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Sertraline in Paired Blood Plasma and Breast-Milk Samples from Nursing Mothers

SEETAL DODD[1], ANDREW STOCKY[2], ANNE BUIST[1], GRAHAM D. BURROWS[1], KAY MAGUIRE[1] and TREVOR R. NORMAN[1]*
[1] *Department of Psychiatry, University of Melbourne, Austin & Repatriation Medical Centre, Heidelberg, Victoria 3084, Australia*
[2] *The Melbourne Clinic, Church Street, Richmond, Victoria, Australia*

Paired blood and breast-milk samples were collected from 10 nursing mothers receiving sertraline. Samples were collected at steady state when the patients had been taking stable doses of 50–150 mg/day over several weeks. Sertraline concentrations in both fluids were determined using a specific, validated HPLC method. Plasma and milk concentrations showed a wide inter-individual variability for the same dose. Mean plasma concentrations were linearly related to dose, but this was not the case for breast-milk concentrations. An overall milk to plasma ratio of $1{\cdot}76 \pm 1{\cdot}72$ was recorded. The average dose to the infants ranged from 1·1 to 31·1 μg/kg, which is less than 2 per cent of the maternal dose per day. Further studies are necessary to determine if these doses are detrimental to the development of the infant. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS — sertraline; post-partum depression; breast feeding; infant exposure

INTRODUCTION

The decision to use psychotropic medications in the post-partum period is controversial (Austin and Mitchell, 1998). Nevertheless, in some cases medication use is essential for the well-being of the mother. In post-partum depression, antidepressant medications are frequently prescribed for lactating women and the question of whether or not to breast feed is raised. An important consideration is the extent to which the drug passes into breast milk and the consequent exposure of the infant to the drug (Buist *et al.*, 1990). For most antidepressant drugs the relative dose received by the infant is less than 2–3 per cent of the maternal dose (Spigset and Hagg, 1998). Despite this relatively low exposure, some adverse effects have been reported in breast-fed infants following maternal consumption of antidepressants (Matheson *et al.*, 1985). Little systematic research has been performed on the excretion of antidepressant drugs into breast milk. Most reports consist of a small series of cases or single case reports. Further case series are necessary to inform clinical decision making, particularly with newer antidepressants which are more likely to be used as the drugs of first choice. The present study reports plasma and breast-milk levels of sertraline in 10 nursing mothers.

METHODS

Patients

Ten breast-feeding women and their infants were enrolled in the study. The mean age of the mothers was 34 years (range 31–37 years). All of the women met DSM-III-R criteria for major depression. Informed consent was obtained from all participants and the protocol was approved by the Ethics in Human Research Committee of the Austin and Repatriation Medical Centre. All subjects received sertraline as their only medication. The sertraline dosage was adjusted until depressive symptoms improved.

Samples

Maternal blood and breast-milk samples were obtained at steady state (more than 2 weeks after a

* Correspondence to: Trevor R. Norman, Department of Psychiatry, University of Melbourne, Austin & Repatriation Medical Centre, Heidelberg, Victoria 3084, Australia.

fixed dose of drug). Blood was collected by venipuncture into 10 ml lithium heparin tubes, centrifuged at 1000 *g* for 10 min, the plasma removed and stored at −20°C in polypropylene tubes until analysed. Milk was expressed by the mother into a plain collection jar and stored at −20°C until analysed.

Analysis of sertraline in plasma and milk

Aliquots of plasma (1·0 ml) were mixed with clomipramine (internal standard, 200 ng in 200 µl) in glass extraction tubes. Sodium carbonate (0·5 ml of 0·6M aqueous solution, pH 10) was added to the plasma and the samples were extracted with 3 ml of hexane-ethyl acetate (90 : 10 v/v) by vortexing for 2 min. After centrifugation (10 min at 1000 *g*) the organic phase was aspirated to a clean glass tube and the compounds back-extracted into hydrochloric acid (0·25 ml of 0·1 M) by vortex mixing. The organic layer was discarded and the aqueous layer dried at 50°C under a stream of air. The residue was reconstituted in mobile phase and injected into the HPLC.

For milk samples aliquots (1 ml) were placed in glass extraction tubes and pre-washed with 4 ml of ethyl acetate by gentle inversion of the stoppered tubes. The mixture was allowed to stand for 5 min and the organic layer discarded. Internal standard (clomipramine, 200 ng in 200 µl) was added and the drugs extracted as for the plasma specimens. Following back-extraction into hydrochloric acid, a third extraction was carried out. Sodium hydroxide (0·25 ml of 6M solution) was added to the acid layer and the drugs extracted into hexane (1 ml). The organic layer was separated into fresh tubes and dried in a stream of air. The residue was reconstituted in mobile phase and injected into the HPLC.

