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Morphine

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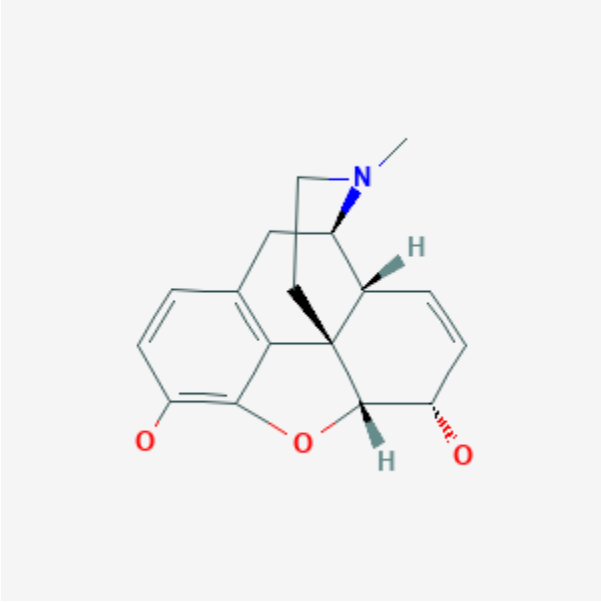

Drug Levels and Effects

Summary of Use during Lactation

Epidural morphine given to mothers for postcesarean section analgesia results in trivial amounts of morphine in their colostrum and milk. Intravenous or oral doses of maternal morphine in the immediate postpartum period result in higher milk levels than with epidural morphine. Labor pain medication may delay the onset of lactation. Maternal use of oral narcotics during breastfeeding can cause infant drowsiness, central nervous system depression and even death, although low-dose morphine might be preferred over other opiates.[1] Newborn infants seem to be particularly sensitive to the effects of even small dosages of narcotic analgesics. Once the mother's milk comes in, it is best to provide pain control with a nonnarcotic analgesic and limit maternal intake of morphine to a 2 to 3 days at a low dosage with close infant monitoring, especially in the outpatient setting.[2] If the baby shows signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness, a physician should be contacted immediately.

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Drug Levels

Morphine is metabolized to inactive morphine-3-glucuronide (60%) and to active morphine-6-glucuronide (10%). Morphine has an oral bioavailability of about 30% in adults. Morphine-6-glucuronide has an oral bioavailability of about 4%,[3] but is probably converted back to morphine in the infant's gut and absorbed as morphine. The plasma clearance of morphine is prolonged in very young infants compared to older infants and children.[4][5] Usual therapeutic intravenous doses of morphine in infants are 10 mcg/kg/hour or 50 to 100 mcg/kg as a single dose. Usual single oral doses of morphine in infants are 100 to 500 mcg/kg.

Maternal Levels. Five lactating mothers who were at least 1 month postpartum were given 1 to 2 doses of either epidural 4 mg or parenteral (intravenous or intramuscular) 5 to 15 mg morphine every 4 to 6 hours for postoperative analgesia. Milk was sampled from each mother 10 times over the 8 hours after her dose. The peak milk level after epidural morphine was 82 mcg/L and occurred 30 minutes after a second dose. The peak milk level after parenteral morphine was about 500 mcg/L and occurred about 45 minutes after a single 15 mg (10 mg intravenous plus 5 mg intramuscular) dose. The half-life in milk was about 3 hours.[6] Using the peak milk levels from this study, an exclusively breastfed infant would receive 75 mcg/kg daily.

Six women who received epidural morphine 5 mg for labor analgesia had their initial colostrum sampled postpartum (range 24-100 hours after epidural). Morphine was undetectable (<0.6 mcg/L) in 4 of the women. The peak morphine level was 4.5 mcg/L and was measured 28 hours after the epidural dose.[7] Considering the small amount of colostrum consumed by the infant, based on the peak level in this study, an exclusively breastfed infant would only receive a negligible amount of morphine from a maternal epidural 5 mg morphine dose for labor analgesia.

