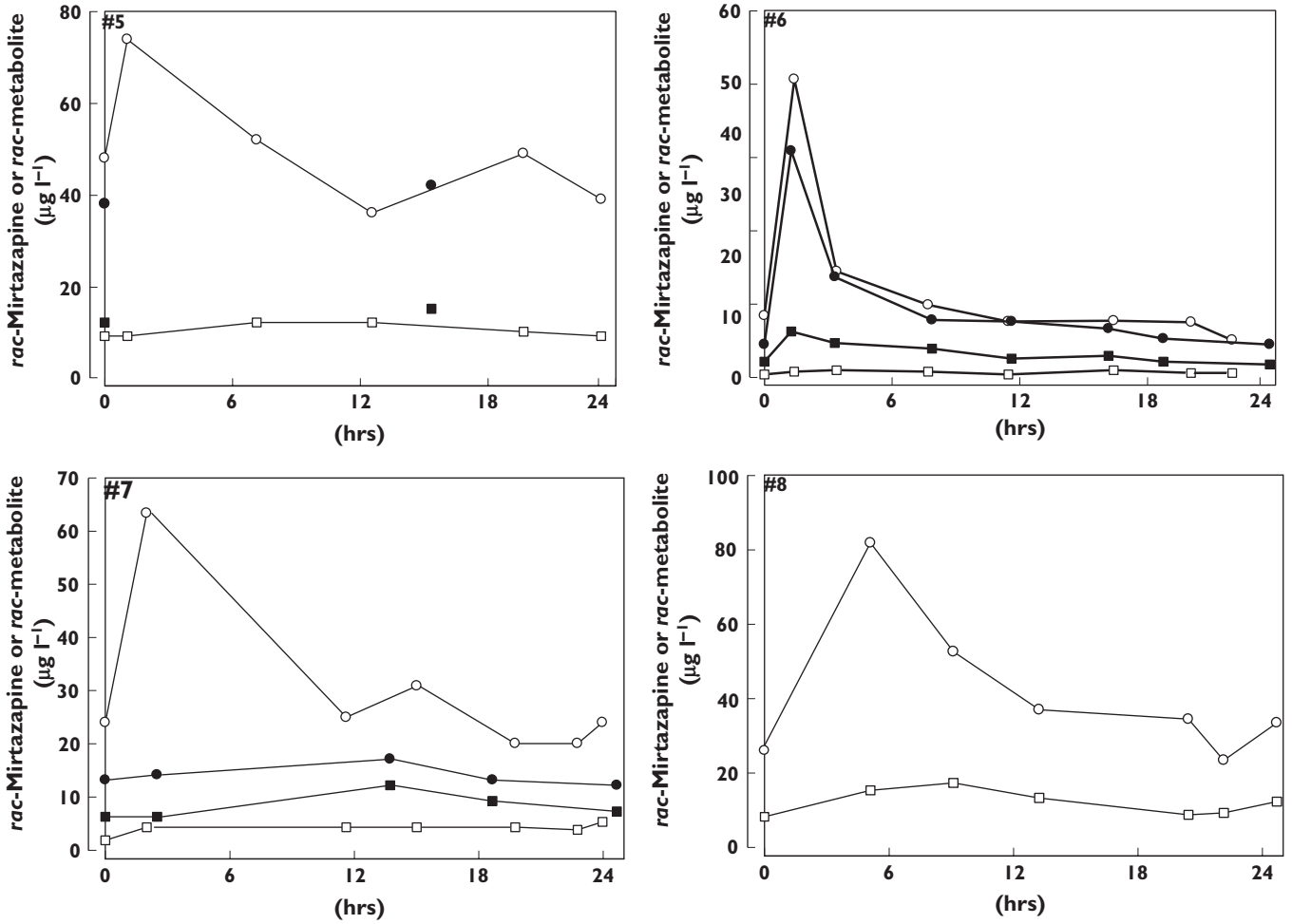

Figure 1
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eight women are shown in Figure 1. The mean (95% CI; $n = 8$) milk C_{av} for mirtazapine was 53 μg l^{-1} (42, 65), while the mean plasma C_{av} ($n = 3$) or $C_{single/dual\ point}$ ($n = 4$) was 47 μg l^{-1} (24, 70). For desmethylmirtazapine, the milk C_{av} was 13 μg l^{-1} (9, 17), while the mean plasma C_{av} or $C_{single/dual\ point}$ was 19 μg l^{-1} (11, 26). The mean ($n = 7$) M/P values were 1.1 (0.7, 1.5) for mirtazapine and 0.6 (0.5, 0.7) for desmethylmirtazapine.

Table 1 summarizes the maternal and infant doses and drug concentrations in infant plasma. The total relative infant dose for the combination mirtazapine and its desmethyl metabolite was a mean of 1.9% of the maternal weight-adjusted dose. This is a conservative estimate, given that desmethylmirtazapine has only 5–10% of the pharmacological activity of the parent drug [10]. Overall, mirtazapine contributed a mean of 80% of the oral antidepressant dose (95% of the pharmacological activity) that the breast-fed infant is calculated to receive. In four of the studies, a blood sample was able to be taken from the infants (Table 1) and analysed for drug content. Mirtazapine was detected in plasma from only one infant (no. 2 at 1.5 μg l^{-1}) and desmethylmirtazapine was not detected in any sample.

