8
Relief of Labor Pain by Systemic Medications and Inhalational Agents

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 into several categories.

Opioids

Opioids 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:

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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 (5–10 mg) or intravenously (2–3 mg), and its peak effect occurs at 1–2 h and 20 min, respectively.[1] Ten healthy nulliparous parturients in active labor were given doses (up to 0.15 mg/kg body weight morphine) for pain relief. The parturients were all significantly sedated and several fell asleep but were awakened by pain during contractions.[2]

Meperidine

This is the most commonly used drug at the present time because of its fast onset. It is used both intramuscularly (50–100 mg) and intravenously (25–50 mg), and its time of onset is 40–50 min and 5–10 min, respectively. Meperidine rapidly crosses the placenta and attains fetal and maternal equilibrium within 6 min.[3]

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 h or 4 h after drug administration.[4] 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 2–3 h of maternal administration (Fig. 8-1).[5] Normeperidine, a metabolite of meperidine, reached its highest fetal concentration after 4 h of maternal administration (Fig. 8-2). They also observed poor Brazelton neonatal neurobehavioral scores at both 12 h and 3 days of age; according to these authors this is related to normeperidine. Thus, the immediate fetal effect observed after the maternal administration of meperidine as shown by low Apgar scores most probably is related to the direct effect

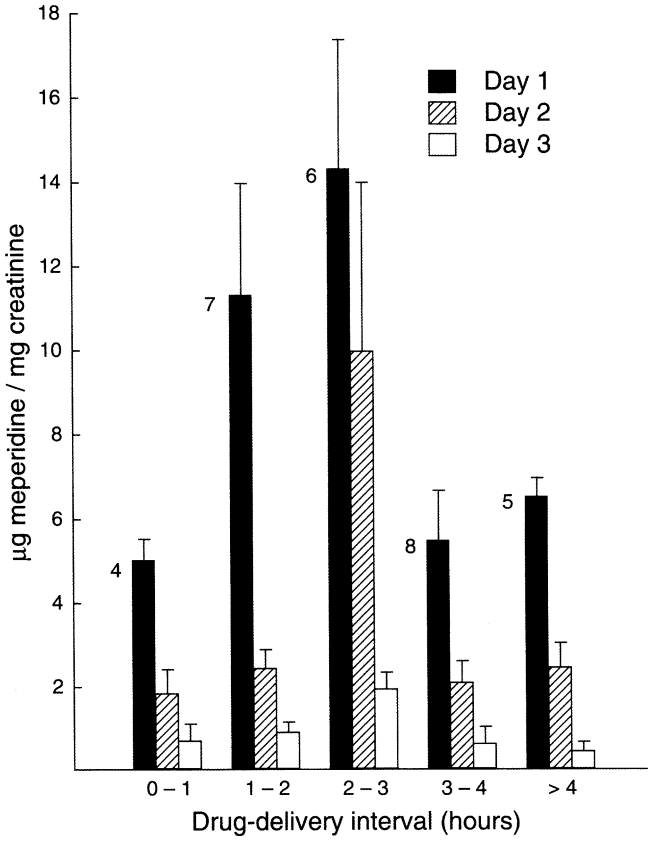

Figure 8–1. Relationship between the meperidine delivery interval and urinary excretion of meperidine by the neonate. (Adapted from Kuhnert et al.[5])

of meperidine; on the other hand, delayed neonatal neurobehavioral changes are probably related to the metabolic product normeperidine. Sosa et al. evaluated the association between the use of meperidine during the first stage of labor and the presence, type, and timing of acidosis in the newborn at birth