Five mothers who had undergone cesarean section delivery at term were given intravenous morphine 7.5 mg after umbilical cord clamping and then 1 to 1.5 mg every 6 minutes via intravenous patient-controlled analgesia (PCA) as needed for up to 48 hours postpartum. When PCA morphine was discontinued, oral morphine 5-30 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 postpartum. Average milk levels from all the mothers studied were about 50 to 65 mcg/L in the first 48 hours postpartum and then dropped to about 20 mcg/L by 72 to 96 hours postpartum. The average cumulative intravenous only dose in the first 48 hours postpartum was about 150 mg. The average cumulative intravenous plus oral morphine dose over the entire 96 hours was about 250 mg.[8] Using the average milk levels reported at each of the 6 collection times from this study, an exclusively breastfed infant would receive about 5 mcg/kg daily. Using the maximum level of 65 mcg/L reported in the first 48 hours postpartum when mothers were receiving intravenous morphine, and assuming 30% oral absorption by the infant, an exclusively breastfed infant would absorb a maximum of about 3 mcg/kg daily equal to 0.3% of the intravenous maternal weight-adjusted daily dosage.

One mother who was 21 days postpartum received oral morphine 10 mg every 6 hours for 4 doses then 5 mg every 6 hours for 2 doses. She had a peak morphine breastmilk level of 100 mcg/L at 1 hour after breastfeeding and 4.5 hours after her first 5 mg dose.[9] Using the peak milk level from this study, an exclusively breastfed infant would receive 15 mcg/kg daily, equal to about 3% of the maternal daily dosage, assuming a daily maternal oral morphine dose of 40 mg.

Epidural morphine 5 mg was given to 30 women immediately following cesarean section and again 24 hours later. There were measurable colostrum morphine levels 12 to 36 hours after delivery in only 3 of the women (range 0.39 to 0.66 mcg/L). The remaining 27 women had undetectable (<0.12 mcg/L) morphine milk levels.[10]

One breastfeeding woman receiving 4 to 8 mg daily of continuous intrathecal morphine had her milk sampled 11 times over 7 weeks postpartum. Levels in milk were undetectable (<8 mcg/L) in 8 of the 11 samples. In 3 of the 11 samples, morphine was detected, but only at levels below the quantification sensitivity of the assay (8 to 25

mcg/L) and was not related to maternal dose.[11] Using the maximum possible milk level of 25 mcg/L from this study, an exclusively breastfed infant would receive about 3 mcg/kg daily from this maternal intrathecal morphine dose regimen.

Seven women who had preterm infants delivered by cesarean section were started on intravenous morphine 7 to 10 mg over 30 to 60 minutes, then 1 mg every 10 minutes by patient-controlled analgesia (PCA) as needed, for up to 48 hours postpartum. Colostrum samples were taken just prior to PCA initiation and again at 12, 24, 36, and 48 hours postpartum. The average cumulative morphine dose was about 60 mg in 48 hours. Three of the women could not produce enough milk for sampling. Morphine and its active 6-glucuronide metabolite were detectable in 3 of the remaining 4 women. There was high intersubject variability with peak milk levels occurring at different times and a wide range of levels measured in each of the women. The peak milk morphine level was 48 mcg/L and the peak 6-glucuronide metabolite level was 1,084 mcg/L. The authors reported median morphine levels of 34, 24, 7, 6.5 and 21 mcg/L and 6-glucuronide levels of 273, 672, 426, 527 and 350 mcg/L at 0, 12, 24, 36 and 48 hours, respectively.[12] Using the reported median milk levels from the 60 mg cumulative 48 hour maternal morphine dose in this study, an exclusively breastfed infant would receive 2.4 mcg/kg daily of morphine and 73 mcg/kg daily of the 6-glucuronide metabolite. Using the peak milk level data from this study, an exclusively breastfed infant would receive an estimated maximum of 7.2 mcg/kg daily of morphine and 163 mcg/kg daily of the 6-glucuronide metabolite.

Twelve women who underwent cesarean section deliveries at 37 to 41 weeks of gestation received a single dose of 2 mg of morphine epidurally. Colostrum was collected at several times during the first 24 hours postpartum. The highest average morphine concentration was reported to be 6.2 mg/L and occurred in colostrum 3.2 hours after the cesarean section. The morphine concentration fell with an average half-life of 2.9 hours. By 6 hours after the dose, the reported concentration was 1.1 mg/L. By 24 hours, the drug was undetectable in colostrum.[13] Note: it is likely that this paper reported the milk concentration values in the wrong units. The values reported were probably in mcg/L, not mg/L.

