7
Relief of Labor Pain by Systemic Medication

Narcotics
- Morphine
- Meperidine
- Alphaprodine (Nisentil)
- Fentanyl
- Remifentanil

Sedatives and/or Tranquilizers
- Barbiturates
- Tranquilizers
  - *Phenothiazines*
  - *Benzodiazepines*

Dissociative Medications

Amnestic Agents

Neuroleptanalgesia

Agonist and Antagonist Agents

Remifentanil

Inhalation Analgesia

Systemic medications have been used exclusively or in association with psychoanalgesia for relief of labor pain during both the first and second stages of labor. These drugs can be classified in the following manner:

1. Narcotics
2. Sedatives and/or tranquilizers
3. Dissociative medications
4. Amnestic drugs
5. Neuroleptanalgesia
6. Agonist-antagonist medications

Narcotics

Narcotics are popular agents for the relief of labor pain either in an early stage before the administration of epidural analgesia or throughout the first and second stages of labor. Because of their faster action and more reliable plasma concentrations, most of these agents are used intravenously. The various narcotics that can be used are as follows:

Morphine

One of the most effective pain relievers, morphine used to be a popular agent; however, because of the *possibility of a higher incidence of neonatal respiratory depression* this agent is not popular for obstetric patients at the present time. It is used either intramuscularly (5 to 10 mg) or intravenously (2 to 3 mg), and its peak effect occurs at 1 to 2 hours and 20 minutes, respectively.[1]

Meperidine

This is the most commonly used drug at the present time because of its fast onset. It is used both intramuscularly (50 to 100 mg) and intravenously (25 to 50 mg), and its time of onset is 40 to 50 minutes and 5 to 10 minutes, respectively. Meperidine rapidly crosses the placenta and attains fetal and maternal equilibrium within 6 minutes.[2] An interesting observation associated with maternally administered meperidine *was the higher incidence of neonatal respiratory depression when the delivery took place during the second and third hour of drug administration. No significant respiratory depression of neonates was observed when delivery took place within 1 hour or 4 hours after drug administration.*[3] Kunhert et al. did an extensive study to explain this interesting observation; these authors measured umbilical cord and neonatal urine concentrations of meperidine and normeperidine *and found that neonatal urine meperidine concentrations showed the highest amount of drug transfer to fetal tissues after 2 to 3 hours of maternal administration* (Fig. 7-1).[4] Normeperidine, a metabolite of meperidine, reached its highest fetal concentration after 4 hours of maternal administration (Fig. 7-2). They also

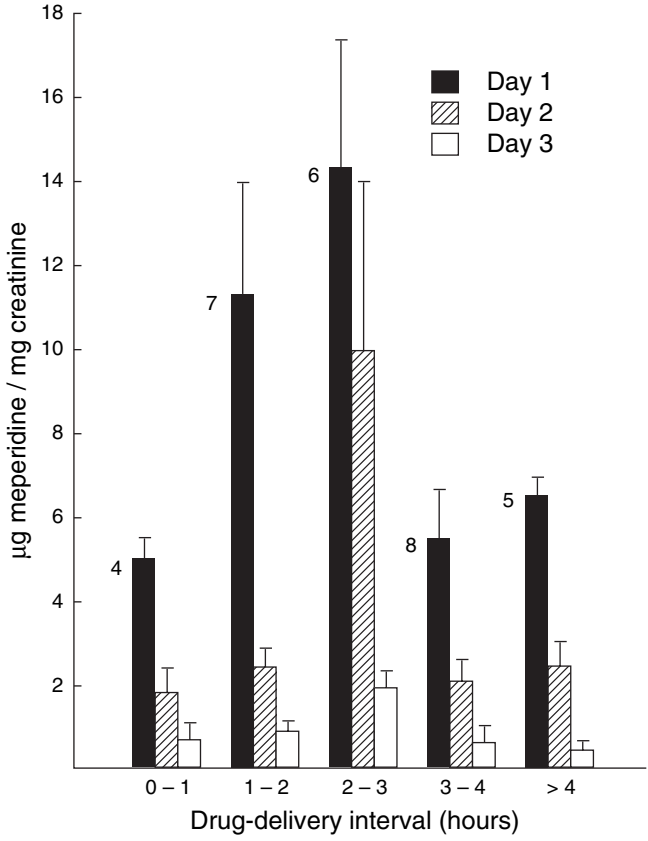

Figure 7–1. Relationship between the meperidine delivery interval and urinary excretion of meperidine by the neonate. (Adapted from Kuhnert BR, Kuhnert PM, Tu AL, et al: *Am J Obstet Gynecol* 1979; 133:909.)

