Use of sertraline, paroxetine and fluvoxamine by nursing women

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Background The pharmacological treatment of depression in nursing women requires information on the magnitude of medication exposure to the infant that may occur through breast milk.

Aims To examine serum concentrations of antidepressants in infants exposed to these medications through breast-feeding.

Method Maternal and infant serum concentrations of sertraline, paroxetine and fluvoxamine were determined with high-performance liquid chromatography (limit of detection=1 ng/ml).

Results No detectable medication was present in any infant exposed to paroxetine (n=16) or fluvoxamine (n=4). Among infants exposed to sertraline (n=30), detectable medication was present in 24% of serum samples. A significant negative correlation was found between infant age and infant serum concentration. Sertraline was significantly more likely to be detected in an infant if the mother's daily dose was 100 mg or higher. No adverse sequelae occurred in any infant.

Conclusions This study shows that paroxetine, fluvoxamine and sertraline produce minimal exposure to infants when taken by nursing mothers.

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When new mothers experience depression, they and their clinicians need to know if antidepressant medications are safe to use while breast-feeding. Several recent reports have examined the extent of exposure that occurs to nursing infants whose mothers take antidepressants (e.g. Altshuler *et al*, 1995; Taddio *et al*, 1996; Mammen *et al*, 1997; Stowe *et al*, 1997; Yoshida *et al*, 1997; Wisner *et al*, 1998; Begg *et al*, 1999; Birnbaum *et al*, 1999; Kristensen *et al*, 1999; Ohman *et al*, 1999; Stowe *et al*, 2000). However, the research literature has consisted largely of single cases or small studies, and methodological differences have limited the information that can be drawn from them (Yoshida *et al*, 1999). To expand this literature, we present measurements of maternal and infant serum concentrations in 50 nursing mother–infant pairs in which the mothers took therapeutic doses of sertraline, paroxetine or fluvoxamine.

METHOD

Fifty nursing mother–infant pairs who presented to UCLA's Pregnancy and Postpartum Mood Disorders Program were included in the study. The women were Caucasian (n=46), Hispanic (n=3) and Asian (n=1), in good physical health, ranging in age from 24 to 41 years old and on standard doses of antidepressant medication, taken once daily for treatment of major depression. Two women additionally were on nortriptyline and another was on alprazolam. None of the infants was on medications of any category. Seventeen women were on antidepressants during pregnancy as well as nursing. Written informed consent was obtained from each mother for collection of serum samples.

Sample collection

Maternal and infant serum samples were obtained at a minimum of 2 weeks following a fixed dose of antidepressant. For women who took the antidepressant during pregnancy, maternal and infant serum samples were obtained a minimum of 2 weeks following delivery. Serum samples were obtained from a total of 50 infants and 48 mothers.

Detection of antidepressant concentrations in serum

The detection of sertraline, desmethylsertraline, paroxetine and fluvoxamine in serum was accomplished via an isocratic high-performance liquid chromatography (HPLC) separation followed by ultraviolet detection at 225 nm. The concentration of each drug (sertraline, desmethylsertraline, paroxetine or fluvoxamine) in the samples was calculated from its peak area ratios by using the slope and intercept of the appropriate calibration curve. The assays had a lower limit of sensitivity of 1 ng/ml, defined by a signal-to-noise ratio of 7 for each drug.

Statistical analysis

The LIFEREG Procedure using SAS software was used to perform a Tobit analysis on the data. The Tobit model is a regression model for left-censored data, assuming a normal distributed error term. The model parameters are estimated by maximum likelihood. A χ^2 test was used to explore whether nursing infants whose mothers took higher daily doses of sertraline (100 mg or more) were more likely to have detectable serum concentrations of medication, as compared with infants of women who took lower doses.

RESULTS

Results of the serum assays for the mother–infant pairs are shown in Table 1. Infant ages ranged from 2 to 60 weeks and weights ranged from 3 to 10 kg at the time of the serum assays.

No detectable medication was present in any infant exposed to paroxetine or fluvoxamine. Detectable medication (parent and/or metabolite) was present in 24% (8/33) of the serum samples obtained from infants exposed to sertraline. Concentrations of sertraline and desmethylsertraline, when present, were 2–8 and 2–12 ng/ml, respectively.

