The accurate assessment and effective treatment of acute pain in children in the hospital setting is a high priority. Evidence is growing that pediatric patients of all ages, even the most extremely premature neonates, are capable of experiencing pain as a result of tissue injuries due to medical illnesses, therapeutic and diagnostic procedures, trauma, and surgery. If pain is not recognized and adequately treated, the resulting physiologic and behavioral responses can be potentially harmful, resulting in long-lasting negative effects on the developing nociceptive system.

The complex processes by which noxious thermal, chemical, or mechanical stimuli are transformed, transmitted, modified, and perceived as pain by an individual are collectively referred to as nociception. Many of these processes lend themselves to pharmacologic interventions that can attenuate or block the transmission of pain. Pain treatment plans that target a single step in the nociceptive process with a single medication may be less effective than plans that target multiple steps by using a combination of analgesics. Although opiates continue to be mainstays in the treatment of moderate to severe acute pain, by combining them with drugs and techniques that target other components of nociceptive pathways it may be possible to reduce the opiate consumption, provide equivalent or superior analgesia, and reduce the incidence and severity of opiate-related adverse drug events such as nausea, vomiting, constipation, pruritus, respiratory and central nervous system depression, and urinary retention. In recent years regional analgesic techniques supplemented with systemic opiate or nonsteroidal anti-inflammatory drug (NSAID) therapy have emerged as invaluable methods for controlling severe acute postoperative pain in
children. It should also be mentioned that especially for the treatment of moderate to severe pain in children, many hospitals now use Pediatric Acute Pain Management Services to develop individual pain treatment plans; closely monitor their implementation, safety, and efficacy; and make adjustments to the treatment plan if necessary to improve analgesia, ensure patient safety, or decrease unwanted side effects of analgesic therapy. This article provides an overview of the most common analgesic medications and techniques used to treat acute pain in children.

**ANALGESIC, ANTIPYRETIC, NONSTEROIDAL ANTI-INFLAMMATORY DRUGS**

NSAIDs are used for mild to moderate pain by themselves or they may used in combination with other agents and techniques for moderate to severe pain. Although they are often categorized as weak analgesics, for pain associated with tissue inflammation, they may be superior to opioids. Their use is not associated with the common adverse reactions associated with opioid therapy: respiratory depression, sedation, physical dependence, nausea, vomiting, constipation, or pruritus. All NSAIDs work by inhibition of cyclooxygenase (COX), the enzyme responsible for metabolizing arachidonic acid. The inflammatory response can be triggered by several mechanisms, all of which result in cell membrane damage, including thermal or mechanical trauma, infectious agents, antigen-antibody complexes, or ischemia. Once released by traumatized or damaged cell membranes, arachidonic acid is metabolized by COX to form prostaglandins and thromboxanes. Prostaglandins and thromboxanes then sensitize peripheral nerve endings and vasodilate vessels causing pain, erythema, and inflammation. Several COX isoenzymes have been identified. The constitutive form of COX (COX-1) is present throughout the body. Prostaglandins produced by COX-1 are essential for a variety of essential functions including: regulation of kidney blood flow, protection of gastric mucosa from damage secondary to gastric acid secretion, and platelet aggregation. Therefore, complications from the use of nonselective COX inhibitors such as ibuprofen, ketorolac, and naproxen include gastric ulceration, bleeding, and impaired renal function. Analgesic efficacy and the risk for bleeding was the subject of a recent review on the perioperative use of NSAIDs. The investigators conclude that although NSAIDs play a valuable part in the management of postoperative pain in children, perioperative bleeding has occurred in children who received NSAIDs. Further, the investigators comment that the available evidence from the literature reviewed fails to establish definitively that NSAID administration is responsible for causing perioperative bleeding. Risk factors for NSAID-induced renal failure include preexisting renal disease, congestive heart failure, hepatic dysfunction, hypovolemia, and the concomitant use of other nephrotoxic drugs such as aminoglycosides, furosemide, or cyclosporine. Neonates may also be at increased risk for oliguria, reduced glomerular filtration rate, and renal compromise associated with NSAID use. NSAIDs should be used cautiously or not at all in patients with any of these risk factors. COX-2 is an inducible isoform of cyclooxygenase. COX-2 is induced by inflammatory mediators in traumatized cells. COX-2 is also a constitutive isoform because it is present in the brain and kidney in the absence of inflammation. Most NSAIDs are nonselective COX inhibitors. The theoretical advantages of using the COX-2 inhibitors relates to a reduction in the incidence of adverse drug reactions. Unfortunately, the initial enthusiasm for COX-2 inhibitors has been tempered by the observation of increased cardiovascular morbidity, myocardial infarction, and stroke due to thrombotic events in adults treated for prolonged periods with these drugs. As a result, 2 COX-2 inhibitors, rofecoxib and valdecoxib, were withdrawn from the market. Celecoxib, another COX-2 inhibitor, has been approved for use in children older than 2 years of age with juvenile rheumatoid arthritis. Celecoxib was generally well tolerated, and seems
to be as effective as naproxen in this patient population.\textsuperscript{23} Although there is some variability in analgesic response to different NSAIDs among patients, initial choice of an agent depends on other factors such as cost, the desired dosing interval, underlying medical conditions, and the patient’s fasting status. The variability in analgesic response to different NSAIDs may be explained in some patients by variable gene expression and polymorphisms in genes encoding enzymes involved in prostaglandin production.\textsuperscript{24}

The oldest drug in this class, acetylsalicylic acid (aspirin), is still commonly used in adults, but use as an analgesic in pediatric patients has nearly stopped due to its association with Reye’s syndrome. However, aspirin is still used for some pediatric patients suffering from rheumatologic conditions.\textsuperscript{25} Aspirin is available in chewable 81-mg tablets as well as tablets of 81 mg and 325 mg for oral use. Aspirin is dosed 10 to 15 mg/kg orally and administered every 4 to 6 hours. Maximum daily dose should not exceed 90 mg/kg per day.

Acetaminophen, the most widely used NSAID for the treatment of fever and pain, is unique among NSAIDs. High levels of peroxides in inflammatory tissue seem to inhibit the ability of acetaminophen to block COX. Peroxide concentrations are low in the brain, thus acetaminophen is an effective COX inhibitor centrally, a potent antipyretic, and a mild analgesic. Because it is a weak COX inhibitor in the periphery, it lacks the troublesome side effects of other NSAIDs but it is a weak anti-inflammatory agent. However, it may have several other antinociceptive effects, including N-methyl-D-aspartate (NMDA) receptor inhibition and activation of descending inhibitory serotonin pathways.\textsuperscript{26}

A recent meta-analysis revealed that acetaminophen and ibuprofen have similar safety profiles, and equivalent efficacy in treating moderate to severe pain in children, but that ibuprofen is a more effective antipyretic.\textsuperscript{27} Others have found that rectal acetaminophen 90 to 100 mg/kg per day did not have additional analgesic effects in 0- to 2-month-old infants with severe postoperative pain receiving continuous intravenous morphine 5 to 10 μg/kg/h after major abdominal surgery.\textsuperscript{28}

In the United States, acetaminophen is available for oral or rectal administration. Two intravenous preparations are available outside the United States, propacetamol and paracetamol (intravenous acetaminophen). Propacetamol is a prodrug of acetaminophen, and is rapidly metabolized to acetaminophen after administration. Though of proven analgesic efficacy perioperatively, it requires reconstitution before administration and is associated with pain during infusion at the intravenous catheter site.\textsuperscript{29} An intravenous acetaminophen preparation may soon be available in the United States, and has also been shown to be effective for treating postoperative pain in a variety of clinical situations and is not associated with pain at the injection site.\textsuperscript{29–33}

Of concern is that acetaminophen is frequently misused, and acetaminophen overdose can lead to hepatic necrosis and failure.\textsuperscript{34} Under normal circumstances, acetaminophen is metabolized in the liver primarily by glucuronidation and sulfation. However, in acetaminophen overdose, an oxidation pathway predominates via cytochrome P450. This oxidation pathway results in the production of a highly hepatotoxic metabolite.

