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ORIGINAL ARTICLE

Alleviating anxiety while breastfeeding: evaluating buspirone transfer into human milk

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Abstract

Purpose Buspirone, an anxiolytic with minimal risk of dependence or respiratory depression, lacks extensive published data on its transfer into human milk during lactation. The objective of this study was to 1) quantify the transfer of buspirone and its active metabolite 1-pyrimidinylpiperazine (1-PP) into human milk, allowing for an estimation of maternal drug exposure to the breastfed infant, and 2) report observations of the infants exposed to buspirone via breastmilk.

Methods Milk samples and health histories were collected from nine lactating mothers who donated milk samples to the InfantRisk Human Milk Biorepository while taking buspirone. The drug concentration–time profile of buspirone and 1-PP was determined using liquid chromatography–mass spectrometry.

Results Buspirone was below the detection level of 1.5 ng/mL in all milk samples with dosages ranging from 7.5 to 30 mg twice daily. However, low levels of active metabolite 1-PP were observed at 7.5 mg twice daily up to 30 mg twice daily. The relative infant dose (RID) calculated ranged from 0.21 to 2.17%, which is below the standard 10% threshold for infant safety. There were no reports of adverse effects in the exposed infants.

Conclusion The levels of buspirone observed in all participants' milk samples were exceedingly low. The subsequently low relative infant dose (RID) in the range of 0.21% to 2.17% is below the 10% threshold for infant safety, suggesting that the transfer of maternal buspirone and its active metabolite (1-PP) into human milk is clinically insignificant and poses minimal risk to a breastfed infant.

Keywords Buspirone · Human milk · Lactation · Breastfeeding · Anxiety · Anxiolytic

Introduction

Early motherhood is a transformative period accompanied by specific concerns about infant safety which may significantly contribute to maternal anxiety (Pawluski et al. 2017). One in 10 women experiences postpartum anxiety that can adversely affect the relationship of the mother and infant (Goodman et al. 2016). Simultaneously, breastfeeding is recommended for the first two years of an infant's life (Eidelman et al. 2012; Meek and Noble 2022). The American College of Obstetricians and Gynecologists (ACOG) clinical practice guideline on the treatment and management of mental health conditions during pregnancy and postpartum recommends selective serotonin reuptake inhibitors (SSRIs) as first-line for perinatal anxiety (strong recommendation, low-quality evidence) and also recommend avoiding benzodiazepines or prescribing sparingly for perinatal anxiety (strong recommendation, moderate quality of evidence) (Miller et al. 2023). However, fear of infant drug exposure via breastmilk with maternal medication use creates a complex clinical treatment conundrum (Davanzo et al. 2016). It has been estimated that almost two in three women prescribed antidepressants before pregnancy discontinued their antidepressant during pregnancy or while lactating due to safety concerns (Grezeskowiak et al. 2014).

The ACOG guidelines do not make any formal recommendations or analyses regarding alternative anxiolytics such as buspirone and what the role of buspirone is in the perinatal period for generalized anxiety disorder or as augmentation for treatment-resistant depression. This may be attributed to a paucity of literature regarding buspirone in

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the antepartum and postpartum periods. As a result, buspirone is one of the most frequently inquired about medications at the InfantRisk Call Center, an evidence-based resource for lactational pharmacovigilance.

Buspirone is a unique oral anxiolytic with a chemical structure distinct from other medications used for anxiety treatment. It was approved for generalized anxiety disorder by the Food and Drug Administration in 1986 and remains a popular option to augment therapy with selective serotonin reuptake inhibitors today (Howland 2015; Garakani et al. 2020). The mechanism of action underlying buspirone's anxiolytic effect is not fully understood, but it is believed to involve serotonergic suppression. It is a partial agonist of 5-HT_{1A} and, to a lesser degree, 5-HT_2 receptors. Buspirone also has low affinity as an antagonist at D_2 receptors (Loane and Politis 2012). Unlike benzodiazepines, buspirone does not have an affinity for GABA receptor complexes, which results in no muscle relaxant or anticonvulsant activity. It does not have a propensity for physical dependence or respiratory depression. Additionally, buspirone does not carry high risk for weight gain or significant sedation at doses less than 20 mg/day. This combination of properties makes buspirone a compelling choice for postpartum women.

