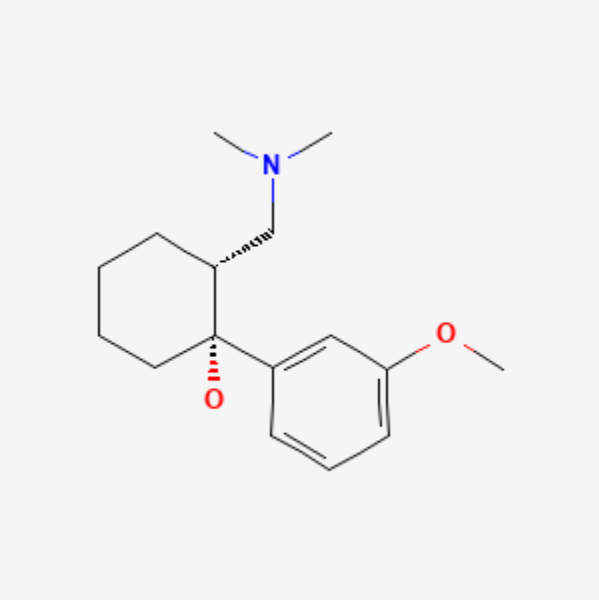
U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006-. Tramadol. [Updated 2023 Dec 15].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Tramadol

Revised: December 15, 2023.

CASRN: 27203-92-5



Drug Levels and Effects

Summary of Use during Lactation

The excretion of tramadol into milk is low and even lower amounts of the active metabolite, O-desmethyltramadol, are excreted. With usual maternal dosage, the amount excreted into breastmilk is much less than the dose that has been given to newborn infants for analgesia and is unlikely to adversely affect nursing infants.[1] Studies in breastfed newborn infants found no adverse effects attributable to tramadol. However, a death occurred in the 8-month-old breastfed infant of a woman addicted to tramadol, but breastfeeding exposure alone might not have accounted for the death. Maternal use of oral opioids during breastfeeding can cause infant drowsiness, which may progress to rare but severe central nervous system depression. Newborn infants seem to be particularly sensitive to the effects of even small dosages of narcotic analgesics. If tramadol is required by the mother of a newborn, it is not a reason to discontinue breastfeeding; however, once the mother's

milk comes in, it is best to provide pain control with a nonnarcotic analgesic and limit maternal intake of oral tramadol to 2 to 3 days at a low dosage with close infant monitoring. The U.S. Food and Drug Administration and the manufacturer recommend against the use of tramadol during breastfeeding.[2] If tramadol is used, monitor infants for increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties or limpness, and contact a physician immediately if any of these occur.

Drug Levels

In adults, tramadol has 70 to 100% oral bioavailability and is metabolized to the active O-desmethyltramadol (M1). Tramadol has a more potent monoamine reuptake inhibitory effect while M1 has a more potent opioid mu-agonist effect. M1 is about 10% as potent as morphine in mu-opiate binding, although some investigators have reported a 450-fold potency difference. Women who are extensive metabolizers of tramadol may have higher than expected serum levels of M1, potentially leading to higher levels of M1 in breastmilk. The capacity of preterm and newborn infants to metabolize tramadol to M1 is limited.[3]

Maternal Levels. The manufacturer reports that in the 16 hours following a 100 mg intravenous dose of tramadol, the cumulative excretion into breastmilk was 100 mcg of tramadol and 27 mcg of M1. No further details are provided.

Detectable levels (>12 mcg/L) of tramadol were found in samples of breastmilk collected 10 hours after a 50 mg maternal dose of intravenous or oral tramadol.[4] No other clinical details or milk levels were reported.

