Paroxetine Levels in Postpartum Depressed Women, Breast Milk, and Infant Serum

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Background: The purpose of this study was to determine the concentrations of paroxetine in maternal serum, breast milk, and infant serum samples and to estimate infant exposure through breastfeeding.

Method: A total of 25 sample sets was obtained: 1 sample set each from 23 mother-infant dyads and 2 sample sets from 1 mother-infant dyad. All mothers met DSM-IV criteria for major depressive disorder. The maternal fixed dosage of paroxetine was 10, 20, or 40 mg/day for a minimum of 30 days before the samples were drawn. Samples were collected 6 hours after dose intake, and the concentration of paroxetine in each sample was determined using gas chromatography/mass spectrometry. The analytic method employed in this study is the most sensitive to date, with the ability to detect drug concentrations as low as 0.1 ng/mL.

Results: Detectable levels of paroxetine were present in all maternal serum samples and in 24 of the 25 breast milk samples. In all of the infant serum samples, the paroxetine concentrations were below the lower limit of quantification. No unusual adverse effects were reported in any of the infants.

Conclusion: The results of this study demonstrate that paroxetine, like the other selective serotonin reuptake inhibitors studied to date, is excreted into the breast milk of nursing mothers.
The mean infant dose of paroxetine was 1.1% of the maternal dose. Although no short-term adverse effects were reported in any of the infants in this study, future studies are needed to address a more systematic method for observing and recording any adverse effects. In addition, future studies should incorporate follow-up studies in order to evaluate possible long-term effects of paroxetine exposure.

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Postpartum depression affects approximately 10% of women within 12 months of childbirth,[1–3] with a peak incidence during the first 4 months. In addition, 30% to 40% of women with postpartum depression also suffer from comorbid anxiety resulting in debilitating panic attacks and frightening intrusive thoughts of harming their infants.[4] A small percentage of postpartum depression patients also experience superimposed psychotic symptoms.[5] The implications of untreated postpartum depression are negative and severe. The mother-infant bonding process, which is mandatory for the child's emotional and cognitive development, is compromised.[6] In addition, children of depressed mothers demonstrate increased incidences of emotional disturbance and poor cognitive performance,[7,8] and these disturbances continue even after the maternal depression has remitted.[9]

Breastfeeding is the best nutritional mode for infants during the first 6 months of life.[10] It encourages positive mother-infant interactions, and it helps in the development of healthy attachment of the infant to his or her mother. In addition, breastfeeding has been linked to possible enhancement of cognitive and academic functioning in older children.[10] Many studies have also found that breastfed infants are less susceptible to infections and illnesses.[10,11] On the basis of such benefits, breastfeeding is strongly endorsed by the American Academy of Pediatrics, and the Academy suggests that women continue breast-feeding their infants for 12 months.[10] Although a growing number of studies have examined the effects of psychotropic drug use during pregnancy and lactation,[12] when new mothers are diagnosed with postpartum depression and prescribed a medication, they are still often reluctant to breast-feed, citing concerns about possible effects on their infants.

Fluoxetine and its main metabolite, norfluoxetine, are present in breast milk at less than 10% of the adult therapeutic dose[13] and are also present in the infant's serum.[14] Three case studies[15–17] have reported symptoms of irritability, vomiting, and short-term seizure-like activity in breastfed infants. However, a study of long-term developmental outcomes reported no abnormalities in infants exposed to fluoxetine through breast milk at a 1-year follow-up.[14]

With respect to sertraline exposure through breast milk, 2 studies have demonstrated very low levels of both sertraline and its metabolite, *N*-desmethylsertraline, in the serum of infants.[18,19] No adverse short-term effects of sertraline exposure have been reported in the literature, and the long-term development of exposed infants has yet to be investigated.

The only case report published on fluvoxamine use during lactation found that 0.5% of the maternal dose was present in the infant, and no adverse behavioral effects were noted.[20] Similarly, case reports of infant citalopram exposure through breast milk showed low amounts of the medication in infant serum relative to maternal doses.[21–23]

The data on paroxetine exposure in the nursing infant are limited, with only 4 reports available.[24–27] To date, these studies have found that the infant is exposed to less than 3% of the maternal dose of paroxetine with no association of negative effects. With the exception of a recent study published by Stowe and colleagues,[24] there are several methodological limitations in the existing reports on paroxetine in lactation, including a failure to report measurement and observation techniques. The number of participants is small; 2 of these studies are case reports, with only a single participant in each report. In addition, in 2 of the 4 reports,[25,26] the concentration of paroxetine in infant serum was not directly measured. Consequently, this database does not allow for definitive conclusions to be made on the safety of paroxetine use during breastfeeding.