There is currently little information regarding the transfer of buspirone or 1-pyrimidinylpiperazine (1-PP), its active metabolite, into human milk. Though buspirone's small molecular size may warrant concern for drug transfer into the milk compartment, it is expected to have limited entry due to high protein binding (86%) and a large volume of distribution, which minimize drug transfer of the drug into milk. Furthermore, the drug's low oral bioavailability decreases systemic exposure in the infant (Mahmood and Sahajwalla 1999). To date, there are no data evaluating maternal buspirone use and excretion into human milk. This study investigates the risk to the breastfed infant with maternal buspirone use by examining the milk and infant outcomes of nine women taking buspirone at dosages of 7.5 to 30 mg twice per day.

Methods

The InfantRisk Human Milk Biorepository (HMB), Texas Tech University Health Sciences Center Amarillo IRB # A21-4214, provided the deidentified materials for this investigation. Electronic consent was obtained from the HMB participants. The HMB collects observational milk samples with various exposures of interest from lactating volunteers. The samples are accompanied by questionnaires with self-reported histories for the breastfeeding dyad. For this study, milk samples were requested from the participants under steady-state conditions at the time points 0, 1, 2, 4, 6, 8, 10, and 12 h post-dose. Mothers were advised to empty both breasts, gently mix the milk, and then aliquot 1–2 oz into a provided collection tube. The collected samples were frozen and shipped overnight to our facility, where they are stored at – 80 °C until further analysis. The HMB was queried for milk donors taking buspirone, resulting in nine deidentified volunteers with corresponding milk samples and health questionnaires pertaining to the maternal-infant dyad. Compliance with ethical standards and approval by the relevant institutional review board (IRB # A21-4214) ensure the protection of participant privacy and welfare throughout the HMB. HMB participant deidentification maintains these protections throughout this study.

This study presents the development and validation of a robust LC–MS/MS (liquid chromatography–tandem mass spectrometry) methodology for analyzing buspirone and its active metabolite in human milk samples. The assay used a Kinetex biphenyl column (100 × 4.6 mm, 5 µm) from Phenomenex with a mobile phase of 30% (vol/vol) water and 70% acetonitrile with a flow rate of 0.4 mL/min. The m/z transitions used were from 386 to 122 for buspirone and 165 to 122 for 1-PP and 294–122 for deuterated internal standard. Blank milk samples obtained from lactating women who were not undergoing any drug therapy were used for the calibration curve. The sample preparation protocol involved simple protein precipitation using organic solvent. The milk concentration–time data sets were subjected to pharmacokinetic analysis, using the log-linear trapezoidal method to calculate the area under the curve (AUC) for 0–12 h and average concentration (C_{avg}); peak concentration T_{max} and relative infant dose (RID).

Relative infant dose was calculated using the formula: relative infant dose (%) = estimated daily infant dose via breast milk (mg/kg/day)/maternal dose (mg/kg/day) × 100. Average infant milk intake was assumed to be 150 mL/kg/day, 75 mL/kg/12 h.

Results

A total of 13 breastfeeding women who were taking buspirone initially consented to the HMB. However, four did not provide their milk samples and were lost to follow-up, resulting in a final sample size of nine participants. Table 1 presents an overview of the demographic characteristics of the women and their infants. The mothers administered buspirone twice a day, with doses ranging from 7.5 to 30 mg.

Understanding the drug concentration–time profile in milk is important for assessing the potential risk of infant exposure and the extent of drug transfer in evaluating the safety of buspirone use in postpartum lactating women. No buspirone levels were observed in any of the collected samples, our level of detection being 1.5 ng/mL. The active metabolite 1-PP was quantitated in all of the milk samples.

