Distribution and excretion of sertraline and *N*-desmethylsertraline in human milk

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Aims To characterise milk/plasma (M/P) ratio and infant exposure, for sertraline and *N*-desmethylsertraline, in breast-feeding women taking sertraline for the treatment of depression.

Methods Eight women (mean age 28 years) taking sertraline (1.05 mg kg^{-1} day^{-1}) and their infants (mean age 5.7 months) were studied. Sertraline and *N*-desmethylsertraline in plasma and milk were measured by high-performance liquid chromatography over a 24 h dose interval at steady-state. M/P values were estimated from area under the plasma and milk concentration-time curves. All milk produced was collected over the dose interval. Infant exposure was estimated as the product of actual or estimated milk production, and average drug concentration in milk, normalized to body weight and expressed as a percentage of the weight-adjusted maternal dose.

Results Mean milk production was 321 ml day^{-1} (range 34–974 ml). Mean M/P values of 1.93 and 1.64 were calculated for sertraline and *N*-desmethylsertraline respectively. Infant exposure estimated from actual milk produced was 0.2% and 0.3% of the weight-adjusted maternal dose for sertraline and *N*-desmethylsertraline (as sertraline equivalents) respectively. When calculated from estimated milk production (0.15 l kg^{-1} day^{-1}), infant exposure was significantly greater ($P<0.0001$) at 0.90% and 1.32% for sertraline and *N*-desmethylsertraline respectively. Neither sertraline nor its *N*-desmethyl metabolite could be detected in plasma samples from the four infants tested. No adverse effects were observed in any of the eight infants and all had achieved normal developmental milestones.

Conclusions Irrespective of the method of calculation of infant exposure, the mean total dose of sertraline and its *N*-desmethyl metabolite transmitted to infants via breast-feeding is low and unlikely to cause any significant adverse effects.

Keywords: sertraline, *N*-desmethylsertraline, human milk, infant dose

Introduction

Depression affects some 3 to 12% of the population each year, and is approximately twice as frequent in women as men [1, 2]. The rate of new psychiatric episodes in women increases markedly in the first 3 months after childbirth, with between 10 and 15% of mothers experiencing depression [3]. Sertraline is a derivative of naphthylamine that belongs to the selective serotonin (5-HT) reuptake inhibitor (SSRI) group of antidepressants [4]. The SSRIs are being prescribed increasingly for the treatment of postnatal depression, posing a dilemma for mothers who wish to breast-feed their infants, but who are concerned about the infant's exposure to the medication. Published information on the distribution of sertraline into human milk is limited to a single case report [5] and a conference abstract outlining a study of nine subjects [6]. Comprehensive characterisation of the transfer of drugs into human milk involves the measurement of milk/plasma (M/P) distribution ratio and the average concentration of drug in milk over a dose interval [7]. Ideally, these data should be obtained by measurement of areas under the milk and plasma concentration-time curves (AUC) at steady state [8]. Using this experimental design, the present study measured M/P ratios and mean infant exposure for sertraline and its major metabolite *N*-desmethylsertraline.

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Methods

Materials

Desipramine hydrochloride was obtained from Ciba-Geigy Australia Ltd. Sertraline and *N*-desmethylsertraline reference standards were obtained from Pfizer Pty Ltd (Australia).

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Isopropylether was obtained from Aldrich Chemical Company Inc. All other chemicals were of analytical grade.

Patients

Eight breast-feeding women, and their infants were enrolled in the study. The women's mean age was 27.9 years (range 23.9–31.6 years) and their mean body weight was 71.1 kg (range 54.0–105.0 kg). Seven of the women were maintained on a single daily oral dose of 50 mg sertraline whilst the eighth was taking 200 mg sertraline once daily. Their infants (six males and two females) had a mean body weight of 7.93 kg (range 4.95–11.3 kg) and were a mean of 5.7 months of age (range 1.8–14.2 months) at the time of the study. Therapy with sertraline had commenced a mean of 2.1 months (range 1.18–4.25 months) prior to the study day and all participants were considered to be at steady-state.