The purpose of the current study was to determine concentrations of paroxetine in maternal serum and breast milk samples from 24 women who chose to continue nursing during antidepressant treatment and in the serum of their infants and to assess the infants' exposure to the medication during breastfeeding.

METHOD

Participants

Thirty mothers referred to the Reproductive Mental Health Programs at St. Paul's and British Columbia Women's Hospitals in Vancouver, British Columbia, Canada, were invited to participate; 24 of 30 women who were being treated with paroxetine for postpartum depression consented to participate. All mothers met DSM-IV criteria for major depressive disorder, with or without a comorbid anxiety disorder. All women included in this investigation were referred within 12 months of childbirth. Thirteen of the mothers were exclusively breast-feeding their infants; for the 11 mothers who were only partially breast-feeding, the number of supplemental feedings was less than 20% of the total daily feedings. All participants were taking paroxetine for the treatment of depression during the postpartum period. Eight mothers were taking clonazepam for the treatment of concomitant anxiety, 2 were taking acetaminophen, and 1 was taking lorazepam. Women with a history of substance abuse or who were taking medications contraindicated with paroxetine were excluded. Written informed consent was obtained for all participants, and collection protocols for the breast milk, maternal serum, and infant serum samples were reviewed with each participant. All patients were recruited after their dose of paroxetine had stabilized (minimum of 30 days). Patients continued on their present dose regimen.

The daily maternal dose of paroxetine was 10 mg (N = 12), 20 mg (N = 10), or 40 mg (N = 3), administered once every morning. Maternal and infant samples were collected approximately 6 hours after dose intake. This sampling time was chosen on the basis of the available studies involving sertraline,[18,19] in which the maximal drug concentration in milk and serum samples was reached 6 to 8 hours after the dose intake. A total of 25 sets of samples were obtained from 24 mother-infant dyads. Maternal blood samples (≈5 mL) were collected via venipuncture, and infant blood samples (≈1 mL) were collected via either heel-prick or venipuncture. All blood samples were collected in Vacutainer tubes without additives. Samples were allowed to clot for 30 minutes and were then centrifuged at 3000 g to separate the serum. Immediately after blood collection, fresh breast milk (foremilk) was collected from all patients via either manual expression or breast pump. All samples were stored at –20°C prior to analysis.

Analytic Procedures

Paroxetine concentrations in breast milk, maternal serum, and infant serum were determined using a modified gas chromatographic/mass spectrometric (GC/MS) procedure (J.K.; D.W. Rurak, D. Phil; K.W.R., unpublished data, September 2000). In brief, serum samples were spiked with paroxetine and maprotiline (internal standard) and basified with 0.5 mL of saturated sodium carbonate; the analytes were then extracted with 7 mL of 0.05 M triethylamine in hexane:isopropanol (98:2 v/v). The organic layer was separated after shaking (20 min) and centrifugation (10 min) and then evaporated to dryness under nitrogen at 35°C. For milk samples, an additional liquid-liquid back-extraction step was added prior to sample drying. The dried residue was reconstituted in 0.1 mL of toluene and derivatized with 0.01 mL of heptafluorobutyric acid anhydride at 60°C for 30 minutes. Following derivative formation, the samples were mixed with 2 mL of 2.5% aqueous ammonia solution containing 0.05 M triethylamine and centrifuged to remove excess derivatizing reagent. The organic layer was then separated and 2 μL was injected onto the GC/MS. The derivatives of paroxetine and the internal standard were separated on a fused silica capillary column (DB5MS 20 m × 0.18 mm internal diameter, 0.18 μm film thickness; J&W Scientific, Folsom, Calif.) with helium as the carrier gas (run time = 10 min). Quantification was performed using

Table 1. Summary of Maternal and Infant Serum and Breast Milk Paroxetine Concentrations, Milk/Serum Ratios, and Estimated Infant Dose From 24 Nursing Mother-Infant Dyads Treated With Paroxetine[a]