Acetaminophen is conveniently available in many preparations including drops (80 mg/0.8 mL), elixir (160 mg/5 mL), chewable tablets (80 mg and 160 mg), tablets (325 mg and 500 mg), and suppositories (80 mg, 120 mg, 325 mg, and 650 mg). Single-dose rectal acetaminophen is administered in a dose of 35 to 45 mg/kg. Repeated rectal dosing is 20 mg/kg every 6 hours in infants and children and every 12 hours in newborns. Oral acetaminophen is administered in a dose of 10 to 15 mg/kg every 4 to 6 hours. The maximum daily acetaminophen dose depends on the age of the patient: the lesser of 4 g or 100 mg/kg per day in children; 75 mg/kg per day in infants; 60 mg/kg per day in newborns longer than 32 weeks’ gestation; and 40 mg/kg per day.
in newborns 28 to 32 weeks’ gestation. It is important to be familiar with all preparations, so that proper instructions may be given to parents of children to avoid accidental overdose. Strict adherence to maximum daily dosing guidelines is important because fatal hepatic necrosis may result from acetaminophen overdose.

Ibuprofen has been the subject of several investigations in children, and analgesic efficacy in a variety of settings has been established. Ibuprofen is another widely used drug in this class, and is available in several formulations for pediatric administration. Adverse events are rare when used for a short time (less than 5 days) in treating acute pain and inflammation due to injury, infection, or illness. For analgesia, ibuprofen can be given as a single dose of 15 mg/kg orally. However, for repeated doses in children aged 6 months to 12 years, ibuprofen should be given as 10 mg/kg every 6 hours orally (maximum daily dose 40 mg/kg). Ibuprofen is available in drops (50 mg/1.25 mL), elixir (100 mg/5 mL), chewable tablets (50 mg and 100 mg), and tablets (200 mg, 400 mg, 600 mg, and 800 mg). Intravenous ibuprofen is not Food and Drug Administration (FDA) approved for the treatment of pain in pediatric patients. Of interest, an intravenous preparation of ibuprofen has been available in North America since 2006 and has been used successfully to treat patent ductus arteriosus in extremely premature infants. Although the adverse events are fewer with intravenous ibuprofen compared with indomethacin in this patient population, oliguria, renal compromise, and renal failure still occur but may be further reduced if ibuprofen is administered orally. The FDA has recently approved intravenous ibuprofen for the treatment of pain and fever in adults.

Naproxen has a longer half-life than ibuprofen, allowing it to be given every 8 to 12 hours. In adults, Naproxen 400 to 500 mg administered orally is effective in treating postoperative pain. In children, naproxen 10 mg/kg orally but not acetaminophen 20 mg/kg orally, administered 30 minutes before adenoidectomy, was found to reduce the need for opiates postoperatively. Naproxen’s safety in newborns and infants has not been established. The usual dose is 5 to 10 mg/kg orally administered every 8 to 12 hours (maximum daily dose 20 mg/kg). Naproxen is available as an elixir (125 mg/5 mL) and tablet (220 mg, 250 mg, 375 mg, and 500 mg).

The pharmacokinetics of ketorolac have now been studied in pediatric patients 0.4 to 32 weeks old, 6 to 18 months old, and 1 to 16 years old. Doses of ketorolac 0.5 mg/kg intravenously result in plasma levels considered therapeutic in adults in most children. In the United States, ketorolac is the only NSAID available for the treatment of pain in pediatric patients that can be given by intravenous as well as oral administration, making it useful in the treatment of postoperative pain in patients who are not able to take medications orally. However, caution is warranted in using ketorolac as acute renal failure, prolongation of bleeding times, and hypersensitivity reactions have been reported in pediatric patients. Some conclude that short-term use (less than 5 days) of ketorolac 0.5 mg/kg intravenously every 6 hours (maximum dose 30 mg) in children 1 to 16 years old who do not have any known contraindication to NSAID use is safe. Analgesic efficacy of ketorolac in children as a sole analgesic for minor surgery as well as an adjuvant for management of severe postoperative pain has been demonstrated in a variety of clinical settings. Ketorolac is available for oral administration as a tablet (10 mg) or intravenous administration as an injectable (15 mg/mL and 30 mg/mL).

**OPIATE ANALGESICS**

Opiates are used for the treatment of moderate to severe pain. Opiates produce analgesia primarily by binding to pre- and postsynaptic cell membranes in the central
nervous system through specific G-protein coupled opioid receptors and acting through a second messenger (cyclic adenosine monophosphate) or K⁺ channels, resulting in neuronal inhibition by decreasing excitatory neurotransmitter release from presynaptic terminals or by hyperpolarizing the postsynaptic neuron. Opioid receptors are classified as μ, κ, and δ. The μ receptor is further subdivided into subclasses μ₁, which mediates supraspinal analgesia and dependence, and μ₂, which mediates respiratory depression, intestinal dysmotility, sedation, and bradycardia. Most commonly used opiates work through μ₁-receptor interaction to produce analgesia. Opiates are classified as agonists, partial agonists, agonist-antagonists, and antagonists. Examples of the μ₁ agonists include morphine, hydromorphone, methadone, fentanyl, sufentanil, remifentanil, codeine, oxycodone, and hydrocodone. Agonist-antagonist opiates, which are agonists at one receptor type and antagonists at another receptor, include naltrexone and pentazocine. Analgesia by agonist-antagonists is mainly κ-mediated, with antagonism or partial agonism at the μ receptor. A partial agonist such as buprenorphine exerts less than full response at a receptor site. Opioid antagonists include naloxone, naltrexone, and nalmefene. Alvimopan and methylnaltrexone, two peripherally acting μ-receptor antagonists, have recently been approved for use in adult patients with opioid-induced bowel dysfunction. Side effects common to opioid agonists include respiratory depression, sedation, nausea, vomiting, pruritus, urinary retention, ileus, and constipation. Less common effects are dysphoria, hallucinations, seizures, and myoclonic movements. There is significant individual variability in the side-effect profiles of the different opiate analgesics. In the presence of unacceptable side effects, switching to a different opiate may result in lessened side effects.

Despite attempts to find a new opiate with equivalent or superior analgesia and a more favorable adverse event profile, morphine remains the standard opiate with which all others are compared. Morphine can be given through multiple routes (intravenous, oral, subcutaneous, aerosolized, intrathecal, epidural, and intra-articular). Morphine is metabolized in the liver to morphine-3-glucuronide (inactive) and morphine-6-glucuronide (active), which are both excreted by the kidneys. In general, the elimination half-life is longer and the clearance is decreased in newborns compared with older children and adults. This difference is especially pronounced in preterm neonates. In addition, less morphine is protein bound in neonates, allowing a greater proportion of unbound morphine to penetrate the brain, thus increasing the risk for respiratory depression. The elimination half-life and clearance reach adult values within 2 months of age. The optimal plasma concentration of morphine needed to achieve analgesia in children is variable based on the existing data. Therefore, careful titration of morphine is required to obtain the desired level of analgesia while monitoring side effects.

