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 (0.151 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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Received 1 March 2001, accepted 10 August 2001.

[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. Creatamotocrit (% 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 µg 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 µg 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 creatamotocrit 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
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
0.151 kg kg⁻¹ day⁻¹ was assumed [21], and this value
was multiplied by the average milk concentration
(AUC(0,24 h)/24 h) to give the absolute infant dose of
V and ODV in mg kg⁻¹ day⁻¹. The infant dose was then
expressed as a percentage of the maternal weight-
normalized dose. Since V and ODV are approximately
equivalent 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 concen-
trations 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 an 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) mg
kg⁻¹ 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 (pKa
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 pKa 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) μg L⁻¹ for V and 286 (160, 412) μg 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 mg kg⁻¹ 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 μg L⁻¹) and ODV (796 μg 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 μg L⁻¹ and 608 μg 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 0.151 kg kg⁻¹ 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 creatamotocrit for the group was 7.5% (6.6, 8.3%).
For creatamotocrit, there were also significant differ-
ences 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 μg L⁻¹, while ODV was detected in four infants at
concentrations ranging from 3 to 38 μg 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 abnormal-
ities. 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
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...
and fluoxetine [24–27]. Compared with the tricyclics and SSRIs, the dual mechanism of action of V in potently 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 μg 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 creataticrit 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 μg l⁻¹) in the plasma of one infant, while low concentrations of ODV (5, 6, 20 and 38 μg 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.

We acknowledge funding from the Women and Infants Research Foundation and Wyeth Australia Pty Ltd. We thank Ruth Barrett-Lennard, Neville Butcher and Cindy Agus for assistance with data collection and analysis, and Medela Inc USA for the loan of a Baby Weigh Scale.

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