Drugs of Choice for Sedation and Analgesia in the Neonatal ICU

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Before 1980, pain in the newborn period was infrequently recognized or treated.1 The reference standard of pain assessment is self reporting which clearly is not possible in the newborn period; thus, clinicians can measure pain only indirectly. Animal and human studies have documented that neonatal pain is associated with both short- and long term consequences.2,3 Further, the enhanced survival of extremely low birth weight babies makes them more susceptible to the effects of pain and stress because of increased exposure. Indeed, one study documented that neonates under 32 weeks’ gestation were exposed to 10 to 15 painful procedures per day, and most of these procedures were untreated.4 Unfortunately, this problem continues. A recent study by Carbajal and colleagues5 has documented the increased occurrence and lack of treatment of neonatal pain in almost 80% of newborns in intensive care!

Analgesia and sedation in the neonatal ICU (NICU) has been fraught with controversy because of concern about the safety of these drugs in the neonatal population, the lack of adequate pharmacokinetic and pharmacodynamic data in this population, difficulty in assessing pain, and lack of long-term neurodevelopmental assessment of survivors for the pain experienced in the neonatal period.6–9 Legitimate concern about safety has led to more governance for moderate sedation privileges for clinicians caring for neonates as well as more emphasis on obtaining consent for sedation,10

This article is being republished due to a drug dosage error that appeared in Clinics in Perinatology, Volume 36, No. 1 (2009), pp.15–26. In the originally published version of the article, Table 1 listed the dosage for Remifentanil as 1 mg/kg. The correct dosage is 1 mcg/kg. This article has been updated to reflect the correct dosage.

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creating roadblocks to giving sedation to neonates undergoing painful procedures. Further, individual differences and decreased morphine metabolism in neonates of younger gestational age may lead to the rapid development of tolerance as well as to the accumulation of the drug in extremely preterm neonates. Thus, the use of sedation and analgesia in the neonatal population, although extremely important, must be done safely and effectively.

OPIOIDS

Opioids are used commonly in modern NICUs. They provide relief from procedural pain (eg, medication before intubation) and from chronic pain (eg, pain caused by necrotizing enterocolitis or ventilation). Several studies and reviews have concluded that opioids should be used selectively. A recent Cochrane review found insufficient evidence to recommend routine use of opioids in mechanically ventilated newborns. The Cochrane review looked at pain scales and found an overall significant effect on pain in the treatment group. No significant effects were seen the treatment group with respect to neonatal mortality, duration of ventilation, short-term or long-term neurodevelopmental outcome, incidence of severe intraventricular hemorrhage (IVH), any IVH, or periventricular leukomalacia (PVL). Given the likely long-term adverse consequences associated with the chronic pain and stress of mechanical ventilation, it is reassuring that short-term adverse effects of analgesia are not more common in the opioid-treated groups.

Morphine

Morphine is the most frequently used opioid analgesic in patients of all ages and is the drug most commonly used for analgesia in ventilated neonates. Morphine has a slow onset of action. Its mean onset of action is 5 minutes, and the peak effect is at 15 minutes. It is metabolized in the liver into two active compounds, morphine-3-glucuronide and morphine-6-glucuronide. The former is an opioid antagonist, and the latter is a potent analgesic. Preterm infants mostly produce morphine-3-glucuronide, which explains why the infant develops tolerance after 3 to 4 days of morphine therapy. Side effects of morphine include hypotension in neonates who have pre-existing hypotension and a gestational age less than 26 weeks, prolonged need for assisted ventilation, and increased time to reach full feeds. Others have suggested that morphine may have a specific effect on pulmonary mechanics, possibly resulting from some as yet undefined direct toxicity such as histamine release and/or bronchospasm. There is even controversy as to whether morphine is effective in the treatment of acute pain.