During the course of the study we collected (post-absorption phase) 14 paired samples of fore- and hind-milk from patients 3, 6, 7 and 8 for analysis. For mirtazapine there was a significant increase in mean concentration (29 μg l^{-1}; 95% CI for difference 18.8, 39.5) between fore- and hind-milk milk (paired $t = 6.06$, $P < 0.001$), while for desmethylmirtazapine there was no significant change between mean concentrations in fore- and hind-milk. On average, the ratio of drug concentration in hind-milk to that in fore-milk was 2.3 (95% CI 1.8, 2.8) for mirtazapine and 1.1 (0.9, 1.2) for desmethylmirtazapine. Creamatocrit (% fat) in these paired fore- (6.2%) and hind-milk (13.7%) samples also

Table 1
Maternal dose of mirtazapine, absolute and relative infant doses and infant plasma concentrations of mirtazapine and desmethylmirtazapine

		Mirtazapine			Desmethylmirtazapine			
Patient	Maternal dose (μg kg^{-1} day^{1})	Absolute infant dose (μg kg^{-1} day^{-1})	Relative infant dose (%)	Infant plasma concentration (μg l^{-1})‡	Absolute infant dose (μg kg^{-1} day^{-1})	Relative infant dose (%)	Infant plasma concentration (μg l^{-1})‡	Total relative infant dose* (%)
1	536	10.0	1.9	<1	2.7	0.5	<1	2.4
2	1967	11.2	0.6	1.5	2.5	0.1	<1	0.7
3	474	6.0	1.3	<4	1.1	0.2	<3	1.5
4	857	7.2	0.8	<1	2.6	0.3	<1	1.2
5	309	7.7	2.5	ND	1.9	0.7	ND	3.1
6	353	9.8	2.8	ND	1.5	0.4	ND	3.1
7	517	5.1	1.0	ND	0.9	0.2	ND	1.2
8	462	7.1	1.5	ND	2.3	0.5	ND	2.1
Mean (95%CI)	495 (407, 696)†	8.0 (6.8, 9.8)	1.5 (0.8, 2.2)		3.0 (2.4, 3.6)	0.4 (0.2, 0.6)		1.9 (1.1, 2.7)

*ND, No plasma sample available. *Expressed in mirtazapine equivalents. †Median (25th & 75th percentiles). ‡Higher limits of detection for some samples as a result of sample volume available for assay.*

approximately doubled (mean increase 7.5%, 95% CI for difference 4.9, 10.1, paired $t = 6.2$, $P < 0.001$).

Discussion

In the present study we measured *rac*-mirtazapine and its *rac*-desmethyl metabolite because the racemate is the form marketed, and because the enantiomers of both parent drug and its metabolite contribute to overall pharmacological activity [9, 10].

Transfer of mirtazapine into milk as measured by a mean M/P of 1.1 was modest, but still twice that for its desmethyl metabolite. Nevertheless, the robustness of our M/P estimates may be questioned as we had AUC data for only three of the patients. Co-transport of mirtazapine into milk with lipid was demonstrated by a significant increase in its concentration between fore- and hind-milk. Moreover, in line with its higher polarity, desmethylmirtazapine transfer was not influenced by milk lipids.

The mean absolute infant dose of mirtazapine was low (8 μg kg^{-1} day^{-1}) compared with the mean maternal dose of 495 μg kg^{-1} day^{-1}. The calculated mean relative infant dose for mirtazapine plus its desmethyl metabolite was some 1.9% (as mirtazapine equivalents) of the weight-adjusted maternal dose. A relative infant dose of <10% of the maternal weight-adjusted dose is generally considered safe [15] and hence mirtazapine is predicted to have a wide margin of safety in breast feeding. Moreover, none of the infants showed any drug-related adverse effects and were achieving developmental milestones. Only very low concentrations of mirtazapine were detected in the plasma of one out of the four infants tested. Hence, the clinical findings in the infants support the predicted low relative infant dose. The low/undetectable infant plasma concentrations could in part be explained if there is significant CYP3A4-dependent first-pass metabolism of mirtazapine (i.e. low bioavailability) in infants, as in adults [9, 18]. Overall, our data for mirtazapine agree with, and substantially extend those in the previous single case report, where mirtazapine alone was measured in milk and plasma taken 15 and 22 h after dose [11].

One of the patients (no. 6) was taking escitalopram as well as mirtazapine. For this patient, the calculated relative infant dose of escitalopram plus desmethylescitalopram was 4% (data not shown). Hence, in considering the breast-feeding risk/benefit analysis for this mother/baby pair, the contributions from both mirtazapine and escitalopram need to be considered.

In summary, the mean relative infant dose of 1.9% for mirtazapine plus its major desmethyl metabolite, suggests that short-term mirtazapine use is safe during breast feeding (notional level of safety <10%). Nevertheless, each decision to breast feed should always be

made on the basis of an individual risk/benefit analysis. Long term follow-up studies of infants exposed to mirtazapine are still needed.

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