Patient No.	Mother Age, y (N = 25)	Mother Weight, kg (N = 25)	Infant Age, mo (N = 25)	Infant Weight, kg (N = 24)	Daily Dose, mg (N = 25)	Concurrent Medication	Paroxetine Concentration (ng/mL)			Milk-to-Plasma Ratio	Infant Exposure		Breast-feeding
							Maternal Serum	Milk	Infant Serum		μg/kg/d	% of Maternal Dose	
1	23	84	3	4.5	10	Clonazepam	7.6	2.1	BLQ	0.28	0.32	0.3	Exclusive
2	28	59	3	3.6	10	Clonazepam	7.0	3.1	BLQ	0.44	0.47	0.3	Exclusive
3	31	77	4	4.0	10	Acetaminophen	4.0	3.2	BLQ	0.80	0.48	0.4	Exclusive
4	38	54	7.5	10.0	10	Lorazepam	6.6	3.2	BLQ	0.48	0.48	0.3	Exclusive
5	31	52	4	3.8	10	...	9.6	2.3	BLQ	0.24	0.35	0.2	Exclusive
6	24	48	3	3.2	10	Acetaminophen	17.2	6.2	BLQ	0.36	0.93	0.4	Exclusive
7	29	59	7	8.6	10	Clonazepam	41.7	20.4	BLQ	0.49	3.06	1.8	Partial
8	31	79	3	10.0	20	...	21.9	19.6	BLQ	0.89	2.94	1.2	Partial
9	29	63	2	4.0	20	...	41.9	51.2	BLQ	1.22	7.68	2.4	Exclusive
10	33	82	3	5.0	40	...	276.1	101.8	BLQ	0.37	15.27	3.1	Exclusive
11	31	66	2	5.9	20	...	36.4	11.0	BLQ	0.30	1.65	0.5	Exclusive
12	29	68	2	4.1	10	...	175.7	19.4	BLQ	0.11	2.91	2.0	Exclusive
13	31	73	4.5	10.0	20	Clonazepam	1.8	3.0	BLQ	1.67	0.45	0.2	Partial
14A[b]	30	70	5	5.4	10	Clonazepam	56.4	41.2	BLQ	0.73	6.18	4.3	Partial
14B	30	70	7	7.3	40	Clonazepam	124.8	93.6	BLQ	0.75	14.04	2.5	Partial
15	33	70	5	8.6	20	Clonazepam	4.0	BLQ	BLQ	N/A	N/A	N/A	Partial
16	36	91	3	6.1	20	...	7.0	1.4	BLQ	0.20	0.21	0.1	Exclusive
17	36	64	4	8.2	10	...	1.1	1.6	BLQ	1.45	0.24	0.2	Partial
18	37	48	10	11.8	20	...	23.1	4.4	BLQ	0.19	0.66	0.2	Partial
19	25	82	1	4.5	20	...	30.8	6.2	BLQ	0.20	0.93	0.4	Exclusive
20	33	82	5	9.1	40	...	8.4	2.6	BLQ	0.31	0.39	0.1	Partial
21	30	63	6	8.6	10	...	133.9	33.3	BLQ	0.25	5.00	3.2	Partial
22	37	91	10.5	10.0	20	...	41.5	13.7	BLQ	0.33	2.06	0.9	Partial
23	40	82	2.5		10	Clonazepam	36.0	10.8	BLQ	0.30	1.62	1.3	Exclusive
24	30	70	5	5.0	20	...	16.0	5.9	BLQ	0.37	0.89	0.3	Partial
Mean	31.4	69.8	4.5	6.7	17.6	...	45.2	19.2	BLQ	0.53	2.88	1.1	
SD	4.3	12.4	2.4	2.6	9.7	...	65.6	27.6		0.41	4.135	1.2	

[a]Abbreviations: BLQ = below assay limit of quantification, N/A = not applicable, as maternal milk levels below limit of quantification.
[b]The daily dose for patient 14 was increased from 10 mg to 40 mg, so 1 sample was taken at each of the 2 dosing levels.

an HP5989A Mass Spectrometer (Hewlett-Packard, Avondale, Pa.) and selected ion monitoring in the negative chemical ionization mode. The mass/charge ratios for the ions monitored were m/z 485 for paroxetine and m/z 453 for the internal standard. The limit of quantification used for the sample analysis in the present study was 0.1 ng/mL, with a linear range from 0.1 to 100 ng/mL ($r^2 > 0.99$). Both intraday and interday precision (relative standard deviation) and accuracy (relative error) were less than 10% at all levels except for the limit of quantification, which had a relative error rate of less than 15%.