observed poor Brazelton neonatal neurobehavioral scores at both 12 hours and 3 days of age; according to these authors this is related to normeperidine. *Thus, the immediate fetal effect that is observed after the maternal administration of meperidine as shown by low Apgar scores most probably is*

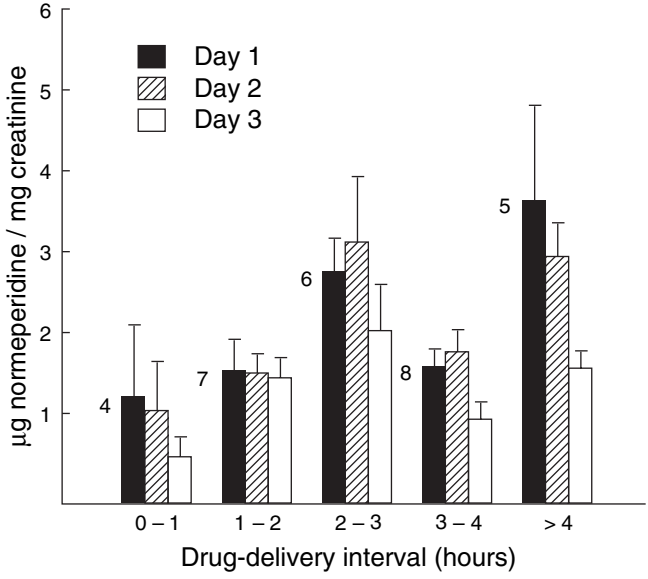

Figure 7–2. Relationship between the meperidine delivery interval and urinary excretion of normeperidine by the neonate. (Adapted from Kuhnert BR, Kuhnert PM, Tu AL, et al: *Am J Obstet Gynecol* 1979; 133:909.)

related to the direct effect of meperidine; on the other hand, delayed neonatal neurobehavioral changes are probably related to the metabolic product normeperidine. Recently neonatal neurobehavior change has been observed from normeperidine excreted from breast milk.[5]

Alphaprodine (Nisentil)

Because of its faster onset and short duration of action, alphaprodine used to be a popular drug among obstetricians, but *this agent was associated with a sinusoidal fetal heart rate pattern.* This drug is not available at the present time.

Fentanyl

Fentanyl is a rapid-acting and short-lasting narcotic, and 100 µg of fentanyl is equipotent to 10 mg of morphine and 100 mg of meperidine. This agent can be used intramuscularly (50 to 100 µg) or intravenously (25 to 50 µg) and will have its peak effect in 7 to 8 minutes and 3 to 5 minutes, respectively. *Interestingly, Eisele and colleagues used 1 µg/kg of fentanyl intravenously before cesarean section and found no differences in Apgar scores, in umbilical cord acid-base values, or in neurobehavioral scores between medicated and control groups.*[6] The main disadvantage of this agent is its short duration: it only lasts for 1 to 2 hours even if used intramuscularly.

Remifentanil

Remifentanil, a new ultra short-acting opioid receptor agonist produces analgesia, however it is quickly metabolized by nonspecific esterases. It crosses the placenta, but it is rapidly metabolized by the neonate. It has been used as a continuous intravenous infusion or patient controlled infusion with some success.[6a] This may be a proper alternative when neuraxial technique is contraindicated. In one report authors used 0.1 mcg/kg/min to 0.2 mcg/kg/min with success.

Sedatives and/or Tranquilizers

These agents can be used either to allay apprehension and anxiety or in conjunction with narcotics to decrease the incidence of nausea and/or vomiting.

Barbiturates

Barbiturates are seldom used at the present time because of their adverse effects in neonates when used in high doses.

Tranquilizers

Phenothiazines

Hydroxyzine (Vistaril) and promethazine (Phenergan) have been used extensively in obstetric cases. These agents

possess effective anxiolytic as well as antiemetic properties *and can decrease the beat-to-beat variability of the fetal heart rate.*

Benzodiazepines

These agents are effective anxiolytic, hypnotic, anticonvulsant, as well as amnestic drugs.

