Distribution of venlafaxine and its O-desmethyl metabolite in human milk and their effects in breastfed infants

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Aims To characterize milk/plasma (M/P) ratio and infant dose, for venlafaxine (V) and its O-desmethyl metabolite (ODV), in breastfeeding women taking venlafaxine for the treatment of depression, and to determine the plasma concentration and effects of these drugs in their infants.

Methods Six women (mean age 34.5 years, mean weight 84.3 kg) taking venlafaxine (median dose 244 mg day⁻¹, range 225–300 mg day⁻¹) and their seven infants (mean age 7.0 months, mean weight 7.3 kg) were studied. V and ODV in plasma and milk were measured by high-performance liquid chromatography over a 12 h dose interval at steady-state. Infant exposure was estimated as the product of estimated milk production rate (0.15 l kg⁻¹ day⁻¹) and average drug concentration in milk, normalized to body weight and expressed as a percentage of the weight-adjusted maternal dose.

Results Mean M/P_{AUC} values of 2.5 (range 2.0–3.2) and 2.7 (range 2.3–3.2) were calculated for V and ODV, respectively. The mean maximum concentrations (95% CI) of V and ODV in milk were 1161 (95% CI, 588, 1734) µg l⁻¹ and 796 (362, 1230) µg l⁻¹. Mean infant exposure was 3.2% (1.7, 4.7%) for V and 3.2% (1.9, 4.9%) for ODV (as V equivalents). V was detected in the plasma of one out of seven infants studied (5 µg l⁻¹), while ODV was detected in four of the infants, at concentrations ranging from 3 to 38 µg l⁻¹. All of the infants in the study were healthy, as reported by their mothers and/or by clinical examination on the study day.

Conclusions The concentrations of V and ODV in breast milk were 2.5 and 2.7 times those in maternal plasma. The mean total drug exposure (as venlafaxine equivalents) of the breastfed infants was 6.4% (5.5–7.3%), which is below the 10% notional level of concern. There were no adverse effects in any of the infants. The data support the use of V in breastfeeding. Nevertheless, since low concentrations of ODV were detected in the plasma of four out of the seven infants studied, we recommend breastfed infants should be monitored closely. Each decision to breast feed should be made as an individual risk:benefit analysis.

Keywords: human milk, infant dose, M/P ratio, O-desmethylvenlafaxine, venlafaxine

Introduction

Venlafaxine (V; 1–2–(dimethylamino)-1–(4-methoxyphenyl)ethyl cyclohexanol HCl) is a novel bicyclic

phenylethylamine antidepressant that inhibits the reuptake of both serotonin and noradrenaline (SNRI) both *in vitro* and *in vivo* [1–4]. This mode of action has proved to be beneficial as the drug lacks many of the side-effects associated with the tricyclic antidepressants and has a different profile to the selective serotonin reuptake inhibitors (SSRIs) [3, 5]. The oral bioavailability of V is around 92% [6]. Peak plasma levels occur 2–4 h after a dose, the steady-state volume of distribution is 6–7 l kg⁻¹

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[1, 2, 7], while the plasma protein binding of V is around 27% [1]. V is metabolized mainly in the liver to its major *O*-desmethyl metabolite (ODV) [6, 8], which has similar antidepressant activity to that of the parent compound [9]. Other metabolites of V include *N*-desmethylvenlafaxine and *N,O*-didesmethylvenlafaxine as well as glucuronide and sulphate conjugates [6]. *O*-Demethylation of V is catalysed by CYP2D6 and the drug has also been shown to be a weak inhibitor of this CYP isoform [10]. More recently, the plasma concentration-time profiles of V and ODV have been shown to be influenced particularly by the CYP2D6*10 genotype [11, 12]. The elimination half-lives for V and ODV are around 4 h and 10 h, respectively [8], and steady-state plasma concentrations of V and ODV are quite variable [7] presumably as a result of interindividual variability in the CYP2D6 genotype.

A major depressive disorder will occur in around 13% of women in the postnatal period, and a substantial number of these women will benefit from the use of antidepressant medication [13]. In recent years the drive to breast feed babies has undergone a resurgence for biological, psychological and social reasons. Lactating women who require treatment with an antidepressant have understandable concerns about the possible transfer of psychotropic medication into the breast milk and thence to their neonate. The safe use of drugs during breastfeeding requires an individualized risk-benefit analysis. To provide the data that underpins such analyses, we have studied the transfer of V and ODV into milk in six lactating women and related this data to plasma concentrations and effects in their breastfed infants.

