Journal of Psychoactive Drugs

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ujpd20

The Pharmacokinetics of Ketamine in the Breast Milk of Lactating Women: Quantification of Ketamine and Metabolites

Philp Wolfson, Rob Cole, Kara Lynch, Cassandra Yun, Jason Wallach, Julane Andries & Melissa Whippo

To cite this article: Philp Wolfson, Rob Cole, Kara Lynch, Cassandra Yun, Jason Wallach, Julane Andries & Melissa Whippo (2022): The Pharmacokinetics of Ketamine in the Breast Milk of Lactating Women: Quantification of Ketamine and Metabolites, Journal of Psychoactive Drugs, DOI: 10.1080/02791072.2022.2101903

To link to this article: https://doi.org/10.1080/02791072.2022.2101903

JOURNAL OF PSYCHOACTIVE DRUGS
https://doi.org/10.1080/02791072.2022.2101903

Taylor & Francis
Taylor & Francis Group

The Pharmacokinetics of Ketamine in the Breast Milk of Lactating Women: Quantification of Ketamine and Metabolites

Philip Wolfson, Rob Cole, Kara Lynch, Cassandra Yun, Jason Wallach, Julane Andries, and Melissa Whippo

The Ketamine Research Foundation, CA, USA

ABSTRACT

Ketamine is a general anesthetic with over 50 years of safe administration that is in increasing use for psychiatric indications. This is evidenced by the recent FDA approval of intranasal esketamine (the S-enantiomer) for the treatment of depression. With respect to ketamine and lactation, incredibly there are no available data on the secretion of ketamine or its metabolites in human breast milk. This information is essential to guide the use of ketamine in breastfeeding women who suffer with postpartum emotional disorders, ongoing depression, PTSD, and more. To address this unmet need, we conducted a pharmacokinetic analysis of the presence of ketamine and several of its major metabolites (norketamine, dehydronorketamine, and hydroxynorketamine isomers) in four women receiving two different intramuscular doses of ketamine – 0.5 mg/kg and 1.0 mg/kg. Our results demonstrate low and rapidly declining levels of ketamine and metabolites in breast milk during the 12-hour post-dosing period. The mean relative infant dose (RID) obtained from AUC estimates for the 0.5 and 1.0 mg/kg doses were 0.650% and 0.766%, respectively. This provides the foundation for studying the use of ketamine during the post-partum period.

ARTICLE HISTORY
Received 31 August 2021
Revised 21 June 2022
Accepted 23 June 2022

KEYWORDS
Ketamine; lactation; postpartum depression; pharmacokinetics; women's health

Introduction

Ketamine was discovered in 1962 and its use as a general anesthetic began in 1970; see (Wallach and Brandt 2018; Morris and Wallach 2014) for detailed reviews of ketamine's origins.

Off-label use of ketamine has been a constant since its discovery. Ketamine has been used in neuropsychiatric research and psychiatric/psychotherapy treatment for decades (Kolp 2007; Wolfson and Hartelius 2016). As the realization of ketamine's clinical utility grows, the treatment of postpartum disorders has come into focus as a possibility for ketamine's effective use, given its demonstrated effectiveness with depressive disorders (Peyrovian et al. 2020). This has raised the importance of assessing any potential risk associated with breast feeding following ketamine administration (Cobb et al. 2015). To address this timely knowledge gap, the pharmacokinetics of ketamine (0.5 and 1.0 mg/kg, IM) in four lactating women was investigated.

Methods

The New England IRB of Needham, Mass, now a part of WCG IRB, approved the study protocol, Ethics and Informed Consent (provided as supplemental material). The Ketamine Research Foundation is a free-standing research organization and received. FDA approval was granted. The study was conducted at the Ketamine Research Foundation's clinical center in San Anselmo, California.