The daily dose of paroxetine for infants was calculated using the following formula: infant dose (weight normalized) = $C_{milk} \times V_{milk} \times F_{BF}$, where C_{milk} is the concentration of paroxetine in the breast milk sample, V_{milk} is the volume of breast milk ingested by each infant per day (estimated to be 150 mL per kg of infant body weight), and F_{BF} is the fraction of breastfeeding for infants who were only partially breastfed. Similar equations have been used in many studies of infants who have been exposed to selective serotonin reuptake inhibitors (SSRIs) through breast milk.[13,25–27] The infant dose was compared with the weight-adjusted maternal dose for each mother-infant pair. For statistical analyses, Spearman rank correlation tests were used, with a significance level of $p < .05$.

RESULTS

Detectable levels of paroxetine were present in all maternal serum samples (1.1–276.1 ng/mL) and in 24 of the 25 breast milk samples (1.4–101.8 ng/mL) (Table 1). Mean maternal serum and breast milk paroxetine concentrations for each dose level are shown in Figure 1. In patient 14, the daily dose was increased from 10 mg to 40 mg; therefore, 2 samples were taken (14A and 14B), one at each dosing level. The increased dose resulted in increases in both maternal serum and breast milk paroxetine concentrations in patient 14.

No significant correlation was found between daily paroxetine doses and maternal serum paroxetine levels in the study population at 6 hours ($r = 0.283$, $p > .05$). On the contrary, a significant correlation between maternal serum and breast milk paroxetine concentration was observed ($r = 0.903$, $p < .05$) (Figure 2). The mean ± SD maternal milk-to-plasma ratio of paroxetine was 0.53 ± 0.41 (range, 0.11–1.67). The mean ± SD calculated normalized daily infant dose was 2.88 ± 4.14 μg/kg (range, 0.21–15.27 μg/kg), which represents 1.1% ± 1.2% of the weight-normalized maternal dose (range, 0.1%–4.3%). In all of the infant serum samples, the paroxetine concentrations were below the limit of quantification

Figure 1. Mean ± SD Paroxetine Concentration in Maternal Serum and Breast Milk at Each Dosing Level: 10 mg/day (N = 12), 20 mg/day (N = 10), and 40 mg/day (N = 3)

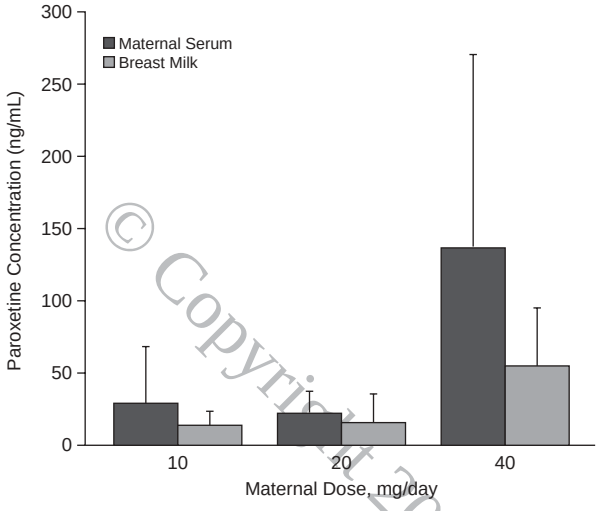
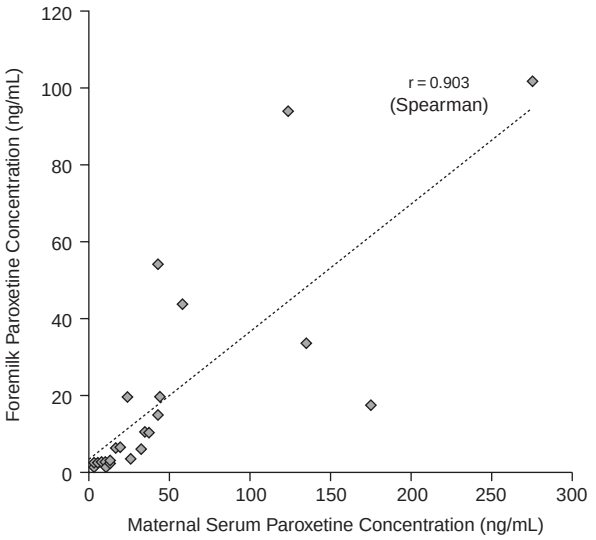


Figure 2. Correlation Between Maternal Serum and Breast Milk Paroxetine Concentrations in 24 Maternal Samples[a]



[a]A significant correlation was observed between the concentration of paroxetine in maternal serum and that in breast milk samples ($r = 0.903$, $p < .05$).