Methods

Patients and study protocol

Six breast-feeding women and their infants were enrolled in the study. The study design was approved by the Research and Ethics Committee of King Edward Memorial and Princess Margaret Hospitals and written informed consent was obtained from all participants.

Data collection

The data collection for the study was as described previously [14]. Briefly, venous blood samples (8 ml; heparinized) were collected from the women via a forearm cannula at 0, 2, 4, 6 and 7 h postdose, and also by venepuncture at 12 h (regular formulation) or 24 h (extended-release formulation). At the same time intervals, both breasts were emptied via an electric or manual breast pump, and 15 ml aliquots were retained for drug assay. A sample of milk was also collected directly into a 1 ml blood-gas syringe (Bard-Parker, Becton-Dickinson, NJ,

USA) and pH was measured using a NOVA StatProfile[®] blood gas analyser (NOVA Biomedical, Waltham MA, USA). Preliminary experiments established that the pH of samples collected using this procedure did not change significantly over a 9 h period (data not shown) and all pH values were measured within this time. Measurements of pH were made on each individual milk sample. Creamatocrit (% fat in milk) for each milk sample was measured as previously described [15]. The remainder of the milk was bottle-fed to the infants as required. The women returned home after 8 h and milk and plasma samples at 12 and 24 h postdose were collected there. All women gave consent for a venous blood sample (0.5–1 ml, heparinized) to be taken from their infants. For all studies, infant health and well being were evaluated by enquiry of the mother together with a full clinical examination by a specialist neonatologist (RK). Infant body weight for age was checked against gender-specific population percentile graphs [16] and where possible, a Denver Developmental Screening Test was performed [17, 18]. Results for the latter were expressed as the quotient of chronological age as a percent.

Materials

V and ODV standards were donated by Wyeth-Ayerst, Princeton, NJ, USA, and norclozapine by Novartis Pharmaceuticals, Basel, Switzerland. All solvents and other chemicals were of analytical or high performance liquid chromatography (h.p.l.c.) grade.

High performance liquid chromatography

Quantification of V and ODV was by h.p.l.c. as described previously [14]. Coefficients of variation (CV) were measured at 100 and 400 $\mu\text{g l}^{-1}$ for both V and ODV. Intra-day CV (both analytes) ranged from 1.1 to 2.6% for plasma and 2.5–3.9% for milk, while interday CV ranged from 1.1 to 3.7% for plasma and from 2.3 to 4.6% for milk. The limit of detection for both analytes in milk and plasma was 1 $\mu\text{g l}^{-1}$.

Data analysis

Data have been summarized as mean (95% CI, or range), or median (25th and 75th percentiles) as appropriate. Differences between milk pH or creatinocrit between patients and collection times were assessed by 2-way ANOVA (SigmaStat, SPSS Chicago IL, USA).

Calculation of milk/plasma ratio and infant dose

Area under the concentration-time profiles (AUC) was calculated using the program Topfit (log trapezoidal rule)

for plasma [19], and rectangular areas for milk (Σ concentration $\times$ collection time) [20]. AUC(0,12 h) data from the five patients with a twice daily regimen were dose-normalized to give an estimated AUC(0,24 h), while patient 6 who was taking a single daily dose of V had data collected to 24 h. Milk/plasma ratios (M/P_{AUC}) were calculated from the AUC data. An infant milk intake of $0.15 \text{ l kg}^{-1} \text{ day}^{-1}$ was assumed [21], and this value was multiplied by the average milk concentration ($AUC(0,24 \text{ h})/24 \text{ h}$) to give the absolute infant dose of V and ODV in $\text{mg kg}^{-1} \text{ day}^{-1}$. The infant dose was then expressed as a percentage of the maternal weight-normalized dose. Since V and ODV are approximately equipotent in their antidepressant activity [9], the infant dose of ODV has been expressed as V equivalents so that total drug exposure can be appreciated.

Measurement of $\log_{10} P$ for V and ODV

The $\log_{10} P$ (octanol:buffer, pH 7.2) value for V and ODV was measured as previously described [20] with concentrations in the buffer phase before and after equilibration being measured by the h.p.l.c. assay described above.

