Transfer of escitalopram and its metabolite demethylescitalopram into breastmilk

Jonathan Rampono,[1] L. Peter Hackett,[2] Judith H. Kristensen,[3] Rolland Kohan,[4] Madhu Page-Sharp[1,5] & Kenneth F. Ilett[1,5]

[1]*Department of Psychological Medicine, Women's and Children's Health Service, Subiaco,* [2]*Clinical Pharmacology & Toxicology Laboratory, PathWest Laboratory Medicine, Nedlands,* [3]*Pharmacy Department, Women's and Children's Health Service and* [4]*Department of Neonatal Services, Women's and Children's Health Service, Subiaco, and* [5]*Pharmacology Unit, School of Medicine and Pharmacology, University of Western Australia, Crawley, Australia*

Correspondence
Dr K. F. Ilett, Pharmacology Unit
M510, School of Medicine and
Pharmacology, University of Western
Australia, 35 Stirling Hwy, Crawley,
6009 Australia.
Tel: + 61 08 9346 2985
Fax: + 61 08 0346 3469
E-mail: ken.ilett@uwa.edu.au

Aims
To investigate the transfer of escitalopram and its demethyl metabolite into milk, the absolute and relative infant doses via milk and to assess any unwanted effects in the breastfed infant.

Methods
Multiple samples of blood and milk were obtained over a dose interval at steady state from eight women who were taking escitalopram for postnatal depression. Drug concentrations in plasma and milk were measured by high-performance liquid chromatography and milk/plasma ratio (M/P$_{AUC}$), absolute infant dose and relative infant dose were estimated by standard methods. Their breastfed infants were also examined clinically and in five infants a blood sample was taken for drug analysis.

Results
The median dose taken by the women was 10 mg day^{-1}. The mean (95% confidence interval) M/P$_{AUC}$ was 2.2 (2.0, 2.4) for escitalopram and 2.2 (1.9, 2.5) for demethylescitalopram. Absolute infant doses were 7.6 µg kg^{-1} day^{-1} (5.2, 10.0) for escitalopram and 3.0 µg kg^{-1} day^{-1} (2.4, 3.6) for demethylescitalopram. The total relative infant dose for escitalopram plus its demethyl metabolite was 5.3% (4.2, 6.4) as escitalopram equivalents. All of the infants had met normal developmental milestones and no adverse effects were seen. Compared with average maternal plasma concentrations (24 µg l^{-1}), the concentrations of the parent drug and its metabolite in plasma from five infants were most commonly below the limit of detection (≤3 µg l^{-1}).

Conclusion
The study shows that escitalopram is safe for use during breastfeeding. Because its absolute infant dose is lower than that for an equivalent antidepressant dose of *rac*-citalopram, it may be preferred over *rac*-citalopram in treating depression in lactating women. Nevertheless, each decision to breastfeed should always be made on the basis of an individual risk:benefit analysis.

Introduction

Because of the 10–15% frequency of depression in the postnatal period, antidepressants are amongst the most frequently used drugs in lactation [1]. Children of depressed mothers may exhibit behavioural problems and delayed language development [2–5]. Thus it is well accepted that treatment of depression in the perinatal period has significant benefits for both mother and infant. We and others have previously studied the transfer of *rac*-citalopram and its demethyl-metabolite into

milk [6–12]. Overall, both drugs had milk/plasma (M/P_{AUC}) transfer ratios of around 2–3, a combined relative infant dose of 2–6% of the maternal weight-adjusted dose and have been considered to be safe for use during breastfeeding. There is only one documented case report of adverse events (disturbed sleep) in a breastfed infant whose mother was taking 40 mg *rac*-citalopram daily [10], although, like most selective serotonin re-uptake inhibitors, citalopram use during pregnancy may result in a short-term serotonin toxicity syndrome in the neonate [12].

In recent years, pharmaceutical companies have been encouraged to market active drug enantiomers rather than racemates in order to produce greater selectivity in primary pharmacological actions and lower side-effects. This trend is important for psychotropic drugs, including antidepressants [13]. The major pharmacological activity resides in the *S*-(+) enantiomer of citalopram (escitalopram) [14–16]. In addition, *R*-(–)-citalopram counteracts the activity of *S*-(+)-citalopram [15], thereby providing a possible basis for the pharmacological and clinical differences observed between citalopram and escitalopram [17].

