Review Article

Drug Therapy

ALASTAIR J.J. WOOD, M.D., *Editor*

ANALGESICS FOR THE TREATMENT OF PAIN IN CHILDREN

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TREATMENT of pain and suffering should be a priority for all clinicians. Previous reviews[1] decried inadequate treatment of pain in infants and children. Surveys in the 1970s and 1980s[2] reported that infants and children were less likely to receive postoperative analgesics than adults. In that era, some neonates underwent surgery with minimal anesthesia,[3] although this practice received some criticism.[4]

Studies over the past 15 years suggest that neonates, infants, and children can receive analgesia and anesthesia safely, with proper age-related adjustments in clinical practice and dosing. Although the emphasis in this review is on the pharmacologic management of pain, several nonpharmacologic approaches, including hypnosis and related cognitive behavioral approaches, have had good efficacy in children with acute or chronic pain.[5,6] Making the hospital environment a less terrifying place may reduce anxiety and fear, which can themselves exacerbate pain.[7] Conversely, nonpharmacologic approaches should not be used as an excuse to withhold appropriate analgesics.

DEVELOPMENT OF NOCICEPTION

Recent studies of the developmental neurobiology of pain have been reviewed elsewhere.[8] Such studies indicate that neonates have considerable maturation of peripheral, spinal, and supraspinal afferent pain transmission by 26 weeks of gestation[9]; respond to tissue injury with specific behavior and with autonomic, hormonal, and metabolic signs of stress and distress[10]; and develop descending inhibitory pathways later than afferent excitatory pathways.[11]

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Several studies[12,13] have examined whether untreated pain in neonates has prolonged behavioral consequences. Infants who were circumcised without anesthesia as neonates showed increased distress during routine immunizations at four to six months of age, as compared with uncircumcised infants or with those who were circumcised as neonates with the use of a topical local anesthetic.[13] These observations are intriguing, although interpretation should be circumspect, pending replication and longer-term controlled studies. Among children with newly diagnosed cancer, those who had inadequate analgesia during a first bone marrow aspiration or lumbar puncture showed more severe distress during subsequent procedures than those who received a potent opioid (oral transmucosal fentanyl citrate) during the first procedure.[14]

DEVELOPMENTAL ISSUES IN PAIN ASSESSMENT AND MEASUREMENT

Children eight or more years of age can generally use visual-analogue pain scales used by adults, which involve rating the intensity of pain on a horizontal ruler. For children from three to eight years old, self-reported measures use either face scales (series of photographs[15] or drawings[16-18] of faces showing increasing degrees of distress) or color-analogue scales (rulers with increasing intensity of red color signifying increasing intensity of pain).[19] Good agreement was reported between the results obtained with a photographic face scale and those obtained with a color-analogue scale among three-to-seven-year-old children who had undergone surgery.[20]

Behavioral observational scales are the primary methods of pain assessment for neonates, infants, and children under four years of age or for children with developmental disabilities.[21] Such scales may score facial expressions,[22] limb and trunk motor responses, verbal responses, or combinations of behavioral and autonomic measures.[23] Some of these scales record "distress," which reflects fear and anxiety as well as pain.[24] Behavioral scales may underrepresent the intensity of persistent pain, as compared with self-reports.[20]

Physiological indexes of pain are useful during surgery and intensive care, although they may be nonspecific. For example, tachycardia may be caused by hypovolemia or hypoxemia, rather than pain. Thus, pain assessment in neonates, infants, and children under four years of age and in children with major disabilities remains a challenge. When clinical signs are unclear, therapeutic trials of comfort measures, feeding, and analgesics may clarify the sources of distress.

GENERAL ASPECTS OF DEVELOPMENTAL PHARMACOLOGY

The pharmacokinetics and pharmacodynamics of analgesics change during development. Age-related trends in several physiological variables relevant to drug action are summarized in Table 1. Different hepatic-enzyme systems for drug metabolism mature at different rates,[25] accounting for many of the observed findings.

