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# Meperidine

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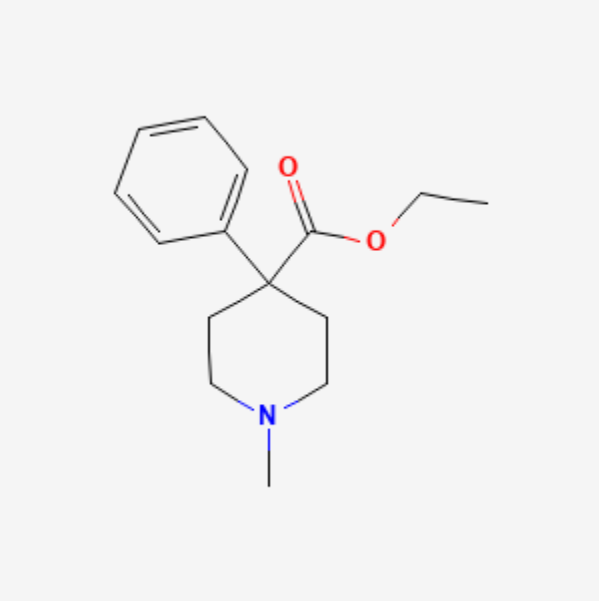


## Drug Levels and Effects

### Summary of Use during Lactation

Intravenous meperidine during labor can interfere with nursing and maternal use of meperidine during breastfeeding can sedate the infants. Postpartum intravenous meperidine can slightly reduce the willingness of infants to breastfeed. Patient-controlled epidural analgesia postpartum appears to be free from these effects. Other agents, such as fentanyl, are preferred for intravenous or intramuscular use, especially while nursing a newborn or preterm infant.[1-3]

A single dose of meperidine for anesthesia or conscious sedation usually does not cause problems in older breastfed infants.[4,5] When a combination of anesthetic agents is used for a procedure, follow the recommendations for the most problematic medication used during the procedure. 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 meperidine 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 meperidine to 2 to 3 days at a low dosage with close infant monitoring. If the baby shows signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, a physician should be contacted immediately.

## Drug Levels

Meperidine is metabolized to the inactive meperidinic acid and to the active metabolite normeperidine which has half the analgesic activity and at least twice the central nervous system excitatory activity of meperidine. The oral bioavailability of meperidine is about 50% in adults. Newborns have impaired meperidine metabolism and possibly a higher oral bioavailability than adults. Newborns may also experience more central nervous system depression from normeperidine than adults. The usual infant oral meperidine dose is 1 to 2 mg/kg while the usual intravenous dose is 1 mg/kg which results in neonatal plasma levels of about 200 to 500 mcg/L.

*Maternal Levels.* In 9 mothers who were 3 to 7 days postpartum and had received a single 50 mg intramuscular dose of meperidine, the highest measured breastmilk level was 130 mcg/L and occurred 2 hours after the dose.[6] Using the peak meperidine milk level from this study, an exclusively breastfed infant would receive about 20 mcg/kg daily of meperidine. However, normeperidine was not measured in the study.

Two breastfeeding mothers who were 8 to 72 hours postpartum and receiving about 500 mg daily of intravenous meperidine had their milk sampled 2 to 4 times over 48 to 72 hours. Relationships between dose timing and milk sampling were not stated. The reported range of measured meperidine milk levels were 165 to 311 mcg/L. Measured normeperidine milk levels were undetectable (<1.6 mcg/L) during the first 12 hours postpartum in 1 patient and reached only 66 mcg/L during the same period in the other patient. In the 36 to 72 hour postpartum period, the reported range of measured normeperidine milk levels were 151 to 333 mcg/L.[7] Using the peak meperidine milk level from this study, an exclusively breastfed infant would receive about 50 mcg/kg daily of meperidine from a maternal intravenous meperidine regimen of 500 mg per day, equal to about 6% of the maternal weight-adjusted dosage. Using the peak normeperidine milk level from this study, an exclusively breastfed infant would receive an additional 50 mcg/kg daily of normeperidine.