Results

The breast-feeding women had a mean age 34.5 years (range 30–41 years) and a mean body weight 84.3 kg (range 62–108 kg). Their infants, including one pair of twins were 3 M and 4 F with a mean age of 7.0 months (range 2.7–10.3 months). Patients 1–5 received Efexor[®] regular formulation twice daily (#1, 112.5 mg morning and night; #2, 150 mg morning and night; #3 and 4, 150 mg in the morning and 112.5 mg at night; #5, 150 mg in the morning and 75 mg at night), while patient 6 received Efexor-XR[®] extended release formulation 225 mg daily in the morning. The median dose of V ingested by the women was 2.91 (range 2.56–3.62) $\text{mg kg}^{-1} \text{ day}^{-1}$. Therapy with V had commenced a mean of 111 (range 18–483) days prior to the study day, and all participants were considered to be at steady-state at the time of study. Patients 1, 2 and 6 commenced V treatment after the birth of their infants, while patients 3, 4 and 5 had commenced venlafaxine before or during their pregnancy. Interestingly, subject 1 (infant age 10.3 months) reported that her milk 'let down' took longer to achieve since she started the drug 1 month previously.

Calculation of the theoretical M/P for V and ODV was undertaken by the method of Begg *et al.* [22]. For V (pK_a 9.4 [23]), the measured $\log P$ octanol:buffer pH 7.2-value of 0.74, a plasma protein binding of 27% [1] and a milk pH of 7.2 yielded a theoretical M/P of 2.33, while for ODV (assuming the same pK_a as V), the measured $\log P$ octanol:buffer pH 7.2-value of 0.5, a plasma protein

binding of 30% [3] and a milk pH of 7.2 yielded a theoretical M/P of 2.21.

Mean plasma and milk concentration-time profiles for V and ODV for all six patients are shown in Figure 1. These plots illustrate clearly the between-patient diversity of plasma V and ODV concentrations that results from CYP2D6 control of drug disposition. For example, subject 1 most likely has the poor metabolizer phenotype, while subject 3 most likely has the extensive metabolizer phenotype. For the group as a whole, maximum plasma concentrations (C_{max} ; mean (95% CI)) were 512 (294, 730) $\mu\text{g l}^{-1}$ for V and 286 (160, 412) $\mu\text{g l}^{-1}$ for ODV and occurred at a mean t_{max} of 2.15 (2.08, 21.7) h after dose for both V and ODV. Subject 6 was the only patient taking the extended-release V formulation and, consistent with her daily dose of $2.56 \text{ mg kg}^{-1} \text{ day}^{-1}$, showed drug concentrations at the lower end of the range for all patients. As expected, the t_{max} values were much later in this patient (5.75 h for V and 7.83 h for ODV). For the milk, details of drug concentration for all patients are shown in Table 1. The mean C_{max} for V (1161 $\mu\text{g l}^{-1}$) and ODV (796 $\mu\text{g l}^{-1}$) occurred at a median of 2.25 h and 2.96 h after dose, respectively. Average (mean) drug concentrations in milk ($C_{average}$) were 638 $\mu\text{g l}^{-1}$ and 608 $\mu\text{g l}^{-1}$ for V and ODV, respectively (Table 1). The mean M/P_{AUC} was 2.5 for V and 2.74 for ODV.

Table 2 summarizes the estimated infant doses of V and ODV as V equivalents. The mean (95% CI) absolute infant doses calculated using an estimated infant milk intake of $0.15 \text{ l kg}^{-1} \text{ day}^{-1}$ were 3.2% (1.7, 4.7%) for V and 3.2% (1.9, 4.9%) for ODV. The mean milk pH for the group was 7.28 (7.23, 7.33) and a two-way ANOVA showed that milk pH varied significantly between patients ($F=9.55$, $P<0.001$) but not between collection times. Mean creatatocrit for the group was 7.5% (6.6, 8.3%). For creatatocrit, there were also significant differences between patients ($F=3.36$, $P=0.033$) but not between collection times.

Infant blood samples were collected at a mean of 6.5 (6.2, 6.8) h after the maternal dose. V was detected in only one of the seven infants at a low concentration of $5 \mu\text{g l}^{-1}$, while ODV was detected in four infants at concentrations ranging from 3 to 38 $\mu\text{g l}^{-1}$ (Table 2). All infants were breastfed 5–6 times daily. Infants 2 and 6 also received supplementary solid food 2–3 times per day and infant 3 received supplementary formula milk (50–120 ml per feed) because her mother had only one breast as a result of a mastectomy for carcinoma. None of the mothers reported any adverse effects in their infants and a full clinical examination revealed no motor or tone abnormalities. Values for the Denver Development quotient were measured in all infants except infant 4 and were normal for age (median = 100%, range 90–125%). However, Infant

Figure 1 Venlafaxine (plasma, ●; milk, ○) and O-desmethylvenlafaxine (plasma, ■; milk, □) concentration-time profiles in the six patients over a dose interval at steady-state.

