Excretion of citalopram in breast milk

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Aims The objective of this study was to measure the secretion of the selective serotonin uptake inhibitor citalopram in breast milk.

Methods The excretion of citalopram in breast milk was studied at steady-state conditions in two patients with depression and in one healthy volunteer after ingestion of a single dose citalopram.

Results Milk/serum concentration ratios based on single pairs of samples from the two patients ranged from 1.16 to 1.88. Based on milk concentration data from the patients, the absolute dose ingested by a suckling infant would be 4.3–17.6 $\mu g\ kg^{-1}\ day^{-1}$, and the relative dose 0.7–5.9% of the weight-adjusted maternal dose. Based on area-under-the-time-concentration curves from the healthy volunteer, the milk/serum ratio was 1.00, the absolute dose to the infant during steady-state conditions would be 11.2 $\mu g\ kg^{-1}\ day^{-1}$ and the relative dose 1.8% of the weight-adjusted maternal dose.

Conclusion The study shows that the relative dose to a suckling infant is close to that reported for fluoxetine, and higher than reported for fluvoxamine, paroxetine and sertraline.

Keywords: breast milk, citalopram, lactation, selective serotonin reuptake inhibitors

Introduction

Post-partum depression is said to occur in 10% of all childbearing women [1], and treatment with antidepressants is sometimes required. Antidepressant therapy for mothers with post-partum depression is complicated by the need to consider possible drug effects on the nursing infant. Tricyclic antidepressants as well as selective serotonin reuptake inhibitors are excreted in breast milk [2–4], but the effects of these drugs on suckling infants are to a great extent unknown. In recent reviews, it is concluded that tricyclic antidepressants, with the exception of doxepin, most probably are safe, whereas fluoxetine should be avoided in lactating mothers [3–5]. So far, no study has been published on the secretion of the selective serotonin reuptake inhibitor citalopram in breast milk.

Methods

Subjects

After giving their informed consent, two patients with depression (Subjects 1 and 2) and one healthy volunteer (Subject 3) participated in this study, which was approved by the Regional Ethics Committee. The subjects had no somatic disease as assessed by medical history, physical examination and routine blood chemistry tests, and they were found to be extensive metabolizers with respect to the polymorphic liver enzymes CYP2C19 and CYP2D6 which are involved in the metabolism of citalopram [6].

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Subject 1 was 27 years old, had a body weight of 67 kg, was treated with citalopram 20 mg day^{-1}, and was studied 2 months post partum. Subject 2 was 30 years old, had a body weight of 70 kg, was treated with citalopram 40 mg day^{-1} and alprazolam 0.75 mg day^{-1}, and was studied 4 months post partum. Serum and pre-feed breast milk samples were obtained immediately before the daily dose, and 4 h later.

Subject 3 was 33 years old, had a body weight of 64 kg, and was studied 10 months post partum. After intake of 40 mg citalopram in a single dose, venous blood samples were taken after 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 and 72 h. Breast milk was obtained after 2, 4, 6, 8, 14, 24, 48 and 72 h, using a manual breast pump. All milk and serum samples were stored at -20° C until analysis.

Analytical procedures

Citalopram and its metabolites desmethylcitalopram and didesmethylcitalopram in serum and breast milk were analysed by a high performance liquid chromatography method based upon another method developed in our laboratory [7]. In short, to 1 ml samples of serum or milk were added 5 ml 0.3 M Na_3PO_4, 400 µl diisopropylether, and 20 µl of a 20 µM internal standard [Lundbeck N-7084; 5-(pyrlidinylpropyliden)-10, 11-dihydro-5H-dibenzo(a,d); H. Lundbeck A/S, Copenhagen, Denmark]. After shaking for 20 min and centrifugation for 10 min, the samples were frozen at -80°C for 15 min and the organic layer was separated and analysed on a straight phase 150 × 4.6 mm Apex Silica column with 3 µm particle size (Jones Chromatography, Mid Glamorgan, United Kingdom). The mobile phase consisted of 65 ml methanol, 345 ml aceto-

nitrile and 1.6 ml 25% ammonia with a flow of 2.2 ml min^{-1}. The injection volume was 50 μl and the ultraviolet detector was operated at 254 nm. The limits of quantitation for citalopram and its metabolites were 5 nmol l^{-1} in serum and 10 nmol l^{-1} in milk. The method was linear at least up to 600 nmol l^{-1}. The intraassay coefficients of variation in serum at 50 nmol l^{-1} were 5.2% for citalopram, 8.5% for desmethylcitalopram, and 6.0% for didesmethylcitalopam. The intraassay coefficients of variation in milk at 100 nmol l^{-1} were 8.3% for citalopram, 10.6% for desmethylcitalopram, and 8.3% for didesmethylcitalopam.