Five mothers who had undergone cesarean section delivery at term were given intravenous meperidine 75 mg after umbilical cord clamping and then 12.5 mg every 6 minutes via intravenous patient-controlled analgesia (PCA) as needed for up to 20 to 48 hours postpartum. When PCA meperidine was discontinued, oral meperidine 50 to 300 mg every 2 to 3 hours as needed was given. Colostrum and milk were sampled from each of the mothers 6 times over 96 hours beginning at 12 hours postpartum. Each mother's individual milk level and meperidine dose were not reported. Two mothers were able to provide enough milk in the 12 to 24 hour postpartum period, 3 were able in the 36 to 48 hour period and 4 were able in the 72 to 96 hour period. The average peak meperidine milk level was about 1100 mcg/L at 12 hours then 450, 250, 200, 150, 100 mcg/L at 24, 36, 48, 72 and 96 hours postpartum, respectively. Milk levels declined while the daily dose of intravenous meperidine in the first 36 hours postpartum remained nearly the same. The average individual cumulative intravenous meperidine dose in the first 12 hours postpartum when the peak milk level occurred was about 350 mg. The cumulative dose in the first 36 hours during mostly intravenous maternal meperidine was about 850 mg. The average cumulative oral meperidine dose over the 48 to 96 hour postpartum period was about 300 mg. The average cumulative intravenous plus oral meperidine dose over the entire 96 hours was about 1300 mg.[8] Using the peak milk level reported in this study, an exclusively breastfed infant would receive 165 mcg/kg daily of meperidine. Using the average milk levels during the first 36 hours postpartum when intravenous dosing predominated and was steady at about 25 mg per hour, an exclusively breastfed infant would receive about 56 mcg/kg daily, equal to 0.6% of the maternal weight-adjusted dosage. Using all the average milk levels reported

over 96 hours postpartum an exclusively breastfed infant would receive about 36 mcg/kg daily, also equal to 0.6% of the maternal weight-adjusted dosage. However, normeperidine was not measured in the study.

Eight breastfeeding women who were 1 month to 1 year postpartum and undergoing gynecological surgery had their milk sampled 3 times after a single intraoperative dose of intravenous meperidine. Seven of the women received 25 mg. Individual meperidine milk levels were not reported. Their average meperidine milk level was 176 mcg/L at 1 to 3 hours after the dose (range 134 to 244 mcg/L in 5 women 1 to 2 hours after the dose and 76 to 318 mcg/L in 3 women 2 to 3 hours after the dose). Only 3 of the women had detectable (>20 mcg/L) meperidine milk levels at 8 to 10 hours after the dose (range 76 to 318 mcg/L). One woman received 75 mg meperidine. Her milk level was 571 mcg/L 4 hours after the dose and 224 mcg/L 8 hours after the dose. None had detectable levels (>20 mcg/L) 24 to 28 hours after their dose. The authors determined that infants in this study received 1.2 to 3.5% of the maternal weight-adjusted dosage.[9]

Twenty women who had a cesarean section delivery were receiving patient-controlled epidural analgesia (PCEA) with meperidine for postpartum analgesia. They received aa mean meperidine dose of 15.9 mg/hour (range 3.7 to 35.2 mg/hour) and a median total dose of 4.5 mg/kg daily (range 1.1 to 7.6 mg/kg daily) during the first 35 to 46 hours postpartum. Breastmilk samples were taken within 2 hours of the end of PCEA and 6 hours later, if possible. Mean meperidine milk concentrations was 421 mcg/L in the first sample and 176 mcg/L in the second. Mean normeperidine milk concentrations was 414 mcg/L in the first sample and 373 mcg/L in the second sample. Absolute infant dosages of meperidine were 20 mcg/kg daily at the time of the first sample and 10 mcg/kg daily at the time of the second. Absolute infant dosages of normeperidine were 21 mcg/kg daily at the time of the first sample and 22 mcg/kg daily at the time of the second. The authors estimated that the combined weight-adjusted maternal dosages of meperidine plus normeperidine was 1.4% and 0.9% for the first milk sample and second sample, respectively.[10]