This study was conducted with four lactating women who agreed to postpone breastfeeding and provide samples of their milk. We collected samples of breast milk from each woman during two separate sessions prior to injection for baseline measurement, and timed for pumping at 3, 6, 9 and 12 hours, i.e., 3-h intervals – choosing greater than the maximum half-life duration (Idvali et al. 1979; Clements, Nimmo, and Grant 1982). These intervals and frequency, as well as small number of participants are supported by breast milk research as per Cobb et al. (2015). Two dosages of ketamine were administered intramuscularly (IM): 0.5 mg/kg and subsequently 1.0 mg/kg, separated by 5–14 days.

The IM route confers rapid onset – 2–5 minutes for effect and a reliable ~93% bioavailability (Grant, Nimmo, and Clements 1981). As examples, the dosages for a 50 kg woman amounted to 25 and 50 mg and for a 70 kg woman 35 mg and 70 mg, respectively, well within therapeutic dosages of IM ketamine for depression and other psychiatric diagnoses (Dore et al. 2019).

CONTACT Philip Wolfson ketamine.research@gmail.com Department of Pharmaceutical Sciences, Saint Joseph's University Philadelphia, PA 19104

An NEIRB approved study Clinical Trial Registration #NCT04285684The Pharmacodynamics of Ketamine in the Breast Milk of Lactating Women: (KRF-LAC)

Supplemental data for this article can be accessed online at https://doi.org/10.1080/02791072.2022.2101903

Participants

Potential participants were approached for an initial screening conversation and if they met inclusion and exclusion criteria were admitted into the study.

The diversity of participants included two women of Latina backgrounds, one Han Chinese woman and one Caucasian woman. No infants were present or involved in the study. Inclusion criteria included age 21–45; postpartum with established lactation for a minimum of 3 months; Ability to pump breast milk and to provide a reservoir for infant feeding prior to the study; or acceptance of feeding with formula; in good health – normal BP/HR; afebrile-temp ascertained; review of systems by MD; absence of diagnosed illnesses; not pregnant–pregnancy tested for before each administration by urine assay.

Exclusion criteria included hypertension with a BP greater than 145/90; concurrent use of any psychiatric medications or other medications determined by the primary investigator to have potential for interaction with the study drug; use of alcohol or other substances such as marijuana within 72 hours of the study; weight <50 kg or >90 kg; pregnancy.

Potential adverse effects included nausea and vomiting – a less than 5% incidence of intolerability to ketamine, transient hypertension, and dissociative effects. Blood pressure was monitored during the experiment. Ketamine is a dissociative anesthetic and participants were informed that they were likely to experience dissociative effects, which could cause anxiety and disorientation, during the first 2 h following ketamine administration, with full recovery to baseline by 3 hours. Given the preparation, participants did well with the dissociative effects.

Procedure

The administration of ketamine followed the basic protocol as per the clinic's practice of ketamine assisted psychotherapy. An MD and a psychotherapist were present throughout the session, with ongoing support during the week following each session, availability thereafter, and a formal four-week follow-up.

Participants were instructed to express milk in full using a Spectra Baby USA – S2 Plus Premier Electric Breast Pump; milk was collected, and the total volumes for each interval measured. A sample aliquot was taken from each interval's total collection and frozen at 0° F (−18°C).

Sample aliquots were transported in ice. The lab processed samples from the first participant as rapidly as possible to enable an estimate for the duration of the collection for subsequent participants by quantifying the amount of ketamine present at intervals to 24 hours for both doses. As the amounts at 12 hours were insignificant, this led to a determination to collect milk at 3-h intervals through 12 hours for the following 3 participants.