Most drugs are transferred into milk by passive diffusion processes and hence maternal drug concentration (controlled by maternal pharmacokinetics) and M/P are major determinants of infant dose via milk [18]. To our knowledge, the only published data for milk transfer of enantiomers are those for methadone following maternal administration of the racemate [19]. In this study, the (M/P) for *R*-methadone was 1.8 times higher than that for *S*-methadone (means of 0.68 and 0.38, respectively). Moreover, average concentrations of *R*-methadone in milk were 181 μg l^{-1} compared with 121 μg l^{-1} for *S*-methadone. The aim of the present study was therefore to investigate the transfer of escitalopram and its demethyl metabolite into milk, to estimate the absolute and relative infant doses via milk and to assess any unwanted effects in the breastfed infant.

Materials and methods

Patients
Eight breastfeeding women who were being treated with escitalopram (Lexapro®) for postnatal depression gave written informed consent and were enrolled in the study.

Study protocol and data collection
The study was approved by the Ethics Committee of the Women's and Children's Health Service, Subiaco, Australia. The mothers were admitted to the research ward at 08.00 h and had a venous catheter inserted in a forearm vein. Venous blood samples (5 ml each, lithium heparin tube) were taken just before the morning dose of escitalopram at around 08.30 h and also at 2, 4 and 6 h after dose. The women were discharged following the 6 h sample and further blood samples were taken by venepuncture at home (by K.F.I.) at 8, 12 and 24 h after dose. The mothers collected milk samples (8 ml each) by hand expression or manual breast pump just before the morning dose and again every time their infant fed during the next 24 h (usually six to seven feeds). For early feeds whilst in the research ward the women usually collected both fore- and hind-milk samples separately, and for all other samples they collected an equal mixture of fore- and hind-milk into a single tube.

Infant health and wellbeing were evaluated by enquiry of the mother, together with a full clinical examination including a Denver development assessment by a specialist neonatologist (R.K.) [20, 21]. Results for the Denver assessment were expressed as the quotient of Denver age/chronological age (as percentage).

Materials
Authentic escitalopram and demethylescitalopram standards were obtained from Lundbeck Australia Pty Ltd, and desipramine hydrochloride (internal standard for the high-performance liquid chormatography assay) from Ciba-Geigy Australia Ltd. All other solvents and chemicals were of analytical grade.

High performance liquid chromatography
Escitalopram and demethylescitalopram in plasma and milk were measured as previously described [9]. Intra- and interday relative standard deviations for the assays in milk and plasma were <6.4% and <13.2%, respectively, over the relevant concentration ranges, with a limit of quantification (LOQ) of 1 μg l^{-1} in both matrices.

Data analysis
Areas under the plasma and milk concentration–time curves (AUC$_{0–24 h}$) were calculated using the mixed log-linear trapezoidal rule as appropriate [22] and the milk to plasma ratio (M/P_{AUC}) was calculated from the relevant AUC measurements. The average drug concentration in milk was calculated as $C_{av} = (AUC_{0–24 h})/\tau$, where τ = the dose interval (nominally 24 h). In graphing the data in Figure 1 and estimating AUC, the concentration values for paired fore- and hind-milk samples were averaged and plotted/analysed against the average of their sampling times. Statistical analysis of data was performed using SigmaStat Ver. 3.1 (SPSS Inc., Chicago, IL, USA).