Hydromorphone is a synthetic derivative of morphine with a longer duration of action (4 to 6 hours) and elimination half-life (3 to 4 hours). Hydromorphone is approximately 10 times more lipophilic than morphine and 5 times more potent. Hydromorphone is often used as a second-line opioid to morphine and is being used more increasingly as a first-line choice, and is described as often having less associated nausea and pruritus than morphine.

Methadone is a synthetic opioid that is noted for its long elimination half-life and duration of action (12 to 36 hours). Traditionally used with opioid-dependent patients, methadone is being increasingly used in cases of acute pain to provide stable levels of opioid analgesia. Methadone has high bioavailability (85%), making it an attractive oral analgesic. The principal metabolite is morphine, which may explain its long duration of action. In addition to being a μ agonist, methadone also is an NMDA
receptor antagonist. These additional qualities make methadone an excellent long-term narcotic for chronic pain. Intraoperative use of methadone has been shown to provide prolonged analgesia in children undergoing major surgery without any increase in major adverse events. Methadone has the potential to increase the QTc in susceptible individuals, so an electrocardiogram is performed before starting the drug.

Fentanyl is a synthetic opioid that is 100 times more potent than morphine. Fentanyl is highly lipophilic, resulting in significant brain penetration. Fentanyl has a short duration of action because of redistribution out of the plasma into body tissues. Once these sites are saturated, the elimination half-life is actually quite long (233 ± 137 minutes in infants 3 to 12 months old; 244 ± 79 minutes in children; and 129 ± 42 minutes in adults). Fentanyl is highly protein bound to α1 acid glycoprotein in the plasma. Neonates have reduced levels of α1 acid glycoprotein, resulting in higher levels of free unbound fentanyl. Metabolism is through glucuronidation in the liver to inactive metabolites that are excreted by the kidney. Because of its potency, hemodynamic stability, and brief duration of action in small doses, fentanyl is an attractive analgesic for short, painful procedures in children, especially in the intensive care unit setting.

Fentanyl can be given in multiple routes: intravenous, epidural, nasal, transmucosal, and transdermal. Epidural fentanyl given as a bolus has its action at spinal sites with a segmental analgesic effect, whereas an epidural infusion acts supraspinally in a nonsegmental manner. Given nasally in a dose of 2 μg/kg, fentanyl provides good analgesia in children who are undergoing myringotomy tube insertion. Fentanyl is available in a candy matrix preparation for transmucosal administration. Transmucosal fentanyl has been used as a premedication for painful procedures, with an onset time of 20 minutes and duration of 2 hours. Fentanyl is sometimes used in opioid-tolerant cancer and sickle cell patients who have frequent bouts of acute pain. Transmucosal fentanyl is more efficient than oral administration because it bypasses the hepatic first-pass metabolism of the oral route, which reduces the availability of fentanyl by 25% to 33%. Transmucosal fentanyl provides good analgesia, but the incidence of nausea with this modality is troublesome. Fentanyl is also available as a patch for transdermal administration, but is not appropriate or recommended for acute pain management in pediatric patients because of the difficulty in quickly and safely titrating an effective dose. Transdermal fentanyl patches (12.5, 25, 50, 75, and 100 μg/h) last for 2 to 3 days. The patch has a long onset time but also a long duration that persists after it is removed.

Codeine is a commonly used oral opiate analgesic often administered in combination with acetaminophen as a tablet or oral solution. However, the parent compound has an extremely low affinity for opioid receptors, and most of the analgesic effect of this drug is due to about 10% of an administered dose being metabolized by the liver, using the P450 cytochrome oxidase pathway (CYP2D6) to produce morphine. Therefore it is not surprising that codeine is one-tenth as potent as morphine. Codeine has a bioavailability of 60% after oral administration, with an onset time of 20 to 30 minutes and an elimination half-life of 2.5 to 3 hours. Codeine is excreted in the urine.

Because codeine is dependent on hepatic CYP2D6 enzyme conversion to morphine to exert analgesic effects, several important pharmacogenetic implications need to be mentioned. There is a large difference in phenotypic expression of 2D6, with about 3% of Caucasians and 40% of people of North African descent being ultrarapid metabolizers, resulting in plasma levels of morphine 50% higher than normal. These individuals may have profound analgesia and a high incidence of opiate-induced adverse drug reactions. In contrast, 7% to 10% of Caucasians are poor metabolizers of codeine by CYP2D6, and receive little or no analgesia after its administration.
recent case report documents the serious effects of ultrarapid metabolization in a neonate who died after exposure to breast milk from his mother who was prescribed oral codeine.\textsuperscript{73}

Oxycodone and hydrocodone are oral analgesics commonly combined with acetaminophen in tablet or liquid form. A new formulation of oxycodone combined with ibuprofen is now available. Oxycodone also is available alone in tablet or liquid form. Caution is advised when prescribing oxycodone liquid because it comes in 1 mg/mL and 20 mg/mL strengths. The usual dosing of oxycodone is 0.05 to 0.15 mg/kg every 4 to 6 hours as needed for pain relief. These analgesics are approximately 10 times more potent than oral codeine. The bioavailability is 60\% after oral administration, with an onset time of 20 to 30 minutes and duration of 4 to 5 hours. Oxycodone and hydrocodone are metabolized in the liver. Oxycodone produces an active metabolite, oxymorphone, that can accumulate in renal failure.\textsuperscript{74} Sustained-release oxycodone is available for more prolonged analgesic needs, but negative publicity over its abuse has made it less desirable to parents.\textsuperscript{75} Hydrocodone dosing is similar to oxycodone but because it is combined with acetaminophen in an oral solution (acetaminophen 500 mg and hydrocodone 7.5 mg per 15 mL), its usefulness in smaller children is limited.

Nalbuphine is a $\kappa$ agonist and a $\mu$ antagonist. Nalbuphine produces equivalent analgesia to morphine up to doses of 200 $\mu$g/kg but increasing the dose beyond this does not result in further analgesia. $\kappa$-Mediated side effects of sedation, dysphoria, or euphoria are likely at higher doses. Nalbuphine is metabolized mainly in the liver and has a half-life of approximately 5 hours. Nalbuphine is usually given intravenously. When given orally, it has a bioavailability of only 20\% to 25\%. Nalbuphine is often used to antagonize $\mu$-mediated side effects from $\mu$-agonist opioids, especially pruritus and urinary retention.\textsuperscript{76,77} Care is needed when using nalbuphine in opioid-dependent children in order not to induce opioid withdrawal.

Naloxone is an antagonist at all opioid receptors. Naloxone is used emergently for respiratory depression at a dose of up to 10 $\mu$g/kg intravenous. Naloxone can also be used to antagonize pruritus and opioid-induced nausea and vomiting (0.25–0.5 $\mu$g/kg/h infusion).\textsuperscript{76,78} Naloxone is metabolized in the liver and has an elimination half-life of 60 minutes.\textsuperscript{54} Because this is a shorter half-life than the $\mu$ agonists it is meant to counteract, continued monitoring of the patient is mandatory. Severe withdrawal can occur when naloxone is given to opioid-dependent patients.

Although not yet approved for use in pediatric patients, alvimopan and methylnaltrexone are approved for use in adults with opiate-induced bowel dysfunction either due to chronic opiate therapy during palliative care (methylnaltrexone) or postoperative ileus after bowel resection surgery (alvimopan).\textsuperscript{79,80} Both drugs bind peripheral $\mu$ receptors throughout the gastrointestinal tract, but do not reverse central analgesic effects of $\mu$ agonists or precipitate withdrawal in opiate-dependant individuals in clinically relevant doses. Methylnaltrexone does not cross the blood-brain barrier due to a highly polar methyl group substitution on the structurally similar compound, naltrexone. Alvimopan is a large, highly polar compound that also does not cross the blood-brain barrier in clinically useful doses.