Table 1 Milk concentrations and M/P ratios for V and ODV.

Patient	t_{max} (h)	Venlafaxine			t_{max} (h)	O-Desmethylvenlafaxine		
		C_{max}^1 ($\mu\text{g l}^{-1}$)	$C_{average}^2$ ($\mu\text{g l}^{-1}$)	M/P_{AUC}		C_{max}^1 ($\mu\text{g l}^{-1}$)	$C_{average}^2$ ($\mu\text{g l}^{-1}$)	M/P_{AUC}
1	1.75	2020	1187	2.40	1.75	335	277	2.61
2	1.67	1096	704	2.05	3.67	561	477	2.26
3	2.25	712	388	2.34	2.25	1120	925	2.75
4	2.25	1230	597	2.04	2.25	1010	651	2.5
5	2.28	1429	597	2.95	4.20	1336	815	3.08
6	5.67	477	354	3.22	7.67	413	502	3.24
Mean	2.25 ³	1161	638	2.50	2.96 ³	796	608	2.74
(95% CI)	(1.75, 2.28)	(588, 1734)	(322, 954)	(2.0, 3.0)	(2.25, 4.2)	(362, 1230)	(358, 858)	(2.36, 3.12)

¹Maximum concentration recorded during the dose interval.

²Average concentration calculated as AUC/dose interval.

³Median (25th and 75th percentiles).

Clinic Healthcare data were available for infant 4 and showed that all normal milestones had been achieved. Infant weights at the time of study were compared with those recorded at birth and related to standard Perinatal/Postnatal Growth Charts. Two infants moved to lower percentiles (infant 1, 90th to 10–25th and infant 6, 50–75th to 3–10th), two stayed in the same percentile

(infant 2, 90th and infant 5, 50th) while two moved to higher percentiles (infants 3 and 4, 3rd to 25th).

Discussion

V is one of two antidepressants that make up the SNRI class [3]. Clinically V has similar efficacy to imipramine

Table 2 Estimated infant dose for V and ODV (as V equivalents), and infant plasma concentrations of V and ODV.

Patient	Venlafaxine	Infant plasma concentration ($\mu\text{g l}^{-1}$)	O-Desmethylvenlafaxine	Infant plasma concentration ($\mu\text{g l}^{-1}$)	Total dose V equivalents (%)
	Infant dose as percentage of maternal dose ¹ (V equivalents)		Infant dose as percentage of maternal dose ¹ (V equivalents)		
1	5.9	5	1.5	<2.5	7.4
2a ²	3.8	<4	2.7	<3	6.5
2b ²	3.8	<4	2.7	<3	6.5
3	2.1	<3	5.2	6.0	7.3
4	2.7	<2	3.1	38.0	5.8
5	2.5	ND ³	3.5	20.0	6.0
6	2.1	ND ³	3.1	3.0	5.2
Mean ⁴	3.2		3.2		6.4
(95% CI)	(1.7, 4.7)		(1.9, 4.9)		(5.5, 7.3)

¹Infant dose = (average milk concentration in $\mu\text{g l}^{-1} \times 0.15 \text{ l kg}^{-1} \text{ day}^{-1} \times 1000$)/mother's dose in mg kg^{-1}) as a percentage.

²Data obtained from twins.

³ND = less than detection limit ($1 \mu\text{g l}^{-1}$).

⁴Twins counted as one observation, $n = 6$.

and fluoxetine [24–27]. Compared with the tricyclics and SSRIs, the dual mechanism of action of V in potentially inhibiting reuptake of both serotonin and noradrenaline and differences in its side-effect profile mean that it is widely used in the treatment of depression, including that occurring in women in the postnatal period.

In the present study we sought to provide quantitative information on the transfer of V and ODV into human milk so that nursing mothers and their medical advisers can make informed decisions on the safety of breastfeeding whilst taking V. Our data complement a short report on V and ODV in milk ($n = 3$) that we published in 1998 [14].