*Infant Levels.* Six breastfed and 6 bottle-fed newborns had meperidine saliva levels measured 2 to 3 hours of age before their first feeding, then again at 24 and 48 hours of age, both times 1.5 hours after a feeding. Their mothers had received a single dose of 100 mg intramuscular meperidine 3 to 4 hours prior to delivery. Meperidine saliva levels in the breastfed newborns were higher at 24 hours of age than at 2 to 3 hours of age. They then decreased slightly by 48 hours of age to levels that were still higher than at 2 to 3 hours of age. In contrast, meperidine saliva levels in the newborns that were bottle-fed decreased over the first 48 hours postpartum. Meperidine was eliminated from saliva very slowly by both groups of newborns. The authors surmised that the higher saliva meperidine levels in the breastfed newborns was caused by oral absorption of meperidine from breastmilk.[9]

Twenty breastfed (extent not stated) infants whose mothers had received patient-controlled epidural analgesia with meperidine had blood samples obtained 48 to 72 hours postpartum at about the time the maternal meperidine was discontinued. Samples were available from 17 infants and averaged 3 mcg/L for meperidine and 0.6 mcg/L of normeperidine. Compared with maternal plasma concentrations obtained at about the same time, infant meperidine and normeperidine concentrations were 1.4 and 0.4% of maternal levels.[10]

## Effects in Breastfed Infants

In 2 controlled studies, repeated maternal post-cesarean section meperidine doses, including patient-controlled analgesia, caused diminished alertness and orientation in 3- to 4-day old, breastfed infants compared to equivalent doses of morphine.[8,11]

Twenty breastfed (extent not stated) infants whose mothers had received patient-controlled epidural analgesia with meperidine for 48 to 72 hours postpartum. They were assessed with the Neurologic and Adaptive Capacity Score (NACS) at a median of 105 minutes after maternal meperidine cessation. The median NACS was 33.5 (range 24 to 38), which is similar to the average score of 35 in healthy infants with no drug effects.[10]

Mothers who were delivering by nonemergency cesarean section using spinal analgesia were given either a single dose of 100 mg of meperidine intravenously after delivery (n = 52) or routine care (n = 49), which consisted of a diclofenac 100 mg suppository. The feeding behaviors of both groups were recorded within 48 hours after delivery. Readiness for feeding in the control group greater than the meperidine group. The mean score of feeding behavior in the meperidine group was slightly, but significantly lower than the control group at 6 and 12 hours after delivery using the infant breastfeeding assessment tool (IBFAT). Several other measures of feeding behavior were not different between the groups.[12]

## Effects on Lactation and Breastmilk

Meperidine can increase serum prolactin.[13] However, the prolactin level in a mother with established lactation may not affect her ability to breastfeed. More importantly, meperidine is likely to interfere with infant nursing behavior when given during labor.[14-16]

In one small study, women given promethazine with meperidine and secobarbital during labor, had the time to lactogenesis II prolonged by 14 hours. Women given meperidine or secobarbital without promethazine had lactogenesis II prolonged 7 hours compared to unmedicated women, but the difference was not statistically significant.[17]

A randomized, multicenter trial compared the initiation rate and duration of breastfeeding in women who received high-dose epidural bupivacaine alone, or one of two low-dose combinations of bupivacaine plus fentanyl. A nonepidural matched control group, some of whom received systemic meperidine, was also compared. Women in the nonepidural group who received systemic meperidine had a lower breastfeeding initiation rate than in the epidural or unmedicated groups.[18]