Tramadol is a moderately potent analgesic that is structurally related to codeine. Tramadol provides analgesia through weak $\mu$-opioid receptor binding, and central inhibition of norepinephrine and serotonin reuptake. Tramadol has an affinity for opioid receptors about 6000 times less potent than morphine, but an active metabolite provides the main opioid analgesic effects, which are only four times less potent than morphine.\textsuperscript{81} As an analogue to codeine, tramadol similarly undergoes metabolism by the CYP2D6 system. This metabolism puts the utility of the drug at an uncertain
level because of phenotypic differences between extensive metabolizers, poor metabolizers, intermediate metabolizers, and ultrarapid metabolizers. In neonates and infants, the CYP2D6 activity increases with maturity, so even genotype extensive metabolizers at this age should be considered to have a poor phenotype response to tramadol until hepatic function improves.82

As an atypical analgesic with opioid receptor binding, tramadol has a decreased side-effect profile of sedation and respiratory depression, and dependence compared with other opiate receptor agonists. However, there is a high incidence of postoperative nausea and vomiting, up to 50%, which limits its usefulness.53 Other side effects include dizziness, pruritus, and constipation. Tramadol is associated with seizures, and should be avoided in patients with a known history of seizure activity or head trauma. In general, tramadol is safe and effective, and can be used for mild to moderate pain relief in children.84,85

OTHER ANALGESICS

**Ketamine**

Ketamine is a phencyclidine derivative and a dissociative anesthetic. Ketamine is a potent analgesic in subanesthetic doses, and is often used for short, painful procedures in children in the emergency room and intensive care unit settings.86,87 Ketamine can be administered intravenously, orally, rectally, and intramuscularly. Because of increased secretions and possible dysphoric effects, ketamine is often combined with an anticholinergic agent and a benzodiazepine. Because of elevations of cerebral blood flow and oxygen consumption, ketamine is not recommended in children who have decreased intracranial compliance. The analgesic effects of ketamine are mediated by NMDA receptor antagonism and possibly μ-receptor agonism. Oral bioavailability is 20% to 25%. Ketamine is highly lipid soluble, with rapid redistribution. Ketamine is N-demethylated in the liver by the cytochrome P450 system.88 Intravenous doses of 0.25 to 0.5 mg/kg can produce intense analgesia for 10 to 15 minutes, although the elimination half-life is 2 to 3 hours. There is increasing literature on the intraoperative and postoperative use of ketamine as an adjunct to opioid analgesia in adults.89 Ketamine can be especially useful in opioid-tolerant patients undergoing procedures.

**α-2 Agonists**

Clonidine is an α2-adrenergic agonist with demonstrated anxiolytic and analgesic benefits in children during the perioperative period.90 Given orally preoperatively (4 μg/kg), clonidine decreases intraoperative anesthetic requirements and postoperative opioid consumption.91,92 Clonidine has been administered intravenously (2 μg/kg) and has been used as an adjuvant to local anesthetics to prolong analgesia or improve analgesia in caudal (1–2 μg/kg), epidural (1 μg/kg), peripheral nerve block (1 μg/kg), and spinal anesthesia (1 μg/kg).90,93–99 When compared with opiates as adjuncts to local anesthetics in continuous epidural infusions, clonidine seems to provide equivalent analgesia and reduce the incidence of opiate-related adverse events (nausea, vomiting, and pruritus).94,95 Clonidine 1 μg/kg as an adjunct to bupivacaine or ropivacaine during peripheral nerve block prolongs the duration of analgesia, but may also increase the incidence of motor block.97

Dexmedetomidine is a centrally acting α2 receptor agonist with an affinity for the receptor that is 8 times that of clonidine.92 Initially studied as a sedative for adults receiving mechanical ventilation, there is now literature on the use of dexmedetomidine in children.92,100–104 In laboratory studies, α2-agonist analgesia mediated in the
spinal cord is possible even in neonates and infants.\textsuperscript{105,106} Although dexmedetomidine is being studied primarily as a sedative, it seems to have analgesic effects in that opioid requirements are decreased with dexmedetomidine therapy. In addition to providing some analgesic benefits and excellent sedation, dexmedetomidine is associated with minimal respiratory depression.

\textbf{\textit{N}-methyl-\textit{D}-Aspartate Receptor Antagonists}

The NMDA receptor has long been known to play a key role in the development of central sensitization following tissue injuries that result in pain.\textsuperscript{107} Ketamine, dextromethorphan, methadone, and magnesium are all known to be NMDA receptor antagonists, and there have been numerous efforts to determine if 3 of these agents (all but methadone) possess any preventative analgesic benefits in the perioperative period. A recent review of these studies determined the evidence was best for dextromethorphan (68\% of dextromethorphan and 57\% of ketamine studies indicated some preventative analgesic benefit could be demonstrated but none of the studies of magnesium revealed such a benefit).\textsuperscript{108} However, even when a benefit was found, others suggested it may be of little clinical significance.\textsuperscript{109} The evidence for analgesic benefit of dextromethorphan in pediatric patients is contradictory.\textsuperscript{110–113} At this time the authors of this review cannot recommend the routine use of dextromethorphan in postoperative pain management protocols for children.

\textbf{\textit{\gamma}-Aminobutyric Acid Agonists}

Benzodiazepines and antispasmodic medications have long been used as adjuvants in the treatment of acute pain. Medical conditions such as cerebral palsy with spastic diplegia, hemiplegia, or quadriplegia, and surgical procedures associated with painful postoperative muscle spasms such as lower extremity tendon releases are situations whereby these agents are very useful, because muscle spasm can lead to tension on surgical incisions, leading to more pain and muscle spasm. But benzodiazepines are also useful in the relief of fear and anxiety in patients without these conditions. Fear and anxiety are factors that can result in magnification of postoperative pain. Also of interest is new literature illuminating the role of \textit{\gamma}-aminobutyric acid (GABA) in the transmission and perception of pain. GABA agonists have shown antinociceptive activity in animal models of acute, inflammatory, and neuropathic pain.\textsuperscript{114} As the primary inhibitory neurotransmitter, GABA is widely distributed throughout the central nervous system, and has many clinical functions beyond pain control, such as anxiolysis, amnesia, muscle relaxation, and anticonvulsant activity. GABA receptors are located along pain transmission pathways from primary afferent A-\textit{\delta} and C fibers through the spinothalamic tract, and in supraspinal sites like the thalamus and periaqueductal gray matter that are involved with pain perception.\textsuperscript{115} Being so ubiquitous is a detriment, as current medications such as baclofen, diazepam, midazolam, and lorazepam are not specific GABA agonists. GABA agonists have serious side effects, primarily sedation and tolerance, which can limit their clinical usefulness. More specific GABA agonists are being developed that do not cause tolerance (CGP44532) and do not cause sedation (CGP35024) at antinociceptive doses.\textsuperscript{115}

In vitro studies have demonstrated that several benzodiazepines interact with \textkappa receptors but not \textmu receptors, and this may explain the clinical observation of analgesic efficacy of benzodiazepines administered in the intrathecal and epidural spaces.\textsuperscript{116} Caudal midazolam 50 \textmu g/kg given alone or in combination with 0.25\% bupivacaine 1 mL/kg reduced postsurgical pain in children undergoing unilateral inguinal hernia repair.\textsuperscript{117} However, before this intervention can be advocated, more studies to determine safety as well as efficacy are needed.
Diazepam and baclofen are two common GABA agonists used in pain management. Diazepam is administered orally (0.1–0.2 mg/kg every 6 hours) or intravenously (0.05–0.1 mg/kg every 6 hours) for centrally mediated muscle relaxation. Baclofen is most often used in chronic painful conditions related to muscle spasticity. Continuous intra-thecal administration of minute doses by an implantable pump is necessary for severe congenital spasms, but oral administration can be used to supplement the infusion or for acute exacerbations of pain due to muscle spasticity. Both medications can cause sedation and respiratory depression, which are increased with the concomitant administration of opiates for pain. Flumazenil (0.01–0.02 mg/kg up to maximum 0.2 mg per dose, with repeat dosing every minute up to 1 mg maximum total dose) can acutely antagonize a diazepam overdose. The acetylcholinesterase inhibitor, physostigmine, is a controversial antagonist of excessive sedation and coma caused by baclofen toxicity. Several case series report contradictory results regarding physostigmine reversal of sedation after accidental baclofen overdose. Knowledge of GABA agonist benefits and side effects is key to their safe integration into a comprehensive acute pain management plan.