Neonates have reduced clearance (normalized to body weight) of many drugs, as compared with infants, children, and adults, largely because of the incomplete maturation of their hepatic-enzyme systems. In contrast, children two to six years of age have greater weight-normalized clearance than adults for many drugs. Higher rates of drug metabolism by cytochrome P-450 in children than in adults are ascribed to a larger liver mass per kilogram of body weight, rather than to age-related changes in intrinsic enzyme catalytic rates.[26] More rapid drug clearance in children than in adults may mean that more frequent drug dosing is required. For example, a sustained-release oral morphine formulation used twice daily in adults requires thrice-daily dosing in children.[27]

Genetic variability in drug metabolism can either enhance or diminish the analgesic effects of drugs in different persons. For example, genetic absence of cytochrome P-450 subtype 2D6, which converts codeine to morphine, may render codeine ineffective as an analgesic.[28]

Renal blood flow, glomerular filtration, and tubular secretion increase in the first weeks of life, approaching adult values by 8 to 12 months. Renal drug clearance may be particularly decreased in preterm neonates.[29]

There are age-related differences in body composition. The fraction of body weight due to water is greater in neonates than in older children. In neonates, a larger fraction of body mass consists of highly perfused tissues, including brain, heart, and viscera, and a lower fraction consists of muscle and fat. Neonates have lower plasma concentrations of proteins that bind drugs, including α_1-acid glycoprotein and albumin. For drugs with a high degree of protein binding, the lower plasma protein concentrations in neonates may lead to an increased fraction of free (unbound) drug and thus to increased drug effect or increased toxicity.

Age-related changes in protein binding of drugs and in brain lipid content may alter drug partitioning and cerebrospinal fluid–blood or brain–blood concentration ratios, independently of changes in the permeability of the blood–brain barrier. Drug entry into the central nervous system depends not only on

TABLE 1. AGE-RELATED PHYSIOLOGICAL TRENDS RELEVANT TO ANALGESIC-DRUG ACTION.*

PHYSIOLOGICAL SYSTEM	AGE-RELATED TREND	CLINICAL IMPLICATIONS
Body compartments	Neonates: decreased fat, decreased muscle, increased water; increased volume of distribution for water-soluble drugs	Increased duration of action for some water-soluble drugs; increased dosing interval
Plasma protein binding	Neonates: decreased concentrations of albumin and α_1-acid glycoprotein	Increased unbound concentrations for highly protein-bound drugs; increased potential for overdosage or toxicity
Hepatic-enzyme systems for drug metabolism	Neonates and infants: immature hepatic cytochrome P-450 subtypes and glucuronyl transferases Children 2–6 yr: increased hepatic mass	Neonates and infants: decreased metabolic clearances; decreased infusion rates or increased dosing intervals Children 2–6 yr: increased metabolic clearance; increased infusion rates or decreased dosing intervals
Renal filtration and excretion of drugs and their metabolites	Neonates and infants: decreased glomerular filtration rates	Neonates and infants: accumulation of renally excreted drugs or active metabolites; decreased infusion rates or increased dosing intervals
Metabolic rate, oxygen consumption, and respiratory function	Neonates and infants: increased oxygen consumption; increased ratio of oxygen consumption to functional residual capacity; decreased fatigue-resistant (type 2) diaphragm fibers; decreased airway caliber; increased resistive work of breathing; decreased pharyngeal and lingual muscle control; decreased rigidity of larynx and subglottic trachea; decreased ventilatory responses to oxygen and carbon dioxide; functional residual capacity near alveolar closing volume	Neonates and infants: respiratory pauses or apnea lead more rapidly to hypoxemia; increased rate of onset and offset of inhalational anesthetics; increased risk of atelectasis or respiratory failure if illness or surgery imposes additional work of breathing; increased risk of hypoventilation due to the combined effects of decreased ventilatory reflexes and responses to opioids or sedatives

*Differences in physiological variables are expressed as increased or decreased relative to the comparable weight-scaled variables in adults. Differences in doses (normalized per kilogram of body mass) or in infusion rate (normalized in milligrams per kilogram per hour) are expressed as increased or decreased relative to comparable variables in adults.

