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BRIEF REPORT

Olanzapine excretion in human breast milk: estimation of infant exposure

Simon Croke[1], Anne Buist[1], L. Peter Hackett[2], Kenneth F. Ilett[3], Trevor R. Norman[1] and Graham D. Burrows[1]

[1] *Department of Psychiatry, University of Melbourne, Austin & Repatriation Medical Centre, Heidelberg, Victoria, Australia*
[2] *Department of Clinical Pharmacology and Toxicology, The Western Australian Institute for Pathology and Medical Research, Nedlands, Western Australia*
[3] *Department of Pharmacology, University of Western Australia, Crawley, Western Australia*

Abstract

Newer antipsychotic drugs offer significant clinical advantages for the treatment of psychosis. In particular for the treatment of postpartum disorders newer agents may be suited due to their favourable side-effect profiles. Of concern is the passage of the drugs into breast milk and what potential risks this poses for an infant who is breastfed. The excretion of olanzapine into the breast milk of five lactating women with postpartum psychosis was examined in this study. Nine pairs of plasma and breast-milk samples were collected and the concentration of olanzapine determined by high-performance liquid chromatography. Single-point milk-to-plasma ratios were calculated and ranged from 0.2 to 0.84 with a mean of 0.46. The median relative infant dose was 1.6% (range 0–2.5%) of the weight-adjusted maternal dose. During the study period, there were no apparent ill effects on the infant as a consequence of exposure to these doses of olanzapine. As with other antipsychotic drugs this study demonstrates that olanzapine passes into breast milk. The long-term effects of exposure in infants exposed to olanzapine requires further investigation.

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Introduction

The association between psychiatric disorders and the postpartum period is well recognized, with up to 20% of all mothers affected (Pritchard and Harris, 1996). Psychosis is the most disabling of these disorders with acute safety risks to both the mother and the infant (Oates, 1997). The highest incidence of postpartum psychosis occurs within 30 d of delivery with most cases occurring within 14 d (Agrawal et al., 1997). Should the disorder be an ongoing illness there are serious consequences for parenting ability and child development (Goodman and Brumley, 1990; Miller and Finnerty, 1996). Despite the consequences and the incidence of the disorder there are no clear guidelines for the use of antipsychotic medication in women who wish to breastfeed their infants. Assessing the risk to the infant of antipsychotic drugs delivered via the breast milk is based on anecdotal evidence or case reports in the literature. In a survey of past reports providing quantitative data on the levels of 'traditional' antipyschotic agents in breast milk, we could find a total of only 32 patients in 11 separate papers (Aaes-Jorgensen et al., 1996; Blacker et al., 1962; Kirk and Jorgensen, 1980; Matheson and Skjaeraasen, 1988; Matheson et al., 1984; Ohkubo et al., 1992; Olesen et al., 1990; Stewart et al., 1980; Whalley et al., 1981; Wiles et al., 1978; Yoshida et al., 1998). The agents reported on were chlorpromazine, haloperidol, trifluoperazine, flupenthixol, zuclopenthixol, chlorprothixene and perphenazine. All were confirmed as appearing in breast milk, with relative infant doses ranging from 0.5–5% of the maternal dose.

With respect to the newer or 'atypical' antipsychotic agents the body of available information is even smaller, despite these agents rapidly becoming the most commonly prescribed antipsychotics in many parts of the world. However, to our knowledge, the only published data for this group are single case reports of risperidone (Hill et al., 2000) and clozapine (Barnas et al., 1994) excretion in human milk. Furthermore there are no controlled studies, which have followed the progress of infants into early childhood, to assess the outcome of exposure to antipsychotics by breastfeeding.

