Excretion of Paroxetine Into Breast Milk

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Background: The study was carried out to quantify the excretion of the selective serotonin reuptake inhibitor paroxetine in breast milk.

Method: In 6 lactating women, the concentrations of paroxetine in breast milk and serum were studied at the times for assumed minimum (24 hours after dose intake) and maximum (4–7 hours after dose intake) drug levels in milk. Moreover, a seventh subject was studied with frequent and regular sampling throughout a dose interval of 24 hours at 2 different dose levels.

Results: The mean milk/serum concentration ratios in the first 6 subjects ranged from 0.39 to 1.11 (overall mean ± SD = 0.69 ± 0.29), and the mean estimated dose to the infants ranged from 0.7% to 2.9% (overall mean ± SD = 1.4% ± 0.79%) of the weight-adjusted maternal dose. Based on area-under-the-curve data from the seventh subject, the milk/serum concentration ratio was 0.69 at a dose of 20 mg/day and 0.72 at a dose of 40 mg/day; the estimated relative doses to the infant were 1.0% and 2.0%, respectively. The mean increase in milk paroxetine concentrations from assumed minimum to assumed maximum was 61% (range, 4%–172%; $p < .01$). The mean paroxetine concentration in hindmilk was 78% higher than in foremilk (range, 16%–169%; $p < .01$), an increase that was parallel to the increase in milk triglyceride levels ($r = 0.83$, $p = .005$). No adverse drug reactions or unusual behaviors were reported in the infants.

Conclusion: The study indicates that the relative dose to a suckling infant for paroxetine is lower than that reported for fluoxetine and citalopram and higher than that reported for sertraline and fluvoxamine.

(J Clin Psychiatry 1999;60:519–523)

During the postpartum period, women have a relatively high incidence of psychiatric illness. The mood disorders during this period are often classified into 1 of 3 categories, depending on their severity: "blues," depression, and psychosis. Postpartum depression affects about 13% of women within the first few months after childbirth.[1] Compared with nonchildbearing women, childbearing women have a 3-fold higher relative risk of depression in the first month postpartum.[2] In most women, the depression subsides within 3 to 6 months of onset, but a longer duration is not unusual. Postpartum depression may also represent the start of recurrent episodes of affective disorders.[3]

Children of mothers with postpartum depression run an increased risk of developing depression as well as impaired concentration ability and deficiencies in social problem solving and intellectual function.[4,5] It has been suggested that these impairments are caused by a reduced quality of the mother-child interaction.[6] Besides the severity of the depression, the duration of the mother's depression appears to significantly increase the risk of the child to develop mental deficiencies: children whose mothers recover within 6 months have less risk than those whose mothers are depressed for a longer time.[7]

Nursing is an important opportunity to enhance the quality of the mother-child interaction and is vigorously promoted because of the substantial body of evidence showing that breastfeeding is superior to bottle-feeding in many ways. These include better protection against diarrhea,[8] otitis media,[9] and respiratory and urinary tract infections.[9–11] Moreover, it has been suggested that breastfeeding may diminish the risk of developing type I diabetes mellitus.[12] Breastfeeding has also been linked to a lower prevalence of atopic eczema and food allergy[13] and to an enhanced antibody response to vaccination.[14]

Postpartum depression does not seem to differ from other depressions with respect to the response to antidepressants.[15] The risks of exacerbation and long duration of the depressive symptoms, as well as the possible cognitive and behavioral consequences for the child, imply that treatment with antidepressants and/or psychotherapy should be considered in postpartum depression. If the mothers are told that they should stop breastfeeding when antidepressant treatment is started, some of them will refuse pharmacologic intervention. If they accept this recommendation, their children will not have the benefits of

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Supported by research funds from the Medical Faculty, Umeå University, Sweden.

The authors acknowledge Kerstin Granberg for excellent clinical assistance.

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breastfeeding. Thus, the essential question is whether or not women can continue breastfeeding during treatment with an antidepressant. In this risk-benefit analysis, knowledge with respect to the excretion of the drug into breast milk is of vital importance.

Several case reports have been published concerning tricyclic antidepressants and breastfeeding (for reviews, see references 16 and 17). Some information is available for the selective serotonin reuptake inhibitors (SSRIs) fluoxetine,[18–21] fluvoxamine,[22,23] citalopram,[24–26] and sertraline,[27,28] and a single case report exists regarding paroxetine.[29] The present study was carried out to investigate the excretion of paroxetine in breast milk more thoroughly and to elucidate the intraindividual and interindividual variability and the role of the milk triglyceride content.