passive permeation, but also on specific carriers for either uptake or exclusion, such as P-glycoproteins.[30]

Children make up a comparatively small market for pharmaceutical companies, which have historically been reluctant to conduct pediatric clinical trials.[31] Pediatric trials are important for defining how infants and children respond to medications and for identifying age-specific toxic effects. A series of federal laws and policies issued over the past seven years to encourage pediatric trials culminated in the "final rule," issued in 2000 and still, at this writing, in effect. Pediatric trials are mandated for all new drugs that, on review by the Food and Drug Administration, are determined to have potential clinical value for a sufficient number of newborns, infants, children, or adolescents.

Most drugs are packaged primarily for adult use, and dose calculations or serial dilutions may produce medication errors. Common patterns of pediatric drug errors[32] include milligram–microgram errors, decimal-point errors, confusion between daily dose and fractional dose (e.g., 100 mg per kilogram per day divided every six hours vs. 100 mg per kilogram per dose every six hours), and dilution errors.

ACETAMINOPHEN, ASPIRIN, AND NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Pediatric use of aspirin has declined since the 1970s, after reports of its association with Reye's hepatic encephalopathy.[33] Aspirin remains useful for rheumatologic conditions and for inhibition of platelet adhesiveness. A comparison of aspirin with ibuprofen in childhood arthritis found that both were equally effective, but that there was better compliance and fewer adverse reactions with ibuprofen.[34] The recommended aspirin dosage is 10 to 15 mg per kilogram every four hours by mouth. Therapeutic plasma aspirin concentrations for fever control are 15 to 20 mg per deciliter. Dosage guidelines for aspirin, acetaminophen, and the nonsteroidal antiinflammatory drugs (NSAIDs) ibuprofen and naproxen are summarized in Table 2.

Acetaminophen (paracetamol) has supplanted aspirin as the most widely used antipyretic and mild analgesic for children. The plasma concentrations effective for fever control and analgesia[35] are 10 to 20 μg per milliliter. The recommended oral dosage is 10 to 15 mg per kilogram every four hours for children. Rectal administration produces delayed and variable uptake; single doses of 35 to 45 mg per kilogram generally produce therapeutic plasma concentrations,[36] with prolonged clearance. Subsequent rectal doses should be smaller (e.g., 20 mg per kilogram), and the interval between doses should be extended to at least six to eight hours.[36,37] Single rectal doses of 20 mg per kilogram produced safe plasma concentrations in preterm neonates.[38]

Daily cumulative acetaminophen doses by the oral or rectal route should not exceed 100 mg per kilogram per day for children, 75 mg per kilogram for infants, 60 mg per kilogram for term and preterm neonates beyond 32 weeks of postconceptional age, and 40 mg per kilogram for preterm neonates from 28 to 32 weeks of postconceptional age. An appropriate rec-

TABLE 2. ORAL DOSAGE GUIDELINES FOR COMMONLY USED NONOPIOID ANALGESICS.

DRUG	DOSE FOR PATIENTS <60 kg	DOSE FOR PATIENTS ≥60 kg	INTERVAL	MAXIMAL DAILY DOSE FOR PATIENTS <60 kg	MAXIMAL DAILY DOSE FOR PATIENTS ≥60 kg
	mg/kg	mg	hr	mg/kg	mg
Acetaminophen	10–15	650–1000	4	100*	4000
Ibuprofen	6–10	400–600†	6	40†‡	2400†
Naproxen	5–6†	250–375†	12	24†‡	1000†
Aspirin§	10–15†§	650–1000†	4	80†‡§	3600†

*The maximal daily doses of acetaminophen for infants and neonates are a subject of current controversy. Provisional recommendations are that daily dosing should not exceed 75 mg per kilogram per day for infants, 60 mg per kilogram per day for term neonates and preterm neonates of more than 32 weeks of postconceptional age, and 40 mg per kilogram per day for preterm neonates 28 to 32 weeks of postconceptional age. Fever, dehydration, hepatic disease, and lack of oral intake may all increase the risk of hepatotoxicity.