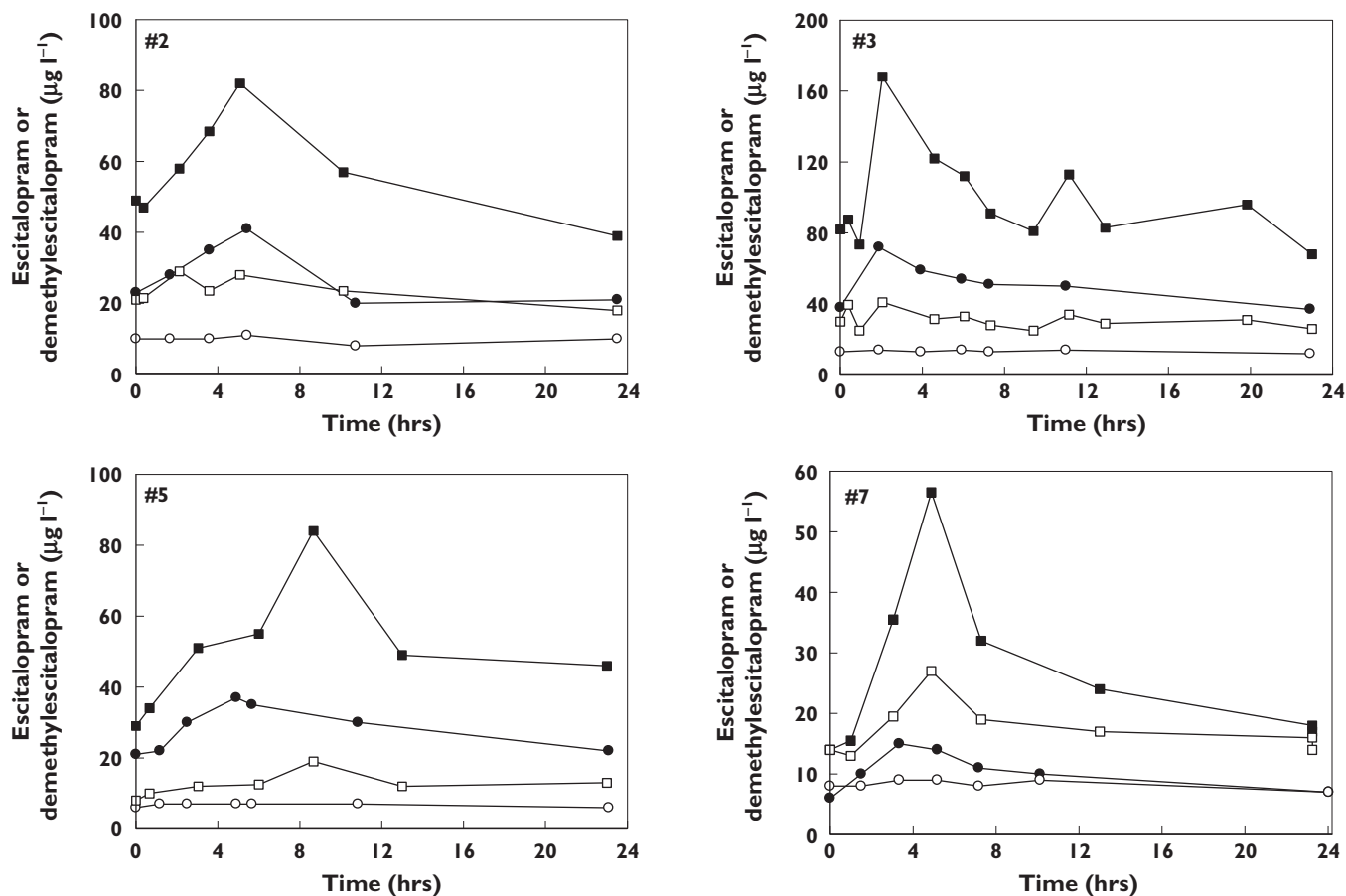Absolute infant dose (μg kg^{-1} day^{-1}) was calculated

Figure 1

Representative milk and plasma concentration–time profiles for escitalopram (■, milk; ●, plasma) and demethylescitalopram (□, milk; ○, plasma) in patients 2 (dose 10 mg), 3 (dose 20 mg), 5 (dose 10 mg) and 7 (dose 10 mg)

as the product of C_{av} and an average infant milk intake of $0.15 \, l \, kg^{-1} \, day^{-1}$ [23]. The relative infant dose was calculated as absolute infant dose/maternal dose ($\mu g \, kg^{-1} \, day^{-1}$) and expressed as a percentage [18]. Maximum concentrations (C_{max}) of drug in milk and plasma and the times of these peaks (T_{max}) were interpolated from the primary data. Data have been summarized as mean [95% confidence interval (CI), or range] or median and range, as appropriate.

Results

The characteristics of the mothers and their infants are summarized in Table 1. The median single daily dose of escitalopram taken by the women was 10 mg (range 10–20 mg) and therapy had commenced a median of 55 days prior to the study day, and they were therefore considered to be at steady state. The infants were five females and three males and all had achieved normal weight for age milestones at the time

of study. The paediatric assessment of the infants revealed no adverse findings and the mean Denver developmental age was 110% (95% CI 99, 121) of the actual age.