Study protocol

The study design was approved by the Research and Ethics Committees of the King Edward Memorial Hospital, Centre for Women's Health. Written informed consent was obtained from all participants. The women were admitted to the research ward at 07.30 h, and had an intravenous cannula inserted into a forearm vein prior to the morning dose of sertraline at 08.00 h. Venous blood samples (8 ml) were collected from the cannula into heparinised tubes, at 0, 1, 2, 3, 4, 6 and 8 h post dose, and by venepuncture at 12 and 24 h. At the same time intervals both breasts were emptied via an electric or manual breast pump and the volume of milk was recorded. Samples of milk (15 ml) were retained for drug assay and the remainder made available to bottle feed the infants. The women were discharged from hospital after the 8 h samples and milk and plasma samples at 12 and 24 h post dose were collected by a research assistant who visited the patient at home. The infants were fed with stored breast milk for the duration of the study. Four women gave consent for a heparinised venous blood sample (0.5–1 ml) to be taken from their infant for subsequent drug assay.

H.p.l.c. analysis of sertraline and N*-desmethylsertraline in plasma and milk*

Aliquots of plasma (0.5 ml) were mixed with desipramine (internal standard; 200 ng in 0.02 ml of an aqueous solution) in 10 ml screw-capped disposable polypropylene tubes. Sodium tetraborate (1 ml of 2% w/v; pH 9.2) was added to the plasma and the samples were extracted with 8 ml of isopropylether by shaking vigorously for 5 min. After centrifugation (5 min at 1500 *g*), the organic phase was aspirated to a clean tube and the compounds back-extracted into 0.2 ml of 0.1 M H_3PO_4 by shaking vigorously for 5 min. After further 5 min centrifugation, the organic phase was aspirated and discarded. The uncapped aqueous acid phase was centrifuged for 10 min at 1500 *g*. The sample was then placed under a stream of N_2 in a water bath at 50° C for 30 s to remove the last traces of isopropylether. Aliquots (0.08 ml) were injected directly onto the h.p.l.c. Unknown samples were interpolated from a linear plot of the peak height ratio for drug : desipramine *vs* known concentrations of drug in plasma. The plasma standard curves were linear over the range (0.05–0.5 mg base l^{-1}) with a correlation coefficient of 0.996–0.997. The within-run coefficients of variation (CV) for the assay were 8.6% and 2.4% at 0.04 and 0.4 mg l^{-1} respectively ($n=5$) for sertraline and 10.9% and 2.4% at 0.04 and 0.4 mg l^{-1} respectively ($n=8$) for *N*-desmethylsertraline. Aliquots of milk were analysed by the method of addition so as to avoid differential variation in recovery of sertraline or *N*-desmethylsertraline and desipramine that may occur when milk samples having differing composition are extracted. Desipramine (internal standard; 200 ng in 0.02 ml of an aqueous solution) was added to 0.5 ml aliquots of milk in 10 ml disposable polypropylene tubes. Each sample was assayed in quadruplicate with the addition of 0, 100, 150 and 200 μg l^{-1} of sertraline or *N*-desmethylsertraline respectively. Sodium tetraborate (1 ml of 2% w/v; pH 9.2) was added to each tube and the samples were extracted as described above for plasma. For each individual sample a standard curve relating added sertraline or *N*-desmethylsertraline concentration and peak height ratio (sertraline or *N*-desmethylsertraline : desipramine) was constructed and the concentration of sertraline or *N*-desmethylsertraline in the sample was obtained from the x-axis intercept. The within-run CVs for the milk assay were 9.5 and 9.7% at 0.05 and 0.4 mg l^{-1} respectively for sertraline and 6.7% and 8.9% at 0.05 and 0.4 mg l^{-1} respectively for *N*-desmethylsertraline ($n=7$). H.p.l.c. analyses were carried out on a system comprising a GBC Model LC 1610 Autosampler, Waters 6000A Solvent Delivery System, Waters 486 Tunable u.v. Absorbance Detector set at 210 nm and a Goerz Model SE120 BBC chart recorder. Analytes were separated on a Beckman Ultraspher® Octyl C_8 column (5 μm; 4.6 mm × 25 cm) using a mobile phase of 43% v/v acetonitrile in an aqueous solution containing 0.086% w/v 1-octanesulphonic acid and 0.01% v/v NNNN-tetramethylenediamine (adjusted to final pH 2.5 with H_3PO_4), pumped at a flow rate of 1.6 ml min^{-1}.

