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Pharmacokinetics of ketamine transfer into breastmilk: a case series

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Introduction

- Ketamine has traditionally been used as a dissociative anesthetic.
- Racemic (intravenous) ketamine has recently gained traction for treatment-resistant depression and acute suicidality due to its immediate effects.
- Ketamine has been successfully used in the literature to manage pain associated with cesarean sections with no adverse effects on breastfeeding.
- Currently, there is insufficient data surrounding the safety and transfer of ketamine into breastmilk.
- Given its off-label usage, there remains lack of consistency in dosing.
- Relative infant dose (RID) is the ratio of a drug's infant dosage via milk to maternal dosage and helps determine the risk of infant exposure to a drug from breastmilk.
  - An RID of <10% is generally considered minimal risk.
- In this case series, we analyze the concentration of racemic ketamine and its active metabolite, norketamine, in the breastmilk of 3 postpartum mothers being treated for depression.

Case Series and Methods

Case 1
- A 34-year-old G2P2 who delivered at 36 weeks and 1 day gestation and is 1-3 months postpartum.
- History of anxiety and depression.
- 49mg ketamine infusions over 2 weeks.

Case 2
- A 42-year-old G1P1 who delivered at 41 weeks and 1 day gestation and is 23 months postpartum.
- History of anxiety, depression, chronic pain, Lyme disease, asthma, hyperlipidemia, infertility, migraines.
- 200mg ketamine infusion daily for 5 days.

Case 3
- 30-year-old G2P2 who delivered at 33 weeks and 6 days gestation and is 1 month postpartum.
- History of anxiety, depression, migraines, arthritis, polycystic ovary syndrome, and infertility.
- 378mg ketamine infusion daily for 5 days.

All patients provided breastmilk following the 4th infusion to allow for adequate ketamine accumulation.

Methods:

- Quantification of ketamine and norketamine was determined using an Agilent Ultivo triple quadrupole LC/MS mass spectrometer.
- A Phenomenex Biphenyl column was used. Isocratic elution was followed using water and acetonitrile with a flow rate of 0.5 mL/min.
- Multiple Reaction Monitoring (MRM) was m/z 238.1 to m/z 125 for ketamine and 224 to 125 for norketamine.
- Extraction from milk was accomplished using protein precipitation with acetonitrile. Blank milk was spiked with appropriate concentrations.

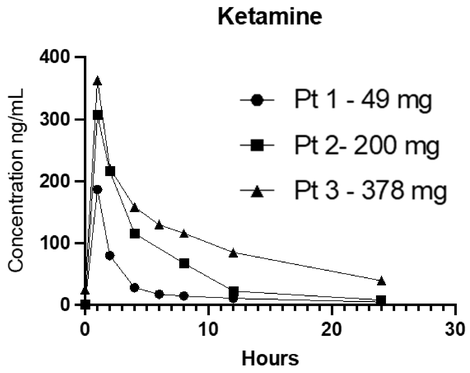

Figure 1: Graph detailing dosage and trajectory breastmilk concentrations of ketamine over a 24-hour period.

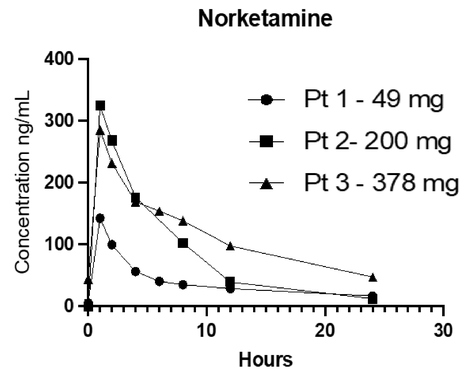

Figure 2. Graph detailing dosage and trajectory of breastmilk concentrations of norketamine over a 24-hour period.

Table 1. Pharmacokinetic parameters of ketamine and norketamine in the breastmilk of 3 women.

Parameter	Patient 1		Patient 2		Patient 3	
	Ketamine	Norketamine	Ketamine	Norketamine	Ketamine	Norketamine
Dose (mg)	49		200		378	
AUC (ng.hr/mL)	551.7	920.4	2050	2050	2735	3006
C_{avg} (ng/mL)	22.98	38.35	61.29	85.41	113.95	125.25
C_{max} (ng/mL)	186.59	142.38	306.63	324.37	363.19	285.04
T_{max} (hour)	1					
Maternal dose (mg/kg/day)	0.607	0.607	2.672	2.67	4.167	4.167
Infant Dose (mg/kg/day)	0.003	0.005	0.009	0.012	0.017	0.018
Relative Infant Dose (%)	**0.57**	**0.95**	**0.34**	**0.48**	**0.4**	**0.45**

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Results and Discussion

- Ketamine and norketamine concentrations were determined in milk samples obtained from 3 subjects. The maximum concentration of both ketamine and norketamine was observed at 1 hour. Ketamine and norketamine concentrations declined over 24-hour period as shown in Figure 1.
- The maternal dose of both ketamine and norketamine ranged from 0.607 mg/kg/day to 4.167 mg/kg/day.
- The total infant dose of ketamine ranged from 0.003 mg/kg/day to 0.0107 mg/kg/day. The total infant dose of norketamine ranged from 0.005 mg/kg/day to 0.012 mg/kg/day.
- Ketamine is most commonly dosed at 0.5 mg/kg, but dosages can range from 0.5 mg/kg to 0.75 mg/kg. Two of our patients were administered significantly higher doses.
- The RID for ketamine ranged from 0.34% to 0.57%, as mentioned in Table 1. The RID for norketamine ranged from 0.45% to 0.95%.
  - Relative infant dose (%) = estimated daily infant dose via breast milk (mg/kg/day) / maternal dose (mg/kgb/day) x 100
- In addition, there were no reported adverse effects seen in the three infants. The reason for such low levels of drug transfer into human milk is likely associated with the structure of the molecule.
- Ketamine has a mean plasma protein binding range between 10% and 50% and a plasma elimination half-life of 2-4 hours.

Conclusion

- ✧ Ketamine is an NMDA-antagonistic anesthetic gaining popularity for off-label management of treatment-resistant depression for breastfeeding mothers.
- ✧ The findings of this study suggest that transfer of ketamine, as well as its active metabolite, norketamine, into breast milk is minimal, as estimated by all relative infant doses (RID) of ketamine under 1%.
- ✧ It was notable that even at high doses, ketamine concentration remained insignificant.
- ✧ Our findings are consistent with a 2021 study preprint which found insignificant levels of intramuscularly administered ketamine in breastmilk after 12 hours.
- ✧ The extremely low RID coupled with limited oral bioavailability of ketamine suggests that infant exposure, and therefore infant risk, of ketamine through breastmilk is lower than previously perceived.
- ✧ Larger-scale research encompassing various dosages and populations is warranted to develop generalizable recommendations.

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