Use of sertraline, paroxetine and fluvoxamine by nursing women

VICTORIA HENDRICK, ALAN FUKUCHI, LORI ALTSHULER, MEL WIDAWSKI, AMY WERTHEIMER and MARTINA V. BRUNHUBER

Background The pharmacological treatment of depression in nursing women requires information on the magnitude of medication exposure to the infant that may occur through breast milk.

Aims To examine serum concentrations of antidepressants in infants exposed to these medications through breast-feeding.

Method Maternal and infant serum concentrations of sertraline, paroxetine and fluvoxamine were determined with high-performance liquid chromatography (limit of detection = 1 ng/ml).

Results No detectable medication was present in any infant exposed to paroxetine (n=16) or fluvoxamine (n=4). Among infants exposed to sertraline (n=30), detectable medication was present in 24% of serum samples. A significant negative correlation was found between infant age and infant serum concentration. Sertraline was significantly more likely to be detected in an infant if the mother’s daily dose was 100 mg or higher. No adverse sequelae occurred in any infant.

Conclusions This study shows that paroxetine, fluvoxamine and sertraline produce minimal exposure to infants when taken by nursing mothers.

Declaration of interest This study was supported by the National Institute of Mental Health, SmithKline Beecham and Pfizer.

When new mothers experience depression, they and their clinicians need to know if antidepressant medications are safe to use while breast-feeding. Several recent reports have examined the extent of exposure that occurs to nursing infants whose mothers take antidepressants (eg. Altshuler et al, 1995; Taddio et al, 1996; Mammen et al, 1997; Stowe et al, 1997; Yoshida et al, 1997; Wisner et al, 1998; Begg et al, 1999; Birnbaum et al, 1999; Kristensen et al, 1999; Ohman et al, 1999; Stowe et al, 2000). However, the research literature has consisted largely of single cases or small studies, and methodological differences have limited the information that can be drawn from them (Yoshida et al, 1999).

To expand this literature, we present measurements of maternal and infant serum concentrations in 50 nursing mother–infant pairs in which the mothers took therapeutic doses of sertraline, paroxetine or fluvoxamine.

METHOD

Fifty nursing mother–infant pairs who presented to UCLA’s Pregnancy and Postpartum Mood Disorders Program were included in the study. The women were Caucasian (n=46), Hispanic (n=3) and Asian (n=1), in good physical health, ranging in age from 24 to 41 years old and on standard doses of antidepressant medication, taken once daily for treatment of major depression. Two women additionally were on nortriptyline and another was on alprazolam. None of the infants was on medications of any category. Seventeen women were on antidepressants during pregnancy as well as nursing. Written informed consent was obtained from each mother for collection of serum samples.

Sample collection Maternal and infant serum samples were obtained at a minimum of 2 weeks following a fixed dose of antidepressant. For women who took the antidepressant during pregnancy, maternal and infant serum samples were obtained a minimum of 2 weeks following delivery. Serum samples were obtained from a total of 50 infants and 48 mothers.

Detection of antidepressant concentrations in serum

The detection of sertraline, desmethylsertraline, paroxetine and fluvoxamine in serum was accomplished via an isocratic high-performance liquid chromatography (HPLC) separation followed by ultraviolet detection at 225 nm. The concentration of each drug (sertraline, desmethylsertraline, paroxetine or fluvoxamine) in the samples was calculated from its peak area ratios by using the slope and intercept of the appropriate calibration curve. The assays had a lower limit of sensitivity of 1 ng/ml, defined by a signal-to-noise ratio of 7 for each drug.

Statistical analysis

The LIFEREG Procedure using SAS software was used to perform a Tobit analysis on the data. The Tobit model is a regression model for left-censored data, assuming a normal distributed error term. The model parameters are estimated by maximum likelihood. A χ² test was used to explore whether nursing infants whose mothers took higher daily doses of sertraline (100 mg or more) were more likely to have detectable serum concentrations of medication, as compared with infants of women who took lower doses.