One mother was taking oral tramadol 300 mg daily during pregnancy and presumably the same dose postpartum for chronic back pain. On approximately day 3 postpartum (time not specified), the breastmilk concentration of tramadol was 1.8 mg/L.[5]

Seventy-five mothers who were 2 to 4 days postpartum provided 3 milk samples from both breasts during the 6 hours following a dose of 100 mg of oral tramadol after taking at least 4 doses. The average milk concentration of tramadol was 748 mcg/L and of M1 was 203 mcg/L. These values translate to an average infant dosage of 112 and 30 mcg/kg daily of the drug and metabolite, respectively. An exclusively breastfed infant would receive maternal weight-adjusted dosages of 2.24% of tramadol and 0.64% of its metabolite.[6]

Reanalysis of the above data using a pharmacokinetic model with first-pass conversion rates based on literature values and simulating a maternal dosage of 100 mg every 6 hours yielded average milk tramadol levels of 0.82 mg/L in extensive metabolizers and 0.99 mg/L in poor metabolizers. Average M1 milk levels were 0.36 mg/L and 0.18 mg/L, respectively. Infant exposure to tramadol and M1 was the same in both phenotype groups and represented 3.1% of the maternal weight-adjusted tramadol dose.[7] Based on this analysis, the average daily dosage of tramadol excreted in milk in poor metabolizers would be 0.15 mg/kg, which is 2.6% of the maternal weight-adjusted tramadol dose, and 1.5% of the recommended daily intravenous neonatal tramadol dose of 10 mg/kg.[3] The average daily dosage of M1 excreted in milk in extensive metabolizers would be 0.054 mg/kg, which represents 2% to 3% of the normal daily neonatal intravenous morphine equivalent dosage.

A woman on methadone maintenance was breastfeeding her neonate. She was reportedly taking tramadol 50 mg orally at an unknown frequency. Foremilk samples were taken on days 12 and 20 postpartum at unknown times relative to the previous dose. Breastmilk on day 12 postpartum contained tramadol 63 mcg/L, O-desmethyltramadol 22 mcg/L, and N-desmethyltramadol 76 mcg/L. Breastmilk on day 20 postpartum contained tramadol 1254 mcg/L, O-desmethyltramadol 388/L, and N-desmethyltramadol 937 mcg/L.[8]

Infant Levels. An infant was born to a mother who as taking 300 mg of tramadol daily for chronic back pain. By day 3, the infant was exclusively breastfeeding and a serum concentration was obtained (time not specified). The infant's tramadol serum concentration was 2 mcg/L. A typical serum tramadol level in neonates given tramadol intravenously for pain is 200 mcg/L.[5]

A woman on methadone maintenance was breastfeeding her neonate. She was reportedly taking tramadol 50 mg orally at an unknown frequency. Oral fluid samples collected from her infant on day 12 at 15:40 had no detectable drug or metabolites. On day 21 at 20:00, the oral fluid contained tramadol 1011 mcg/L, O-desmethyltramadol 1499 mcg/L, and N-desmethyltramadol 406 mcg/L. The infant's urine on day 12 contained no detectable tramadol, O-desmethyltramadol or N-desmethyltramadol. The infant's urine on day 20 contained 14 mcg/L of tramadol and <10 mcg/L of O-desmethyltramadol of N-desmethyltramadol.[8]

Effects in Breastfed Infants

Seventy-five breastfed infants whose mothers were breastfeeding and taking tramadol 100 mg every 6 hours following a cesarean section were compared to 75 matched infants at 2 to 4 days of age. Forty-nine percent of the mothers taking tramadol and all of the control mothers were taking other opiates (primarily oxycodone) and 61% of and 58%, respectively, also were taking a nonsteroidal anti-inflammatory agent (primarily diclofenac). Examination by a pediatrician revealed no difference between the groups using the Neurologic and Adaptive Capacity Score.[6]