A randomized, controlled trial conducted in the Netherlands compared the analgesic effect of morphine versus placebo infusions for a duration of 7 days in 150 newborns who received mechanical ventilation. The findings of the study suggested that routine morphine infusion in preterm newborns who received ventilatory support neither improved pain relief nor protected against poor neurologic outcome (defined as severe IVH, PVL, or death within 28 days). The NEurologic Outcomes and Preemptive Analgesia in Neonates (NEOPAIN) trial included ventilated preterm neonates from 16 centers in the United States and Europe. It compared the effect of morphine versus placebo infusions, following a loading dose, on the neurologic outcomes of the ventilated neonates. The results suggested that continuous morphine infusion did not reduce early neurologic injury in ventilated preterm neonates. The poor neurologic outcome was defined as severe IVH, PVL, or death. Hypotension occurred more frequently in the morphine group than the placebo group.
One study assessed the long-term outcome at age 5 to 6 years of prematurely born children (< 34 weeks’ gestation) who by randomization received morphine in the neonatal period to facilitate mechanical ventilation. This study looked at children from two trials. The first included 95 infants who were assigned randomly to receive morphine alone, pancuronium alone, or both morphine and pancuronium. The second trial included 21 infants who received morphine and 20 infants who received placebo. Each child was assessed using three scales: the full-scale Weschler Preschool and Primary Scale of Intelligence, the Movement Assessment Battery for Children, and the Child Behavior Checklist. No adverse effects on intelligence, motor function, or behavior were found in the children treated with morphine.

**Fentanyl**

Fentanyl is an opioid analgesic that is 50 to 100 times more potent than morphine. It is used frequently because it provides rapid analgesia. It may be used as a slow intravenous push every 2 to 4 hours or as a continuous infusion. Tolerance may develop, and withdrawal symptoms may occur after 5 or more days of continuous infusion. In a blinded, randomized, controlled trial, a single dose of fentanyl given to ventilated preterm newborns significantly reduced pain behaviors and changes in heart rate. It also increased growth hormone levels. In another study, fentanyl provided the same pain relief as morphine but with fewer side effects. In other studies, fentanyl use resulted in lower heart rates and lower behavioral stress scores and pain scores than seen with placebo; however, the infants receiving fentanyl required higher ventilator rates and peak inspiratory pressures at 24 hours. Fentanyl also may be used transdermally in patients who have limited intravenous access.

Side effects of fentanyl include bradycardia, chest wall rigidity, and opioid tolerance after prolonged therapy.

**Methadone**

Methadone is a potent analgesic with a rapid onset of action and prolonged effect. It has minimal side effects, high enteral bioavailability, and a low cost.

**Other Opiates**

Other opiates include the short-acting drugs sufentanil, alfentanil, and remifentanil. All are useful for short procedures such as intubation. Sufentanil and alfentanil are metabolized by the liver, which is immature in preterm neonates, resulting in increased drug levels with repeated infusions, especially in preterm neonates. Remifentanil, on the other hand, is cleared rapidly by plasma esterases and is unaffected by the maturity of the liver enzyme system, making it attractive for short neonatal surgery or other procedures when rapid recovery is anticipated.

**BENZODIAZEPINES**

The benzodiazepines are anxiolytic drugs that have limited analgesic effect but are commonly used in NICUs to produce sedation and muscle relaxation and to provide amnesia (in older patients). This class of drugs inhibits gamma-aminobutyric acid A receptors. The main complications include myoclonic jerking, excessive sedation, respiratory depression, and occasional hypotension.

**Midazolam**

The most commonly used benzodiazepine in the NICU is midazolam. When administered with morphine, it provides better sedation than morphine alone in ventilated patients, without adverse effects. The minimal effective dose for most neonates is
200 \(\mu g/kg\) with a maintenance dose of 100 \(\mu g/h\). It can be given orally, although in neonates the bioavailability of oral midazolam is only half that of intravenous midazolam. Intranasal midazolam has been shown to be effective for fundoscopic examinations in older children, but this mode of delivery has not been tested in neonates. One recent review found no apparent clinical benefit of midazolam compared with opiates in mechanically ventilated neonates. Further, midazolam was associated with worse short-term adverse effects (death, severe IVH, or PVL) in the NOPAIN trial compared with morphine alone. In summary, midazolam seems to provide sedative effects in mechanically ventilated neonates, but it should be used with caution because of reported adverse effects, particularly when used alone.

**Lorazepam**

Lorazepam is a longer-acting benzodiazepine that frequently is used in preterm neonates. Its duration of action is 8 to 12 hours. It also is an effective anticonvulsant for neonates refractory to phenobarbital. Unfortunately, one of its main side effects is myoclonic jerking, which mimics seizure activity. It has been shown (along with morphine) to adhere to the tubing in patients treated with extracorporeal membrane oxygenation (ECMO), increasing dosing requirements by 50% in those patients.