The mean M/P-values for V and ODV were 2.5 and 2.74, respectively, and were within the same range as our previous preliminary observations [14]. The average concentrations of V and ODV in milk also were similar (638 and $608 \mu\text{g l}^{-1}$, respectively) and led to mean relative infant doses of 3.2% for V and 3.2% for ODV. Thus, despite significant intersubject variability in individual plasma and milk concentration–time profiles, relative infant dose is remarkably similar in all nine patients now studied. Combining the infant dose exposure data from the present study with that of our previous study [14] gave mean infant doses of 3.3% (2.4–4.3) for V, 3.6 (2.5–4.7) for ODV (as V equivalents) and an overall dose of 6.8% (5.6–8).

Prediction of M/P on theoretical grounds has been recommended as a means of estimating infant exposure when maternal plasma concentrations of drug are the only data available [28]. Using this method we calculated an M/P of 2.33 for V and 2.21 for ODV. These values were very similar to those observed in our study (2.5 and 2.74, respectively) and testify to the robustness of the prediction algorithm for basic drugs. Our data for milk pH and creatinocrit suggest that these factors are likely to be

a source of between-subject variability in M/P and drug transfer into milk.

The safety of V for the infant appears to be satisfactory, as no adverse effects were noted in our present or previous studies. In the present study, all seven infants had normal Denver quotients and with two exceptions, had achieved standard growth milestones. The latter exceptions are most likely examples of ‘catch-down’ growth [29] that occurs normally in many young children as a result of both hormonal and other control factors [30, 31]. V itself was only detected at a very low concentration ($5 \mu\text{g l}^{-1}$) in the plasma of one infant, while low concentrations of ODV (3, 6, 20 and $38 \mu\text{g l}^{-1}$) were present in four of the seven infants. These ODV concentrations correspond to 1.8%, 12.8%, 5.7% and 1.9%, respectively, of the average plasma concentrations measured in their mothers. The presence of mainly ODV in the infant's plasma indicates that all had significant capacity to metabolize the V that comprised approximately 50% of the drug they ingested. Clearance of ODV by the infants did not appear to be an issue, although our data in this area are limited. Nevertheless, we would suggest that particular care should be taken with preterm and very young neonates where hepatic drug metabolizing enzyme levels would be expected to be low.

In summary, all of the infants in the study were healthy as reported by their mothers and/or by clinical examination on the study day. Moreover, overall drug plus primary metabolite transfer was 6.4% of the weight-adjusted maternal dose and lower than the notional 10% level of concern [21]. Nevertheless ODV was detected in plasma from four of the seven infants, albeit at relatively low concentrations. Therefore we would recommend cautious use of V in breastfeeding women, provided that each

decision to breast feed is made on the basis of a thorough risk:benefit analysis. As is appropriate with breastfeeding when drugs are taken routinely by the mother, frequent regular checks of the infant's progress should be made. In the case of V, occasional monitoring of ODV in the infant's plasma could be undertaken as an additional safety measure, particularly in preterm infants or very young neonates.