†Higher doses may be used in selected cases for treatment of rheumatologic conditions in children.

‡Dosage guidelines for neonates and infants have not been established.

§Aspirin carries a risk of provoking Reye's syndrome in infants and children. If other analgesics are available, aspirin should be restricted to indications for which an antiplatelet or antiinflammatory effect is required, rather than being used as a routine analgesic or antipyretic in neonates, infants, or children. Dosage guidelines for aspirin in neonates have not been established.

tal regimen for a preterm neonate 30 weeks of postconceptional age would be 20 mg per kilogram every 12 hours. Excessive dosing has produced hepatic failure in both infants and children.

NSAIDs are widely used for children. Systematic reviews have found few differences among NSAIDs for analgesia in adults and little advantage of injected over oral administration.[39] Pharmacokinetic studies of several NSAIDs in children found weight-normalized clearance and volumes of distribution greater than those in adults, but similar elimination half-lives.[40]

Adverse gastrointestinal or renal events from short-term use of either ibuprofen or acetaminophen appear to be quite rare in children.[41] Some studies comparing acetaminophen and NSAIDs have found no difference in analgesic effectiveness,[42] whereas others have found better analgesia with NSAIDs.[43] NSAIDs may increase the risk of bleeding after tonsillectomy.[44] NSAIDs provide good postoperative analgesia and result in lower opioid requirements than in control groups not receiving NSAIDs.[45]

Selective cyclooxygenase-2 (COX-2) inhibitors[46] have been designed to retain the analgesic and anti-inflammatory effects of NSAIDs while reducing the risk of gastric irritation and bleeding. There are few published studies of the pediatric use of selective COX-2 inhibitors,[47] except for nimesulide,[48] which is not available in the United States. Additional large-scale studies are needed to evaluate efficacy and cost–benefit and risk–benefit issues.

OPIOIDS

The indications for opioids include postoperative pain, pain due to sickle cell disease, and pain due to cancer. The suggested dosage guidelines for subjects who have never received opioids are presented in Table 3. As with adults, the risk of addiction (compulsive drug-seeking behavior) appears low among children receiving opioids for pain. Over the past 15 years, opioids in infants and children have received intensive study.

Pharmacokinetics of Opioids in Neonates, Infants, and Children

The weight-normalized clearance of several opioids is diminished in neonates and reaches mature values over the first two to six months of life.[50-53] The elimination half-life of morphine, in a pooled analysis, averaged 9 hours in preterm neonates, 6.5 hours in term neonates, and 2 hours in older infants and children.[2] The active metabolites of morphine are excreted by the kidneys and can accumulate in neonates because renal function is not yet mature. Delayed renal clearance of morphine metabolites may contribute to the analgesic, respiratory depressant, and rarely, convulsant effects of morphine in the neonate. Fentanyl clearance may be impaired during and after abdominal surgery in neonates.[50]

Opioid Pharmacodynamics and Clinical Outcomes in Neonates, Infants, and Children

The respiratory-reflex responses to airway obstruction, hypercapnia, and hypoxemia are immature at birth and mature gradually over the first two to three months of life in both preterm[54] and term[55] neonates. Neonates and infants with chronic lung disease[56] have impaired ventilatory reflexes, which might increase their risk of opioid-induced respiratory depression. Case series and outcome studies of children not undergoing intubation suggest a higher frequency of opioid-induced respiratory depression among neonates than among infants over six months of age or older children.[57-59] However, morphine infusions during the postoperative period in intubated neonates are associated with low behavioral pain scores and good hemodynamic stability.[60]

In infants three to six months of age, the analgesic effects of morphine or fentanyl are similar to, and the ventilatory depression is no greater than, that seen in adults with similar plasma concentrations of morphine[61,62] or fentanyl.[63] Some of the cited studies assessed ventilatory drive in infants breathing through endotracheal tubes; studies conducted in intubated infants may underestimate the risk of airway obstruction or hypoventilation in non-intubated infants.