Representative milk and plasma concentration–time profiles for four of the eight women are shown in Figure 1. Maximum drug concentrations in milk and plasma, the times at which they occurred and the M/P_{AUC} values are summarized in Table 2. C_{max} and C_{av} for escitalopram and demethylescitalopram were consistently higher in milk than in plasma and the M/P for both drugs was 2.2. In addition, for escitalopram the median T_{max} was significantly greater (Wilcoxon rank signed test $T = -34$, $P = 0.023$) in milk than in plasma, indicating a delay in equilibration between the two compartments. By contrast, for demethylescitalopram, which exhibited a flatter concentration–time profile, T_{max} was similar in milk and plasma.

Table 3 summarizes the weight-corrected maternal

escitalopram doses, as well as the calculated infant doses and measured drug concentrations in the infant's plasma. The total relative infant dose for the combination escitalopram and its metabolite was a mean of 5.3%

Table 1
Characteristics of the mothers and their infants

Group	Parameter
Mothers	
Age (years)	32 (24–42)*
Weight (kg)	68 (56–85)*
Escitalopram dose (mg day^{-1})	10 (10–20)†
Duration of treatment (days)	55 (23–240)†
Infants	
Sex (M/F)	3/5
Gestational age (months)	39.1 (35.3–40.1)†
Chronological age (months)	3.6 (1.5–9.5)†
Birth weight (kg)	3.3 (2.5–3.8)†
Weight on study day (kg)	5.9 (3.7–10.5)†

Mean (range). †Median (range).

of the maternal weight-adjusted dose. Overall, escitalopram contributed some 70% of the oral dose that the breastfed infant is calculated to receive. In five of the studies, a blood sample was able to be taken from the breastfed infants (Table 3) and analysed for drug content. The limit of detection (LOD) in these samples varied according to the volume of plasma that was available. Both escitalopram and its metabolite were undetectable in four of the samples and were present in one infant (patient 7) at very low levels of 3 µg l^{-1} and 2 µg l^{-1}, respectively.

During the course of the study we collected 24 paired samples of fore- and hind-milk for drug analysis. For escitalopram there was a significant difference (paired $t = 5.3$, $P < 0.001$) between fore- and hind-milk means of 9 µg l^{-1} (95% CI for difference 6.5, 12.4). For demethylescitalopram the median fore- (21 µg l^{-1}) and hind-milk (24 µg l^{-1}) concentrations were also significantly different (Wilcoxon rank signed test $T = -13$, $P < 0.001$). On average, the ratio of drug concentration in hind-milk to that in fore-milk was 1.2 (95% CI 1.12, 1.28) for escitalopram and 1.23 (1.1, 1.36) for demethylescitalopram.

Table 2
Escitalopram and demethylescitalopram C_{max}, T_{max} and C_{av} for milk and plasma and their M/P$_{AUC}$ values

Patient	Milk			Plasma			M/P$_{AUC}$
	C_{max} (µg l^{-1})	T_{max} (h)	C_{av} (µg l^{-1})	C_{max} (µg l^{-1})	T_{max} (h)	C_{av} (µg l^{-1})	
Escitalopram							
1	64	2.8	47	38	1.5	28	1.7
2	82	5.1	56	41	5.4	25	2.2
3	168	2.1	99	72	1.9	49	2.0
4	57	5.9	39	23	4.1	18	2.0
5	84	8.7	53	37	4.9	28	1.9
6	73	11.3	58	39	2	25	2.3
7	57	4.9	27	15	3.3	9	2.7
8	37	10.3	28	15	3.4	12	2.4
Mean (95% CI)	78 (51, 105)	5.5 (4.4, 9.1)*	51 (35, 67)	35 (22, 48)	3.4 (2.0, 4.3)*	24 (15, 33)	2.2 (2.0, 2.4)
Demethylescitalopram							
1	36	1	28	9	1	20	2.3
2	29	2.1	25	11	5.4	23	2.4
3	41	2.1	49	14	3.9	31	2.3
4	22	5.9	18	10	7.1	18	1.9
5	19	8.7	28	7	4.9	13	2.0
6	26	4.7	25	14	4.2	23	1.8
7	27	4.8	10	9	4.3	18	2.1
8	17	16.1	12	6	2.1	15	3.1
Mean (95% CI)	27 (21, 33)	4.8 (2.1, 6.6)*	24 (16, 32)	10 (8, 12)	4.3 (3.5, 5.0)*	20 (16, 24)	2.2 (1.9, 2.5)

Median (25th and 75th percentiles).