**Local Anesthetics**

Local anesthetics reversibly bind sodium channels. Once bound, the channels are inactive and stop the propagation of nerve signals to the brain. These drugs prevent the transmission of pain. The two classes of local anesthetics are amides and esters, which describe the central bond between the aromatic ring and amine group found in each class. Amides are metabolized by the liver, whereas esters are broken down by plasma esterases. Carl Koller, in 1884, was the first physician to use a local anesthetic for surgical anesthesia. Koller applied a cocaine solution topically for ophthalmologic surgery. Today local anesthetics are administered topically, subcutaneously, transdermally, intravenously, perineurally, or administered in the intrathecal or epidural space.

The selection of local anesthetic depends on the metabolic maturity of the child as well as the delivery site. In children, tetracaine and bupivacaine are most commonly used intrathecally due to their prolonged half-lives, because neonates and infants have higher rates of cerebrospinal fluid (CSF) turnover and larger ratios of CSF volume to weight, which decrease the effectiveness of local anesthetics. Epidurally, ropivacaine, bupivacaine, and 2-chloroprocaine are commonly used. Ropivacaine has replaced bupivacaine at the authors’ institution due to decreased toxicity in neonates and infants. Bosenberg and colleagues showed that although ropivacaine provided effective analgesia in infants, the plasma concentration of unbound ropivacaine was not influenced by the duration of infusion for up to 48 to 72 hours. This result contrasts with bupivacaine in infants, in whom the unbound concentration of bupivacaine (considered the toxic moiety) during epidural infusion increased until the end point of 48 hours. 2-Chloroprocaine avoids much of the potential toxicity of amides because plasma esterase activity, though measurably reduced in neonates, is sufficient for ester metabolism. Besides a larger therapeutic window, ropivacaine has a better side-effect profile, with less motor blockade than an equipotent analgesic dose of bupivacaine.

Toxicity of local anesthetics and the technical expertise required to deliver the drugs to the site of action are the two main reasons local anesthetic use is not as ubiquitous in the pediatric population. Table 1 lists commonly accepted maximum doses of local anesthetics. With the advent of lipid infusions for acute local anesthetic toxicity, the use of regional techniques is expanding in children. There is a case report of
a successful treatment of local anesthetic overdose with 20% lipid infusion in a child receiving a regional anesthetic for postoperative pain control.124

When using local anesthetics to block the transmission of pain, preventing systemic toxicity requires more vigilance with children. Most regional techniques are performed under general anesthesia or heavy sedation to allow the placement of a needle the child would not otherwise tolerate. This technique eliminates many of the signs of central nervous system toxicity such as agitation, confusion, twitching, drowsiness, apnea, and sensory disturbances (tinnitus, metallic taste, diplopia, circumoral paresthesias). Cardiovascular signs such as hypotension, bradycardia, and ventricular arrhythmias might be the only signs of acute toxicity in an anesthetized child. Measures taken to prevent toxicity include gentle aspiration on the syringe before incremental, small-volume injections, using pharmacologic markers like epinephrine when appropriate, and monitoring the patient until the peak blood concentration occurs.

**TECHNIQUES FOR POSTOPERATIVE PAIN MANAGEMENT**

**Measuring Pain**

Just as it would be inconceivable to manage hypertension without knowing the patient’s blood pressure, to effectively manage pain one must have a gauge of the patient’s pain intensity. Pain assessment tools are an essential prerequisite for pain treatment plans in children. Tremendous advances have been made in recent years, but assessing the perceived pain in neonates, infants, and nonverbal or developmentally delayed children is still a difficult challenge. There are dozens of pain assessment measures now available to guide clinicians in managing pain. Table 2 lists examples of pediatric pain scales. Children of 8 years and older can reliably report pain on the visual analog scale used in adult pain management. Younger children between 3 and 7 years of age can report pain using face scales (a series of drawings depicting increasing levels of distress) after undergoing surgery.131 The younger the child, the less likely he or she can make clear delineations between levels of pain using pain scales.132

For neonates and infants, pain assessment tools often rely on behavioral observations by caregivers and physiologic changes in the patient, which is often the case in cognitively impaired children as well. Problems arise in that pain is a subjective experience that cannot completely translate from patient to patient. An infant’s behavioral response to a heel lance with facial grimacing, crying, and motor activity might mimic the behavior found in another infant who is experiencing hunger. Most infants with colic manifest pain facies that rate highly in infant focused pain scales, yet pain management plans are not offered to these children.133 Another problem is that

<table>
<thead>
<tr>
<th>Table 1 Local anesthetic maximal doses (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>2-Chloroprocaine</td>
</tr>
<tr>
<td>Lidocaine</td>
</tr>
<tr>
<td>Bupivacaine</td>
</tr>
<tr>
<td>Ropivacaine</td>
</tr>
<tr>
<td>Levobupivacaine</td>
</tr>
</tbody>
</table>

Abbreviation: NR, not recommended.
physiologic responses such as an increased heart rate, which could be a sign of pain or hypovolemia, are not specific or sensitive to pain alone. However, due to the lack of a reliable, validated, biologic marker, current pediatric pain scales must be used and updated as research allows.

**Postoperative Pain Management Strategies**

Traditionally acute pediatric pain was managed with opiate analgesics alone, but fear of severe adverse events such as central nervous system and respiratory depression related to their use often resulted in inadequate pain control. Now, successful pain management strategies target several of the complex elements of pain transduction, transmission, modulation, and perception. Balanced or multimodal analgesia plans with NSAIDs acting on the periphery, regional anesthetic blockade of peripheral nerves, nerve roots, or spinal cord, and opiates acting centrally have become increasingly popular to maximize acute pain control in pediatric patients. This balanced approach can minimize the occurrence of adverse drug reactions attributed to each component of the multimodal plan because generally lower doses of each component are required to produce equivalent or superior analgesia. Shortfalls in the opioid-only strategy such as delays in dosing, inadequate dosing, intramuscular route of delivery, and failure to recognize an individual patient’s pain can all be ameliorated by long-acting regional techniques including continuous peripheral nerve catheters, scheduled dosing of NSAIDs, patient-controlled analgesia, and management of breakthrough pain with additional opiates.