Calculation of infant dose

The absolute infant sertraline or *N*-desmethylsertraline (as sertraline equivalents) dose was calculated by two separate methods, both assuming an oral bioavailability of 100%. In method A, the measured cumulative drug excretion over 24 h was divided by the infant's body weight to give a dose in mg kg^{-1}. In method B, an average infant intake of 0.15 l milk kg^{-1} day^{-1} was assumed [9], and this value was multiplied by the average milk concentration (AUC_{milk}/dose interval time) to give a dose in mg kg^{-1}. For both methods, the infant dose was then expressed as a percentage of the maternal weight-normalised dose.

AUC(0,24 h) for the plasma and milk concentration-time profiles was calculated using the trapezoidal rule. Oral plasma clearance of sertraline was calculated as dose/$AUC_{plasma\ 0-24\ h}$.

Statistical evaluation of data

Data have been summarised as mean ± s.e.mean or mean (range) as appropriate. Differences between means were assessed using Student's *t*-test.

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Results

Typical plasma and milk concentration-time data and cumulative milk excretion for sertraline and *N*-desmethylsertraline are shown for patient 1, in Figure 1 a and b respectively. The mean total volume of milk collected from the patients over the 24 h period of the study was 321 ml (range 34–974 ml). Volunteer 5 was able to produce only very small amounts of milk.

Table 1 outlines the maternal dose, AUC for the milk and plasma concentration-time curves for both sertraline and *N*-desmethylsertraline, and the M/P ratio values derived from this data for both analytes. Mean oral plasma clearance of sertraline was 1.72 ± 0.21 l h^{-1}. The mean M/P ratios calculated from AUC data for sertraline and *N*-desmethylsertraline were 1.93 ± 0.16 and 1.64 ± 0.19 respectively.

Table 2 summarizes the calculated infant dose of sertraline and *N*-desmethylsertraline as sertraline equivalents. Infant dose was calculated by two different methods. The mean absolute infant doses calculated by Method A, using actual cumulative drug excretion, were $0.20\% \pm 0.05\%$ for sertraline and $0.30\% \pm 0.09\%$ for *N*-desmethylsertraline. Doses calculated by Method B, assuming an estimated infant intake of 0.15 l kg^{-1} day^{-1} were $0.90 \pm 0.09\%$ for sertraline and $1.32 \pm 0.15\%$ for *N*-desmethylsertraline. Mean values for Method B were significantly higher than those for Method A for both sertraline ($t = 6.7$, $P < 0.0001$) and *N*-desmethylsertraline ($t = 5.9$, $P < 0.0001$). The concentrations of both sertraline and *N*-desmethylsertraline were less than 5 μg l^{-1} (limit of detection) in the four infants whose blood was sampled (Table 2). All infants in the study appeared to be feeding well and achieving the normal developmental milestones, which were assessed by examination of the Personal Health Record book of each infant and discussion with the mother. No drug-related or other adverse effects were reported by the mothers.

Discussion

After oral administration, sertraline is slowly absorbed, with peak concentrations occurring after 6–8 h [10]. Sertraline has a volume of distribution of 20 l kg^{-1}, and is approximately 99% bound to plasma proteins [10]. It undergoes sequential oxidation and conjugation in the liver and is excreted mainly as metabolites in urine and faeces [10]. The primary metabolite, *N*-desmethylsertraline, is formed by cytochrome P4503A4. It has approximately eight times less activity than sertraline in the inhibition of 5-HT uptake