(0.1 ng/mL). Neither remarkable adverse effects nor unusual infant behaviors were reported by any of the mothers nor observed by any of the investigators during the study session.

DISCUSSION

The present study is the largest to date, involving 24 mother-infant dyads, and is 1 of only 3 reports[24,27] of paroxetine that have directly measured the serum concentrations of the drug in nursing infants. The results of this study demonstrate that paroxetine, like the other SSRIs, is excreted in the breast milk of nursing mothers, with considerable individual variability in maternal serum and breast milk concentrations, and that nursing infants are exposed to this agent through their mothers' milk. These results confirm and extend the findings of a recently published study of paroxetine exposure in 16 breastfed infants.[24]

In the present study, the maternal milk-to-plasma ratio of paroxetine was highly variable, ranging from 0.11 to 1.67. These data were recently confirmed by Stowe and colleagues,[24] who suggest that both the portion of breast milk sampled and the timing of the sampling affect the milk-to-plasma ratio, thus making this formula of limited use in estimating the daily infant dose of paroxetine.

Monitoring the infant serum concentration provides valuable information to determine the degree of exposure. The most direct and relevant indicator of infant exposure is obtained by measuring medication levels in the infant. Single-point determination of infant serum concentration appears to be the most practical method of determining secondary infant exposure. Ideally, pharmacokinetic profiling through multiple blood sampling would provide more useful information on infant drug exposure. However, multiple blood sampling from an infant without a clear indication of complications would be unacceptable and may further aggravate maternal anxiety, depression, and feelings of guilt.

This study employed the most sensitive analytic method reported to date for detecting and quantifying SSRI concentrations in breast milk and serum samples. The limit of quantification obtained in this study was 0.1 ng/mL, whereas previous studies of SSRI concentrations in milk and serum samples have reported values ranging from 1 ng/mL to 20 ng/mL. All of the infant serum samples in the present study were found to be below this limit of detection, indicating that paroxetine was present in only trace amounts in the serum of these infants.

In order to reduce infant exposure, several past studies have suggested discarding a portion of breast milk at the time when the medication concentration in the milk is expected to be at a maximum.[19,26] The merits of discarding this portion of milk, however, may not be applicable in a practical setting. First, determination of the average period of highest drug concentration in milk may not be feasible owing to individual variation in pharmacokinetics. Second, the psychological impact on nursing mothers must be considered; by instituting a regimen of milk disposal, mothers may become concerned enough to decide to discontinue either breastfeeding or medication.

Although the results of this study are promising in that no measurable levels of paroxetine were detected in the serum of infants, several limitations to these findings must

be addressed. First, 8 of the mothers took the antianxiety medication clonazepam at some point during this study. The effects, if any, that concurrent clonazepam use may have on the metabolism or excretion of paroxetine and the other SSRIs have yet to be determined. Second, although no adverse infant behaviors were reported by any of the mothers, the long-term effects of chronic paroxetine exposure through breast milk have yet to be studied. Third, the generalizability of the present findings to very young infants must be addressed. Hepatic maturation in the infant is highly variable, although it usually occurs by 3 months of age.[28] Although only 5 infants in the present study were below 3 months of age, the results are promising in that all of these infants had nonquantifiable levels of paroxetine in their serum, as was the case for the older infants.

The decision to treat nursing mothers with antidepressants should be based on a risk-benefit assessment for each patient. The substantial risk of untreated depression on the well-being of both mother and infant must be balanced against the risk of commonly prescribed antidepressants on the nursing infant. In cases where the benefits of drug treatment outweigh the risks, the use of the SSRI paroxetine is a good choice when accompanied by careful therapeutic monitoring. Accepting the necessity of pharmacologic intervention, the goal of these treatments should be focused on minimizing fetal and neonatal exposure while maximizing clinical improvement in the mother.

CONCLUSION

The current study provides a detailed investigation of paroxetine excretion into breast milk and extends the rapidly growing data on the safety of SSRIs for lactating women. This study is unique in that it involves the largest sample size of any of the SSRI lactation studies and introduces a more sensitive assay methodology than is currently being used to investigate drug concentrations in milk and serum samples. Future research should focus on standardizing the assay techniques and data collection procedures to allow for easier interpretation of the findings.

Drug names: citalopram (Celexa), clonazepam (Klonopin and others), fluoxetine (Prozac), fluvoxamine (Luvox), lorazepam (Ativan and others), paroxetine (Paxil), sertraline (Zoloft).

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