Individual children have widely variable pain perceptions of similar conditions, resulting in different analgesic needs. These differences are based on past experiences, culture, and genetics. Individuals will also vary in pain control requirements depending on time, activity, and level of emotional stress. At rest, the perceived pain is usually less than when the child is changing position, taking a deep breath, receiving needed nursing care, undergoing a dressing change, or undergoing diagnostic and therapeutic procedures. Likewise, anxiety and pain can increase when the child must undergo multiple procedures, diagnostic tests, or participate in regular physical therapy or routine nursing care and physical examinations. Effective pain management plans take a proactive position in dealing with background pain, and

<table>
<thead>
<tr>
<th>Scale</th>
<th>Type</th>
<th>Ages</th>
<th>Scoring Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIPP&lt;sup&gt;125&lt;/sup&gt;</td>
<td>Behavioral and physiologic parameters</td>
<td>Term and preterm infants</td>
<td>Gestational age, Behavioral state, Heart rate, SpO&lt;sub&gt;2&lt;/sub&gt;, Facial expression</td>
</tr>
<tr>
<td>CRIES&lt;sup&gt;126&lt;/sup&gt;</td>
<td>Behavioral and physiologic parameters</td>
<td>32–60 weeks</td>
<td>Crying, increased O&lt;sub&gt;2&lt;/sub&gt;, Increased vital signs, Expression, Sleeplessness</td>
</tr>
<tr>
<td>FLACC&lt;sup&gt;127&lt;/sup&gt;</td>
<td>Behavioral parameters</td>
<td>&lt;3 years or unable to self-report</td>
<td>Face, Legs, Activity, Cry, Consolability</td>
</tr>
<tr>
<td>Faces&lt;sup&gt;128&lt;/sup&gt;</td>
<td>Self-report</td>
<td>3–12 years</td>
<td>Happy face to saddest face yield numeric 0–10 score</td>
</tr>
<tr>
<td>VAS&lt;sup&gt;129,130&lt;/sup&gt;</td>
<td>Self-report</td>
<td>Children &gt;7 years</td>
<td>0 = no pain, 10 = maximum pain</td>
</tr>
</tbody>
</table>

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<sup>125</sup> Kraemer & Rose
<sup>126</sup> Kraemer & Rose
<sup>127</sup> Kraemer & Rose
<sup>128</sup> Kraemer & Rose
<sup>129</sup> Kraemer & Rose
<sup>130</sup> Kraemer & Rose
have allowances to provide adequate analgesia for breakthrough pain experienced for any reason.

**Patient-Controlled Analgesia**

Patient-controlled analgesia (PCA) is an excellent delivery system for treating moderate to severe pain in children as young as 5 years old in some circumstances, with proper education and routinely in normal 7-year-old children. There are reports of younger children successfully using PCA, especially in patients with chronic needs. When used with adequate monitoring, PCA is a safe, effective method of delivering opioids. PCA has a high patient, family, and staff satisfaction. The high rate of success is related to meeting patient needs. PCA provides a highly reliable dispensing system that the patient can use to titrate opioids to individual needs. Patients can receive immediate relief of pain without being subjected to the inherent delays of hospital care that are out of their control, such as understaffing and other patients' need for more emergent attention. More responsibility and control for the minute to minute management of pain is given to the patient who can titrate down their demand for opiates during periods of lesser pain at rest, or increase their demand for opiates with more frequent button pushes when they are experiencing more pain associated with various activities. The patient feels the pain and self-administers medication until a satisfactory improvement is perceived.

Opioids have serious side effects that are mitigated with the appropriate use of PCA. Most institutions have monitoring requirements in place for the safe delivery of narcotics. Minimum safety measures should include continuous respiratory rate, pulse oximetry, heart rate with frequent blood pressure monitoring, pain assessment, and level of consciousness. As the blood concentration of the infused opiate increases due to increased demand from the patient, the side effects of somnolence and sedation become more clinically significant and will prevent the child from administering an opiate overdose. In this situation it is understood that the patient is the only one to activate the PCA demand button. In other situations, nurses and parents can safely deliver narcotics via PCA to children younger than 6 years or with developmental delay, but different parameters must be set to prevent accidental overdose by caregivers. A recent study showed that PCA by proxy had the same prevalence of adverse events compared with PCA by the patient, but the need for rescue intervention was greater in patients on PCA by proxy. By allowing the patient or proxy to control pain with frequent, small doses of medications, PCA systems maintain a narrower range of plasma concentration of opioids with lower peaks and higher troughs, resulting in less respiratory and central nervous system depression and more consistent pain control.

The infusion pump is programmed to deliver a specified (demand) dose of medication when the system is activated, typically by depressing a button. The minimum time between delivered doses is the lockout time, designed to prevent drug accumulation and to allow the effect of the drug to begin before a second dose is administered. During the lockout time, no demand doses are delivered regardless of how many times the button is pushed. Finally, a total maximum dose is set as a final precaution against overdosing. The total maximum dose is usually calculated in 1- or 4-hour limits. The pump will not administer any medication once this maximum dose is reached, until time passes to allow for the patient to eliminate the narcotic. The pump records data on the patient's drug usage including number of attempts and actual opioid injections. This information can be useful in changing the parameters on the pump to achieve better pain control.
Basal infusions are another component of PCA systems. Basal infusions allow for a continuous infusion of medication independent of the demand dosing. The goal of the basal infusion is to provide some nominal pain relief during sleep when the patient would not be activating the PCA pump, and has been advocated by some investigators for pediatric patients expected to experience severe postoperative pain, such as adolescents after posterior spinal fusion.\textsuperscript{134} This infusion would seem to prevent acute troughs in blood levels and therefore reasonably blunt an acute exacerbation of pain. However, there is literature that shows no differences in pain scores or demand dosing between patients with or without basal infusions, and that basal infusions constitute a risk factor for increasing adverse respiratory events in children.\textsuperscript{137–139} Opioid-naïve patients are especially at risk with basal infusions, which should most likely be avoided except in rare instances like posterior spinal fusion. Although potentially useful, basal infusions circumvent the inherent safety balance between PCA usage in an alert patient and a narcotic-induced somnolence to prevent overuse of the PCA system. Table 3 lists the PCA dosing guidelines for several opiate analgesics.

As safe and effective as the PCA infusion is, there are problems that need to be addressed. Patients invariably will maximize the PCA and still need more opioid for pain control. Medications used for other purposes might sedate the patient, thus preventing him or her from using the PCA. Finally, the pump itself might fail. All of these situations and others require orders for the nurse to give additional pain relief, usually the same medication as found in the pump, given intravenously every 3 hours for severe, breakthrough pain. Side effects of the opioids are often encountered even with frequent, small doses so rescue orders are part of the authors’ PCA treatment plan. For severe respiratory depression, naloxone\textsuperscript{10} \textmu g/kg intravenously will reverse the opioid effect. The half-life of the opioid antagonist is usually shorter than the offending opioid, so vigilance is necessary to prevent a recurrence of sedation. Ondansetron \text{100 to 150} \textmu g/kg intravenously every 8 hours is used as first-line treatment for nausea and vomiting. For opioid-induced pruritus, nalbuphine \text{50} \mu g/kg every 4 hours can be effective, as well as naloxone infusion of \text{0.25} \mu g/kg every hour for severe pruritus, especially with neuraxial opioids. Adjunct medications for inflammation and muscle spasms are also routinely ordered with PCA.