**BARBITURATES**

Barbiturates are used commonly in neonates for sedation and analgesic effects, despite a lack of evidence for pain relief.

**Phenobarbital**

Phenobarbital usually is considered the drug of choice for seizure control. Despite minimal animal evidence for antinociception, it often is used for analgesia. It also is used in conjunction with opioids for sedation, although there is little recent evidence that it is effective. Classically, phenobarbital has been used for neonatal abstinence syndrome, but recent work by Ebner and colleagues has demonstrated that opiates shorten the time required for treatment. Because of its anticonvulsant effects, however, phenobarbital is an attractive adjunct for patients who have seizures.

**Thiopental**

Thiopental is a short-acting barbiturate used for anesthetic induction. It is used sparingly in the NICU, but one randomized, controlled trial showed a decreased time needed for intubation and maintenance of heart rate and blood pressure with thiopental compared with placebo during nasotracheal intubation.

**Chloral Hydrate**

Chloral hydrate is used for hypnosis when sedation but not analgesia is required for certain procedures such as MRI. Apnea and bradycardia may occur in ex-preterm infants undergoing procedural sedation with doses as little as 30 mg/kg. Side effects were inversely related to gestational age. The usual dose is 50 to 100 mg/kg. A dose of 75 mg/kg administered orally is more efficacious than a 0.2-mg/kg dose of intravenous midazolam and has comparable side effects (apnea, bradycardia).

**KETAMINE**

Ketamine is a dissociative anesthetic used for anesthesia, analgesia, and sedation. It causes bronchodilation and mild increases in blood pressure and heart rate. Cerebral blood flow is relatively unaffected with ketamine, making it an attractive choice for...
some unstable hypotensive neonates requiring procedures such as cannulation for ECMO. Animal studies have raised concern about the neurodegenerative effects of ketamine although ketamine in clinically relevant doses is neuroprotective in the presence of inflammatory pain. Nevertheless, extrapolating animal to human data is problematic at best, and there has been no credible evidence that ketamine is detrimental to the developing human brain in the presence of pain. Clearly, more study is needed to determine the safety and efficacy of this anesthetic.

### PROPOFOL

Propofol has become popular as an anesthetic agent for young children, but it has not been studied extensively in neonates. One study compared propofol with morphine, atropine, and suxamethonium for intubation and found that propofol led to shorter intubation times, higher oxygen saturations, and less trauma than the combination regimen in neonates. Propofol should be used with caution in young infants, however, because clearance is inversely related to neonatal and postmenstrual age. Thus with intermittent bolus or continuous administration this drug can accumulate in young immature neonates, leading to toxicity.

### ACETAMINOPHEN

Acetaminophen acts by inhibiting the cyclo-oxygenase (COX) enzymes in the brain and has been well studied in newborns. It is useful for mild pain, in conjunction with other pain relief, or after circumcision.

### LOCAL ANESTHETICS

#### Lidocaine

Lidocaine inhibits axonal transmission by blocking Na⁺ channels. Lidocaine is used commonly for penile blocks for circumcisions. In this circumstance, its use has demonstrated effectiveness in decreasing pain response to immunizations as long as 4 months after circumcision compared with neonates who received placebo. The ring block has been shown to be a more effective than a dorsal penile root block or eutectic mixture of local anesthetics (EMLA) cream in relieving the pain of circumcision.

#### Topical Anesthetics

Topical anesthetics have demonstrated effectiveness for certain types of procedural pain such as venipuncture, lumbar puncture, or immunizations. Complications include methemoglobinemia and transient skin rashes. In preterm neonates with thin skin, the concern for methemoglobinemia is accentuated.

Unfortunately, topical anesthetics are not effective in providing pain relief for the heel prick, one of the most common skin-breaking procedures, because of increased skin thickness. Newer topical anesthetics include 4% tetracaine and 4% liposomal lidocaine. Although the newer agents have a shorter onset of action, they are no more effective in pain relief.