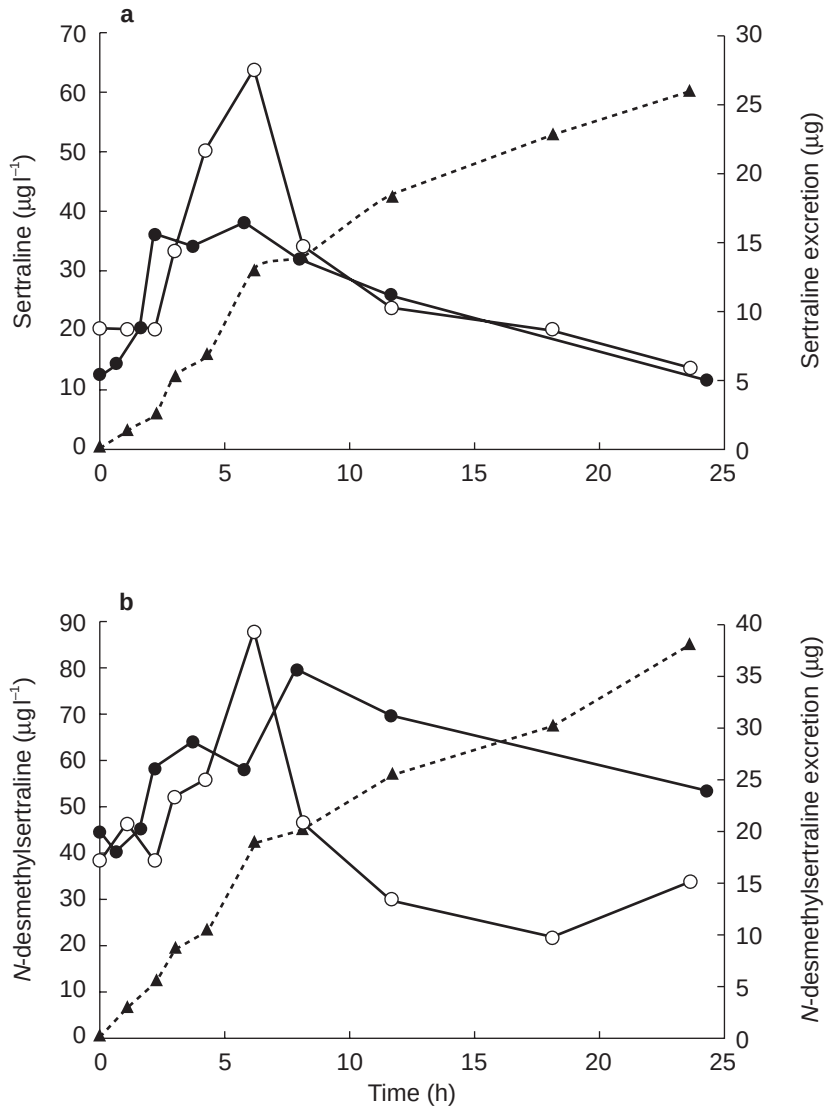

Figure 1 Data for one 24 h dose interval in patient 1. Milk (○) and plasma (●) concentrations of sertraline (a) and *N*-desmethylsertraline (b), together with cumulative excretion of both sertraline and *N*-desmethysertraline in milk (▲).

Table 1 Maternal dose, AUC for plasma and milk and M/P ratios for sertraline and *N*-desmethylsertraline.

		Sertraline			N-*desmethylsertraline*		
Volunteer	*Maternal dose (mg kg^{-1})*	*AUC[1] plasma (μg l^{-1} h)*	*AUC[1] milk (μg l^{-1} h)*	*M/P*	*AUC[1] plasma (μg l^{-1} h)*	*AUC[1] milk (μg l^{-1} h)*	*M/P*
1	0.833	588	670	1.14	1524	920	0.60
2	0.847	377	860	2.28	684	1205	1.76
3	0.649	588	1002	1.70	888	144	1.62
4	3.333	2209	4640	2.10	3853	7897	2.05
5	0.476	583	858	1.47	484	1066	2.20
6	0.926	398	1014	2.55	577	1206	2.09
7	0.602	499	1084	2.17	974	1283	1.32
8	0.769	648	1323	2.04	1533	2255	1.47
Mean ± s.e.mean	1.05 ± 0.33	736 ± 213	1431 ± 463	1.93 ± 0.16	1315 ± 389	1997 ± 867	1.64 ± 0.19

[1]Note that AUC values are not dose corrected.

Table 2 Estimated infant dose for sertraline and *N*-desmethylsertraline (as sertraline equivalents), and infant plasma concentrations of sertraline and *N*-desmethylsertraline.

	Sertraline			N-*desmethylsertraline*		
	Infant dose as % maternal dose		*Infant plasma*	*Infant dose as % maternal dose*		*Infant plasma*
Volunteer	*Method A[1]*	*Method B[2]*	*(mg l^{-1})*	*Method A[1]*	*Method B[2]*	*(mg l^{-1})*
1	0.414	0.511	[3]NS	0.634	0.729	[3]NS
2	0.387	0.654	[3]NS	0.555	0.955	[3]NS
3	0.093	1.022	[3]NS	0.117	1.529	[3]NS
4	0.339	0.889	< 5	0.590	1.574	< 5
5	0.046	1.175	[3]NS	0.059	1.520	[3]NS
6	0.148	0.699	< 5	0.195	0.865	< 5
7	0.096	1.165	< 5	0.112	1.436	< 5
8	0.077	1.120	< 5	0.126	1.968	< 5
Mean ± s.e.mean	0.20 ± 0.05	0.90 ± 0.09		0.30 ± 0.09	1.32 ± 0.15	