Infant Levels. In a term infant, the measured plasma morphine level was 1.2 mcg/L. The measurement was taken 108 hours after the mother's last dose of morphine and no morphine was detected in her milk. The mother's dose was not reported.[14]

One mother of a term 21-day-old breastfeeding infant received a 10-day tapering dose of oral morphine beginning with 50 mg every 6 hours. On day 9 she received 10 mg every 6 hours then 5 mg every 6 hours on day 10. The infant's serum morphine level was 4 mcg/L measured 1 hour after breastfeeding and 4 hours after the first 5 mg dose on day 10. Because this serum level occurred while the mother was taking a lower morphine dose, the authors surmised that the infant likely had serum milk levels in what they considered a therapeutic range of over 20 mcg/L during the time the mother was taking higher morphine doses.[9]

Effects in Breastfed Infants

In a term infant with unexplained apnea and bradycardia with cyanosis while hospitalized in the first week of life, the measured plasma morphine in the infant was 1.2 mcg/L. The measurement was taken 108 hours after the mother's last dose of morphine and no morphine was detected in her milk. The mother's dose was not reported.[14]

Breastfed newborns of mothers using intravenous PCA morphine for postcesarean analgesia were more alert and better oriented after postpartum day 3 than infants of mothers using intravenous PCA meperidine and nonbreastfed control infants. There was no difference in newborn respiratory rates. The authors stated that the mothers of nonbreastfed infants had greater parity than the breastfeeding mothers which, combined with a presumed lower desire to breastfeed, may have contributed to the lower behavioral and alertness scores in the nonbreastfed newborns.[8][15]

A study of pregnant being treated for opiate dependency with slow-release oral morphine at a clinic in Vienna were followed as were their newborn infants. Compared to infants who were not breastfed (n = 91), breastfed infants (n = 21) had lower average measures of neonatal abstinence, lower dosage requirements of morphine (5.23 mg vs 8.75 mg), shorter durations of treatment for neonatal abstinence (10.2 vs 18.1 days) and shorter hospital stays (19.7 vs 31 days).[16]

A search was performed of the shared database of all U.S. poison control centers for the time period of 2001 to 2017 for calls regarding medications and breastfeeding. Of 2319 calls in which an infant was exposed to a substance via breastmilk, 7 were classified as resulting in a major adverse effect, and one of these involved morphine. A one-month-old infant was exposed to fentanyl, morphine, oxycodone, and unspecified benzodiazepines. The infant was admitted to the intensive care unit and described as being agitated and irritable and having tachycardia, confusion, drowsiness, lethargy, miosis, respiratory depression, acidosis, and hyperglycemia. The dosages, routes of administration, and extent of breastfeeding were not reported and the infant survived.[17]

Effects on Lactation and Breastmilk

Morphine can increase serum prolactin.[18] However, the prolactin level in a mother with established lactation may not affect her ability to breastfeed.

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, blinded study in 250 women receiving a cesarean section at term compared the effects on breastfeeding of postpartum intrathecal morphine 300 to 500 mcg to a control group who received a non-opiate for pain.. Systemic morphine or meperidine could be give to control mothers for severe breakthrough pain. All mothers also received midazolam 2 mg after cord clamping and oxytocin. At 2 months of age, there was no difference in the breastfeeding rates between the two groups, although infant weight gain was about 5% lower in the spinal morphine group.[20]

A prospective study in an Australian hospital compared mothers who received epidural fentanyl analgesia, subcutaneous morphine or neither during labor and delivery. When controlled for labor induction, instrumental delivery and special care nursery admission, no difference was seen between the 3 groups in breastfeeding rates at discharge or at 6 weeks postpartum.[21]

Alternate Drugs to Consider

(Analgesia) Acetaminophen, Butorphanol, Fentanyl, Hydromorphone, Ibuprofen

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Substance Identification

Substance Name

Morphine

CAS Registry Number

57-27-2

Drug Class

Breast Feeding

Lactation

Analgesics, Opioid

Narcotics