Calibrators containing ketamine, norketamine, dehydronorketamine, and hydroxynorketamine (Cerriliant, Round Rock Texas, USA) were prepared in drug-free breast milk at 10 concentrations ranging from 0.1 to 100 ng/ml. Ketamine-D4 and norketamine-D4 wereF used as internal standards. Breast milk samples (200 μl) were prepared using protein precipitation and EVOLUTE EXPRESS CX SPE cartridges (Biotage, Uppsala, Sweden) following the manufacturers recommended protocol. LC-MS/MS data was acquired with a Sciex QTRAP4500 system (AB Sciex, Framingham, MA, USA) in positive ion mode. Chromatographic separations were performed on a 130 Å, 2.5 µm, 2.1 mm × 50 mm Waters XBridge BEH Phenyl XP Column (Milford, MA, USA) using a 4-min linear gradient from 10% to 33% with 0.1% formic acid in water and acetonitrile. A more detailed description of the method and its validation is planned for a later publication.

Graphpad Prism 9.3.0 was used for $AUC_{0\text{-}12}$ calculations using the area under curve analysis to provide total peak areas and 95% confidence intervals.

Results

Mean breast milk concentrations are presented in Table 1. Concentrations of ketamine and metabolites in breast milk were dose dependent (Figure 1) with the higher 1.0 mg/kg dose giving consistently higher breast milk concentrations of ketamine and metabolites. Modest interparticipant variation (~twofold difference between lowest and highest concentrations) was observed. As anticipated, ketamine concentrations rapidly declined over the time course measured, consistent with the plasma elimination rate of ketamine (Bolze and Boulieu 1998). The decline of metabolites was slightly slower than that for ketamine, consistent with reported plasma pharmacokinetics (Bolze and Boulieu 1998)

$AUC_{0\text{-}12}$ data are presented in Table 2. In one participant, breast milk levels were also measured at 24 and 30 hours (Supplemental Table 1) following the 1.0 mg/kg doses. The calculated $AUC_{0\text{-}30}$ for ketamine and metabolites (Supplemental Table 2) as well the representative ketamine $AUC_{0\text{-}30}$ graph for this single participant (Supplemental Figure 1) are provided.

Relative infant dose (RID) is defined as the ratio of the infant daily dose (mg/kg/day)/Mother's daily dose (mg/kg/day) × 100. An absolute infant dose (mg/kg/

Table 1. Breast milk concentrations (ng/ml) of ketamine and metabolites. Concentrations reported as mean ± standard deviation.

Time (h)					
Compound	Dose of Ketamine	3	6	9	12
Ketamine					
	0.5 mg/kg	51.2 ± 18.8	22.6 ± 8.4	10.6 ± 5.4	4.5 ± 4.4
	1.0 mg/kg	125.0 ± 44.1	48.2 ± 17.3	21.6 ± 13.9	18.5 ± 6.7
Norketamine					
	0.5 mg/kg	42.6 ± 10.5	28.6 ± 5.2	18.8 ± 5.1	8.7 ± 6.4
	1.0 mg/kg	92.7 ± 14.8	62.4 ± 12.9	37.3 ± 10.5	32.3 ± 10.3
Dehydronorkertamine					
	0.5 mg/kg	0.56 ± 0.3	0.55 ± 0.2	0.45 ± 0.3	0.21 ± 0.1
	1.0 mg/kg	2.0 ± 1.1	1.8 ± 1.1	1.4 ± 0.7	1.1 ± 0.6
Hydroxynorketamine					
	0.5 mg/kg	29.9 ± 9.0	28.3 ± 10.2	25.6 ± 8.0	17.5 ± 9.9
	1.0 mg/kg	64.1 ± 21.1	66.9 ± 13.1	54.6 ± 11.2	41.5 ± 9.8

