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Maternal Metyrapone Use During Breastfeeding: Safe for the Breastfed Infant

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Context: Metyrapone is an inhibitor of endogenous adrenal corticosteroid synthesis, which has been proven to be a viable option in controlling maternal serum cortisol concentrations during pregnancy. The infant exposure to maternally ingested metyrapone through breast milk is, however, largely unknown.

Case Description: We report the excretion of metyrapone into breast milk and subsequent infant exposure from a lactating woman on 250 mg of metyrapone three times daily. Due to limited supply of breast milk, the infant was fed ~50% breast milk and 50% formula. At steady state, the average concentrations in the studied breast milk and absolute and relative infant doses were 176 μg/L, 26.45 μg/kg/d, and 0.7%, respectively, for metyrapone, and 310 μg/L, 46.52 μg/kg/d, and 1.21% for its active metabolite metyrapol. The breastfed infant was found to have a plasma metyrapone concentration of 0.05 μg/L, with no evidence of disruption to his adrenocortical axis biochemically.

Conclusion: These findings indicate that maternal metyrapone use during breastfeeding did not pose a notable risk to this breastfed infant. The infants' exposure to metyrapone was further minimized by avoiding nursing for 2 to 3 hours after each metyrapone dose.

Freeform/Key Words: metyrapone, metyrapol, breastfeeding, milk, infant dose, lactation

The pharmacological effect of metyrapone and its active metabolite metyrapol is to reduce cortisol production by inhibiting the 11-β-hydroxylation reaction in the adrenal cortex. As with many medications where there is minimal data, the manufacturer's product information states that patients on metyrapone should not breastfeed [1]. Only one case has reported excretion into breast milk. Hotham *et al.* [2] calculated that a fully breastfed infant would receive ~9 μg/kg daily or 0.1% of the weight-adjusted maternal dose of metyrapone, inferring that metyrapone exposure to a breastfed infant was unlikely to cause adverse effects. The patient in that study chose not to breastfeed, so the subsequent infant exposure and absolute safety of metyrapone use while breastfeeding remains unknown.

Abbreviations: AID, absolute infant dose; AUC0-6, Area under the concentration-time curve; Cavg, average concentration in milk; Ke, elimination constant; RID, relative infant dose.

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1. Case Study

A 27-year-old previously well primigravid woman presented at 24 weeks' gestation with severe hypertension and was diagnosed with ACTH-independent Cushing's syndrome secondary to a left adrenal adenoma. Adrenalectomy was deemed too high a risk thus the patient was managed with metyrapone at an average daily dose of 750 mg titrated to a target urinary free cortisol of 300 to 400 nmol/24 hours. The maternal antenatal course was complicated by hypokalemia, hypertension, gestational diabetes mellitus, and peripartum cardiomyopathy. Serial scans revealed a large for gestational age fetus with reassuring growth and wellbeing. At 32 weeks' gestation, delivery was necessitated given deteriorating maternal cardiac ejection fraction. A live male infant weighing 2014 g (58th centile) was delivered. Apgar scores were 9 at 1 minute and 9 at 5 minutes. The infant required admission to the special care nursery until 37 weeks of age with complications related to prematurity, however, remained in good condition with no evidence of inhibition of adrenal 11-β hydroxylase as evidenced by normal serum potassium and cortisol levels, and normal blood pressure recordings.

Postpartum the patient remained on metyrapone, 250 mg three times daily while awaiting left adrenalectomy. Concomitant drug treatment included bisoprolol 10 mg and captopril 12.5 mg twice a day. From the establishment of lactation, until ~7 months' postpartum, the patient elected to feed her infant with ~50% breast milk and 50% formula due to inadequate supply of breast milk to sustain exclusive breastfeeding.

At 5 weeks' postpartum, the patient requested that we collect her breast milk so that the transfer of metyrapone into her breast milk could be analyzed. Further to this, she requested that her infant be tested for metyrapone exposure and any sequelae. Written informed consent was obtained from the patient on behalf of herself and her son to carry out the required testing procedures as well as to publish this case report and the accompanying tables and figures.

2. Methods

A. Breast Milk Collection and Storage

Breast milk collection was undertaken on four occasions using an electric breast pump. Breast milk samples were stored frozen at −20°C before analysis.

During collection one, the first 10 mL of breast milk expressed from one breast was collected immediately pre metyrapone dose. Two hundred fifty milligrams of metyrapone was then ingested, and 10 mL of breast milk was collected from the same breast, every 30 minutes for 6 hours until immediately prior to the next dose of metyrapone.

Collection two was performed 3 days later. Immediately preingestion of metyrapone, the first 10 mL of fore-breast milk was collected, the breast was emptied via electronic pump, and then a residual 10 mL of hind breast milk was collected.