Four mothers (nos 5, 16, 24 and 49) titrated their dose of the antidepressant

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Table 1 Serum concentrations of antidepressants in 50 nursing mother–infant pairs

Pair	Maternal medication	Dose (mg/day)	Exposed to antidepressant during pregnancy and delivery	% Breast-feeding (*v.* formula)	Infant age at serum sample (weeks)	Infant weight at serum sample (kg)	Maternal medication concentration (ng/ml)	Infant medication concentrations (ng/ml)	Maternal metabolite concentration (ng/ml)	Infant metabolite concentration (ng/ml)
1	Sertraline	25	No	100	12	6.7	4	<1	4	<1
2	Sertraline	25	No	90	13	5.4	0	<1	13	<1
3	Sertraline	25	No	100	5	3.7	5	<1	20	<1
4	Sertraline	25	No	100	3	3.5	7	<1	9	<1
5a	Sertraline	50	No	100	4	4.6	15	<1	39	2
6	Sertraline	50	No	100	28	7.8	18	<1	15	<1
7	Sertraline	50	No	100	16	4.4	28	<1	51	<1
8	Sertraline	50	No	100	39	9.1	15	<1	48	<1
9	Sertraline	50	No	100	10	3.7	3	<1	9	<1
10	Sertraline	50	Yes	50	4	3.4	42	<1	64	<1
11	Sertraline	50	Yes	80	6	3.9	30	<1	35	<1
12	Sertraline	50	Yes	50	6	4.7	19	<1	77	<1
13	Sertraline	50	Yes	100	60	9.6	8	<1	23	<1
14	Sertraline	50	No	100	17	7.7	6	<1	16	<1
15	Sertraline	50	Yes	100	11	5.4	30	8	50	4
16a	Sertraline	75	No	50	26	8.1	19	<1	77	<1
17	Sertraline	75	No	100	17	6.3	82	<1	182	<1
18	Sertraline	75	Yes	50	5	4.1	92	<1	210	<1
19	Sertraline	100	No	100	9	4.9	45	<1	75	<1
20	Sertraline	100	No	100	2	5.5	50	<1	124	12
21	Sertraline	100	No	80	12	6.4	14	<1	27	<1
22	Sertraline	100	No	70	52	10.0	14	<1	36	<1
23	Sertraline	100	Yes	100	10	4.1	46	<1	128	<1
24a	Sertraline	100	No	100	8	5.0	89	<1	265	11
25	Sertraline	100	No	50	44	7.8	64	<1	102	<1
26	Sertraline	125	No	100	14	6.8	48	<1	164	2
5b	Sertraline	150	No	80	36	9.3	31	<1	61	<1
16b	Sertraline	150	No	50	37	8.6	64	<1	84	<1
27	Sertraline	150	No	100	7	4.5	35	<1	120	4
28	Sertraline	150	Yes	100	8	4.7	53	2	133	2
24b	Sertraline	150	No	100	19	7.3	7	<1	16	<1
29	Sertraline	150	Yes	100	3	3.7	102	<1	182	26
30	Sertraline	200	No	100	16	5.5	n/a	<1	n/a	<1
31	Paroxetine	5	No	100	16	5.1	<1	<1	n/a	n/a
32	Paroxetine	10	No	100	3	4.6	10	<1	n/a	n/a
33	Paroxetine	10	Yes	100	3	3.7	28	<1	n/a	n/a
34	Paroxetine	20	Yes	100	2	4.0	42	<1	n/a	n/a
35	Paroxetine	20	No	100	11	6.4	18	<1	n/a	n/a
36	Paroxetine	20	No	100	12	6.4	24	<1	n/a	n/a
37	Paroxetine	20	Yes	100	13	5.3	36	<1	n/a	n/a
38	Paroxetine	20	No	100	14	7.8	<1	<1	n/a	n/a
39	Paroxetine	20	No	100	16	4.3	38	<1	n/a	n/a
40	Paroxetine	20	No	50	19	5.2	27	<1	n/a	n/a
41	Paroxetine	20	No	40	19	7.3	27	<1	n/a	n/a
42	Paroxetine	20	Yes	95	26	8.6	64	<1	n/a	n/a
43	Paroxetine	20	No	100	4	3.0	21	<1	n/a	n/a
44	Paroxetine	20	Yes	100	6	5.3	76	<1	n/a	n/a
45	Paroxetine	25	Yes	100	7	4.6	84	<1	n/a	n/a
46	Paroxetine	30	No	99	11	5.9	136	<1	n/a	n/a
47	Fluvoxamine	100	Yes	100	8	4.7	140	<1	n/a	n/a
48	Fluvoxamine	100	No	100	13	6.8	<1	<1	n/a	n/a
49a	Fluvoxamine	100	No	100	9	5.2	n/o	<1	n/a	n/a
49b	Fluvoxamine	150	No	100	12	5.9	n/o	<1	n/a	n/a
50	Fluvoxamine	150	Yes	100	6	6.0	n/o	<1	n/a	n/a