Address for correspondence: Dr S. Croke, Department of Psychiatry, University of Melbourne, Austin & Repatriation Medical Centre, Heidelberg, Victoria, Australia
Tel.: 61-3-9496 2940 *Fax*: 61-3-9496 2360
E-mail: simon.croke@armc.org.au

Olanzapine is an atypical antipsychotic, which acts at both dopamine D2 and 5-HT-2A receptors in the central nervous system (Stephenson and Pilowsky, 1999). It has been shown to be effective in the treatment of various psychotic disorders (Tollefson et al., 1997). Following oral doses the drug is well absorbed and is extensively metabolized in the liver, principally by the cytochromes P4501A2 and P4502D6 (Stephenson and Pilowsky, 1999). At least 10 metabolites have been identified; the main metabolic pathways are N-glucuronidation, allylic hydroxylation, N-oxidation and N-demethylation. Olanzapine-*N*-oxide and *N*-desmethyl-olanzapine along with olanzapine-*N*-glucuronide have been detected in urine. For the most part, the metabolites of olanzapine do not appear to be pharmacologically active, or are only weakly active (Fulton and Goa, 1997; Perry et al., 1997; Stephenson and Pilowsky, 1999). The primary aim of our study was to quantify the excretion of the olanzapine in breast milk of five nursing mothers receiving the drug for the treatment of postpartum psychosis. A secondary aim was to test the algorithm put forward by Begg et al. (1992) for predicting the milk/plasma (M/P) ratio of basic drugs such as olanzapine on theoretical grounds.

Methods

Patients

Consecutive patients admitted to the Mother–Baby Psychiatric Unit at the Austin and Repatriation Medical Centre were considered for inclusion in the study. To be eligible for the study patients had to meet the DSM-IV diagnostic criteria for either schizophrenia and other psychotic disorders or mood disorder with psychotic features (American Psychiatric Association, 1994). As this was not an efficacy study no formal ratings of the severity of illness were made and the decision to treat was based on clinical criteria. Based on the clinical global impression of illness all cases met least moderate to severe criteria. Doses of olanzapine were at the discretion of the treating clinician. All patients were advised of the lack of clinical information concerning the use of olanzapine in breast-feeding and its passage into milk. Nevertheless some elected to continue with treatment and provide specimens for the study. Olanazapine was continued for a minimum of 5 d to ensure that steady-state plasma concentrations had been achieved before plasma and breast-milk samples were collected. Doses of olanzapine were administered at 22:00 hours each evening as a single oral regimen. The study protocol was approved by the Committee on Human Research and Ethics of the Austin and Repatriation Medical Centre and all subjects gave written informed consent.

Analysis of olanzapine in plasma and milk

Plasma

Aliquots of plasma (1 ml) were mixed with ascorbic acid (10 μl of 25% aqueous solution) and mexiletine (internal standard, 15 μl of 10 μg/ml) in glass extraction tubes. Olanzapine was analysed by HPLC using a method established in our laboratory (Dusci et al., unpublished observations). Briefly, plasma was alkalinized with sodium carbonate (pH 10) and extracted with a hexane : dichloromethane (8 : 15) mixture by shaking vigorously for 5 min. The organic phase was back-extracted into hydrochloric acid and an aliquot injected onto the HPLC. Unknowns were interpolated from a standard curve run with each batch of samples. Standard curves were linear over the range 2–120 μg/l ($r > 0.996$).

Milk

In our experience variable milk matrix composition can sometimes affect the recovery of analytes. Therefore, milk samples were analysed by the 'method of addition'. Aliquots (4×1 ml) were placed in separate glass extraction tubes and 0, 10, 20 and 30 ng of olanzapine standard respectively were added. The specimens were then extracted as described above for plasma. The peak height ratio (olanzapine : internal standard, *y*-axis) for each sample was regressed (linear; $r > 0.0995$) against the concentration of added olanzapine (*x*-axis). The equation to this line was used to calculate the negative *x*-axis intercept that is the estimated concentration of olanzapine originally present in each milk sample.