Five days later, the collection one protocol was repeated for collection three; however, milk was collected hourly rather than half hourly for patient ease.

Collection four was undertaken to provide a sample of the milk the infant was receiving in a realistic feeding scenario. Over a 24-hour period, during each feed, a random mixed sample of 10 mL of expressed breast milk from either breast was collected and stored for analysis. During this collection, the patient ingested 250 mg of metyrapone three times daily, avoiding breastfeeding for ~2 to 3 hours post each dose.

B. Infant Testing

At 5 weeks' postpartum, the infant had a corrected gestational age of 37 weeks. At 10:16 AM, he underwent blood testing for 11-deoxycortisol, ACTH, and cortisol, as well as serum metyrapone and metyrapol levels, 1-hour post exposure to 40 mL of expressed breast milk collected 3 hours post maternal ingestion of 250 mg of metyrapone. We were unable to repeat

hormonal measurements, or perform dynamic testing to further assess the infants' adrenocortical axis at a later gestational age, as his treating pediatric team found his growth and development to be appropriate with no indication clinically to warrant further testing.

C. Laboratory Methods

Metyrapone and metyrapol were measured with Ultra Performance Liquid Chromatography (BEH C_{18} 2.1x50 mm column at 45°C) coupled to a Quattro Premier XE mass spectrometer (Waters, Milford, MA). Acetonitrile (150 μL) with metyrapone-d6 (Alsachim, France) internal standard was added to 50 μL of sample. Ten microliters of supernatant was chromatographically resolved over 2 minutes with 2 mmol/L ammonium acetate plus 0.1% formic acid and a linear methanol gradient. Mass transitions (mz) were monitored in positive ionization mode: metyrapol 229.3 > 121; metyrapone 227.2 > 120.9 0; metyrapone d6 233.1 > 126.9. The detection limits for metyrapone and metyrapol were 0.2 and 0.5 μg/L and imprecision at 25 and 250 μg/L were < 7%. Cortisol, 11-deoxycortisol, and aldosterone were measured with tandem mass spectrometry [3]. ACTH was assayed on an Immulite 2000 analyzer (Siemens, Munich, Germany).

D. Data Analysis

Metyrapone and metyrapol milk concentration-time data sets were analyzed using traditional pharmacokinetic principles. The terminal elimination t1/2 was calculated from log-linear regression analysis of the data pairs, and the elimination constant (Ke) was calculated as in 2/t1/2. Area under the concentration-time curve (AUC0-6) was measured using the log-linear trapezoidal rule. The average concentration in milk (Cavg) over one dose interval at steady state was calculated as AUC0-6/6 hours. Absolute (AID) and relative (RID) infant doses were calculated using an average milk intake of 0.15 L/kg/d.

3. Results

The measured concentrations of metyrapone and metyrapol in breast milk collected at 30-minute intervals after a 250-mg morning dose are depicted in Fig. 1. The apparent t1/2 and Ke values of metyrapone and metyrapol were 32.9 minutes (0.55 hours), and 66.8 minutes (1.11 hours) and 0.6004 and 0.6229, respectively. AUC, Cavg, AID, and RID for the concentration of metyrapone and metyrapol in milk collected at 30-minute intervals are summarized in Table 1. Table 2 represents the same data for milk collected at 60-minute intervals. The difference between the data from collections one and three likely reflects the early concentration peak of metyrapone and metyrapol post dose ingestion, which is missed in the hourly data series.

The concentrations detected in fore and hind-milk were found to be similar, with metyrapone measured at 2.1 μg/L and 2.3 μg/L respectively, and metyrapol at 22 μg/L in both samples. This suggests that milk composition does not affect the measurable drug or drug metabolite concentration.

Metyrapone and metyrapol milk concentrations at steady state vs time over 24 hours, where the patient took 250 mg of metyrapone at 0800 hours, 1415 hours, and 2000 hours and subsequently breastfed providing mixed samples of every feed given for analysis are depicted in Fig. 2.

The infant plasma concentration of metyrapone was 0.05 μg/L and metyrapol was 4 μg/L. Comparative concentrations measured in the mother's serum were 41.5 and 338 μg/L, respectively. The infant's ACTH was 160 ng/L (10–180 ng/L), the cortisol was 98 nmol/L (15–340 nmol/L), and 11-Deoxycortisol was 2 nmol/L (<25.0 nmol/L). His sodium was 133 mmol/L (133–144 mmol/L), and potassium was 4.8 mmol/L (4.2–6.7 mmol/L).