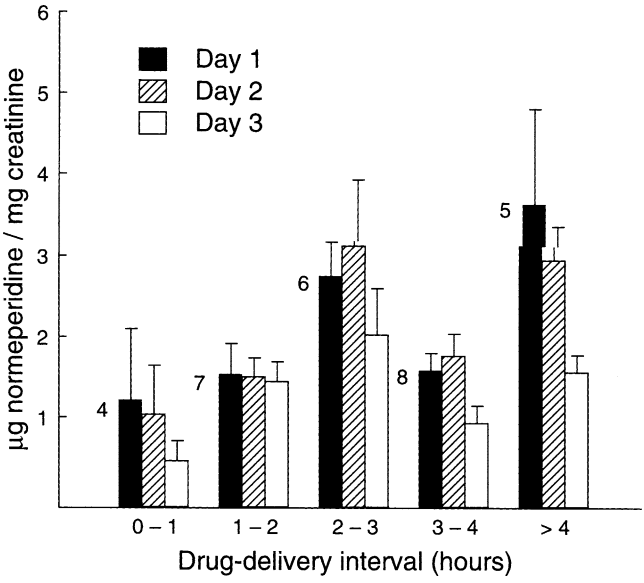

Figure 8–2. Relationship between the meperidine delivery interval and urinary excretion of normeperidine by the neonate. (Adapted from Kuhnert et al.[5])

and found that there was an increased risk of acidosis at birth in the meperidine group as compared to the control group.[6] Neonatal neurobehavioral change has also been observed from normeperidine excreted from breast milk.[7]

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 (50–100 µg) or intravenously (25–50 µg) and will have its peak effect in 7–8 min and 3–5 min, respectively. The main disadvantage of this agent is its short duration: it only lasts for 1–2 h even if used intramuscularly.

Fentanyl can be used via patient-controlled intravenous analgesia (PCIA) technique to provide labor analgesia. In one study,[8] patients received an initial IV dose of 100 μg of fentanyl incrementally over 1–5 min. If the pain was not adequately relieved, an additional 50 μg was given and repeated every 5 min until the patient reported adequate pain relief. The PCIA pump was initially set to give aliquots of 25–50 μg fentanyl with a lockout interval of 10 min. The lockout period and bolus dose were increased or decreased to achieve desired comfort level. Although this technique did not provide better analgesia than conventional patient-controlled epidural analgesia, it offers a good alternative method where a regional anesthesia is contraindicated. Just like any systemic analgesic techniques, intravenous fentanyl produces more maternal and neonatal sedation compared to regional anesthesia.[8] On the contrary, fentanyl administered as single dose does not have significant neonatal effects. 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.[9] Recently Frolich et al. also demonstrated that 1 μg/kg of fentanyl and midazolam 0.02 mg/kg given intravenously before the cesarean delivery did not have any adverse neonatal effects (Can J Anaesth 2006;53:79–85).

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.

In one study,[10] 20 term parturients requesting labor analgesia were randomized to receive one of two regimens of intravenous remifentanil. The initial settings in both groups consisted of an infusion of 0.025 μg/kg/min and a PCA bolus of 0.25 μg/kg and a lockout interval of 2 min. In Group A, the infusion was increased in a stepwise manner from 0.025 μg/kg/min to 0.05 μg/kg/min, 0.075 μg/kg/min, and 0.1 μg/kg/min as required; the bolus was kept constant at 0.25

μg/kg. In Group B, the bolus was increased from 0.25 μg/kg to 0.5 μg/kg, 0.75 μg/kg, and 1 μg/kg as necessary; the infusion was kept constant at 0.025 μg/kg/min. Maternal pain, satisfaction and sedation scores, remifentanil requirement, and side effects were recorded. Mean pain and patient satisfaction scores, and cumulative doses of remifentanil were similar in the two groups. The overall incidence of side effects was greater in Group B ($P = 0.0007$), with drowsiness observed in 100% of patients, as compared to 30% in Group A ($P = 0.003$). The minimum oxygen saturation levels were 94.3% +/– 2.6% and 92.2% +/– 3.8% in Groups A and B, respectively ($P = 0.19$). The authors concluded that although pain and satisfaction scores were similar in both groups, the regimen used in Group A was associated with fewer side effects compared to the Group B dosing regimen. However, there is a potential for respiratory depression and mandates close respiratory monitoring. When compared to epidural analgesia, this technique is not superior.[11]

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.

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 (2.5–10 mg) diazepam did not affect Apgar scores or neonatal acid–base values; however, lower Scanlon neurobehavioral scores were observed at 4 h.[12,13] *In larger doses diazepam can produce neonatal hypotonia, lethargy, and hypothermia.* In the past, diazepam has been used to treat convulsions following local anesthetic toxicity or in eclamptic patients. Midazolam has replaced diazepam for these indications.