Continuous opioid infusions during the postoperative period have been used extensively in older infants and children, with generally good efficacy and safety,[64] although with a substantial incidence of peripheral side effects.[65] Starting rates of morphine infusion ranged from 0.01 mg per kilogram per hour in infants under 6 months of age[66] to 0.025 to 0.04 mg per kilogram per hour in children over 12 months of age. In neonates, the weight-scaled rates of opioid infusion should be lower, and the repeated weight-scaled intermittent doses should be smaller, less frequent, or both, than in infants and children.

Neonates receiving opioids should have continuous electronic monitoring, preferably by pulse oximetry, and they should be observed in a setting that permits rapid intervention for airway management, because respiratory-rate monitoring alone may be an inadequate predictor of impending apnea. Studies have not firmly established either morphine or fentanyl as the preferred opioid for neonates or infants.[67]

Patient-Controlled Analgesia in Children

The safety and efficacy of patient-controlled analgesia for children as young as six years are supported by the results of controlled trials.[68] The variables for patient-controlled analgesia should be individualized. Addition of a low-dose basal infusion improves pain scores and patient satisfaction according to some

TABLE 3. INITIAL DOSAGE GUIDELINES FOR OPIOID ANALGESICS.*

DRUG	EQUIANALGESIC DOSES		USUAL STARTING INTRAVENOUS OR SUBCUTANEOUS DOSES AND INTERVALS		PARENTERAL:ORAL DOSE RATIO	USUAL STARTING ORAL DOSES AND INTERVALS	
	PARENTERAL	ORAL	CHILD <50 kg	CHILD ≥50 kg		CHILD <50 kg	CHILD ≥50 kg
Codeine	120 mg	200 mg	NR	NR	1:2	0.5–1.0 mg/kg every 3–4 hr	30–60 mg every 3–4 hr
Morphine	10 mg	30 mg (long-term)	Bolus: 0.1 mg/kg every 2–4 hr	Bolus: 5–8 mg every 2–4 hr	1:3 (long-term)	Immediate release: 0.3 mg/kg every 3–4 hr	Immediate release: 15–20 mg every 3–4 hr
		60 mg (single dose)	Infusion: 0.03 mg/kg/hr	Infusion: 1.5 mg/hr	1:6 (single dose)	Sustained release: 20–35 kg: 10–15 mg every 8–12 hr 35–50 kg: 15–30 mg every 8–12 hr	Sustained release: 30–45 mg every 8–12 hr
Oxycodone	NA	15–20 mg	NA	NA	NA	0.1–0.2 mg/kg every 3–4 hr	5–10 mg every 3–4 hr
Methadone†	10 mg	10–20 mg	0.1 mg/kg every 4–8 hr	5–8 mg every 4–8 hr	1:2	0.1–0.2 mg/kg every 4–8 hr	5–10 mg every 4–8 hr
Fentanyl	100 μg (0.1 mg)	NA	Bolus: 0.5–1.0 μg/kg every 1–2 hr Infusion: 0.5–2.0 μg/kg/hr	Bolus: 25–50 μg every 1–2 hr Infusion: 25–100 μg/hr	NA	NA	NA
Hydromorphone	1.5–2 mg	6–8 mg	Bolus: 0.02 mg every 2–4 hr Infusion: 0.006 mg/kg/hr	Bolus: 1 mg every 2–4 hr Infusion: 0.3 mg/hr	1:4	0.04–0.08 mg/kg every 3–4 hr	2–4 mg every 3–4 hr
Meperidine (pethidine)‡	75–100 mg	300 mg	Bolus: 0.8–1.0 mg/kg every 2–3 hr	Bolus: 50–75 mg every 2–3 hr	1:4	2–3 mg/kg every 3–4 hr	100–150 mg every 3–4 hr

*Doses are for patients over six months of age. In infants under six months, initial per-kilogram doses should begin at roughly 25 percent of the per-kilogram doses recommended here. Higher doses are often required for patients receiving mechanical ventilation. All doses are approximate and should be adjusted according to clinical circumstances. Recommendations are adapted from previous summary tables, including those of a consensus statement from the World Health Organization and the International Association for the Study of Pain.[49] NA denotes not applicable, and NR not recommended.