[1]Infant dose, (cumulative dose over 24 h in μg/(infant body wt in kg × 1000)/mother's dose in mg kg^{-1})) as a %.
[2]Infant dose, (average milk concentration in μg l^{-1} ⋆ 0.15 l kg^{-1} day^{-1} 1000)/mother's dose in mg kg^{-1}) as a %.
[3]NS, no sample.

in vitro and is inactive in animal models of depression and other *in vivo* tests [10]. The half-life ($t_{1/2}$) of sertraline is 25–26 h, while that for the *N*-desmethyl metabolite ranges from 66–80 h [10].

The plasma concentrations of sertraline and *N*-desmethylsertraline, and the oral clearance of sertraline, for our patients, were similar to previously reported values [11, 12]. The total milk volumes (mean 321 ± 108 ml day^{-1}) measured in this study were low by comparison with the range of 700–800 ml day^{-1} reported by others [9, 13] and the mean of 726 ± 134 ml day^{-1} which we reported in a study of the distribution and excretion of sumatriptan into human milk [14]. Sertraline and/or its metabolites, the underlying depressive illness, and individual variability in physiological control factors are possible contributors to the low milk volumes. An inefficient pumping technique, or the possibility that an infant may have been breast fed during the evening, may have also affected the volume of milk collected. It is of interest to note that sertraline has modest ability (K_i = 260 nM) to block the uptake of [^{3}H]-dopamine in rat brain synaptosomes [15]. Since the secretion of prolactin by the anterior hypothalamus is sensitive to D_2-receptor activation [16] and since mean plasma concentrations of sertraline were around 1000 nM in our study, it is possible that sertraline itself is in part responsible for the low milk production rate. Prolactin secretion is also mediated by serotonin, with raised serum prolactin levels reported in some patients treated with SSRIs [17]. The M/P ratios measured in this study for sertraline and *N*-desmethylsertraline were high (1.9 and 1.6 respectively), but within the range of values for basic amines with similar pKa values [18]. The range of M/P values for sertraline (1.14–2.55) in our study is considerably higher than the value of 0.63 which can be calculated from the data in the single case reported by Altshuler *et al.* [5]. However, this latter calculation may be unreliable as it is based on the average of several milk concentrations divided by a single observation of plasma sertraline concentration.

Infant dose was calculated by two different methods. Method B, which assumes an average milk intake of 0.15 l kg^{-1} day^{-1} gave mean values that were approximately 4-fold higher than those calculated by Method A which was based on actual total milk production volumes. Nevertheless, it should be noted that on average infants only consume some 76% of the available milk [19]. The lower values for method A probably reflect total milk collection volumes at the low end of the expected normal range, together with the abnormally low milk volumes obtained from volunteer 5. In the context of total dose of pharmacologically active drug received by the infant via the milk, the difference between methods A and B is of little practical significance.

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Our estimated mean infant dose for sertraline (0.9% of maternal dose; Method B) can be compared with published values of 0.45% [5] and 0.3–2.6% [6] (both calculated by Method B and assuming an average maternal dose of 1 mg kg^{-1}). Similarly, our estimated mean infant dose for *N*-desmethylsertraline (1.3% as sertraline equivalents) can be compared with a range of 0.5–5.0% that can be calculated from the data of Winn *et al.* [6].

The biological significance of the intake of sertraline and its *N*-desmethyl metabolite can be considered from four perspectives. Firstly, the calculated mean total dose of both drugs is 2.2% of the maternal dose and this is well below the notional 10% level of concern suggested by Begg *et al.* [20]. Secondly, the dose of pharmacologically active drug may be restricted to that from sertraline itself, as *N*-desmethylsertraline has only one eighth of the SSRI potency of sertraline, and has no effect in antidepressant testing models [10]. Thirdly, our data show that neither sertraline or *N*-desmethylsertraline could be detected in the infant's plasma. Fourthly, a recent report [21] has shown that maternal sertraline treatment causes a significant decrease in uptake of 5-HT by platelets from breast-feeding mothers but that no such effect was seen in their infants. Overall, the absolute dose of sertraline and its *N*-desmethyl metabolite transmitted to infants via breast-feeding is low, and is unlikely to cause any significant adverse effects. The effects of perinatal infant exposure to sertraline on long-term cognitive development of the exposed infant cannot be evaluated at present. However, studies of infants whose mothers had taken the related SSRI fluoxetine [22] or the tricyclic antidepressant dothiepin [23] during pregnancy have shown that neurodevelopment was normal.