A national survey of women and their infants from late pregnancy through 12 months postpartum compared the time of lactogenesis II in mothers who did and did not receive pain medication during labor. Categories of medication were spinal or epidural only, spinal or epidural plus another medication, and other pain medication only. Women who received medications from any of the categories had about twice the risk of having delayed lactogenesis II (>72 hours) compared to women who received no labor pain medication.[19]

A randomized, nonblinded study compared the use of intramuscular meperidine 100 mg to intranasal (mean dose 486 mcg) or subcutaneous (mean dose 300 mcg) fentanyl for labor analgesia. More women in the meperidine group had difficulty establishing lactation (79%) than in the intranasal (39%) or subcutaneous (44%) fentanyl groups. Mothers who received meperidine reported more sedation, had longer labors, and their infants were more likely to be admitted to the nursery.[20,21]

Analysis of an Australian database of 1835 pregnant women found that the 285 women who received meperidine during labor were 41% more likely to have discontinued breastfeeding by 6 weeks of age.[22]

A study of lactose, protein, sodium and potassium concentrations in the breastmilk found slightly higher lactose concentrations in the milk of mothers who delivered vaginally and received no meperidine compared to those who had a Cesarean section followed by patient-controlled analgesia with meperidine in the first 72 hours postpartum. Between 72 and 165 hours postpartum, vaginally delivered mothers without meperidine had lower sodium and protein content and higher potassium content in milk than those who received meperidine. However, by 72 hours postpartum, both groups had evidence of adequate secretory activation.[23]

A retrospective case-control study conducted in two hospitals in central Iran compared breastfeeding behaviors in the first 2 hours postdelivery by infants of 4 groups of primiparous women with healthy, full-term singleton births who had vaginal deliveries. The groups were those who received no medications during labor, those who received oxytocin plus scopolamine, those who received oxytocin plus meperidine, and those who received oxytocin, scopolamine and meperidine. The infants in the no medication group performed better than those in

all other groups, and the oxytocin plus scopolamine group performed better than the groups that had received meperidine.[24]

Use of a combination of meperidine 50 mg and levallorphan 0.625 mg (Pethilorphan) per dose intramuscularly as a last resort for severe labor pain was studied retrospectively in a hospital in Japan that did not use epidural analgesia. It was often used with hydroxyzine 50 mg or promethazine 25 mg intramuscularly. Outcomes were compared to those of women who received no meperidine. Although women who received meperidine plus levallorphan had several indications of more difficult labor and delivery, there was no difference in the rates of suckling difficulties or breastfeeding rates at discharge or 1 month postpartum between the groups. No differences between dosages of meperidine received was found.[25]

A randomized, partially blinded study in a hospital in Thailand compared intravenous meperidine and fentanyl for pain during active labor. Mothers received either meperidine 50 mg (n = 46) or fentanyl 50 mcg (n = 46) initially and then every 1 (fentanyl) or 2 (meperidine) hours as requested by the mother. The percentages of infants who breastfed in the first 24 hours were only 61% for meperidine and 54% for fentanyl, although the difference was not statistically significant. Care of the infants (e.g., skin-to-skin in the first hour) was not reported.[26]

A multicenter, prospective cohort study in Hong Kong of 1277 women who gave birth found that women who received meperidine for labor pain relief (almost 20% of women) had a 31% reduced likelihood of breastfeeding in the first hour postpartum. The difference was statistically significant. Epidural opioids did not cause this problem.[27]

A randomized study compared intravenous meperidine 50 mg to inhaled nitrous oxide for labor analgesia. A higher percentage of mothers receiving nitrous oxide were able to breastfeed immediately after birth (95% vs 88%), but the difference was not statistically significant. There were no differences in breastfeeding rates at 24 hours after delivery or formula use.[28]

## Alternate Drugs to Consider

Acetaminophen, Butorphanol, Fentanyl, Hydromorphone, Morphine

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# Substance Identification

## Substance Name

Meperidine

## CAS Registry Number

57-42-1

## Drug Class

Breast Feeding

Lactation

Milk, Human

Analgesics, Opioid

Narcotics

Opiates