Milk triglyceride concentrations were determined by enzymatic hydrolysis with subsequent determination of glycerol, using a commercial kit (Triglycerides GPO-PAP; Boehringer Mannheim, Mannheim, Germany). Milk pH was determined using a Corning pH Meter 240 (Corning Glass Works, Corning, New York, USA) with an Ingold U402-M6-S7/100 glass electrode (Mettler-Toledo AG, Urdorf, Switzerland).

Data analyses and calculations

The absolute daily dose of citalopram ingested by the infant per kg body weight (D_{inf}) was calculated using the equation

$$D_{inf} = C_{ss(milk)} \times V_{milk} \quad (1)$$

where $C_{ss(milk)}$ = steady state concentration in milk and V_{milk} = daily volume ingested by the infant; assumed to be 0.15 l kg^{-1} body weight. For dosage calculations, concentrations in moles per liter were converted into grams per liter (1 mol of citalopram = 324.4 g).

The relative daily citalopram dose ingested by the infant (D_{rel}) was calculated using the equation

$$D_{rel} = D_{inf}/D_{mat} \times 100 \quad (2)$$

where D_{mat} = maternal daily citalopram dose kg^{-1} body weight.

For Subject 3, pharmacokinetic parameters were calculated using the pharmacokinetic programme package Siphar/Win, version 1.13 (Simed SA, Créteil, France). The terminal elimination rate constant (λ_z) was calculated by means of the peeling procedure. Areas under the serum and milk time-concentration curves (AUC) were calculated by means of the linear trapezoidal rule from 0 to 72 h, and thereafter by means of λ_z from 72 h to infinity. Mean residence time (MRT) was calculated as AUMC/AUC, in which AUMC is the area under the concentration-time product *vs* time curve from zero to infinity. Oral clearance was calculated as dose/AUC, assuming complete absorption. $C_{ss(milk)}$ was estimated as AUC/24 h.

Results

Subjects 1 and 2

Serum and milk concentrations of citalopram, milk pH and triglyceride concentrations, and milk/serum concentration ratios (M/S ratios) are presented in Table 1. Assuming that the citalopram concentrations measured after 0 and 4 h represent minimum and maximum, respectively, the absolute dose ingested by the infant (D_{inf}) can be estimated to be between 13.9 and 17.6 μg kg^{-1} day^{-1} for Subject 1, and between 4.3 and 10.9 μg kg^{-1} day^{-1} for Subject 2. The relative dose ingested by the infant (D_{rel}) can be estimated to be 4.6–5.9% for Subject 1, and 0.7–1.8% for Subject 2.

On another occasion, milk was obtained from Subject 1 at the start and end of a feed. Milk citalopram concentrations at that time were 280 and 355 nmol l^{-1}, respectively, and milk triglyceride concentrations were 46.0 and 66.3 mmol l^{-1}, respectively. Thus, milk citalopram concentrations increased by 27% and milk triglyceride concentrations by 44% during this feed.

The mothers observed no adverse effects in the infants.

Subject 3

Oral clearance of citalopram was 370 ml min^{-1}, and the elimination half-life was 30.8 h. No metabolites were detected in serum or in milk. The time course of citalopram in milk roughly paralleled the respective serum time profile (Figure 1), although it was somewhat delayed (MRT_{serum} = 35.5 h, MRT_{milk} = 39.5 h). AUC for milk and serum were 5561 and 5540 nmol l^{-1} h, respectively, giving an M/S ratio of 1.00. Milk pH was high, ranging from 7.7 to 8.1. Milk triglyceride concentrations varied between 33.6 and 49.2 mmol l^{-1} the first 24 h, and were 26.1 and 20.8 mmol l^{-1} after 48 and 72 h, respectively. Based on AUC values, the absolute dose ingested by the infant during steady state conditions (D_{inf}) would be 11.2 μg kg^{-1} day^{-1}, and the relative dose (D_{rel}) would be 1.8%.

Discussion

The weight-adjusted daily citalopram dose ingested by the infants was calculated to be 0.7–5.9% of the maternal dose on the basis of concentration data from the patients, and 1.8% on the basis of AUC data from the healthy volunteer. Since errors always are associated with estimates from single concentrations, the relative dose calculated on the basis of AUC data probably is the more reliable. Ideally, more than two samples should have been obtained also from the patients. The intention with the patient sampling was to obtain one sample representing the trough milk concentration (at the time of the dose intake), and one sample representing a concentration close to maximum (4 h after the dose intake). The average drug exposure to the infant during a 24 h period would be somewhere between these two extreme values. In the healthy volunteer, who was followed more closely than the two patients, the maximum milk concentration of 122 nmol l^{-1} was found 6 h after a single dose intake. The increases in milk concentrations between 0 and 4 h in Subjects 1 and 2 were 75 and 136 nmol l^{-1}, respectively. Considering that Subject 1 was treated with 20 mg day^{-1} and Subjects 2 and 3 were treated with 40 mg day^{-1}, the increases from the trough to the highest concentrations measured correspond well with each other. Consequently, it seems reasonable to conclude that the concentrations found in Subjects 1 and 2 after 4 h are close to maximum, and that the time to achieve the maximum milk concentration was extraordinarily long in Subject 3. However, we cannot completely rule out that

Table 1. Milk pH and triglyceride concentrations, milk and serum concentrations of citalopram and metabolites, and milk/serum concentration ratios in two lactating mothers.