Diazepam. A popular anxiolytic drug, diazepam has been used extensively in obstetric practice. In small doses (2.5 to 10 mg) diazepam did not affect Apgar scores or neonatal acid-base values; however, lower Scanlon neurobehavior scores were observed at 4 hours.[7] *In larger doses diazepam can produce neonatal hypotonia, lethargy and hypothermia. Sodium benzoate, which is used as a buffer in the injectable solution, can displace the bilirubin from albumin and can cause hyperbilirubinemia.* Diazepam still remains the drug of choice to treat convulsions following local anesthetic toxicity or in eclamptic patients.

Midazolam. Because of its fast onset and short half-life this agent has become very popular in nonobstetric cases. Because of its potent anterograde amnestic effect, one has to be careful when using it for parturients.[8]

Dissociative Medications

Ketamine has been used as an induction agent during general anesthesia for cesarean section. In small intravenous doses (10 to 15 mg) it may be a useful analgesic drug. The possibility of delirium and hallucinations during emergence from cesarean section following large doses of ketamine may be a problem. The use of diazepam during induction can decrease the incidence of this drawback. Other untoward side effects include hypertension, increased salivation, as well as increased involuntary movements. An *increased intensity of uterine contractions has also been observed following the use of ketamine*

(*>1 mg/kg intravenously*)[9]; neonatal depression can also occur in this dose range.

Amnestic Agents

Scopolamine (hyoscine) is a potent amnestic agent and also possesses mild sedative properties. It was used in combination with morphine for "twilight sleep." Scopolamine crosses the placenta and can cause fetal tachycardia and a loss in beat-to-beat variability.

Neuroleptanalgesia

Innovar (droperidol, 2.5 mg/mL, plus fentanyl, 0.05 mg/mL), although extensively used in general surgical cases, has never become popular in the obstetric population.

Agonist and Antagonist Agents

Butorphanol (Stadol) and nalbuphine are extremely popular at the present time for the relief of labor pain. One to 2 mg of butorphanol has been found to be as effective as 40 to 80 mg of meperidine for relieving labor pain. Butorphanol was associated with less drowsiness as well as less nausea and/or vomiting. *However, the use of butorphanol was associated with a 75% incidence of a transient sinusoidal fetal heart rate pattern.*[10] Because of the problem with the sinusoidal pattern, although benign, as well as maternal somnolence, butorphanol is rarely used at Brigham and Women's Hospital at the present time. Nalbuphine (Nubain), 10 mg intravenously, has become the drug of choice. In a double-blind randomized study using intravenous increments of nalbuphine, 3 mg, vs. meperidine, 15 mg, by patient-controlled analgesia during the first stage of labor, better maternal analgesia was observed with nalbuphine; there were no differences between the two in the maternal or neonatal side effects.[11]

Sedatives, tranquilizers, and narcotics have been used in parturients for a long time; newer agents might be more effective and less detrimental to both mother and baby.

Remifentanil

Remifentanil is the newest opiate marketed for intravenous use. A case report that included three patients was published from England. The authors used patient-controlled intravenous remifentanil for pain during labor for three thrombocytopenic parturients. A bolus of 0.5 mcg/kg with a lockout period of 2–3 min allowed successful demand anesthesia with each contraction. The authors mentioned that there was an initial period during which the expectant mothers learned to anticipate the next contraction and to deliver a bolus close to thirty seconds before the initiation of the contraction. In such cases remifentanil was associated with excellent analgesia, and the doses ranged from 426–1050 mcg/hour. They reported one episode of maternal sedation and fetal heart rate decelerations, which may have been due to excessive demand dosing; however, as the authors mentioned, mothers and neonates tolerated remifentanil without problems. Remifentanil has a unique advantage because of its rapid metabolism by tissue esterase; hence it does not accumulate in the fetus.[11a]

Inhalation Analgesia

Inhalation analgesia is still being used in different parts of the United States. At Brigham and Women's Hospital inhalation analgesia by mask is not used, for fear of maternal aspiration.