Chromatography was performed using a Shimadzu LC-IOAT liquid chromatograph with a SIL-10AXL autoinjector and a SPD-10A UV-visible detector set at a wavelength of 205 nm. Data were collected using a CBM-10A communications bus module interfaced to a PC. Separations were achieved with an Alphabond C18, 150 × 3·9 mm column with a 7·5 × 4·6 mm guard column (Alltech, Baulkham Hills, Australia) and a mobile phase of 50 mM KH_2PO_4 acetonitrile (40 : 60 v/v) at a flow rate of 1·0 ml/min. Retention time was 5·3 min for sertraline and 6·2 min for clomipramine. For both plasma and milk, the limit of detection was 5 ng/ml. The assay demonstrated linearity in the range 10–200 ng/ml. The within run coefficient of variation was < 15 per cent at 10 and 80 ng/ml for both milk and plasma.

Calculation of infant dose

An average milk intake of 0·15 l/kg/day was assumed (Bennett, 1996), together with an oral bioavailability of 100 per cent. Using the concentration of drug in breast milk, the dose to the infant can be calculated. In the absence of breast-milk concentrations, the infant dose can be calculated according to the formula $C_{ss} \times M/P \times V_{milk}$ where C_{ss} is maternal steady state concentration and M/P is the milk to plasma ratio (Atkinson *et al*., 1988).

RESULTS

Paired plasma and breast-milk samples were collected from 10 women treated with sertraline for a minimum of 2 weeks. Doses of drug ranged from 50 to 150 mg/day. Individual data for sertraline concentrations are presented in Table 1. Mean plasma (±SD) sertraline concentration was 29 (±17) ng/ml and mean milk concentration was 47 (±62) ng/ml. For each subject, a milk to plasma ratio was calculated and ranged from 0·12 to 5·18, with a mean of 1·76 ± 1·72. The ratio did not appear to depend on dose, the correlation between dose and ratio being not statistically significant ($r = -0{\cdot}08$; $p > 0{\cdot}1$, Spearman rank correlation). While breast-milk concentrations were not linearly related to dose ($r = 0{\cdot}26$, $p > 0{\cdot}1$, Spearman rank correlation) plasma concentrations showed a significant linear relationship to dose ($r = 0{\cdot}92$, $p < 0{\cdot}0005$, Spearman rank correlation).

For the women treated, clinical response to sertraline was regarded as satisfactory. Formal ratings of the severity of depression were not made, but based on clinical impression at the time of the specimen collection, all were rated as mild to moderately ill.

DISCUSSION

The data from this study confirm that sertraline passes into the breast milk of nursing mothers, often at levels exceeding those in the plasma. A notable feature of the breast-milk levels is their wide inter-individual variation for patients receiving the same oral dose. The dose of drug to which the infant is exposed by breast feeding is relatively small, rang-

Table 1. Sertraline concentrations from paired samples of plasma and breast milk from 10 women

Pair	Time since last dose (h)	Daily dose (mg)	Plasma sertraline (μg/l)	Milk sertraline (μg/l)	Milk to plasma ratio	Infant dose* (μg/kg)
1	4	50	17·0	17·0	1·00	2·6
2	12	50	11·4	8·9	0·78	1·3
3	30	50	11·0	23·0	2·09	3·5
4	26	50	23·0	100·0	4·35	15·0
5	3	50	20·0	41·0	2·05	6·2
6	6	100	29·3	30·7	1·05	4·6
7	12	100	27·8	18·6	·67	2·8
8	20	150	48·6	16·0	·33	2·4
9	1	150	62·7	7·3	·12	1·1
10	26	150	40·0	207·0	5·18	31·1
Mean ± SD			90 ± 46	47 ± 62	1·76 ± 1·72	7·06 ± 9·36

* Infant consumes 0·15 l/kg breast milk per day.

ing from 1·1 to 31·1 μg/kg (Table 1). Expressed as a percentage of the maternal dose, this is less than 2 per cent. Confirmation of this low exposure was obtained in two infants for whom blood specimens were obtained. In neither sample was sertraline detected. The result needs to be interpreted with caution since the volume of blood was small (~0·5 ml) and the detection limit of the assay relatively modest. Using a conservative estimate of the minimum quantifiable amount of drug as twice the detection limit, i.e. 10 ng/ml, it can be estimated that these infant samples contained < 20 ng/ml of sertraline. Clinical observations suggested no untoward effects in the infants as a result of this level of exposure to sertraline. In previous studies, both detectable levels of sertraline in infant plasma and adverse effects of the exposure have been reported. Sertraline levels of < 5 ng/ml were measured in the serum of three infants following breast feeding by sertraline-treated mothers and desmethylsertraline levels were ⩽10 ng/ml in nine children from a group of 11 mother–infant pairs studied (Stowe *et al*., 1997). In similar studies, sertraline levels in the infants were either not detected (Altshuler *et al*.,, 1995; Kristensen *et al*., 1998) or near the limit of detection of the drug assay (Mammen *et al*., 1997; Wisner *et al*., 1998). Despite these low concentrations of drugs, two probable cases of adverse neonatal reactions have been reported (Rohain, 1997). Agitation, sedation and developmental difficulties which reversed on drug cessation were noted in these two infants.