RESULTS

Results of the serum assays for the mother–infant pairs are shown in Table 1. Infant ages ranged from 2 to 60 weeks and weights ranged from 3 to 10 kg at the time of the serum assays.

No detectable medication was present in any infant exposed to paroxetine or fluvoxamine. Detectable medication (parent and/or metabolite) was present in 24% (8/33) of the serum samples obtained from infants exposed to sertraline. Concentrations of sertraline and desmethylsertraline, when present, were 2–8 and 2–12 ng/ml, respectively.

Four mothers (nos 5, 16, 24 and 49) titrated their dose of the antidepressant...
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n/o, not obtained; n/a, not available.
upwards to help their mood and obtained repeat serum samples on themselves and
their infants after being on the higher medication dosage for at least 1 week.
Maternal dosage of sertraline correlated highly with infant serum concentration
of desmethylsertraline after controlling for infant age, gestational exposure and
breast-feeding exposure (parameter estimate=0.09, d.f.=1, P=0.03). Maternal
serum concentrations of sertraline and desmethylsertraline correlated highly with
infant serum concentration of desmethylsertraline (parameter estimate=0.20, d.f.=1,
P<0.001 and parameter estimate=0.07, d.f.=1, P=0.008, respectively) after con-
trolling for infant age, gestational exposure and breast-feeding exposure. This analysis
used all the available maternal and infant serum samples shown in Table 1.
A significant negative correlation was found between infant age and infant serum
concentration of desmethylsertraline after controlling for maternal dosage, gestational
exposure and breast-feeding exposure (parameter estimate=-1.46, d.f.=1, P=0.002).
Among women who breast-fed fully, the likelihood of their infants having a detect-
able level of medication (sertraline or des-
methylsertraline) was significantly higher
if their dose was 100 mg or more ($\chi^2= 6.81$, d.f.=1, P=0.009).

Mothers were questioned about poten-
tial adverse sequelae to their infants and
did not report any such findings. Specific
enquiries were made regarding gastro-
intestinal symptoms (e.g. vomiting, watery
stool), lethargy, changes in sleep patterns
and easy bruising. None of the women in
the study was on other medications and
the infants were in good health.

DISCUSSION
This study found that serum concentrations
of medication were undetectable in all in-
fants exposed to paroxetine or fluvoxamine
and in the majority of infants exposed to
sertraline while nursing. When medication
was present in the sertraline-exposed in-
fants, it was usually in the form of the
metabolite desmethylsertraline. Maternal
serum concentrations of sertraline and
desmethylsertraline correlated highly with
infant serum concentrations of desmethyl-
sertraline. Maternal dosage of sertraline
also correlated highly with infant serum
concentrations of desmethylsertraline; doses of 100 mg or above were significantly
more likely to produce detectable concen-
trations in the infant. A significant negative
correlation emerged between infant age and
serum concentration of desmethyl-
sertraline.

This study’s findings suggest that
paroxetine, fluvoxamine and sertraline are reasonable choices for nursing women
requiring treatment for depression. In
comparison with fluoxetine, these medi-
cations appear to produce less exposure
to nursing infants and have not been linked
with the adverse events of neonatal irrit-
ability, sleep disturbance and poor feeding
that have been reported in association with
fluoxetine exposure through breast-feeding
(Lester et al, 1993; Brent & Wisner, 1998;
Chambers et al, 1999; Kristensen et al, 1999).
For infants that are healthy and
full-term, these findings provide no reason
to discourage nursing among women taking
paroxetine, fluvoxamine or sertraline at
standard therapeutic dosages. The use of
additional medications that are commonly
taken in the post-partum period (e.g. anti-
histamines, decongestants, pain medi-
cations) should be kept to a minimum
until more is known about whether such
combinations are safe for the nursing infant
(Mitchell, 1999).

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