In the United Kingdom inhalation analgesia has been used with great success during both the first stage as well as the second stage of labor. *Entonox is a mixture of 50% oxygen and 50% nitrous oxide delivered in a cylinder.* This is connected with a mask for use by the parturient. *One of the main problems with this agent (entonox) is the possibility of separation of the gas mixture when the temperature reaches –7°C*; in such a situation parturients will inhale 100% oxygen first, followed by nitrous oxide, and this can cause severe complications. Parturients can self-administer this agent; however, constant communication between the woman and the administrator is absolutely vital. One should start to inhale 30 seconds before the onset of the contraction so that an adequate brain

concentration can be achieved at the peak of the uterine contraction. Besides N_2O, the other inhalation agents that have been used are methoxyflurane and trichloroethylene (Trilene). Enflurane 1% with oxygen or isoflurane 0.75% in oxygen have been compared with N_2O/O_2 (50%) for relief of labor pain and found to be more effective than N_2O/O_2 mixture. However, these agents never became popular in the United States. Two recent inhalational agents, desflurane and seroflurane, are undergoing trials. Desflurane, because of its extreme stability from biodegradation, may be a better choice in obstetric anesthesia.[12]

The effect of the inhalation agents on uterine activity and neonates will depend upon the concentrations of the agents used. In smaller concentrations, no detrimental effect on uterine contraction or neonates has been observed. If general anesthesia is ever indicated for vaginal delivery, then one must take all precautions (nonparticulate antacid, preoxygenation, cricoid pressure, endotracheal tube with an inflated cuff) to avoid any complication. *Occasionally a high concentration of inhalation anesthetics may be necessary to relax the uterus for manipulation by the obstetrician.*[13] Sevoflurane or desflurane also may be used. *Major indications for these manipulations are (1) extraction of the head during a breech delivery, (2) internal version and extraction of the second baby during the delivery of twins, (3) extraction of a retained placenta, and (4) reduction of uterine inversion.* To minimize postpartum bleeding, one should immediately shut off the inhalation anesthetics following uterine relaxation.

References

1. Way WL, Costley EC, Way EL: Respiratory sensitivity of the newborn infant to meperidine and morphine. *Clin Pharmacol Ther* 1965; 6:454.
2. Shnider SM, Way EL, Lord MJ: Rate of appearance and disappearance of meperidine in fetal blood after administration of narcotic to the mother. *Anesthesiology* 1966; 17:227.
3. Shnider SM, Moya F: Effects of meperidine on the newborn infant. *Am J Obstet Gynecol* 1964; 89:1000.
4. Kuhnert BR, Kuhnert PM, Tu AL, et al: Meperidine and normeperidine levels following meperidine administration during labor II. Fetus and neonate. *Am J Obstet Gynecol* 1979; 133:909.

5. Whittels B, Scott DT, Sinatra RS: Exogenous opioids in human breast milk and acute neonatal neurobehavior: A preliminary study. *Anesthesiology* 1990; 73:864.
6. Eisele JH, Wright R, Rogge P: Newborn and maternal fentanyl levels at cesarean section. *Anesth Analg* 1982; 61:179.
7. Rolbin SH, Wright RG. Shnider SM, et al: Diazepam during cesarean section—effects on neonatal Apgar scores, acid-base status, neurobehavioral assessment and maternal and fetal plasma norepinephrine levels (abstract). Presented at the Annual Meeting of the American Society of Anesthesiologists, New Orleans, 1977, p 449.
8. Kanto J, Aaltonen L, Erkkola R: Pharmacokinetics and sedative effect of midazolam in connection with cesarean section performed under epidural analgesia. *Acta Anaesthesiol Scand* 1984; 28:116.
9. Marx GF: Postpartum uterine pressure with different doses of ketamine. *Anesthesiology* 1979; 50:163.
10. Hatjis CG, Meis PJ: Sinusoidal fetal heart rate pattern associated with butorphanol administration. *Obstet Gynecol* 1986; 67: 377.
11. Frank M, McAteer EJ, Cattermole R, et al: Nalbuphine for obstetric analgesia: A comparison of nalbuphine with pethidine for pain relief in labour when administered by patient controlled analgesia. *Anaesthesia* 1987; 42:697.
11a. Jones R, Pegrum A, Stacey RGW: Patient-controlled analgesia using remifentanil in the parturient with thrombocytopenia. *Anaesthesia* 1999; 54:459.
12. Jones RM: Desflurane and seroflurane: Inhalation anesthetics for this decade. *Br J Anaesth* 1990; 65:527.
13. Munson ES, Majer WR, Caton D: Effects of halothane cyclopropane and nitrous oxide on isolated human uterine muscle. *J Obstet Gynecol Br Commonw* 1969; 76:27.