n/o, not obtained; n/a, not available.

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upwards to help their mood and obtained repeat serum samples on themselves and their infants after being on the higher medication dosage for at least 1 week.

Maternal dosage of sertraline correlated highly with infant serum concentration of desmethylsertraline after controlling for infant age, gestational exposure and breast-feeding exposure (parameter estimate=0.09, d.f.=1, P=0.03). Maternal serum concentrations of sertraline and desmethylsertraline correlated highly with infant serum concentration of desmethylsertraline (parameter estimate=0.20, d.f.=1, $P<0.001$ and parameter estimate=0.07, d.f.=1, P=0.008, respectively) after controlling for infant age, gestational exposure and breast-feeding exposure. This analysis used all the available maternal and infant serum samples shown in Table 1.

A significant negative correlation was found between infant age and infant serum concentration of desmethylsertraline after controlling for maternal dosage, gestational exposure and breast-feeding exposure (parameter estimate=−1.46, d.f.=1, P=0.002). Among women who breast-fed fully, the likelihood of their infants having a detectable level of medication (sertraline or desmethylsertraline) was significantly higher if their dose was 100 mg or more (χ^2= 6.81, d.f.=1, P=0.009).

Mothers were questioned about potential adverse sequelae to their infants and did not report any such findings. Specific enquiries were made regarding gastrointestinal symptoms (e.g. vomiting, watery stool), lethargy, changes in sleep patterns and easy bruising. None of the women in the study was on other medications and the infants were in good health.

CLINICAL IMPLICATIONS

- This study found that the use of fluvoxamine, paroxetine and sertraline by nursing women produces minimal medication exposure to the infants.
- The presence of low detectable serum concentrations of medication was not associated with adverse effects in the infants.
- Maternal serum concentrations and dosage of medication can be employed to estimate infant serum concentrations.

LIMITATIONS

- Use of maternal reports rather than paediatric examinations in assessing for potential medication-related adverse events in the infants.
- Single serum measurement of medication in the mother–infant pairs.
- Lack of evaluation of infants' long-term outcomes associated with their early exposure to antidepressant medications.

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DISCUSSION

This study found that serum concentrations of medication were undetectable in all infants exposed to paroxetine or fluvoxamine and in the majority of infants exposed to sertraline while nursing. When medication was present in the sertraline-exposed infants, it was usually in the form of the metabolite desmethylsertraline. Maternal serum concentrations of sertraline and desmethylsertraline correlated highly with infant serum concentrations of desmethylsertraline. Maternal dosage of sertraline also correlated highly with infant serum concentrations of desmethylsertraline; doses of 100 mg or above were significantly more likely to produce detectable concentrations in the infant. A significant negative correlation emerged between infant age and serum concentration of desmethylsertraline.

This study's findings suggest that paroxetine, fluvoxamine and sertraline are reasonable choices for nursing women requiring treatment for depression. In comparison with fluoxetine, these medications appear to produce less exposure to nursing infants and have not been linked with the adverse events of neonatal irritability, sleep disturbance and poor feeding that have been reported in association with fluoxetine exposure through breast-feeding (Lester *et al*, 1993; Brent & Wisner, 1998; Chambers *et al*, 1999; Kristensen *et al*, 1999). For infants that are healthy and full-term, these findings provide no reason to discourage nursing among women taking paroxetine, fluvoxamine or sertraline at standard therapeutic dosages. The use of additional medications that are commonly taken in the post-partum period (e.g. antihistamines, decongestants, pain medications) should be kept to a minimum until more is known about whether such combinations are safe for the nursing infant (Mitchell, 1999).

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