4. Discussion

The main objective in performing this study was to elicit the safety of breastfeeding an infant using breast milk from a lactating mother treated with metyrapone 250 mg three times

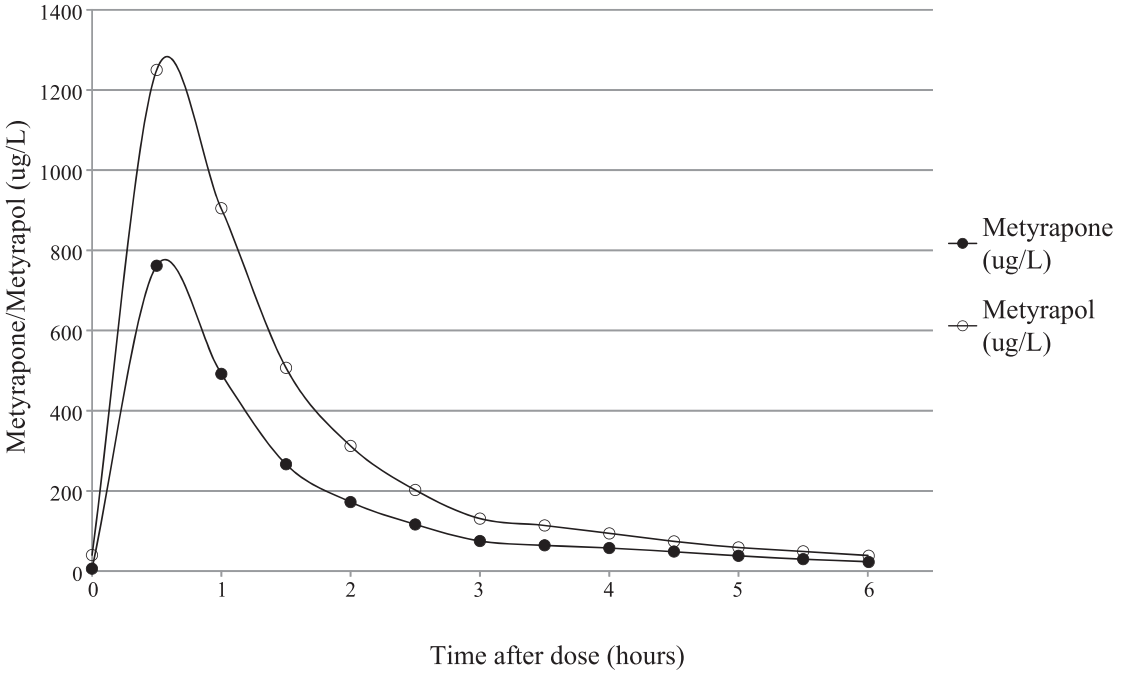

Figure 1. Metyrapone and metyrapol milk concentrations at steady-state vs time following maternal ingestion of 250 mg of metyrapone. Metyrapone (filled circles) and metyrapol (open circles) milk concentrations at steady-state vs time following maternal ingestion of 250 mg of metyrapone at 0 h (total daily dose = 750 mg, administered in divided doses, 6 hourly). Breast milk obtained at 30-min intervals after drug administration, revealed a maximum concentration of 761.7 μg/L of metyrapone, and 1250 μg/L of its active metabolite metyrapol at 30 min after dosing. Drug concentrations in milk rapidly declined over 6 h. The estimated daily infant dose for metyrapone from breast milk is 26.45 μg/kg, which represents 0.69% of the lowest approved pediatric dose.

daily. In this study, we demonstrated that metyrapone and its active metabolite metyrapol were excreted into breast milk exposing the studied breastfed infant to both the parent drug and its metabolite at concentrations well below the national level of concern for safety with no observed effect on his adrenal axis.

The ideal assessment of infant exposure to a drug is the measurement of drug concentration in their plasma [4]. Timing the collection of the infant's blood sample was based on the milk ingestion patterns normally used and the likely t1/2 of metyrapone and metyrapol in the infant. Metyrapone was detected in the infant's serum at a maximum concentration of 4.05 μg/L (metyrapone 0.05 μg/L and metyrapol 4 μg/L). At this low concentration there did not appear to be substantial biochemical evidence of a metyrapone effect on neonatal adrenocortical function as evidenced by the normal cortisol, ACTH, and 11-deoxycortisol levels detected. However, this should be interpreted with caution as this is based on a single sample and the ACTH, although normal, was toward the upper end of the normal range. Furthermore, the cumulative stress related to the degree of prematurity of the neonate coupled

Table 1. AUC, Cavg, AID, and RID for Metyrapone and Metyrapol in Milk Collected at 30-min Intervals After Drug Administration

Parameter	Metyrapone	Metyrapol
AUC0-6h μg·h/L	1057.89	1860.94
Cavg (μg/L)	176.31	310.16
AID (μg/kg/d)	26.45	46.52
RID (%)	0.69	1.21

Table 2. AUC, Cavg, AID, and RID for Metyrapone and Metyrapol in Milk Collected at 60-min Intervals After Drug Administration

Parameter	Metyrapone	Metyrapol
AUC0-6h μg·h/L	60.16	113.37
Cavg (μg/L)	10.03	18.89
AID (μg/kg/d)	1.5	2.83
RID (%)	0.04	0.074

with the multiple routine procedures required during his special care nursery stay may have also had an impact on his hypothalamic pituitary adrenal axis, further confounding the test results, and we cannot adjust for this potential effect.