The data in this study generally agree with other reports that the milk to plasma ratio for sertraline is about 2 and that based on this ratio the infant dose is about 2–3 per cent of the maternal dose. While such exposure is low and can be used to reassure breast-feeding mothers, other kinetic factors need to be taken into account in relation to recommendations as to the timing of the feeding. Differences in breast-milk concentrations have been noted with respect to fore milk and hind milk for sertraline (Stowe *et al*., 1997) and other antidepressants (Buist *et al*., 1993). Hind milk tends to have higher concentrations than fore milk due to its more lipophilic nature. The relationship of the time of the dose to the time of breast feeding can also help to reduce the exposure of the infant to the drug. Peak breast-milk concentrations tend to lag behind those in plasma. For sertraline it has been estimated that peak breast-milk concentrations occur 7–8 h after a dose, with a minimum at 22–24 h (Stowe *et al*., 1997). Breast feeding is probably best carried out immediately before a dose.

In this study *N*-desmethyl sertraline, the main metabolite of sertraline, was not quantitated. In predictive animal pharmacological models of depression this metabolite is inactive, while its effect on serotonin reuptake is significantly less than that of the parent drug (Doogan and Caillard, 1988). It is unlikely that this metabolite contributes to any therapeutic activity of the compound, but its role in adverse effects cannot be ignored. Further studies are necessary to explore this potential relationship. In breast-feeding women treated with sertraline (and other antidepressants), routine monitoring of breast-milk drug levels may be justified. Monitoring of infant plasma levels may also be justified, par-

ticularly where the child demonstrates adverse effects or developmental difficulties.

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REFERENCES

Altschuler LL, Burt VK, McMullen M, Hendrick V. 1995. Breastfeeding and sertraline: a 24 hour analysis. *J Clin Psychiat* **56**: 243–245.

Atkinson HC, Begg EJ, Darlow BA. 1988. Drugs in human milk — clinical pharmacokinetic considerations. *Clin Pharmacokin* **14**: 217–240.

Austin MPV, Mitchell PB. 1998. Use of psychotropic medications in breast-feeding women: acute and prophylactic treatment. *Australian N Zealand J Psychiat* **32**: 778–784.

Bennett PN. 1996. *Drugs and Human Lactation* (2nd edn). Elsevier: Amsterdam; 67–74.

Buist A, Norman TR, Dennerstein L. 1990. Breast feeding and the use of psychotropic medication: a review. *J Affect Disord* **19**: 197–206.

Buist A, Norman TR, Dennerstein L. 1993. Plasma and breast-milk concentrations of dothiepin and northiaden in lactating women. *Hum Psychopharmacol* **8**: 29–33.

Doogan DP, Caillard V. 1988. Setraline: a new antidepressant. *J Clin Psychiat* **49** (Suppl.): 46–51.

Kristensen JH, Ilett KF, Dusci LJ, Hackett LP, Yapp P, Wojnar-Horton RE, Roberts MJ, Paech M. 1998. Distribution and excretion of sertraline and N-desmethylsertraline in human milk. *Br J Clin Pharmacol* **45**: 453–457.

Mammen OK, Perel JM, Rudolph G, Foglia JP, Wheeler SB. 1997. Sertraline and norsertraline levels in three breastfed infants. *J Clin Psychiat* **58**: 100–103.

Matheson I, Panele H, Alertsen AR. 1985. Respiratory depression caused by N-desmethyldoxepin in breast milk. *Lancet* **ii**:1124.

Rohain A. 1997. Drug distribution in human milk. *Australian Prescriber* **20**: 84.

Spigset O, Hagg S. 1998. Excretion of psychotropic drugs into breast milk: pharmacokinetic overview and therapeutic implications. *CNS Drugs* **9**: 111–134.

Stowe ZN, Owens MJ, Landry JC, Kilts CD, Ely T, Llewellyn A, Nemeroff CB. 1997. Sertraline and desmethylsertraline in human breast milk and nursing infants. *Am J Psychiat* **154**: 1255–1260.

Wisner KL, Perel JM, Findling RL. 1996. Antidepressant treatment during breast-feeding. *Am J Psychiat* **153**: 1132–1137.