†Methadone requires additional vigilance because it can accumulate and produce delayed sedation. If sedation occurs, doses should be withheld until sedation resolves. Thereafter, doses should be substantially reduced, the interval between doses should be extended to 8 to 12 hours, or both.

‡The use of meperidine should generally be avoided if other opioids are available, especially with long-term use, because its metabolite can cause seizures.

reports[68] but produces more episodic hypoxemia at nighttime according to others.[69] We routinely prescribe basal infusions for children with cancer or sickle cell disease. Patient-controlled morphine treatment in children typically starts with a bolus dose of 0.02 mg per kilogram, a lockout interval of seven minutes, and a four-hour maximum of 0.3 mg per kilogram. If a basal infusion is used, it is typically begun at 0.01 to 0.015 mg per kilogram per hour.

Nurse-activated patient-controlled analgesia is now widely used for infants[70] as a convenient way to prevent delays in relieving episodic pain. Activation of the button for patient-controlled analgesia by parents ("parent-controlled analgesia") is widely accepted in palliative care. However, its use for postoperative pain is controversial because of the potential for either overdosing or underdosing subjects who have not received opioids before. If parent-controlled analgesia is to be considered, we recommend a formal education program for parents, together with protocols for close observation by the nursing staff.

Meperidine (pethidine) in low doses is useful to treat postoperative shivering or rigors after amphotericin infusion, but it has no particular advantages as an analgesic. Morphine resulted in better analgesia and no more side effects than meperidine in a double-blind comparison in which patient-controlled analgesia was used.[71] Meperidine can produce dysphoria and seizures from accumulation of its metabolite, normeperidine. The clinical usefulness of hydromorphone appears to be similar to that of morphine; it is roughly five times as potent as morphine in children.[72] Fentanyl provides analgesia with a rapid onset and short duration of effect for brief, painful procedures. With repeated dosing or with prolonged infusions, fentanyl becomes longer-acting.[73,74] Rapid administration of fentanyl can produce chest-wall rigidity that responds to naloxone in some cases; in other cases, neuromuscular blockade and positive-pressure ventilation are required.[75]

Two novel formulations of fentanyl may be useful in selected patients. Oral transmucosal fentanyl permits rapid onset of analgesia for brief, painful procedures[14,76] in hospitalized children in whom intravenous access is not available. In adults, the analgesic effect of 800 μg of oral transmucosal fentanyl is roughly equivalent to that of 10 mg of intravenous morphine.[77] Oral transmucosal administration is effective because it bypasses the efficient first-pass hepatic metabolism of fentanyl that occurs after enteral absorption.

Transdermal fentanyl provides a consistent analgesic effect for selected patients, such as children with severe pain due to cancer.[78] Transdermal fentanyl has a slow onset and some variability in absorption, and it is contraindicated as initial treatment for patients who have not received opioids before. Oral or intravenous methadone is useful because of its prolonged duration of action.[79] However, because of slow and variable clearance, methadone requires careful assessment and titration to prevent delayed sedation. Methadone elixir is useful as a long-acting opioid for patients unable to swallow whole sustained-release opioid tablets. Agonist–antagonists such as pentazocine[80] and drugs such as buprenorphine[81] that act at kappa receptors offer no apparent advantages over mu-agonist opioids.