Table 1 Demographic characteristics of participants

Parameter	Value
Maternal age (years)	32 ± 3.8 (26–37)
Number of pregnancies	1 (1–2)
Gestational age at delivery (weeks)	38.3 ± 1.6 (34–39)
Birth weight (grams)	3183.5 ± 724 (1723–4139)
Taking concomitant maternal medications	
Yes	8 (88.9%)
No	1 (11.1%)
Infant's gender	
Male	5 (55.6%)
Female	4 (44.4%)
Exclusive breastfeeding	9 (100%)
Infant age at time of sampling	1–3 months ($n=3$)
	4–6 months ($n=2$)
	7–11 months ($n=4$)

The values are presented as mean ± SD (range) or *n* (%)

Milk concentrations of 1-PP were low throughout the time profile and relatively dose proportional (Fig. 1). As doses varied, individual pharmacokinetic results are presented for each participant (Table 2). The infant daily doses were estimated at 0.0004–0.0075 mg/kg/day and the relative infant doses were calculated as 0.21% to 2.17%. Moreover, none of the mothers reported any adverse effects in their infants.

Discussion

In this study investigating buspirone concentrations in maternal milk samples, there was low transfer of buspirone and its active metabolite 1-PP into human milk, even at the maximum labeled dose (60 mg per day). The relative infant dose (RID), a weight-adjusted measure of infant exposure, averaged less than 1% with a maximum of 2.17%. It is commonly accepted that a drug with a RID below 10% is probably safe, though a stricter threshold

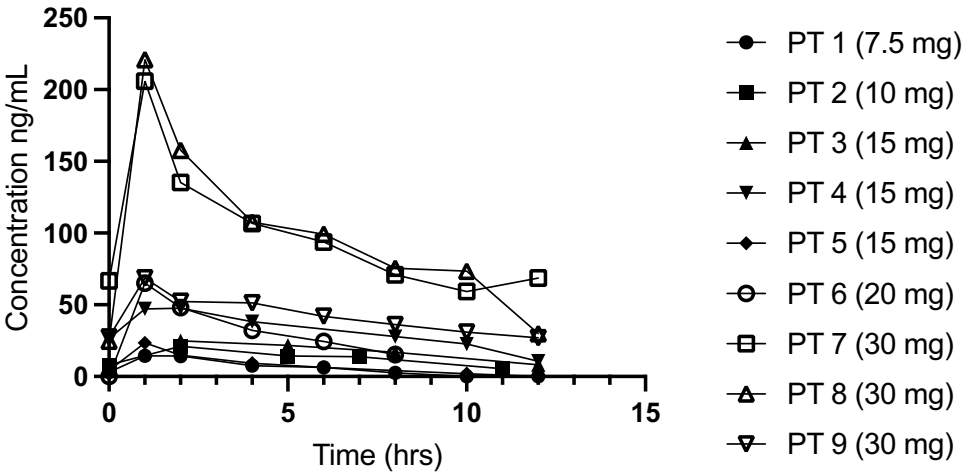

Fig. 1 Buspirone active metabolite (1-PP) concentration over a 12-h dosing period in human milk. Milk concentrations of 1-PP peaked 1-h post dose and fell over the dosing period. Drug concentrations were dose proportional with inter-participant variability. Baseline values supported the presumption of steady-state conditions

Table 2 Individual patient pharmacokinetic data

Participant number	Weight (kg)	Dose (mg BID)	Maternal weight adjusted dose mg/kg/12 h	Milk AUC 12 ng*h/mL	Infant daily dose (mg/kg/12 h)	Relative infant dose
1	70.7	7.5	0.11	71	0.0004	0.42%
2	58.9	10	0.17	148.6	0.0009	0.55%
3	65.7	15	0.23	178.7	0.0011	0.49%
4	78.01	15	0.19	386.3	0.0024	1.26%
5	55.7	15	0.27	91.33	0.0005	0.21%
6	77.1	20	0.26	266.3	0.0016	0.64%
7	88.9	30	0.34	1172	0.0073	2.17%
8	65.7	30	0.46	1212	0.0075	1.66%
9	99.7	30	0.30	508.5	0.0031	1.06%
Average	*73.4*	*19.2*	*0.26*	*448.3*	*0.0028*	*0.94%*

of 5% is sometimes applied to psychoactive medications (Larsen et al. 2015). Based on available pharmacokinetic information and animal models, the active metabolite 1-PP has around 25% of the activity of buspirone and it is also available in 20-fold greater concentrations in the serum (Bristol-Myers Squibb 2010). Given that 1-PP based on animal models has 20-fold higher concentrations in the serum, it is unsurprising that 1-PP was detected in this study while buspirone was not. To date, there is only one case report available with a lactating mother taking buspirone 15 mg three times daily that analyzed untimed milk samples along with maternal and infant plasma levels. This case report did not identify buspirone in any of the milk or infant plasma samples, but the findings were limited by not reporting an established level of detection (Brent and Wisner 1998).