An 8-month-old infant was brought to an emergency department (ED) in Egypt with altered mental status, hypoxia, hypotension and a low hematocrit. In the ICU, the infant had a positive urine drug screen for tramadol and a negative urine test for cannabinoids and opiates. Two doses of naloxone improved her blood gases and 2 days later her mental status had improved. The infant's parents stated that they were addicted to tramadol and the mother was breastfeeding the infant. The infant was discharged on day 3 after admission. Thirty-six hours later, the infant again presented to the ED with cardiopulmonary arrest, with a 4 on the Glasgow coma scale and generalized clonic-tonic seizures. The infant died from cardiac arrest 3 days after admission. The mother stated that she had breastfed the infant after the initial discharge from the hospital. The author speculates that mother or infant might be an ultra-rapid CYP2D6 metabolizer leading to high levels of the active metabolite, because this variant is relatively prevalent in those of Mediterranean origin. However, neither genetic testing nor measurement of tramadol in milk or the infant were performed.[9] This case cannot definitely be attributed to breastmilk exposure alone, because the sudden onset of the symptoms at 8-months of age seems implausible. It is somewhat more likely that the baby ingested the tramadol directly.

A hospital in Japan provided postpartum mothers with a combination tablet containing tramadol 37.5 mg and acetaminophen 325 mg every 6 hours for 3 days if they requested a pain medication. A retrospective analysis found that of 148 mothers who received the drug, all infants were breastfed and none of the infants had an adverse reaction, such as drowsiness, difficulty breastfeeding or breathing problems.[10] The relatively low dose and short duration of therapy may have reduced the risk of adverse reactions.

A cross-sectional survey of mothers who had breastfed their infant in the past 12 months identified 142 mothers who had taken one or more medications while nursing. One of the mothers who was taking tramadol reported that her infant developed drowsiness, which caused her to change the time of feeding.[11]

Effects on Lactation and Breastmilk

Tramadol can increase serum prolactin.[12] However, the prolactin level in a mother with established lactation may not affect her ability to breastfeed.

A randomized study compared tramadol and naproxen for post-cesarean section pain. Patients received the drugs either on a fixed schedule or as needed. No difference in breastfeeding rates were seen among the groups.[13]

In a study in China, women with a scheduled cesarean section were randomized to receive intravenous patient-controlled analgesia with either sufentanil or tramadol. Postpartum prolactin levels were higher in the tramadol group (348 mcg/L) than in the sufentanil group (314 mcg/L). The onset of lactation was sooner in the tramadol

group (21.4 hours) than in the sufentanil group (25.1 hours). Both of these difference were statistically significant.[14] Injectable tramadol is not available in the United States.

A nonrandomized, nonblinded study in a Serbian hospital of women near term who underwent cesarean section compared general anesthesia (n = 284) to spinal or epidural anesthesia (n = 249). Spinal anesthesia consisted of hyperbaric bupivacaine 12 mg and fentanyl 0.01 mg; epidural anesthesia consisted of isobaric bupivacaine 0.5% (0.5 mg per 10 cm height) and fentanyl 0.05 mg. General anesthesia consisted of propofol 2.3 mg/kg and succinylcholine 1.5 mg/kg for induction and intubation, followed by an anesthetic gas mixture and oxygen. Reportedly, nitric oxide (possibly nitrous oxide) was 50% of the gas before delivery and 67% after delivery. Sevoflurane was also used in some cases. After delivery and cord clamping, mothers received fentanyl 3 mcg/kg and rocuronium 0.5 mg/kg intravenously for placental delivery. After surgery, neuromuscular block reversal was performed with neostigmine and atropine. All patients received 1 mg/kg of diclofenac every 8 h for 24 hours after delivery and 98% of general anesthesia patients also received 100 mg of tramadol and 78.5% received acetaminophen 1 gram. No regional anesthesia patients received tramadol or acetaminophen. Patients receiving one of the regional anesthetic protocols established lactation sooner (56% and 29% after 18 and 24 hours, respectively), while 86% of women receiving general anesthesia did not establish lactation until 36 to 48 hours after surgery.[15]

A randomized, double-blind study was performed in pregnant women scheduled for cesarean section under spinal anesthesia with bupivacaine and fentanyl. Patients received either 100 mg diclofenac (n = 100), 100 mg tramadol (n = 100) or placebo (glycerin suppositories) n = 100, all given as rectal suppositories every 8 hours for the first 24 hours after surgery. The time to initiate breastfeeding was significantly shorter among mothers who received tramadol than a placebo, 1.7 vs 4.1 hours with breastfeeding support and 3.7 vs 6.2 hours without support. Diclofenac was slightly more effective than tramadol among mothers who received no support (3.5 vs 3.7 hours).[16]