Chromatography was performed using a Merck LiChrospher 60 RP Select B column (250 mm × 4 mm i.d.), a mobile phase of 12% acetonitrile in 0.5% phosphoric acid containing 0.05% triethylamine, delivered at a flow rate of 1.2 ml/min. Analytes were detected by their UV absorbance at 200 nm. The coefficients of variation for plasma assay were: intra-day (4.6 and 2.4%, at 6 and 120 μg/l, respectively) and inter-day (8.2 and 3.9%, at 6 and 120 μg/l, respectively). For milk, the coefficients of variation were: intra-day (6.3 and 3.4%, at 6 and 120 μg/l, respectively) and inter-day (6.3 and 3.3%, at 6 and 120 μg/l, respectively).

Measurement of $\log_{10} P$ for olanzapine

The $\log_{10} P_{(\text{octanol : buffer, pH 7.2})}$ value for olanzapine was measured as previously described (Rampono et al., 2000) with concentrations in the buffer phase before and after equilibration being measured using the HPLC assay described above.

Results

The log $P_{(\text{octanol}:\text{buffer, pH } 7.2)}$ value for olanzapine was 2.02, indicating that the drug has a substantial lipid solubility. Calculation of the theoretical M/P ratio for olanzapine was undertaken by the method of Begg et al. (1992) using the above log *P* value, the higher (relevant) of the its two pK_a values (5 and 7.4), a plasma protein binding of 93% as calculated by Baselt (2000) and a milk pH of 7.2 yielded a theoretical M/P ratio of 0.38.

A total of 5 women aged 21–35 yr (mean 26.2 yr) provided a total of 9 paired plasma and breast-milk specimens. One subject provided 3 pairs of specimens, two subjects 2 specimens and the remaining subjects provided 1 specimen. Each woman was the mother of a singleton child, whose ages ranged from 3 wk to 6 months. Patient A weighed 80.5 kg, the others ranged from 55.4 to 59 kg. At the time of medication stabilization, infants and their mothers were in-patients, and both infants and the mother–infant interaction under close observation, including sleep patterns, weight and milestone assessment.

During the admissions, which ranged from 8 d to 5 wk, there were no clinically significant health or developmental problems observed in the infants despite their mothers receiving olanzapine throughout. One infant developed an upper respiratory tract infection that was not considered related to ingestion of olanzapine through the breast milk. Doses of olanzapine ranged from 2.5 to 10 mg/d.

Table 1 reports the olanzapine plasma and milk concentrations, as well as M/P ratios and relative infant dose at various times after dose for the 5 women. The M/P ratio was variable ranging from 0.2 to 0.84 with a mean of 0.46. Relative infant dose was calculated directly from the olanzapine concentration in milk, using an average milk consumption of 0.15 l/kg . d for each infant, and assuming 100% bioavailability (Bennett, 1966):

$$\text{relative infant dose} = \frac{[\text{milk concentration } (\mu\text{g/l}) \times 0.15 \text{ l/kg . d} \times 100]}{(\text{maternal dose } (\mu\text{g})/\text{maternal body weight})}.$$

For patients A–E the average or single calculated values for relative infant dose were 2.2, 2.5, 0, 1.4 and 1.6% respectively of the weight-adjusted maternal dose.

Discussion

Prediction of M/P ratios on theoretical grounds has been recommended as a means of estimating drug concentration in milk and hence infant exposure, when maternal plasma concentrations of drug are the only data available (Begg et al., 1992). Using this method we predicted an M/P ratio of 0.38 for olanzapine. This value is similar to those measured in our present study (mean 0.46, range 0.2–0.8). Thus, our data suggest that the algorithm for predicting the M/P ratio of basic drugs gave a robust estimate for olanzapine and may be useful for other basic drugs where milk transfer is unknown.