Time after dose intake (h)	*Milk triglyceride concentration (mmol l^{-1})*	*Milk pH*	*Serum citalopram/ desmethylcitalopram/ didesmethylcitalopram concentrations (nmol l^{-1})*	*Milk citalopram/ desmethylcitalopram/ didesmethylcitalopram concentrations (nmol l^{-1})*	*Milk/serum citalopram concentration ratio*
Subject 1					
0 (24)	35.3	6.76	152/48/6	286/NQ/NQ	1.88
4	40.7	6.60	214/49/NQ	361/NQ/NQ	1.69
Subject 2					
0 (24)	17.2	6.63	76/36/17	88/NQ/NQ	1.16
4	15.0	6.79	136/38/11	224/NQ/NQ	1.65

NQ = not quantifiable (limit of quantitation 5 nmol l^{-1} in serum, 10 nmol l^{-1} in milk).

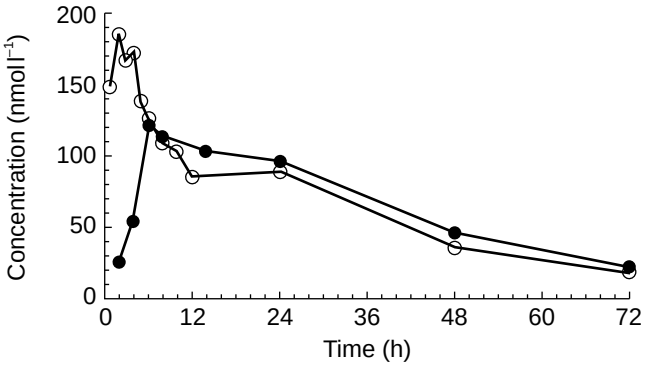

Figure 1 Concentrations of citalopram in serum (○) and breast milk (●) from a healthy, lactating woman after a single oral dose of 40 mg citalopram. The metabolites desmethylcitalopram and didesmethylcitalopram were not detected, either in serum (limit of quantitation 5 nmol l^{-1}) or in milk (limit of quantitation 10 nmol l^{-1}). Area under the curve for milk: area under the curve for serum = 1.00.

using the 4 h time point from Subjects 1 and 2 will be an underestimation of the maximum dose to the infant.

In addition to the significance of whether equilibrium of distribution has been reached or not, milk triglyceride content and milk pH may account for some of the variability in the M/S ratios [8, 9]. Concentrations of lipophilic drugs are generally increased in milk with high triglyceride levels [2], and Subject 1, who had higher triglyceride levels than Subject 2, also had higher M/S ratios of citalopram. The milk triglyceride content also increases during a feed, and the concentrations of tricyclic antidepressants such as nortriptyline, doxepin and dothiepin have been reported to increase by 50–100% in milk during a feed [9–11]. In the present study, we observed a 27% increase in the milk concentration of citalopram during a feed. This is somewhat lower than for tricyclic antidepressants and consistent with the lower octanol/water partition coefficient for citalopram (3.7) than for nortriptyline (50.1) [12, 13]. As citalopram is a weak base (pKa 9.5), it tends to concentrate in milk with a low pH compared with milk with a high pH. Thus, the remarkably high milk pH could be one factor contributing to the relatively low M/S ratio in Subject 3.

Data on the excretion in breast milk are available also for other selective serotonin reuptake inhibitors. For fluoxetine, the relative dose to the infant can be estimated to be 1.2–6.2% based on three single case reports [14–16], and 6.5 ± 1.3% (mean ± s.d.; maximum 17.2%) based on a recent study of 11 cases [17]. (Our own calculations, based on the information presented in the reports [14–17], including the active metabolite norfluoxetine and assuming a maternal body weight of 70 kg when not stated). For fluvoxamine, sertraline and paroxetine, the relative dose to the infant can be calculated to be 0.5%, 0.45 and 0.34%, respectively [18–20]. Drug disposition data for selective serotonin reuptake inhibitors in infants are lacking, and it is therefore unknown whether the differences in relative doses to the infant are of clinical importance. Nevertheless, a possible association between colic in an infant and the intake of fluoxetine with milk has been described [16], and it is recommended that the administration of fluoxetine should be avoided in lactating mothers [3–5]. Taking into account that the relative citalopram dose to the infant is close to the values reported for fluoxetine, it seems pertinent to be cautious also with the administration of citalopram to lactating mothers.

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