Table 3
Maternal dose of escitalopram, absolute and relative infant doses, and infant plasma concentrations of escitalopram and demethylescitalopram

		Escitalopram			Demethylescitalopram			
Patient	Maternal dose ($\mu g\ kg^{-1}\ day^{-1}$)	Absolute infant dose ($\mu g\ kg^{-1}\ day^{-1}$)	Relative infant dose (%)	Infant plasma concentration ($\mu g\ l^{-1}$)	Absolute infant dose ($\mu g\ kg^{-1}\ day^{-1}$)	Relative infant dose*(%)	Infant plasma concentration ($\mu g\ l^{-1}$)	Total relative infant dose* (%)
1	179	7.0	3.9	ND	3.2	1.8	ND	5.7
2	139	8.3	6.0	<5	3.6	2.6	<3	6.1
3	235	14.9	6.3	<3	4.6	2.0	<2	8.3
4	299	5.8	1.9	ND	2.7	1.0	ND	2.9
5	180	8.0	4.5	ND	2.0	1.1	ND	5.6
6	267	8.7	3.3	<1	3.4	1.3	<1	4.6
7	143	4.1	2.9	3	2.7	2.0	2	4.8
8	154	4.3	2.8	<1	2.3	1.5	<1	4.3
Mean	199	7.6	3.9		3.0	1.7		5.3
(95% CI)	(157, 241)	(5.2, 10.0)	(2.8, 5.0)		(2.4, 3.6)	(1.3, 2.1)		(4.2, 6.4)

Expressed in escitalopram equivalents. ND, No plasma sample available.

Discussion

Escitalopram oral pharmacokinetics are characterized by a T_{max} of 4 h, plasma albumin binding of around 80%, a volume of distribution (V_d/F) of 12–36 l, a $t_{1/2\beta}$ of 30 h and an oral clearance of 36 l h^{-1} [24]. Its main metabolite is demethylescitalopram (28–31%) and there is also a small amount of didemethylescitalopram (<5%) [24]. Comparative data for oral administration of R-(−) citalopram alone are not available but after oral administration of 40–60 mg day^{-1} of *rac*-citalopram for 6 weeks, the average serum concentration of S-(+)-citalopram was 61% of that for R-(−)-citalopram, while the average serum concentration of S-(−)-demethylescitalopram was 71% of that for R-(+)-desmethylescitalopram [25]. Moreover, the mean $t_{1/2}$, steady-state volume of distribution and oral clearance for R-(−)-citalopram were 47 h, 16.4 l kg^{-1} and 0.26 l kg^{-1} h^{-1}, respectively, compared with 35 h, 18.3 l kg^{-1} and 0.48 l kg^{-1} h^{-1}, respectively, for S-(+)-citalopram. The mean $t_{1/2}$ for R-(−)-demethylescitalopram was significantly longer (70 h) than that for S-(+)-demethylescitalopram (51 h). These data show that the S-(+) enantiomer of citalopram has a higher oral clearance that that of the corresponding R-(−) enantiomer and suggest that there is a similar higher clearance for the S-(+)-desmethylescitalopram compared with that for its R-(−)-enantiomer. As the R-(−)-enantiomer accounts for some two-thirds of steady-state concentrations following administration of *rac*-citalopram [25], the total drug load to the breastfed infant would be

markedly reduced with escitalopram compared with *rac*-citalopram. In addition, the recommended dose ranges of escitalopram (10–20 mg) [24] and citalopram (20–60 mg) [26] suggested better efficacy for escitalopram and led us to hypothesize that the absolute infant dose of escitalopram would be lower than that for *rac*-citalopram, conferring a higher safety margin when the drug is used to treat depression in breastfeeding women.

As expected, in the present study the median dose of escitalopram (10 mg) was significantly lower (Mann–Whitney rank sum test $T = 76.5$, $P = 0.014$) than that reported (20 mg) in our earlier study of the transfer of *rac*-citalopram into milk in lactating women [9]. In addition, the absolute infant dose for escitalopram [mean (95% CI) 7.6 µg kg^{-1} day^{-1} (5.2, 10.0)] was also significantly lower (52%) than that for *rac*-citalopram [14.5 µg kg^{-1} day^{-1} (8.3, 20.6)] in our earlier study (t-test, $t = -6.9$, $P = 0.023$). By contrast, the absolute infant doses of demethylescitalopram [3.0 µg kg^{-1} day^{-1} (2.4, 3.6)] and *rac*-demethylcitalopram [5.4 µg kg^{-1} day^{-1} (2.2, 8.6)] were not significantly different, indicating that exposure to this metabolite, which has a long $t_{1/2}$ [25], is independent of the dose forms used in our present and previous studies. Overall, we conclude that absolute infant dose is lower when escitalopram is used instead of citalopram at clinically comparable antidepressant doses. The lower absolute infant dose results because the R-enantiomer is not present.