Equipotency tables are useful for conversion from one opioid to another or for conversion from one route of administration to another. Studies of opioid-tolerant adults with cancer showed that, when treatment was being changed from one opioid to another, the analgesic and respiratory depressant effects of the second opioid appeared much stronger than those predicted by conversion ratios that had been derived from studies of subjects who had not received opioids before. This phenomenon, known as "incomplete cross-tolerance," is especially pronounced when the second opioid is methadone,[82] and it is probably due to the fact that the *d*-isomer of methadone can act as an antagonist at the *N*-methyl-D-aspartate subclass of glutamate receptors.[83,84]

Mild respiratory depression can be managed by repeatedly awakening the patient, encouraging deep breathing, and withholding further doses until the effects subside. In urgent situations, assisted ventilation or naloxone (10 to 20 μg per kilogram) may be needed. The use of naloxone in opioid-tolerant patients carries a risk of producing withdrawal reactions; the hemodynamic consequences can be especially severe in patients with cardiac disease. If the circumstances are not too urgent, incremental dosing with naloxone (e.g., 2 μg per kilogram every 30 seconds until the respiratory rate and tidal volume increase) may reverse excessive opioid effects without evoking severe pain or withdrawal reactions. If naloxone is administered, close observation is recommended and repeated doses may be needed.

Nonrespiratory side effects of opioids, including nausea, ileus, itching, and urinary retention, are common among infants and children[65] and may cause considerable distress. Many opioid side effects can be ameliorated by drug therapy directed at the side effect (e.g., antiemetics to treat nausea and vomiting, antihistamines to treat itching, and laxatives to treat constipation).

LOCAL ANESTHETICS

Local anesthetics are now widely used in children. Their safety is quite acceptable, although excessive plasma concentrations can produce seizures and cardiac depression. The amino-amides (e.g., lidocaine and

bupivacaine) have a narrower therapeutic index for neonates than for children or adults because of decreased metabolic clearance,[85,86] with resultant drug accumulation during infusions[86]; decreased plasma concentrations of α_1-acid glycoprotein, leading to higher concentrations of unbound local anesthetic; and hard-to-recognize warning signs of impending toxic effects in preverbal neonates and infants. The maximal recommended doses of lidocaine are 4 mg per kilogram without epinephrine and 5 mg per kilogram with epinephrine in neonates and 5 to 7 mg per kilogram in children. The maximal recommended doses of bupivacaine, with or without epinephrine, are 2 mg per kilogram in neonates and 2.5 mg per kilogram in children.[85]

Topical formulations are useful for needle procedures. For repair of lacerations, combinations of tetracaine with epinephrine (adrenaline) and cocaine, known as TAC, are widely used.[87] Cocaine-free preparations are equally effective.[88] Several formulations provide analgesia for intact skin and are effective for needle procedures, including a cream containing both lidocaine and prilocaine (EMLA, AstraZeneca),[89] and tetracaine gel (Ametop, Smith and Nephew [not yet available in the United States]).[90] EMLA is safe and more effective than placebo for circumcision of newborns,[91] although it is less effective than ring block.[92]

Regional anesthesia is commonly administered, with excellent efficacy and safety, to anesthetized children for postoperative analgesia,[93] peripheral-nerve block,[94] and epidural analgesia.[95-97] Epidural analgesia is effective even in premature and term neonates.[97] Epidural analgesia in neonates and infants requires specific expertise on the part of physicians and nurses and close observation, as well as modifications in technique and drug selection.[98]

Ropivacaine[99] and levobupivacaine[100] are two new local anesthetics that are attractive because they involve less potential cardiac risk than bupivacaine in the event of overdose.[101] Clonidine is an attractive adjuvant to epidural local anesthetics, because it prolongs or intensifies analgesia and also produces less nausea, ileus, itching, urinary retention, and respiratory depression than opioids.[102]

Children undergoing outpatient surgery frequently report high pain scores, partly because of parental reluctance to administer analgesics.[103] Although peripheral-nerve blocks and caudal blocks provide good analgesia, the duration of analgesia is generally less than eight hours. Thus, parents should be encouraged to administer analgesics before pain is severe.