The recommended dose of metyrapone for the diagnostic evaluation of ACTH independent Cushing syndrome in a child 1 month to 18 years of age is 15mg/kg orally every 4 hours for six doses with treatment doses ranging from 250 mg to 6 g orally daily [5]. In the present case, the AID for metyrapone and metyrapol combined is 72.97 (26.45 metyrapone, 46.52 metyrapol) μg/kg/d. This is 820-fold less than the lower end of the diagnostic dose range for metyrapone in infants. The total RID (metyrapone plus metyrapol) of 1.9% of the weight-adjusted maternal dose is also well below the notional 10% level of concern for safety in breastfeeding [6].

There are several limitations of this report. Maternal comorbidities, concomitant medications, and frequency of feeding in a primigravid mother all potentially influenced the subsequent concentration of drug excreted into her breast milk. Furthermore, the degree of prematurity of the neonate and the mixed breast and formula feeding potentially affected the profile of drug absorption, distribution, metabolism, and excretion thus the reported results may not reflect all infants exposed to metyrapone in breast milk.

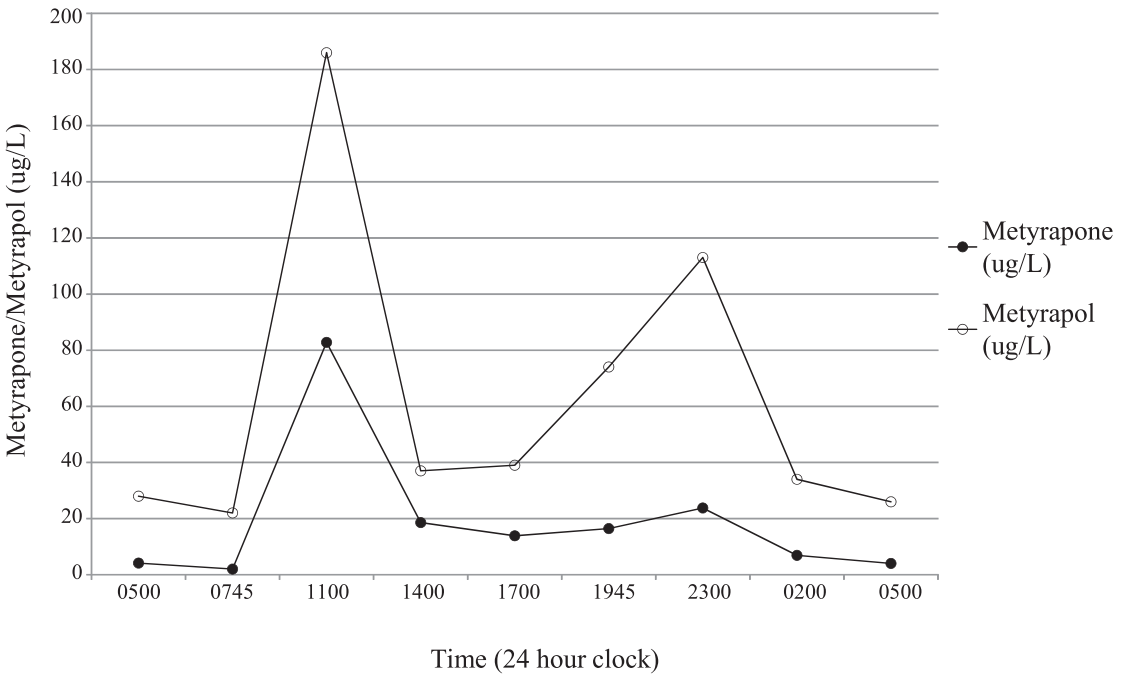

Figure 2. Metyrapone and metyrapol milk concentrations at steady state vs time over 24 h. Metyrapone (filled circles) and metyrapol (open circles) milk concentrations at steady state vs time over 24 h, where the patient took 250 mg of metyrapone at 0800 AM, 1415 PM, and 2000 PM, and breast fed providing mixed samples of every feed given for analysis.

5. Conclusion

Metyrapone and metyrapol excretion into breast milk is minimal, and the low AID, RID, and concentration of metyrapone detected in the serum of a well infant with no detectable sequelae of exposure to metyrapone as evidenced by normal ACTH, cortisol, and 11-deoxycortisol levels indicates the likely safety for a mother to breastfeed while using the drug. Exposure of the infant can be further minimized by avoiding nursing for 2 to 3 hours after each dose.

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Disclosure Summary: The authors have nothing to disclose.

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