METHOD

Subjects

After giving their informed consent, 7 somatically healthy patients participated in this study, which was approved by the Ethics Committee at Umeå University. The patients were recruited from a large pool of patients referred to 2 psychiatric clinics in the area. Their specific diagnoses according to DSM-IV criteria were major depressive disorder (N = 5) and panic disorder (N = 2). The patients were 28 through 35 (mean = 30.1) years old. Their body weights are presented in Table 1. As the polymorphic liver enzyme cytochrome P450 2D6 (CYP2D6) is of major importance for the metabolism of paroxetine,[30] patients were tested with CYP2D6 genotyping[31] after inclusion in the study. All were found to be extensive metabolizers of CYP2D6 substrates. Each subject had been treated with a constant dose of paroxetine for at least 8 days prior to the study days. All subjects took paroxetine once daily in the morning.

Sampling Procedures

In 6 subjects, milk and serum samples were obtained in the morning, 24 hours after the previous dose had been ingested. A new dose was then ingested immediately. Four to 7 hours later, 1 or 2 milk/serum sample pairs were collected. The sampling times were chosen in order to obtain samples representing the trough (minimum) milk concentration and a concentration assumed to be close to maximum.[24] The seventh subject was followed with milk and serum sampling at steady-state 0, 1, 2, 3, 4, 6, 8, and 24 hours after dose intake on 2 occasions (at doses of 20 mg/day and 40 mg/day, respectively) with an interval of 7 weeks.

The mothers were encouraged to breast-feed their infants on all sampling occasions if possible. Several foremilk (before breastfeeding) and hindmilk (at the end of the feed) pairs of milk samples could therefore be obtained. Milk was collected by manual expression, usually from both breasts on the same occasion. However, in the seventh subject, milk from the left and right breast was collected separately during the second sampling period. Blood was collected from the antecubital vein and centrifuged within 30 minutes. Milk and serum were frozen at –20°C until the day of analysis.

Analytical Procedures

Paroxetine in serum and breast milk was assayed by a high-performance liquid chromatography (HPLC) method based upon a method published earlier.[9,13] In brief, 5 mL of 0.3-M Na_3PO_4, 400 µL of diisopropyl ether, and 20 µL of a 20-µM internal standard (imipramine) were added to 1-mL samples of serum or milk. After shaking for 20 minutes and centrifugation for 10 minutes, the samples were frozen at –80°C for 15 minutes. Then, the organic layer was separated on a straight-phase 150 × 4.6–mm Apex Silica column with 3-µm particle size (Jones Chromatography, Mid Glamorgan, United Kingdom) and analyzed on a Waters LC module I (Waters Chromatography, Milford, Mass.) with the ultraviolet detector set at a wavelength of 294 nm. The mobile phase consisted of 65 mL of methanol, 345 mL of acetonitrile, and 1.7 mL of 25% ammonia.

The limit of quantitation for paroxetine was 5 ng/mL in serum and milk, and the method was linear at least up to 300 ng/mL in serum and milk. The intra-assay coefficients of variation were 7.5% in milk and 5.9% in serum at 30 and 50 ng/mL, respectively. The interassay coefficients of variation at the same concentrations were 15.2% in milk and 6.9% in serum.

Milk triglyceride concentrations were determined by enzymatic hydrolysis with subsequent determination of glycerol using a commercial kit (Triglycerides GPO-PAP; Boehringer Mannheim, Mannheim, Germany).

Calculations and Statistics

Areas under the curve (AUC) for serum and milk concentrations from 0 to 24 hours were calculated by means of the trapezoidal rule, using the pharmacokinetic program package Siphar/Win, version 1.13 (Simed SA, Créteil, France). The infant paroxetine dose per kg body weight (D_{infant}) was related to the maternal paroxetine dose per kg body weight using the equation $D_{infant} = C_{milk} \times V_{milk} / D_{mother}$ where C_{milk} = paroxetine concentration in milk, V_{milk} = daily volume ingested by the infant, assumed to be 150 mL/kg, and D_{mother} = maternal daily paroxetine dose per kg body weight.

The statistical tests employed were the Wilcoxon test for paired differences and the Spearman rank correlation test. A p value less than .05 was considered statistically significant.