The main finding of the study is that olanzapine passes into the breast milk, but at concentrations lower than those occurring in plasma. Maternal plasma concentrations were generally in line with those reported in the literature for other groups receiving similar doses to those

Table 1. Olanzapine dosage, sample time after administration, milk and plasma concentrations, M/P ratio, and relative infant dose

Patient	Maternal dose (mg)	Time after dose (h)	Olanzapine in milk (mg/l)	Olanzapine in plasma (mg/l)	M/P ratio	Relative infant dose (%)
A	10	11	21	25	0.84	2.54
A	10	23	16	31	0.52	1.93
B	2.5	22	7	14	0.5	2.48
C	2.5	12	< 1	8	–	0
D	2.5	12	5	11	0.45	1.72
D	2.5	12	3	10	0.3	1.03
E	2.5	11	8	15	0.53	2.66
E[a]	2.5	16	4	12	0.33	1.33
E	2.5	23	2	10	0.2	0.66

[a] Infant of E, plasma 15 h post-maternal dose < 1 μg/l.

used in the present study (Fulton and Goa, 1997). The concentration of olanzapine in milk was approximately proportional to dose. In the present study our estimates of the M/P ratio and olanzapine concentration in milk were obtained from between 1 and 3 paired milk and plasma samples per patient, and there was significant between-patient variability for these two measurements. Robust estimates of both the M/P ratio and average drug concentration in milk (the primary factors that allow estimation of infant dose) are best obtained from measurements of the area under the milk and plasma concentration–time curves over a dose interval (AUC). Hence, we suggest that further studies of olanzapine excretion in milk should be conducted using a multiple sampling strategy that would facilitate analysis by the AUC method.

Where maternal plasma concentration of olanzapine is the only measurement available, the product of the M/P ratio and plasma concentration can be used to estimate the concentration in milk. In turn the concentration in milk is then used to calculate relative infant dose. In the present study, relative infant dose was calculated directly from the measured concentration of olanzapine in milk, without the need to use the M/P ratio. The median value for relative infant dose of 1.6% (range 0–2.5%) is well below the notional 10% level of concern reported by Bennett (1996) for 'safe' breastfeeding.

With our limited number of concentration measurements in milk, we cannot accurately evaluate the utility of trying to decrease infant dose exposure by 'pumping and dumping' milk produced at around the time of the peak concentrations in plasma. However, this strategy is unlikely to be worthwhile given the long plasma half-life of olanzapine in women (37 h; Eli Lilly Product Information, Zyprexa) which would suggest a small peak-to-trough variation in both plasma and milk concentration across a 24-h dose interval. In addition, the low level of the calculated relative infant dose also suggests that avoiding feeding at the peak is unlikely to result in a significant reduction in infant exposure.

In one case the patient consented to have her infant give plasma for the analysis of olanzapine. The sample was collected 15 h after the maternal dose and olanzapine was not detected (assay limit of detection $< 1\ \mu g/l$) suggesting that the drug did not accumulate excessively. Nevertheless the result needs to be interpreted cautiously as the infant was 4 months old at the time of sampling, an age at which liver enzymes are near adult levels of activity. Furthermore, the sample was collected long after the maternal dose when breast milk levels are likely to be close to the trough. These data confirm that infant exposure to the drug through the breast milk is relatively low.

The shortcomings of this study need to be acknowledged. First, there were relatively few patients in the study. Secondly, relative infant dose was estimated from milk concentrations measured in only 1–3 samples from each patient, rather than from an average concentration measured over the whole dose interval. Thirdly, we did not quantify olanzapine metabolites that might have contributed to overall infant drug exposure. Nevertheless, since the *N*-10-glucuronide of olanzapine does not cross the blood–brain barrier (Eli Lilly Product Information, Zyprexa), and the major *N*-desmethyl-, N-oxide and 2-hydroxy metabolites have little or no pharmacological activity (Fulton and Goa, 1997; Perry et al., 1997; Stephenson and Pilowsky, 1999), metabolites in milk are unlikely to be a significant issue.

The present study highlights the paucity of data available for the newer antipsychotics with respect to their safety and toxicity during breastfeeding. Clearly, more detailed studies are necessary to delineate both the amount of drug that passes into the breast milk and the long-term consequences for the intellectual and physical development of children so exposed.

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