### COMMON PROCEDURES

Common neonatal procedures and advantages and disadvantages of drug therapy are summarized in Table 1.
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Drugs</th>
<th>Advantages of Treatment</th>
<th>Disadvantages of Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical ventilation</td>
<td>Fentanyl (1–3 μg/kg)</td>
<td>Improved ventilator synchrony, lower pain scores</td>
<td>Prolonged time on assisted ventilation, prolonged time to full feeds, increased bladder catheterization, hypotension</td>
<td>Use sedation as needed, not preemptively; midazolam was associated with adverse short-term effects in NOPAIN trial.</td>
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<tr>
<td></td>
<td>Morphine (0.1 mg/kg)</td>
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<td></td>
<td>Midazolam (0.1–0.2 mg/kg)</td>
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<tr>
<td>Circumcision</td>
<td>Lidocaine (1 mL) EMLA</td>
<td>Less pain response up to 4 months post-procedure</td>
<td>Allergic reaction, bruising at injection site</td>
<td>Ring block is more effective than dorsal penile nerve root block.</td>
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<td>Heel lance</td>
<td>Sucrose</td>
<td>Shorter crying, reduced changes in heart rate</td>
<td>None</td>
<td>EMLA cream is not effective.</td>
</tr>
<tr>
<td>Venipuncture, arterial puncture,</td>
<td>Topical anesthetic (EMLA)</td>
<td>Lower Premature Infant Pain Profile scores, less crying</td>
<td>Local reaction, rare methemoglobinemia</td>
<td>Other nonpharmacologic treatments are effective.</td>
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<tr>
<td>lumbar puncture</td>
<td>Sucrose</td>
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<tr>
<td>Intubation</td>
<td>Morphine (0.1 mg/kg)</td>
<td>Shorter time to intubation, less trauma, less desaturation, better maintenance of vital signs</td>
<td>None</td>
<td>There is no accepted premedication. Opiates are the class most common used.</td>
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<td></td>
<td>Fentanyl (1–3 μg g/kg)</td>
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<td></td>
<td>Remifentanil (1 mcg/kg)</td>
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<td>Midazolam (0.2 mg/kg)</td>
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<td></td>
<td>Propofol (2–6 mg/kg)</td>
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<td>Ketamine (1 mg/kg)</td>
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<td></td>
<td>Suxamethonium (2 mg/kg)</td>
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<tr>
<td>Procedure/Condition</td>
<td>Analgesia</td>
<td>Sedation</td>
<td>Possible Complications</td>
<td>Additional Information</td>
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<tr>
<td>More invasive procedures (eg, cannulation for ECMO)</td>
<td>Propofol (2–6 mg/kg) Ketamine (1 mg/kg) Fentanyl (1–3 mcg/kg)</td>
<td>Maintenance of cardiovascular stability</td>
<td>Questionable neurotoxicity with ketamine</td>
<td>Ketamine may be neuroprotective.</td>
</tr>
<tr>
<td>Postsurgical pain</td>
<td>Fentanyl (1–3 µg g/kg) Morphine (0.1 mg/kg) Acetaminophen (15 mg/kg)</td>
<td>Lowered neuroendocrine response, faster recovery</td>
<td>Respiratory depression, hypotension with opiates</td>
<td>Use acetaminophen only for mild pain.</td>
</tr>
<tr>
<td>Endotracheal suctioning</td>
<td>Midazolam (0.2 mg/kg) Morphine (0.1 mg/kg) Fentanyl (1–3 µg/kg)</td>
<td>Anxiolitic</td>
<td>Respiratory depression, hypotension, dependence</td>
<td>Pain usually is not treated.</td>
</tr>
<tr>
<td>Imaging (MRI)</td>
<td>Chloral hydrate (50–100 mg/kg)</td>
<td>Sedation</td>
<td>Respiratory depression, hypotension</td>
<td>Chloral hydrate provides sedation only.</td>
</tr>
</tbody>
</table>
FUTURE DIRECTIONS

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDS) are used extensively for pain relief in children and adults, but they are used mainly for patent ductus arteriosus (PDA) closure in neonates. They act by inhibiting the COX-1 and COX-2 enzymes responsible for converting arachidonic acid into prostaglandins, thus producing their analgesic, antipyretic, and anti-inflammatory effects. The analgesic effects of NSAIDS have not been studied in neonates, although both ibuprofen and indomethacin have been studied for use in PDA closure. Concern about side effects of renal dysfunction, platelet adhesiveness, and pulmonary hypertension have limited their study for this indication. Ibuprofen, however, has demonstrated beneficial effects on cerebral circulation in human studies as well as beneficial effects on the development of chronic lung disease in baboon experiments, making it an attractive analgesic in preterm neonates. Nonpharmacologic approaches such as acupuncture, massage therapy, sucrose, and music are also safe and effective.

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REFERENCES