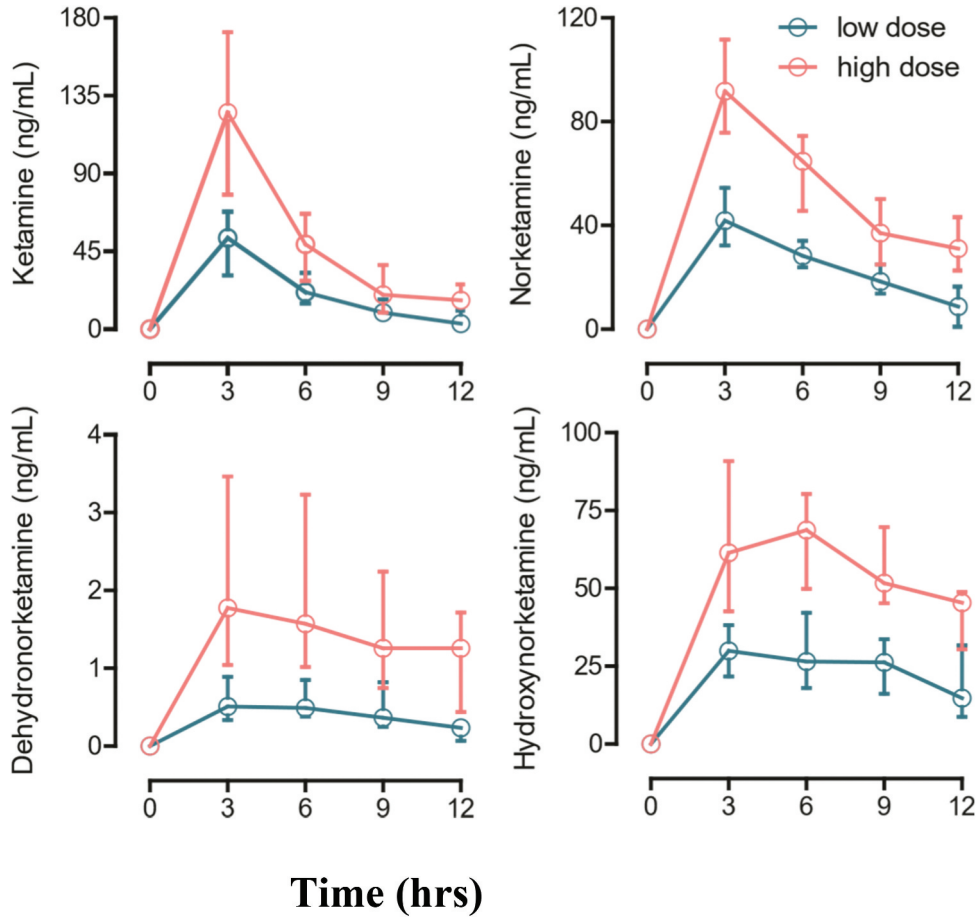

Figure 1. Graphs of quantitative analysis of ketamine and metabolites in breast milk for all four participants. Each data point shown as mean ± SD.

day) is equal to the mean milk concentration ($AUC_{0-\infty}$ divided by 12 h) multiplied by the estimated infant milk ingestion of 0.15 L/kg/day. Thus, the mean absolute infant dose was determined to be 612.8 ng*h/mL/12 h) × 150 mL/kg/day = 7,660 ng/kg/day. This gives a mean RID for the 1 mg/kg dose based on the AUC_{0-12} (612.8 ng*h/mL), of (0.00766 mg/kg/1.0 mg/kg) * 100 = 0.766% (Jensen and Bennett 1996). The comparable mean RID for the 0.5 mg/kg dose is 0.650%. A single participant in which breast milk was collected past 12 hours showed minimal secretion post-12 hours, supporting the use of 12-h excretion profiles in this calculation (Supplemental Figure 1).

Table 2. Mean $AUC_{0\text{-}12}$ calculations of ketamine and metabolites in breast milk.

Compound	Ketamine Dose (mg/kg)	AUC (95% CI) ng h/mL
Ketamine	0.5	259.8 (170.3–349.2)
	1.0	612.4 (406.2–818.7)
Norketamine	0.5	283.2 (226.7–339.6)
	1.0	625.8 (528.5–723.0)
DHNK	0.5	5.0 (3.2–6.8)
	1.0	17.4 (10.2–24.6)
HNK	0.5	277.7 (205.9–349.5)
	1.0	619.1 (502.2–736.0)