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. However, as mentioned above, midazolam, 0.02 mg/kg, in combination with fentanyl, 1 μg/kg given intravenously before the cesarean delivery did not have any adverse neonatal effects. This approach seems to be a good option in very anxious patients prior to cesarean delivery.

Dissociative Medications

In small intravenous doses (10–15 mg) ketamine may be a useful analgesic drug.[14] The onset of action is about 30 s and lasts for 4 min. Bolus doses up to 0.25 mg/kg are suggested.[15] We have occasionally used 0.5 mg/kg bolus intravenous dose followed by 0.5 mg/kg/h infusion in patients to provide labor analgesia where regional analgesia was not an option. This was used in conjunction with fentanyl PCIA. Undesirable hallucinations were minimal. However, the quality of analgesia obviously will not match that from regional analgesia. Nonetheless, ketamine provides another option of systemic analgesia during labor.

Ketamine has been used as an induction agent during general anesthesia for cesarean section. The possibility of delirium and hallucinations during emergence from cesarean section following large doses of ketamine may be a problem. The use of

midazolam 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*);[16] 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 popular at the present time for the relief of labor pain. One to two milligrams of butorphanol has been found to be as effective as 40–80 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 transient sinusoidal fetal heart rate pattern.*[17] 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), 5–10 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.[18] The half-life of nalbuphine in the neonate has been estimated to be 4.5 h and therefore the neonatal respiratory monitoring is required in newborns born to mothers receiving nalbuphine for the labor and delivery.[19]

Inhalation Analgesia

Inhalation analgesia is still being used in different parts of the United States and more often in Europe. A survey from Ontario noted that nitrous oxide was available in 75% of hospitals. Hospitals without the availability of epidural analgesia were more likely to have nitrous oxide analgesia than those with epidural analgesia (89% vs. 70%).[20]

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 and available in cylinders in United Kingdom.* This mixture may be administered by unsupervised midwives in Great Britain in settings where regional anesthesia is not available. The flow of the gases from the cylinder to the mask can be controlled by one-way valve to limit pollution of the labor suite. *One of the main problems with this agent (Entonox) is the possibility of unreliable concentrations being delivered from the Entonox cylinder when the ambient temperature reaches –7°C;* in such a situation, nitrous oxide becomes liquid in the cylinder. Under these circumstances, parturients will inhale 100% oxygen initially, followed by very high concentrations of nitrous oxide, and this can result in maternal hypoxia. Parturients can self-administer this agent; however, constant communication between the woman and the administrator is absolutely vital. One should start to inhale 30 s before the onset of the contraction so that an adequate brain concentration can be achieved at the peak of the uterine contraction. With intermittent inhalation of nitrous oxide, accumulation over time is negligible, and the neonate eliminates most of the gas within minutes of birth.[21]

Besides N_2O, the other inhalation agents that have been used in the past are methoxyflurane, trichloroethylene (Trilene),

enflurane, and isoflurane. Enflurane 1% in 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.[22,23] More recently, newer inhalational agents with low blood gas solubility, desflurane and sevoflurane, have been trialed during labor and delivery. In one study, the authors compared the efficacy of Entonox with sevoflurane 0.8% during labor and they concluded that self-administered sevoflurane at subanesthetic concentration (0.8%) can provide useful pain relief during the first stage of labor, and to a greater extent than Entonox. Although greater sedative effects were experienced with sevoflurane, it was preferred to Entonox.[24] In another study, the authors compared desflurane (1–4.5%) in oxygen to nitrous oxide (30–60%) in oxygen for labor analgesia. They found that analgesia scores were similar for both groups with more amnesia in desflurane group (23% vs. 0% $P < 0.05$). Blood loss did not differ significantly: 364 ml for the desflurane group and 335 ml for the nitrous oxide group. There were no significant differences for neonatal Apgar score at 1 min or at 5 min or the NACS at 2 h or 24 h between the two groups. Hence, desflurane in subanesthetic doses seems to be safe and effective inhalation agent for normal delivery but might be associated with greater sedation.[25]

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) similar to those mandatory during general anesthesia. *Occasionally a high concentration of inhalation anesthetics may be necessary to relax the uterus for manipulation by the obstetrician.*[26,27] *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.

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