Medication selection for anxiety and depression in the perinatal period can be affected by lactation status. Patients and providers alike share in the struggles of clinical-decision making during pregnancy and breastfeeding (McDonald et al. 2011). Some of the struggles that providers face center on risk and benefits given the available evidence. However, even with evidence, surveys indicate that providers recommended breastfeeding patients abstain from breastfeeding with medications not associated with infant harm (Jayawickrama et al. 2010). Breastfeeding mothers face an equally difficult dichotomous dilemma of balancing being a "good mother" protecting their baby from untoward harm and being "responsible" acting on medical advice from their providers (McDonald et al. 2011). Breastfeeding women as a result have 17% higher perceptions of risks of using medications during lactation compared to during pregnancy. Breastfeeding women also have "negative feelings like anxiety or guilt" when using medications (Spiesser-Robelet et al. 2017).

However, information suggests that many of these concerns are not supported by evidence. Based on current information, citalopram, fluoxetine, sertraline, and paroxetine have been evaluated in breastfeeding women and have not been identified as causing adverse effects in infants (Hale and Krutsch 2023). However, augmenting antidepressant therapy can be a challenge in this population. With bupropion there have been two case reports of infant seizures while exposed to bupropion in milk, and with venlafaxine there has been a case report of failure to thrive in one infant exposed to venlafaxine in utero and in lactation (Chaudron and Schoenecker 2004; Neuman et al. 2014; Tran et al. 2016). Though ACOG's clinical practice guidelines recommend avoiding or limiting benzodiazepines in lactating women when possible, there is some evidence that infant sedation was associated with the number of CNS depressants rather than simply benzodiazepine use (Kelly et al. 2012). Regardless, the anxious patient may not find these findings reassuring.

Buspirone is an attractive option to explore for breastfeeding women as its safety profile is palatable. There are no strong or moderate suggestions of infant harm from case reports of maternal buspirone use (Brent and Wisner 1998). Additionally, buspirone has no suspected impact on milk production; it has been suggested to increase prolactin (Maskall et al. 1995). Buspirone does have a major drug-drug interaction involving the enzyme cytochrome P450 3A4 (CYP3A4). When buspirone is used with inhibitors of CYP3A4 (e.g., grapefruit juice, ritonavir, itraconazole, erythromycin, diltiazem), it blocks the conversion of buspirone to its active metabolite 1-PP which can significantly increase the serum concentration of buspirone and it is recommended to use a lower daily dose 2.5 mg per day. Limitations of this study include small sample size and the absence of corresponding maternal or infant plasma samples.

Conclusion

In this analysis of nine breastfeeding mothers taking up to the maximum dose of 60 mg per day, no buspirone and minimal active metabolite 1-PP was found in breast milk samples. The relative infant dose (RID), a weight-adjusted measure of infant exposure, was well below even the strictest safety parameters, averaging less than a 1% RID with a maximum of 2.17%. Therefore, our results suggest that maternal buspirone poses low risk of infant harm. Given the relatively sparse literature available on buspirone in breastfeeding, this research adds information for breastfeeding women who are advised to take buspirone to treat generalized anxiety disorder or as augmentation therapy for depression.

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Data availability The data that support the findings of this study are available from the corresponding author, LC, upon reasonable request.

Declarations

Conflict of interest K.K. has consulted for Adnovate Clinical Development Strategies Ltd and co-authors Hale's Medications and Mothers' Milk. All other authors have no relevant financial or non-financial interest to disclose. All other authors certify that they have no affiliations

with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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