GENERAL ANESTHESIA FOR NEONATES AND INFANTS

General anesthesia has become much safer for neonates and infants over the past 30 years, and the risk of cardiac arrest or death during general anesthesia in infants has decreased by a factor of more than 20.[104,105] Even the most critically ill neonates can tolerate anesthesia for major surgery.[106] Autonomic and hormonal–metabolic stress responses in neonates are blunted to varying degrees by high-dose opioid anesthesia,[107] epidural local anesthetics,[108] and inhalational anesthetics.[109]

TREATMENT OF PAIN DUE TO CANCER

Pain in children with cancer may be caused by tumor progression; by consequences of treatment, such as mucositis; or by needle procedures, including bone marrow aspiration. For needle procedures, both pharmacologic approaches (topical and infiltration anesthesia, conscious sedation, and general anesthesia) and nonpharmacologic approaches[5] (hypnosis and cognitive–behavioral programs) are efficacious. The optimal combination of pharmacologic and nonpharmacologic approaches should be individualized.

The majority of children with advanced cancer can be made comfortable with titrated oral doses of opioids and appropriate management of side effects.[110] If oral administration is not tolerated, the alternatives include intravenous, continuous subcutaneous,[111] and transdermal[78] opioid administration. A retrospective survey of parents' recollections suggests a need for improved interventions for pain as well as for a range of other symptoms, especially fatigue and sleep disturbance, among children with terminal cancer.[112] Methylphenidate is useful in antagonizing opioid-induced sedation. Marked escalation of opioid doses (e.g., by 100 times or more) may be required, primarily among patients with solid tumors metastatic to the spine or central nervous system.[110] Some of these patients have pain resistant to high-dose opioids but can be made comfortable and alert by epidural or subarachnoid infusions of local anesthetics and opioids.[113] Management of cancer pain is best approached in the context of broad-based supportive or palliative care[114] programs not limited to pharmacologic interventions.

PHARMACOLOGIC MANAGEMENT OF CHRONIC NONCANCER PAIN

Chronic pain can be a burden for children and families and can impair social functioning and school attendance. It is useful to distinguish between nociceptive pain and neuropathic pain. Nociceptive pain involves the detection of tissue injury or inflammation by a normally functioning nervous system. Neuropathic pain persists because of abnormal excitability in the peripheral or central nervous system. Neuropathic pain in children is commonly post-traumatic.[115] Prolonged pain after amputation is not rare in children.[116] Evidence in adults supports the efficacy of

tricyclic antidepressants and several anticonvulsants, especially gabapentin,[117] in several conditions involving neuropathic pain.[118] Antidepressants and anticonvulsants are commonly used for children with neuropathic pain, despite a lack of controlled studies. Our impression is that they can be effective in children, as they are in adults, although they can have side effects.

Recurrent headaches are common in children.[119] Abortive and preventive therapies for migraine in children have been studied.[120] Sumatriptan, a serotonin 1B/1D receptor agonist, appears effective and safe as an abortive treatment.[121] Dihydroergotamine,[122] ibuprofen, and acetaminophen[123] were more effective than placebo in interrupting episodes of migraine, and ibuprofen appeared to be more effective than acetaminophen.[123] For prevention of migraine, trials have reported efficacy with beta-blockers,[124] calcium-channel blockers,[124] and antidepressants.[125,126] Yet other trials found beta-blockers to be no more effective than placebo[127] and less effective than self-hypnosis.[127]

Children with sickle cell disease who have vaso-occlusive episodes should receive opioids as needed to relieve pain. Studies emphasize oral dosing[128] of potent opioids and NSAIDs, home treatment,[129] and reduced reliance on emergency departments or inpatient admission.

In several other chronic, debilitating conditions in childhood, there is a restricted role for long-term episodic or regularly scheduled administration of opioids as a component of a comprehensive pain-management program.

With knowledge of principles that influence drug dosage, actions, and interactions, clinicians should generally be able to provide effective relief of acute pain, pain due to cancer, and several types of chronic pain in infants and children with a wide margin of safety.

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CORRECTION

Analgesics for the Treatment of Pain in Children

Analgesics for the Treatment of Pain in Children . In Table 3, on page 1098, in the column for ``Usual Starting Intravenous or Subcutaneous Doses and Intervals´´ for children weighing less than 50 kg, the dose of morphine given by infusion should be 0.03 mg/kg/hr rather than 0.3 mg/kg/hr. The Web version of the table has been corrected. We regret the error.

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