RESULTS

A total of 58 milk/serum samples were analyzed. The milk concentrations of paroxetine ranged from 5.3 to 145 ng/mL and the serum concentrations from 11 to 188

Table 1. Milk and Serum Paroxetine Concentrations, Milk/Serum Concentration Ratios, and Estimated Infant Doses in Samples From 7 Lactating Women Treated With Paroxetine

Patient No.	Body Weight, kg	Dose, mg/d	Time Postpartum, wk	Milk Paroxetine Concentration, ng/mL[a]	Serum Paroxetine Concentration, ng/mL[a]	Milk/Serum Concentration Ratio[a]	Relative Dose Received by the Infant, %[a,b]
1	64	20	7	75 (66–85)[c]	54 (45–65)[c]	1.39 (1.31–1.47)	3.6 (3.2 –4.1)
		30	16	92 (84–111)[c]	115 (108–118)[c]	0.80 (0.73–0.94)	3.0 (2.7–3.5)
		40	20	88 (45–145)[c]	164 (137–188)[c]	0.54 (0.34–0.88)	2.0 (1.1–3.5)
2	63	20	20	24 (15–37)[c]	17 (11–22)[c]	1.46 (0.71–2.00)	1.1 (0.7–1.8)
		30	30	29 (13–55)[c]	33 (24–39)[c]	0.76 (0.31–1.19)	0.8 (0.4–1.4)
3	67	20	22	33 (20–51)[d]	43 (42–44)[d]	0.77 (0.48–1.16)	1.7 (1.0–2.6)
4	65	20	6	18 (15–21)[e]	43 (32–54)[e]	0.43 (0.39–0.47)	0.9 (0.8–1.0)
5	69	40	8	46 (31–60)[f]	116 (94–137)[f]	0.39 (0.33–0.44)	1.2 (0.8–1.6)
6	52	10	9	8.0 (5.3–9.5)[g]	16 (14–18)[g]	0.51 (0.38–0.61)	0.7 (0.5–0.9)
7	60	20	11	23[h]	33[h]	0.69[h]	1.0[h]
		40	18	90[h,i]	125[h]	0.72[h,i]	2.0[h,i]

[a]Mean (range) unless otherwise noted.
[b]Infant paroxetine dose per kg body weight expressed as a percentage of the maternal paroxetine dose per kg body weight.
[c]Samples obtained 0 (24), 4, and 6 hours after last dose, both foremilk and hindmilk.
[d]Samples obtained 0 (24) and 6 hours after last dose, both foremilk and hindmilk.
[e]Samples obtained 0 (24) and 7 hours after last dose, foremilk only.
[f]Samples obtained 0 (24) and 4 hours after last dose, foremilk only.
[g]Samples obtained 0 (24), 4, and 6 hours after last dose, foremilk only.
[h]Based on area-under-the-curve (AUC) values 0–24 hours after dose intake at steady-state conditions (value given = AUC value/24).
[i]Mean concentration, right and left breast.

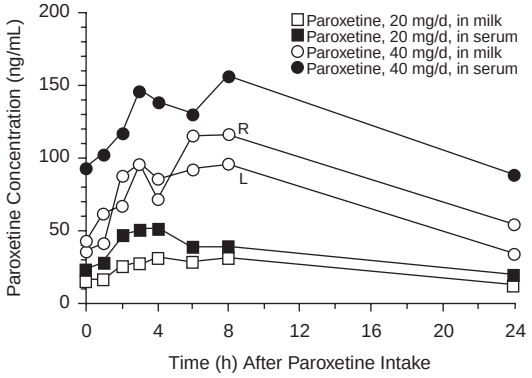
ng/mL (see Table 1). Single milk/serum concentration ratios varied from 0.31 to 2.00 (see Table 1). In the first 6 patients, the individual mean milk/serum ratios ranged from 0.39 to 1.11 (overall mean ± SD = 0.69 ± 0.29). In the same subjects, the estimated individual mean relative doses to the infants ranged from 0.7% to 2.9% (overall mean ± SD = 1.4% ± 0.79%) of the weight-adjusted maternal dose. Based upon AUC values from subject 7 (Figure 1), the milk/serum ratios were 0.69 and 0.72, respectively, and the relative doses to the infant were estimated to be 1.0% and 2.0%, respectively.

Ten pairs of foremilk/hindmilk samples from the same feeds were available. Based upon these (Figure 2), a mean increase in paroxetine concentrations of 78% (range, 16%–169%) from foremilk to hindmilk (mean = 33.4 vs. 52.2 ng/mL; $p < .01$) was observed. Moreover, there was a significant positive correlation between the relative increase in triglyceride levels and the relative increase in paroxetine concentrations (9 samples; $r = 0.83$, $p = .005$). The differences in paroxetine concentrations between the right and left breast in subject 7 (see Figure 1) were also significantly correlated to the differences in triglyceride content ($r = 0.98$; $p < .001$).