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References

- Morton WA, Sonne SC, Verga MA. Venlafaxine: a structurally unique and novel antidepressant. *Ann Pharmacother* 1995; **29**: 387–395.
- Holliday SM, Benfield P. Venlafaxine. A review of its pharmacology and therapeutic potential in depression. *Drugs* 1995; **49**: 280–294.
- Kent JM. SNaRIs, NaSSAs, and NaRIs: new agents for the treatment of depression. *Lancet* 2000; **355**: 911–918.
- Harvey AT, Rudolph RL, Preskorn SH. Evidence of the dual mechanisms of action of venlafaxine. *Arch Gen Psychiat* 2000; **57**: 503–509.
- Pinder RM. Designing a new generation of antidepressant drugs. *Acta Psychiat Scand (Suppl.)* 1997; **391**: 7–13.
- Howell SR, Husbands GEM, Scatina JA, Sisenwine SF. Metabolic disposition of 14C-venlafaxine in mouse, rat, dog, rhesus monkey and man. *Xenobiotica* 1993; **23**: 349–359.
- Troy SM, Parker VD, Fruncillo RJ, Chiang ST. The pharmacokinetics of venlafaxine when given in a twice-daily regimen. *J Clin Pharmacol* 1995; **35**: 404–409.
- Klamerus KJ, Maloney K, Rudolph RL, Sisenwine SF, Jusko WJ, Chiang ST. Introduction of a composite parameter to the pharmacokinetics of venlafaxine and its active O-desmethyl metabolite. *J Clin Pharmacol* 1992; **32**: 716–724.
- Muth EA, Moyer JA, Haskins T, Andree TH, Husbands GEM. Biochemical, neurophysiological, and behavioural effects of Wy-45, 233 and other identified metabolites of the antidepressant venlafaxine. *Drug Dev Res* 1991; **23**: 191–199.
- Otton SV, Ball SE, Cheung SW, Inaba T, Rudolph RL, Sellers EM. Venlafaxine oxidation *in vitro* is catalysed by CYP2D6. *Br J Clin Pharmacol* 1996; **41**: 149–156.
- Fukuda T, Nishida Y, Zhou Q, Yamamoto I, Kondo S, Azuma J. The impact of the CYP2D6 and CYP2C19 genotypes on venlafaxine pharmacokinetics in a Japanese population. *Eur J Clin Pharmacol* 2000; **56**: 175–180.
- Fukuda T, Yamamoto I, Nishida Y, et al. Effect of the CYP2D6*10 genotype on venlafaxine pharmacokinetics in healthy adult volunteers. *Br J Clin Pharmacol* 1999; **47**: 450–453.
- O'Hara M, Swain M. Pares and risk of posnatal depression: a meta-analysis. *Int Rev Psychiat* 1996; **8**: 37–54.
- Ilett KF, Hackett LP, Duscil LJ, et al. Distribution and excretion of venlafaxine and O-desmethylvenlafaxine in human milk. *Br J Clin Pharmacol* 1998; **45**: 459–462.
- Silprasert A, Dejsarai W, Keawvichit R, Amatayakul K. Effect of storage on the creatinocrit and total energy content of human milk. *Human Nutrit Clin Nutrit* 1987; **41**: 31–36.
- Hamill PV, Drizd TA, Johnson CL, Reed RB, Roche AF. *NCHS growth curves for children birth-18 years*. United States. Vital Health Statistics – Series 11: Data from the National Health Survey.: 1–74, 1977.
- Frankenburg WK, Dodds JB. The Denver development screening test. *J Pediat* 1967; **71**: 181–191.
- Rossiter EJ. The use of developmental screening and assessment instruments by paediatricians in Australia. *J Paediat Child Health* 1993; **29**: 357–359.
- Thomann P. Non-compartmental analysis methods manual. In *Topfit 2.0 Pharmacokinetic and Pharmacodynamic Data Analysis System for the PC*, ed. by Heinzel G, Woloszczak R, Thomann P. Stuttgart: Gustav Fischer 1993; Chapter 2, pp 5–66.
- 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**: 263–268.
- Bennett PN. Use of the monographs on drugs. In *Drugs and Human Lactation*, 2nd edn, ed. Bennett PN. Amsterdam: Elsevier, 1996; pp 67–74.
- 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.
- Baselt RC. *Disposition of Toxic Drugs and Chemicals in Man*. 5th edn, ed. by Baselt RC. Foster City CA. Chemical Toxicology Institute, pp 874–876, 2000.
- Clerc GE, Ruimy P, Verdeau-Palles J. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. The Venlafaxine French Inpatient Study Group. *Int Clin Psychopharmacol* 1994; **9**: 139–143.
- Dierick M, Ravizza L, Realini R, Martin A. A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. *Prog Neuro-Psychopharmacol Biol Psychiat* 1996; **20**: 57–71.
- Costa e Silva J. Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. *J Clin Psychiat* 1998; **59**: 352–357.
- Schweizer E, Feighner J, Mandos LA, Rickels K. Comparison of venlafaxine and imipramine in the acute treatment of major depression in outpatients. *J Clin Psychiat* 1994; **55**: 104–108.
- Atkinson HC, Begg EJ. Prediction of drug distribution into human milk from physicochemical characteristics. *Clin Pharmacokinet* 1990; **18**: 151–167.
- Ackland FM, Preece MA. Catch-up growth. *Pediatrician* 1987; **14**: 226–233.
- Luo ZC, Low LC, Karlberg J. Fetal size to final height in Hong Kong Chinese children. *J Pediat Endocrinol Metab* 2000; **13**: 269–279.
- Ong KK, Ahmed ML, Sherrieff A, et al. Cord blood leptin is associated with size at birth and predicts infancy weight gain in humans. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *J Clin Endocrinol Metab* 1999; **84**: 1145–1148.