**Continuous Intravenous Opiate Infusion**

In young children with moderate to severe pain who cannot use a PCA due to age, physical disability, or cognitive impairment, a continuous intravenous (CIV) infusion can provide stable pain relief. Steady plasma drug levels are one benefit compared with intermittent bolus dosing. There is a decreased reliance on often busy nursing staff. As with PCA, rescue medication must be ordered for breakthrough pain. Because of the pharmacokinetics of infusions, a bolus dose is usually given as the

<table>
<thead>
<tr>
<th>Drug</th>
<th>Demand Dose (\mu g/kg)</th>
<th>Lockout Interval (min)</th>
<th>Basal Infusion (\mu g/kg/h)</th>
<th>1-h/4-h Limit (\mu g/kg)</th>
<th>As Needed IV Rescue Dose (\mu g/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>20</td>
<td>8–10</td>
<td>0–20</td>
<td>100/300</td>
<td>50</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>4</td>
<td>8–10</td>
<td>0–4</td>
<td>20/60</td>
<td>10</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.5</td>
<td>6–8</td>
<td>0–0.5</td>
<td>2.5/4</td>
<td>0.5–1.0</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>20</td>
<td>8–10</td>
<td>0–20</td>
<td>100/300</td>
<td>50</td>
</tr>
</tbody>
</table>
infusion is started to achieve a therapeutic drug level. Careful, slow titration is warranted in neonates and infants as the pharmacokinetics of narcotics differ widely according to age. Morphine has an elimination half-life of 9 hours in preterm infants, 6.5 hours in neonates, and 2 hours in older infants and children. The CIV frequently provides a foundation for pain control at rest, but any increase in activity or nursing care necessitates intermittent administration of rescue analgesic medication for so-called breakthrough pain (Table 4).

**Epidural Analgesia**

Continuous epidural analgesia (CEA) has become an indispensable tool for managing severe postoperative pain in neonates, infants, and children after a wide variety of surgical procedures. CEA reduces the surgical stress response and hospitalization time, and may improve outcomes in specific pediatric populations. Dolin and colleagues collected pooled postoperative pain scores from 165 studies and found

<table>
<thead>
<tr>
<th>Table 4: Opioid Dosing Regimens</th>
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<tbody>
<tr>
<td><strong>Opioid</strong></td>
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<tr>
<td>Morphine</td>
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<td></td>
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<tr>
<td>Hydromorphone</td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Methadone</td>
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<tr>
<td>Nalbuphine</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Codeine</td>
</tr>
<tr>
<td>Oxycodone</td>
</tr>
<tr>
<td>Hydrocodone</td>
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</tbody>
</table>
that the mean incidence of moderate to severe pain in patients with a PCA was 35.8% and 10.4%, whereas patients with CEA had incidences of 20.9% and 7.8%.

The placement of the tip of the epidural catheter close to the center of the surgical dermatomes to be blocked is an essential prerequisite for adequate pain relief, especially in neonates when the potential for local anesthetic toxicity greatly reduces the volume of epidural infusate that can be safely administered. In infants, a caudal insertion site for the catheter is frequently chosen because a styled catheter can be easily advanced to thoracic levels. Another insertion point is the interspace of L5 and S1, called the modified midline Taylor approach, which also allows for a relatively easy advancement of the catheter to high lumbar and thoracic levels.\(^\text{143}\) Whenever an epidural catheter is threaded from a caudal or lower lumbar entry site to a thoracic level, intraoperative confirmation of the correct desired position of the epidural catheter is performed by radiography after administration of a nonionic contrast medium (0.3 mL of Omnipaque 180 [iohexol], GE Health Care), or by fluoroscopy with an opaque stylet in place, or with contrast. Tsui and colleagues\(^\text{144}\) have described a technique using nerve stimulation to confirm epidural catheter placement. Ultrasound-guided epidural catheter insertion and placement is another safe method in infants.\(^\text{145}\)

Most, if not all epidural catheters are placed under general anesthesia. A large study in Great Britain and Ireland, consisting of 10,633 epidurals in children, did not correlate any problems to the use of general anesthesia while placing the epidurals.\(^\text{146}\) Of course, precautions still are necessary when the child is anesthetized to ensure incorrect placement. Several anatomic differences between children and adults regarding epidural catheter placement merit discussion. The distance from skin to the epidural space or depth is the most obvious difference between adults and children. Other anatomic differences are the softer ligamentum flavum in children, making a false loss of resistance during placement of the epidural catheter more common in children. The conus medullaris ends at L3 in neonates and does not reach the adult L1 level until 1 year of age. Infants have a higher CSF volume to weight ratio, as well as a faster rate of CSF production and absorption than adults. Locating the epidural space with a loss-of-resistance technique should be conducted with saline as opposed to air to avoid air embolus, cord compression, or a patchy block.\(^\text{147}\)

The risk of local anesthetic toxicity is one of many problems that need to be continually monitored during CEA. A dedicated team of physicians and nurses should be immediately available to manage any emergent problems with pain control or side effects in patients with CEA. The epidural insertion site should be evaluated daily by a member of the pain management team for signs of infection. Standardized protocols and order sets include patient monitoring parameters as well as neurologic assessment (mental status, motor check, and pain scores) every 4 hours. Standard safety equipment includes a working intravenous line, breathing circuit, mask, oxygen, and suction at the bedside for each patient with a CEA. Instructions for the patient’s nurse on contacting members of the pain management service should be readily available. A specialized team of caregivers can anticipate medication side effects of CEA and proactively address these problems.

A common problem with CEA includes inadequate pain control. This problem is often due to incorrect dermatomal placement, catheter problems (kinking, obstruction, leaking, or breaking) pump malfunction, insufficient solution concentration/rate, or catheter migration/dislodgement from the original location. First, testing the catheter with a safe, short-acting bolus medication to ensure its continued usefulness is recommended (Table 5). If the epidural is functioning, then changing the rate or concentration, or adding adjuvants within the infusion may improve pain control.
Inadequate or failed CEA should be expeditiously replaced with another strategy for pain control such as CIV or PCA in appropriate children. The medications used in CEA, specifically the opiates, are significant sources of side effects. Motor block is a late sign of compartment syndrome and also a direct effect of local anesthetics. Decreasing the concentration of the local anesthetic solution and also the rate can allow a sensory block and pain relief to remain without the disconcerting feeling of paralysis. Systemic local anesthetic toxicity is rare with infusions, but infants with immature hepatic function and decreased protein binding are at a greater risk. Table 6 lists CEA dosing guidelines. Opioid adjuvants to CEA infusions commonly cause nausea, vomiting, pruritus, urinary retention, sedation, and respiratory depression. Reducing the amount of opiate in the epidural solution is an option, but medications to counteract the opioid-induced side effects are usually required, as if the opiates were given intravenously.

Patient-controlled epidural analgesia (PCEA) combines the benefits of CEA and PCA. Children 5 years or older have the ability to effectively use this technique. As with PCA, the analgesic benefit is that the patient can adjust the pain medication to meet an increase in pain sensation due to episodes of increased activity or care. The basal infusion is administered at 0.1 to 0.2 mL/kg/h. Demand doses range form 0.05 to 0.1 mL/kg with a lockout time of 20 to 30 minutes, to accrue a total dose of 0.2 to 0.4 mL/kg/h (the total hourly dose should not exceed 20 mL).

Intrathecal Morphine

Intrathecal morphine has been used for many years to treat pain in children following a variety of surgical procedures. An early report using relatively high doses of morphine 20 μg/kg (n = 29) and 30 μg/kg (n = 27) reported satisfactory analgesia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ropivacaine (mg/mL)</th>
<th>Fentanyl (μg/mL)</th>
<th>Morphine (μg/mL)</th>
<th>Clonidine (μg/mL)</th>
<th>Rate Ropivacaine (max. mg/kg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn 0–2 months</td>
<td>1 (0.5–1.0)</td>
<td>0.2</td>
<td>NR</td>
<td>0.04</td>
<td>0.2 (0.15–0.25)</td>
</tr>
<tr>
<td>Infant</td>
<td>1 (0.5–1.5)</td>
<td>2 (2–5)</td>
<td>25</td>
<td>0.4</td>
<td>0.25 (0.15–0.3)</td>
</tr>
<tr>
<td>Child (lumbar)</td>
<td>1.5 (1–2)</td>
<td>2 (2–5)</td>
<td>25–50</td>
<td>0.4–0.6</td>
<td>0.3 (0.2–0.4)</td>
</tr>
<tr>
<td>Child (thoracic)</td>
<td>1.5 (1–2)</td>
<td>2 (2–5)</td>
<td>NR</td>
<td>0.4–0.6</td>
<td>0.3 (0.2–0.4)</td>
</tr>
</tbody>
</table>

Abbreviation: NR, not recommended.