The paroxetine concentration-time profiles in milk during the first 6 hours after dose are shown in Figure 3. There was a mean increase of 61% (range, 4%–172%) from the paroxetine concentration 0 (24) hours after dose intake to the highest concentration measured 4 to 7 hours later (mean = 44.3 vs. 78.5 ng/mL; $p < .01$).

The increases in serum and milk trough paroxetine concentrations in the 3 subjects studied at different dose levels are shown in Figure 4. In 2 of the subjects (subjects 1 and 2), the increases in the milk concentrations were small despite the relatively great increases in the corresponding serum level. In the third subject (subject 7), the increase in milk paroxetine concentration was roughly parallel to the corresponding increase in serum at the dose level of 20 to 40 mg/day.

Figure 1. Concentration-Time Profile of Paroxetine in Milk and Serum During a Dose Interval of 24 Hours at Steady State in a Subject First Treated With Paroxetine, 20 mg/day, and Then With Paroxetine, 40 mg/day[a]



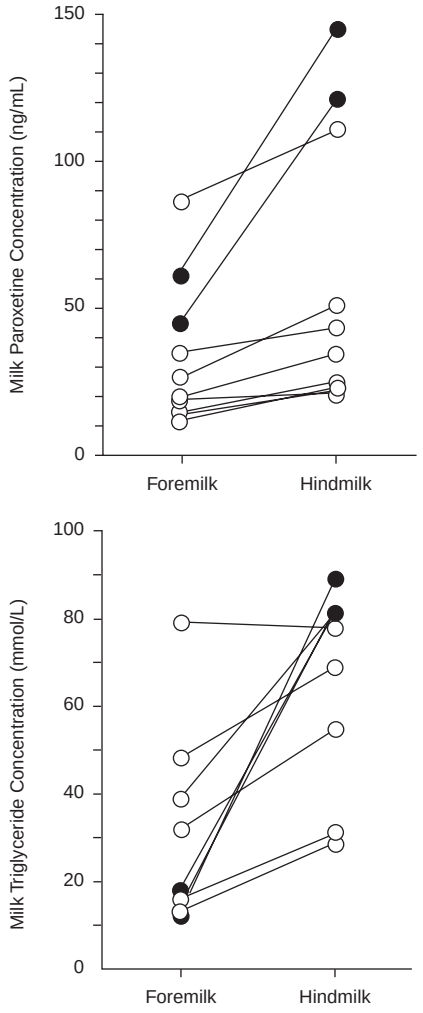
[a]At the dose of 20 mg/day, milk was collected from both breasts, and at the dose of 40 mg/day, from each breast separately. In milk from the right breast, the mean ± SD triglyceride content was generally higher than in milk from the left breast (67.0 ± 14.5 vs. 51.3 ± 19.7 mmol/L). Abbreviations: L = left breast, R = right breast.

The mothers observed no adverse effects or unusual behavior in the infants, and the infants thrived normally during maternal paroxetine treatment.

DISCUSSION

The present study demonstrates that a considerable time-dependent, dose-dependent, and interindividual

Figure 2. Paroxetine Concentrations in Foremilk and Hindmilk (top panel) and Triglyceride Concentrations in Foremilk and Hindmilk (bottom panel) From the Same Feeds[a]



[a]In 1 sample, the milk volume obtained was too low to make it possible to determine the triglyceride content. Two subjects, who had considerable increases both in paroxetine concentration and in triglyceride concentration, are shown separately (filled symbols).

Figure 3. Mean Milk Concentrations of Paroxetine (foremilk samples only) at 0, 4, and 6 Hours After Intake of Paroxetine

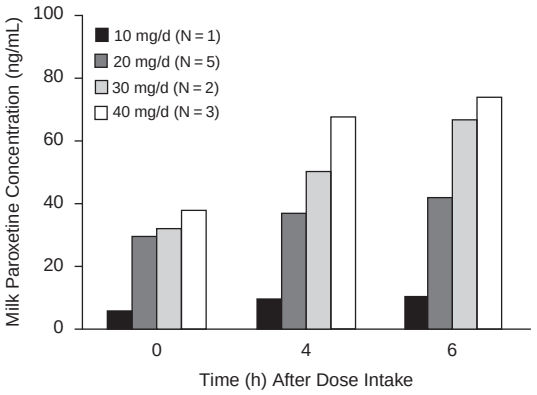
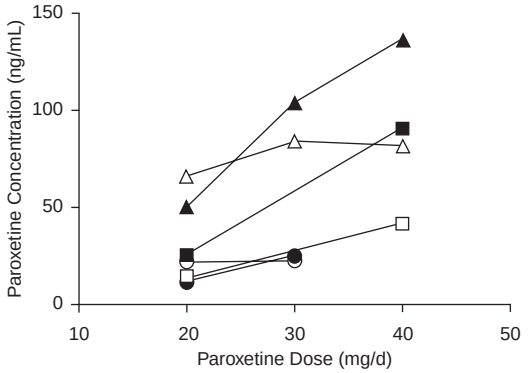