The relative infant doses for escitalopram [3.9% (2.8,

5.0)] and demethylescitalopram [1.7% (1.3, 2.1)] in the present study were, as expected, similar to those reported for *rac*-citalopram [3.7% (2.6, 4.8)] and *rac*-demethylcitalopram [1.4% (0.9, 1.9)] in our earlier study [9]. Hence, when comparing infant exposure from a pure enantioner drug formulation to that from a clinically comparable dose of its racemate formulation, the relative infant dose may not reveal the whole story and recourse to a comparison at the level of the absolute dose is more appropriate and informative.

In calculating total relative infant doses (escitalopram plus demethylescitalopram; see Table 3), we have valued the contribution of demethylescitalopram in escitalopram 'equivalents', using the parent:metabolite molecular weight ratio. Hence, our total relative infant dose calculation is very conservative in that S-(+)-demethylescitalopram has only 15% of the activity of escitalopram in inhibiting 5-hydroxytryptamine reuptake into rat brain synaptosomes [14]. Moreover, demethylescitalopram is less polar [9] and therefore less likely to enter the brain.

The M/P_{AUC} values for escitalopram [2.2 (2.0, 2.4)] and demethylescitalopram [2.2 (1.9, 2.5)] in the present study were similar to those we reported for *rac*-citalopram [1.8 (1.2, 2.3)] and *rac*-demethylcitalopram [1.8 (1.1–2.5)] [9]. The lack of a significant difference suggests that the R-enantiomers of citalopram and its demethylmetabolite transfer to milk similarly to their respective S-enantiomers. Infant exposure is thus dependent primarily on maternal plasma concentration of the pure enantioner(s) and is unlikely to be influenced by chirality.

On the basis of the lower absolute infant dose calculations above, we conclude that escitalopram is preferred to *rac*-citalopram in the treatment of depression during lactation. Our assessment of the eight breastfed infants in our study revealed no adverse effects and low or undetectable plasma drug levels in five of the infants where a blood sample was able to be taken. The actual concentrations (or the LODs) for the infant sample as percent of the C_{av} in maternal plasma were 14% (4, 31) for escitalopram mean (range), and 20% (12, 36) for demethylescitalopram. These percentages are conservatively estimated, in that the LODs for two of the infant samples were high due to the small sample volumes available. While our positive clinical observations suggest that escitalopram has a low potential for causing adverse events in the breastfed infant, it should be remembered that our cohort is small and there is one case of an adverse event for *rac*-citalopram [10].

Overall, with a mean relative infant dose of 5.3% of the weight-adjusted maternal dose for escitalopram plus its major demethyl metabolite, our study shows that escitalopram is safe (notional level of safety <10%) for use during breastfeeding and, because the absolute infant dose is lower, it should be preferred over *rac*-citalopram in treating depression in lactating women. Nevertheless, each decision to breastfeed should always be made on the basis of an individual risk:benefit analysis.

References

1 O'Hara MW, Zekoski EM, Philipps LH, Wright EJ. Controlled prospective study of postpartum mood disorders: comparison of childbearing and nonchildbearing women. J Abnorm Psychol 1990; 99: 3–15.

2 Sinclair D, Murray L. Effects of postnatal depression on children's adjustment to school. Teacher's reports. Br J Psychiatry 1998; 172: 58–63.

3 Murray L, Fiori-Cowley A, Hooper R, Cooper P. The impact of postnatal depression and associated adversity on early mother–infant interactions and later infant outcome. Child Dev 1996; 67: 2512–26.

4 Zekoski EM, O'Hara MW, Wills KE. The effects of maternal mood on mother–infant interaction. J Abnorm Child Psychol 1987; 15: 361–78.

5 Lee CM, Gotlib IH. Adjustment of children of depressed mothers: a 10-month follow-up. J Abnorm Psychol 1991; 100: 473–7.