Discussion

Peak breast milk levels of ketamine and metabolites were maximal at the 3-h time point (Figure 1). If there is a desire to obtain more accurate estimates of C_{max} and T_{max} earlier time points should be obtained in future studies. Reported AUC levels following IM ketamine were not found following a literature search. However, peak ketamine and norketamine levels in breast milk are consistent with ketamine and norketamine plasma levels following IM administration of 0.5 mg/kg doses (Dick et al. 1985, Grant, Nimmo, and Clements 1981). For example, Grant, Nimmo, and Clements (1981) reported a C_{max} of 240 ng/mL ketamine and 90 ng/mL norketamine in 6 adult participants given 0.5 mg/kg ketamine. Estimated C_{max} from a pediatric population-based PK model also suggest similar levels (Hornik et al. 2018). The plasma concentration curves in these studies also exhibit similarities to those observed here with rapid decline in ketamine levels over the hours following dosing. This suggests equilibrium between ketamine plasma and breast milk compartments, and it does not appear ketamine or norketamine are concentrated in breast milk above plasma levels. Future work comparing plasma and breast milk levels can further investigate this observation.

RID is a common measure to assess risk of infant exposure (Hotham and Hotham 2015). The mean RID obtained from the AUC for the 0.5 and 1.0 mg/kg doses are 0.650% and 0.766%, respectively. A RID <10% is generally considered acceptable (Hotham and Hotham 2015) and thus the findings presented here suggest ketamine has a low lactation risk. The RID calculation does not consider the poor oral bioavailability of ketamine, as observed in adults (Dinis-Oliveira 2017; Fourcade and Lapidus 2016). Thus, accounting for low oral bioavailability it is conceivable that exposure in infants is incredibly low. No adverse effects were reported by any of the 4 participants or their infants in the immediate follow-up period and at the 4-week follow-up.

The absence of data before hour 3 post-dose could be viewed as a significant limitation of this study. However, even if peak concentrations were not captured, it is biologically implausible that the resulting RID would increase by an order of magnitude, to reach the 10% threshold. While a 10-fold increase is unlikely, an increase of 3–4 times is possible, based on the serum pharmacokinetic profile (Grant, Nimmo, and Clements 1981). To be clear, this is a study that is not focused on ascertainment of the timing of peak levels, but rather on the pharmacokinetic profile over time of ketamine and its metabolites in breast milk. Given ketamine's low oral bioavailability and documented safety in neonates and infants, it is likely that breastfeeding can safely be resumed as soon as the mother feels able to do so; that is once the mother feels awake, alert, and is able to hold her infant, as with most anesthetics (Cobb et al. 2015).

Conclusions

Our data provide the first quantification of ketamine and its major metabolites in human breast milk. These findings show low concentrations of ketamine and metabolites in breast milk with a rapid decline in concentration within several hours post-dosing. The mean relative infant dose (RID) obtained from AUC estimates for the 0.5 and 1.0 mg/kg doses were 0.650% and 0.766%, respectively. Thus, anticipated exposure of babies to the levels of ketamine and metabolites observed in this study represent only a tiny fraction of amounts in common clinical use in humans, including in pediatrics. These findings provide evidence supporting the safe resumption of breastfeeding for lactating mothers. The low exposure to the infant from the predicted exposure levels based on our study would not lead to clinically relevant effects in breast-fed infants. We believe this study will help open the door for further explorations of ketamine in the treatment of emotional disorders of the postpartum period.

Author notes

The authors confirm that the Principal Investigator for this study is Philip E Wolfson MD, and that he had direct clinical responsibility for patients. All authors confirm the Originality of this text and this Research

Each of the authors state that there are no conflicts of interest and no relationships with commercial interests.

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Written informed consent was obtained from all participants and the Informed Consent as approved by both the FDA and the IRB is appended.