Figure 4. Effect of Maternal Paroxetine Dose on Serum and Breast Milk Paroxetine Concentrations in 3 Women



[a]Only foremilk samples obtained 24 hours after the last dose are included. Filled symbols = serum; open symbols = milk. Triangles = subject 1, circles = subject 2, squares = subject 7.

variability exists in the excretion of paroxetine in breast milk. The variability in milk paroxetine concentrations during a dose interval was generally less than the corresponding variability in serum, but was nevertheless relatively high. Thus, by avoiding breastfeeding during the peak concentration phase in breast milk, infant exposure to paroxetine can be reduced to some extent. If the infant is not nursed during the night, the daily exposure will be lower if the mother ingests the drug in the evening rather than in the morning.

Another important factor for the variability in milk paroxetine concentrations is the milk triglyceride content. This is as expected for a lipophilic drug and has been observed also for citalopram and sertraline.[24,28] A somewhat surprising finding was that the milk paroxetine concentration in 2 of the 3 subjects was relatively stable despite increases in daily maternal doses within the 20- to 40-mg interval. This finding is not consistent with the current knowledge of the processes of drug excretion into breast milk. One possible, although speculative, explanation is that paroxetine binding to lipids or proteins in the milk might be saturated in some subjects; however, to our knowledge, such processes have not been described earlier. The increase in the relative infant dose for subject 7, from whom the most conclusive data are available, is consistent with the dose-dependent pharmacokinetics of paroxetine.[32] As the relative infant dose for paroxetine, in contrast to drugs with linear elimination kinetics, increases with increasing maternal doses, this calculation might be less informative for paroxetine than for other drugs. The demonstration of a definitive relationship between maternal dose and breast milk concentration or relative infant dose would require a larger study group with more than 2 or 3 dose levels for each subject.

For practical reasons, serum or urine from the infants was not obtained in the current study, and the infant paroxetine levels could therefore not be investigated. As such knowledge is important to provide more direct information about infant exposure, studies including infant serum levels are highly warranted. Moreover, studies in a greater number of subjects, including a control group, are needed to determine whether any infant symptoms could be associated with paroxetine exposure. Ideally, long-term neurobehavioral development should also be investigated.

Data on the excretion in breast milk are available also for other SSRIs. For fluoxetine, the relative dose to the infant can be estimated to be 1.2% to 6.2% based on single case reports,[18–20] and 6.5% ± 1.3% (mean ± SD) based on a study of 11 patients.[21] For citalopram, the relative dose has been reported to be 0.7% to 5.9%,[24] 5%,[25] and 5% to 9%,[26] respectively. For fluvoxamine, the relative dose has been calculated to be 0.5%,[22,23] and for sertraline, 0.45%[27] and 1.04% ± 0.46% (mean ± SD).[28] Thus, the relative dose of paroxetine to the infant seems to be lower than for fluoxetine and citalopram, but higher than for fluvoxamine and sertraline. However, because the SSRIs are metabolized by different hepatic enzymes that may mature at different rates in the infant,[17] the clinical importance of the differences in infant doses is largely unknown.

In the present study, no clinical signs of adverse drug reactions were observed in the infants. On the contrary, a possible association between intake of fluoxetine through breast milk and colic in an infant has been described, and high infant plasma concentrations were detected.[21] Therefore, fluoxetine treatment is generally discouraged during breastfeeding. Although no adverse drug reactions have been reported for other SSRIs,[22–29] the number of subjects exposed is too small to conclude with certainty that breastfeeding could be considered as safe with these drugs.

If lactating mothers wish to breast-feed during paroxetine treatment, they should be treated with the lowest possible effective dose in order to minimize infant exposure. Moreover, the mothers should be observant for possible adverse effects in the infant, such as poor suckling, irritability, increased crying, and diarrhea. By avoiding breastfeeding during the peak concentration phase in breast milk, for example by ingesting the daily dose in the evening if the infant is not nursed during the night, infant exposure might be reduced to some extent.

Drug names: citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft).

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