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References

1 Angst J. Epidemiology of depression. [Review]. *Psychopharmacol* 1992; **106**: Suppl: S71–4.
2 Kessler RC, McGonagle KA, Zhoo S, *et al.* Lifetime and 12 month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiat* 1994; **51**: pp. 8–19.
3 Kendell RE, Chalmers JC, Platz C. Epidemiology of puerperal psychoses *Br J Psychiat* 1987; **150**: 662–673.
4 Murdoch D, McTavish D. Sertraline. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depression and obsessive-compulsive disorder. [Review] *Drugs* 1992; **44**: 604–624.
5 Altshuler LL, Burt VK, McMullen M, Hendrick V. Breastfeeding and sertraline: a 24-hour analysis. *J Clin Psychiat* 1995; **56**: 243–245.
6 Winn SS, Drawer PO, Stowe ZN, *et al.* Sertraline in breast milk and nursing infants. *Proc 148th Ann Meeting Am Psychiat Assocn, Miami, FL* 1995; p73 (Abstract # NR72).
7 Ilett KF, Kristensen JH, Wojnar-Horton RE, Begg EJ. Drug distribution in human milk. *Aust Prescriber* 1997; **20**: pp. 35–40.
8 Begg EJ, Atkinson HC. Modelling of the passage of drugs into milk. [Review]. *Pharmacol Ther* 1993; **59**: 301–310.
9 Bennett PN. Use of the monographs on drugs. In *Drugs and human lactation*, 2nd Edn, Amsterdam: Benneth PN ed, Elsevier, 1996: pp 67–74.
10 Doogan DP, Caillard V. Sertraline: a new antidepressant. [Review]. *J Clin Psychiat* 1988; **49**: Suppl: 46–51.
11 Demolis JL, Angebaud P, Grange JD, Coates P, Funck-Brentano C, Jaillon P. Influence of liver cirrhosis on sertraline pharmacokinetics. *Br J Clin Pharmacol* 1996; **42**: 394–397.
12 Gupta RN, Dziurdzy SA. Therapeutic monitoring of sertraline [letter]. *Clin Chem* 1994; **40**: 498–499.
13 Allen JC, Keller RP, Archer P, Neville MC. Studies in human lactation: milk composition and daily secretion rates of macronutrients in the first year of lactation. *Am J Clin Nutrit* 1991; **54**: 69–80.
14 Wojnar-Horton RE, Hackett LP, Yapp P, Dusci LJ, Paech M, Ilett KF. Distribution and excretion of sumatriptan in human milk. *Br J Clin Pharmacol* 1996; **41**: 217–221.
15 Bolden-Watson C, Richelson E. Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. *Life Sci* 1993; **52**: 1023–1029.
16 Neville MC, Walsh CT. Effects of drugs on milk secretion and composition. In *Drugs and human lactation*, 2nd Edn, Bennett PN ed. Amsterdam: Elsevier, 1996: pp 15–46.
17 Egberts ACG, Meyboom RHB, De Koning FHP, Bakker A, Leufkens HGM. Non-puerperal lactation associated with anti depressant drug use. *Br J Clin Pharmacol* 1997; **44**: 277–281.
18 Atkinson HC, Begg EJ. Prediction of drug distribution into human milk from physicochemical characteristics. *Clin Pharmacokinet* 1990; **18**: 151–167.
19 Daly SE, Hartmann PE. Infant demand and milk supply. Part 1: Infant demand and milk production in lactating women. [Review]. *J Hum Lact* 1995; **11**: 21–26.
20 Begg EJ, Atkinson HC, Duffull SB. Prospective evaluation of a model for the prediction of milk: plasma drug concentrations from physicochemical characteristics. *Br J Clin Pharmacol* 1992; **33**: 501–505.
21 Epperson CN, Anderson GM, and McDougle CJ. Sertraline and breast-feeding. *N Engl J Med* 1997; **336**: pp. 1189–1190.
22 Nulman I, Rovet J, Stewart DE, *et al.* Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med* 1997; **336**: pp. 258–262.
23 Buist A, Janson H. Effect of exposure to dothiepin and northiaden in breast milk on child development. *Br J Psychiat* 1995; **167**: 370–373.

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