Alternate Drugs to Consider

Acetaminophen, Ibuprofen, Morphine

References

1. Palmer GM, Anderson BJ, Linscott DK, et al. Tramadol, breast feeding and safety in the newborn. Arch Dis Child 2018;103:1110-3. PubMed PMID: 29599166.
2. United States Food and Drug Administration. FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. 2017;April 20. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm
3. Allegaert K, Rochette A, Veyckemans F. Developmental pharmacology of tramadol during infancy: ontogeny, pharmacogenetics and elimination clearance. Paediatr Anaesth 2011;21:266-73. PubMed PMID: 20723094.
4. Kmetec V, Roskar R. HPLC determination of tramadol in human breast milk. J Pharm Biomed Anal 2003;32:1061-6. PubMed PMID: 12899994.
5. Hartenstein S, Proquitte H, Bauer S, et al. Neonatal abstinence syndrome (NAS) after intrauterine exposure to tramadol. J Perinat Med 2010;38:695-6. PubMed PMID: 20707626.
6. Ilett KF, Paech MJ, Page-Sharp M, et al. Use of a sparse sampling study design to assess transfer of tramadol and its O-desmethyl metabolite into transitional breast milk. Br J Clin Pharmacol 2008;65:661-6. PubMed PMID: 18294329.
7. Salman S, Sy SK, Ilett KF, et al. Population pharmacokinetic modeling of tramadol and its O-desmethyl metabolite in plasma and breast milk. Eur J Clin Pharmacol 2011;67:899-908. PubMed PMID: 21394525.

8. Gesseck AM, Nanco CR, Hendricks-Muñoz KD, et al. Neonatal exposure to tramadol through mother's breast milk. J Anal Toxicol 2021;45:840-6. PubMed PMID: 34037761.
9. Hussien R. Tramadol intoxication in an 8-months-old infant through breastfeeding: A case report. J Clin Toxicol 2017;7:335. doi:10.4172/2161-0495.1000335
10. Nagae Seika P, Taizan K, Mariko S, et al. Safety of tramadol hydrochloride/acetaminophen combination tablet use for postpartum pain. J Obstet Gynaecol Res 2021;47:2919. Abstract ISP-39-8.
11. Ahmadzai H, Tee LBG, Crowe A. Adverse drug reactions in breastfed infants: A cross-sectional study of lactating mothers. Breastfeed Med 2022;17:1011-17. PubMed PMID: 36315169.
12. Seitz W, Kirchner E, Schaps D, et al. Endocrine reaction pattern in the course of a one-phase tramadol-N2O combination anesthesia. Anasth Intensivther Notfallmed 1982;17:325-31. PubMed PMID: 6297329.
13. Sammour RN, Ohel G, Cohen M, Gonen R. Oral naproxen versus oral tramadol for analgesia after cesarean delivery. Int J Gynaecol Obstet 2011;113:144-7. PubMed PMID: 21435642.
14. Chi X, Li M, Mei W, Liao M. Comparison of patient-controlled intravenous analgesia with sufentanil versus tramadol in post-cesarean section pain management and lactation after general anesthesia - a prospective, randomized, double-blind, controlled study. J Pain Res 2017;10:1521-7. PubMed PMID: 28740418.
15. Stanisic DM, Kalezic N, Rakic A, et al. Comparison of post-cesarean pain perception of general versus regional anesthesia, a single-center study. Medicina (Kaunas) 2022;59:44. PubMed PMID: 36676668.
16. Hooda R, Malik N, Pathak P, et al. Impact of postoperative pain on early initiation of breastfeeding and ambulation after cesarean section: A randomized trial. Breastfeed Med 2023;18:132-7. PubMed PMID: 36800334.

Substance Identification

Substance Name

Tramadol

CAS Registry Number

27203-92-5

Drug Class

Breast Feeding

Lactation

Milk, Human

Analgesics, Opioid

Narcotics