Acknowledgments

The study was entirely funded by the non-profit Ketamine Research Foundation.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the The Ketamine Research Foundation;

ORCID

Philip Wolfson http://orcid.org/0000-0003-0867-0861

References

Bolze, S., and R. Boulieu. 1998. HPLC determination of ketamine, norketamine, and dehydronorketamine in plasma with a high-purity reversed-phase sorbent. *Clinical Chemistry* 44 (3):560–64. doi:10.1093/clinchem/44.3.560.

Clements, J., W. Nimmo, and I. Grant. 1982. Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. *Journal of Pharmaceutical Sciences* 71 (5):539–42. doi:10.1002/jps.2600710516.

Cobb, B., R. Liu, E. Valentine, and O. Onuoha. 2015. Breastfeeding after anesthesia. *Translational Perioperative and Pain Medicine* 1 (2):1–7.

Dinis-Oliveira, R. J. 2017. Metabolism and metabolomics of ketamine: A toxicological approach. *Forensic Sciences Research* 2 (1):2–10. doi:10.1080/20961790.2017.1285219.

Dore, J., B. Turnipseed, S. Dwyer, A. Turnipseed, J. Andries, G. Ascani, C. Monnette, A. Huidekoper, N. Strauss, and P. Wolfson. 2019. Ketamine assisted psychotherapy (KAP): Patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *Journal of Psychoactive Drugs* 51 (2):189–98. doi:10.1080/02791072.2019.1587556.

Fourcade, E. W., and K. A. Lapidus. 2016. The basic and clinical pharmacology of ketamine. In Mathew, SJ and Zarate J (Eds.)*Ketamine for treatment-resistant depression*, 13–29. Cham: Adis.

Grant, I. S., W. S. Nimmo, and J. A. Clements. 1981. Pharmacokinetics and analgesic effects of im and oral ketamine. *British Journal of Anaesthesia* 53 (8):805–10. doi:10.1093/bja/53.8.805.

Hornik, C. P., D. Gonzalez, J. van den Anker, A. M. Atz, R. Yogev, B. B. Poindexter, K. C. Ng, P. Delmore, B. L. Harper, C. Melloni, et al. 2018. Population pharmacokinetics of intramuscular and intravenous ketamine in children. *The Journal of Clinical Pharmacology* 58 (8):1092–104. doi:10.1002/jcph.1116.

Hotham, N., and E. Hotham. 2015. Drugs in breastfeeding. *Australian Prescriber* 38 (5):156. doi:10.18773/austprescr.2015.056.

Idvall, J., Ahlgren, I., Aronsen, K.F. and Stenberg, P., 1979. Ketamine infusions: pharmacokinetics and clinical effects. British Journal of Anaesthesia, 51(12), pp.1167–73.

Jensen, A. A., and P. N. Bennett. 1996. *Drugs and human lactation: A comprehensive guide to the content and consequences of drugs, micronutrients, radiopharmaceuticals, and environmental and occupational chemicals in human milk*. Amsterrdam: Elsevier Science Limited.

Kolp, E., M. S. Young, H. Friedman, E. Krupitsky, K. Jansen, and L. O'-Connor. 2007. Ketamine enhanced psychotherapy: Preliminary clinical observations on its effects in treating death anxiety. *International Journal of Transpersonal Studies* 26:1–17.

Morris, H., and J. Wallach. 2014. From PCP to MXE: A comprehensive review of the non- medical use of dissociative drugs. *Drug Testing and Analysis* 6 (7–8):614–32. doi:10.1002/dta.1620.

Peyrovian, B., R. S. McIntyre, L. Phan, L. M. Lui, H. Gill, A. Majeed, D. Chen-Li, F. Nasri, and J. D. Rosenblat. 2020. Registered clinical trials investigating ketamine for psychiatric disorders. *Journal Psychology Research* 1–12.

Wallach, J., and S. D. Brandt. 2018. 1, 2-Diarylethylamine-and ketamine-based new psychoactive substances. In Maurer HH & Brandt SD (Eds.) *New psychoactive substances*, 305–52. Cham: Springer.

Wolfson, P., and G. Hartelius, The ketamine papers. MAPS. 2016