Table 5
Example of bolus testing of epidural

<table>
<thead>
<tr>
<th>3% Chloroprocaine Epidural Test Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Weight (kg)</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>0–10</td>
</tr>
<tr>
<td>11–25</td>
</tr>
<tr>
<td>26–40</td>
</tr>
<tr>
<td>41–70</td>
</tr>
<tr>
<td>&gt;70</td>
</tr>
</tbody>
</table>
of 22 hours or more in children following open heart surgery. Clinically significant respiratory depression occurred between 3.5 and 4.5 hours after intrathecal morphine administration in six patients receiving morphine 30 μg/kg versus three children who received the lower dose. Since this time several reports comparing high- and low-dose intrathecal morphine for postsurgical pain in children have shown that analgesic benefit is not improved by increasing the dose of intrathecal morphine. Intrathecal morphine 2 or 5 μg/kg administered intraoperatively provided equivalent analgesia and side-effect profiles in children after spinal fusion surgery, but the children who received morphine 5 μg/kg had lower blood loss. Intrathecal morphine 4 to 5 μg/kg provided satisfactory analgesia in 187 children after a variety of surgical procedures, with minimal respiratory depression. Thus it seems that the ideal dose of intrathecal morphine is 2 to 5 μg/kg.

### Regional Anesthesia

Regional anesthesia in children is increasingly popular, not only as an adjunct to anesthesia but as a technique for managing postoperative pain. One reason for the renewed interest in pediatric regional anesthesia is that the use of nerve stimulators and ultrasound has improved the success rate of nerve blocks and theoretically may make placement of blocks safer in anesthetized children. This differs from the standard in adults whereby blocks are placed under minimal to no sedation so that one can confirm analgesia, and so that the adult patients can communicate the occurrence of paresthesias if they occur, or symptoms indicate intravascular injection of local anesthetics. Giaufre and colleagues presented data in more than 9000 peripheral nerve and regional field block techniques, and reported zero complications despite the fact that 89% of the patients were under “light general anesthesia.” Moreover, studies indicate that in animals use of volatile anesthetics for general anesthesia confers some protection against cardiotoxicity in the event of an accidental overdose of local anesthetic. Using ultrasound is safe and has been shown to be efficacious in pediatric regional anesthesia. Ultrasound guidance of regional anesthetic blockade is reviewed in greater detail elsewhere in this issue. Whenever possible, regional anesthesia should be used as part of a comprehensive pediatric pain management program, but implementation should always focus on safety and minimizing risks.

The caudal block is one of the most commonly performed regional anesthetics in pediatrics. For the majority of hernia surgery, the caudal block is the technique of choice, but it can also yield excellent analgesia for lower extremity surgery, and has been reported for patent ductus arteriosus ligation. Typical doses include ropivacaine 0.1% to 0.2% and bupivacaine 0.125% to 0.25% with epinephrine in volumes of 0.5 to 2 mL/kg (not to exceed toxic doses measured in mg/kg). The relatively short duration of analgesia following a single-injection block can be mitigated adding clonidine, 1 to 2 μg/kg, to prolong the block. Motor block with higher concentrations of bupivacaine are a major complaint in ambulatory children. One of the most frequent complications with caudals is inadvertent needle placement into the vasculature, intrathecal space, or even bone in very young children; yet, this rate remains low (overall morbidity 0.7 per 1000), due to methods of detection including ultrasound visualization, aspiration of the needle or catheter, and test dosing with epinephrine. The caudal block is a mainstay of pediatric regional anesthesia, with a long history of safety.

All peripheral nerve blocks used in adult patients can be performed in children too. Table 7 lists examples of common peripheral nerve blocks. Pediatric regional anesthesia is incorporating single-shot and continuous (via percutaneously placed
catheters) nerve blocks as part of a balanced pain management strategy aimed at reducing side effects and inefficiencies associated with traditional opiate-based plans. Prolonged analgesia via continuous nerve blocks or very long duration local anesthetics will allow patients to recover safely at home. This therapy will require standardized, advanced ultrasound-guided regional anesthesia training and newer pharmacologic treatments to come into routine practice.162,163

**SUMMARY**

During the past 2 to 3 decades, pediatric pain management has gained tremendous knowledge with respect to the understanding of developmental neurobiology, developmental pharmacology, the use of analgesics in children, the use of regional techniques in children, and of the psychological needs of children in pain. A wide range of opioid, NSAID, and nontraditional medications are available to treat a variety of pain types.

Teams of health care professionals specializing in managing pain in children are designing pain management plans for their patients that are proactive, and not only covering baseline pain but also anticipating breakthrough pain associated with nursing care, physical therapy, wound care, and diagnostic and therapeutic procedures, and prescribing contingent analgesics to be administered if needed during these events. Titration is an optimal way to approach opioid dosing, to maximize comfort and safety while minimizing side effects. Careful assessment and reassessment of pain and response to analgesics is required to tailor care to individual patients. Many adverse effects of opioids are idiosyncratic, so changing from one to another can resolve many problems such as itching, dysphoria, and nausea. Children are now benefiting from many techniques for effective management of pain in adult patients (PCA, CEA, PCEA, and continuous peripheral nerve blocks), as experience has shown that they are safe and effective in pediatric populations.

**REFERENCES**


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Table 7

<table>
<thead>
<tr>
<th>Region</th>
<th>Block</th>
<th>Effective Analgesia</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper extremity</td>
<td>Interscalene</td>
<td>Shoulder/arm/elbow</td>
<td>SS/CPNB</td>
</tr>
<tr>
<td></td>
<td>Infraclavicular</td>
<td>Elbow/forearm</td>
<td>SS/CPNB</td>
</tr>
<tr>
<td></td>
<td>Axillary</td>
<td>Forearm/hand</td>
<td>SS/CPNB</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>Femoral</td>
<td>Thigh/knee</td>
<td>SS/CPNB</td>
</tr>
<tr>
<td></td>
<td>Sciatic</td>
<td>Leg/ankle/foot</td>
<td>SS/CPNB</td>
</tr>
<tr>
<td></td>
<td>Ankle</td>
<td>Foot</td>
<td>SS</td>
</tr>
<tr>
<td>Trunk</td>
<td>Ilioinguinal/iliohypogastric</td>
<td>Inguinal hernia/lower abdomen</td>
<td>SS</td>
</tr>
<tr>
<td></td>
<td>Rectus sheath</td>
<td>Umbilicus/superficial abdomen</td>
<td>SS</td>
</tr>
<tr>
<td></td>
<td>Intercostal/paravertebral</td>
<td>Thoracic</td>
<td>SS/CPNB</td>
</tr>
<tr>
<td></td>
<td>Lumbar plexus</td>
<td>Hip/pelvis/leg</td>
<td>SS/CPNB</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Penile</td>
<td>Penis</td>
<td>SS</td>
</tr>
<tr>
<td></td>
<td>Supraorbital/supratrochlear</td>
<td>Forehead/headache</td>
<td>SS</td>
</tr>
<tr>
<td></td>
<td>Greater/lesser occipital</td>
<td>Occiput/headache</td>
<td>SS</td>
</tr>
</tbody>
</table>

Abbreviations: SS, single shot; CPNB, continuous peripheral nerve block.