6 Spigset O, Carieborg L, Ohman R, Norstrom A. Excretion of citalopram in breast milk. Br J Clin Pharmacol 1997; 44: 295–8.

7 Jensen PN, Olesen OV, Bertelsen A, Linnet K. Citalopram and desmethylcitalopram concentrations in breast milk and in serum of mother and infant. Therap Drug Monit 1997; 19: 236–9.

8 Ohman R, Norstedt B, Vitols WS. Citalopram and metabolite levels in plasma and breast milk in two nursing women. Br J Clin Pharmacol 1997; A179.

9 Rampono J, Kristensen JH, Hackett LP, Paech M, Kohan R, Ilett KF. Citalopram and demethylcitalopram in human milk; distribution, excretion and effects in breast fed infants. Br J Clin Pharmacol 2000; 50: 263–8.

10 Schmidt K, Olesen OV, Jensen PN. Citalopram and breast-feeding: serum concentration and side effects in the infant. Biol Psychiatry 2000; 47: 164–5.

11 Nordeng H, Bergsholm YK, Bohler E, Spigset O. Excretion of selective serotonin reuptake inhibitors in breast milk. Tidsskr Nor Laegeforen 2001; 121: 199–203.

12 Heikkinen T, Ekblad U, Kero P, Ekblad S, Laine K. Citalopram in pregnancy and lactation. Clin Pharmacol Ther 2002; 72: 184–91.

13 Baumann P, Zullino DF, Eap CB. Enantiomers' potential in psychopharmacology—a critical analysis with special emphasis on the antidepressant escitalopram. Eur Neuropsychopharmacol 2002; 12: 433–44.

14 Hyttel J, Bogeso KP, Perregaard J, Sanchez C. The pharmacological effect of citalopram residues in the (S)-(+)-enantiomer. J Neural Transm Gen Sect 1992; 88: 157–60.

15 Sanchez C, Bergqvist PB, Brennum LT, Gupta S, Hogg S, Larsen A, Wilborg O. Escitalopram, the S-(+)-enantiomer of citalopram, is a selective serotonin reuptake inhibitor with potent effects in animal models predictive of antidepressant and anxiolytic activities. Psychopharmacology (Berl) 2003; 167: 353–62.

16 Mork A, Kreilgaard M, Sanchez C. The R-enantiomer of citalopram counteracts escitalopram-induced increase in extracellular 5-HT in the frontal cortex of freely moving rats. Neuropharmacology 2003; 45: 167–73.

17 Sanchez C, Bogeso KP, Ebert B, Reines EH, Braestrup C. Escitalopram versus citalopram: the surprising role of the R-enantiomer. Psychopharmacology (Berl) 2004; 174: 163–76.

18 Hale TW, Ilett KF. Drug Therapy and Breastfeeding. From Theory to Clinical Practice, 1st edn. London: The Parthenon Publishing Group 2002: 1–94.

19 Begg EJ, Malpas TJ, Hackett LP, Ilett KF. Distribution of R- and S-methadone into human milk at steady state during ingestion of medium to high doses. Br J Clin Pharmacol 2001; 52: 681–5.

20 Frankenburg WK, Dodds JB. The Denver development screening test. J Pediatr 1967; 71: 181–91.

21 Rossiter EJ. The use of developmental screening and assessment instruments by paediatricians in Australia. J Paediatr Child Health 1993; 29: 357–9.

22 Begg EJ, Duffull SB, Hackett LP, Ilett KF. Studying drugs in human milk: time to unify the approach. J Hum Lact 2002; 18: 319–28.

23 Bennett PN. Use of the monographs on drugs. In: Drugs and Human Lactation, 2nd edn, ed Bennett PN. Amsterdam: Elsevier 1996: 67–74.

24 Anonymous. Lexapro (escitalopram) Product Information. In: E-MIMS Ver 5.00.0106. St Leonards, Australia: MultiMedia Australia Pty Ltd 2005.

25 Sidhu J, Priskorn M, Poulsen M, Segonzac A, Grollier G, Larsen F. Steady-state pharmacokinetics of the enantiomers of citalopram and its metabolites in humans. Chirality 1997; 9: 686–92.

26 Anonymous. Cipramil (rac-citalopram) Product Information. In: E-MIMS Ver 5.00.0106. St Leonards, Australia: MultiMedia Australia Pty Ltd 2005.