Special Article

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The Pediatric Pain Service: Management of Acute Pain in Children

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Everything you ever wanted to know about acute pain management and couldn't find in a single resource: where, when, how....

THE TREATMENT and alleviation of pain is a basic human right that exists regardless of age. Unfortunately, even when their pain is obvious, children frequently receive no treatment, or inadequate treatment, for pain and for painful procedures. The newborn and critically ill child are particularly vulnerable. The common "wisdom" that children neither respond to, nor remember, painful experiences to the same degree that adults do is simply untrue.

Unfortunately, even when physicians decide to treat children in pain, they rarely prescribe potent analgesics, adequate doses, or utilize pharmacologically rational dosing regimens because of their over-riding concern that children may be harmed by the use of these drugs. This is not at all surprising because physicians are taught throughout their training that opiates cause respiratory depression, cardiovascular collapse, depressed levels of consciousness, vomiting, and, with repeated use, addiction. Rarely, if ever, are the appropriate therapeutic uses of these drugs, or rational dosing regimens, discussed. Indeed, until very recently, it was difficult to find pain and its medical management even mentioned in any of the current textbooks of pediatric medicine and surgery.

Nurses are taught to be wary of physicians' orders (and patients' requests) as well. The most common prescription order for potent analgesics, "to give as needed" (pro re nata, "prn"), has come to mean "to give as infrequently as possible". The "pro" order also means that either the patient must ask for pain medication or the nurse must identify when a patient is in pain. Neither of these requirements may be met by children in pain. Children less than 7 years of age may be unable to adequately verbalize when or where they hurt. Alternatively they may be afraid to report their pain. Many children will withdraw or deny their pain in an attempt to avoid yet another terrifying and painful experience - the intramuscular injection or "shot". Finally, several studies have documented the inability of nurses and physicians to correctly identify and treat pain even in post-operative pediatric patients.

Fortunately, the past 5 years has seen a virtual explosion in the development of pediatric pain services, primarily under the direction of pediatric anesthesiologists. These pain service teams provide the pain management for acute, postoperative, terminal, neuropathic and chronic pain. The purpose of this review is to highlight[1] the component services necessary for a multi-disciplinary pediatric pain service and[2] the recent advances in opioid and local anesthetic pharmacology and therapeutic interventions, which are useful in the treatment of childhood pain. Specifically I will[1] review the components of a multi-disciplinary pain service[2], how pain is assessed in children[3], delineate the role of opioid receptors in the mechanism of opioid analgesia[4], provide a phar-

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macokinetic and pharmacodynamic framework regarding the use of opioids and local anesthetics in children, and[5] provide guidelines for pain management using patient controlled analgesia, methadone, spinally administered opiates, and continuous epidural infusions using bupivacaine or lidocaine alone and in combination with fentanyl.

THE PEDIATRIC PAIN SERVICE

The multi-disciplinary approach to pain management has become the most widely accepted model in current clinical practice. Indeed, this is true whether one designs an acute pain service (e.g., for the management of post-operative pain, terminal pain of malignancies, and vase-occlusive crisis in sickle cell disease) or an acute and chronic pain service (e.g., for the treatment of reflex sympathetic dystrophy, chronic abdominal pain, and Headache). The crucial component services involved in a multi-disciplinary approach are listed in table I. Usually under the medical direction of an anesthesiologist, *a pain service can only be successful if the department of nursing is fully integrated into its design and function from the outset.* In fact, after deciding to start a pain service, the single most important priority of the director is to select and secure the funding for a dedicated nurse clinician, whose only clinical and administrative responsibilities are the pain service. Anything else will ultimately lead to failure.

The goals of the pain service are to select the appropriate drugs, methods and techniques of delivery that are appropriate for an individual patient's needs. A 24-hour availability is necessary as well as regular follow up by skilled and knowledgeable physicians. Furthermore, it is the duty of the pain service to provide the medical and nursing services of the hospital with periodic education updates, printed protocols, and standardized orders for the various pain therapy modalities the service utilizes.

Additionally, the pain service must maintain continuing quality assurance reviews of all problems that arise and/or may potentially arise.

PAIN ASSESSMENT

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Pain is a subjective experience; operationally, it can be defined as "what the patient says hurts" and exists "when the patient says it does". Infants, pro-verbal children, and children between the ages of 2 and 7 (Piaget's "pro - operational thought stage") may be unable to describe their pain or their subjective experiences. This has led many to conclude that children don't experience pain in the same way that adults do. Clearly, children do not have to know or be able to express the meaning of an experience in order to have the experience.

Table I. Services involved in a multidisciplinary pediatric pain service

Anesthesiology	Oral - Maxillofacial Surgery	Physical therapy
Neurology	Orthopedics	Pediatric - Psychology
Neurosurgery	Pediatrics Hematology - Oncology	Surgery
Nursing	Pharmacy	Urology

On the other hand, because pain is essentially a subjective experience, it is becoming increasingly clear that the child's perspective of pain is an indispensable facet of pediatric pain management and an essential element in the specialized study of childhood pain. Indeed, pain assessment and management are inter-dependent and one is essentially useless without the other.

The goal of pain assessment is to provide accurate data about the location and intensity of pain as well as the effectiveness of measures used to alleviate or abolish it.

Validated, reliable instruments currently exist to measure and assess pain in children over the age of three. These instruments which measure the quality and intensity of pain are "self- report measures" and make use of pictures or word descriptors to describe pain. Pain intensity or severity can be measured in children as young as 3 years of age by using either the Oucher scale (developed by Dr. Judy Beyer), a two part scale with a vertical numerical scale (0-100) on one side and six photographs of a young child on the other, or a visual analogue scale, or a 10 cm line with a smiling face on one end and a distraught, crying face on the other. In my practice I use the 6 face pain- scale developed by Dr. Donna Wong (and is found in the Harriet Lane Handbook).

This scale is attached to the vital sign record and nurses are instructed to use it or a more age-appropriate self - report measure whenever vital signs are taken. Alternatively, color, word - graphic

rating scales, and poker chips have been used to assess the intensity of pain in children as well. In infants and newborns pain has been assessed by measuring physiologic responses to a nociceptive stimuli, such as blood pressure and heart rate changes or by measuring levels of adrenal stress hormones.

Alternatively, behavioral approaches have utilized facial expression, body movements, and the intensity and quality of crying as indices of response to nociceptive stimuli.

Finally, it is important to accurately define the location of pain as well. This is readily accomplished by using either dolls or action figures or by using drawings of body outlines, both front and back.

PAIN MANAGEMENT NON-OPIOID (OR "WEAKER") ANALGESICS

The "weaker" or "milder" analgesics, of which acetaminophen (Tylenol®), salicylate (aspirin), and ibuprofen (Motrin®) are the classic examples, comprise a heterogeneous group of non-steroidal anti inflammatory drugs (NSAID) and non-opioid analgesics. They provide pain relief primarily by blocking peripheral prostaglandin production. These analgesic agents are administered enterally via the oral or, on occasion, the rectal route and are particularly useful for inflammatory, bony, or rheumatic pain. Parenterally administered NSAIDS, such as ketorolac, are now available for use in children in whom the oral or rectal routes of administration are not possible. Unfortunately, regardless of dose, the non-opioid analgesics reach a "ceiling effect" above which pain can not be relieved by these drugs alone (table II). Indeed, because of this, these weaker analgesics are often administered in combination with other more potent opioids such as codeine or oxycodone.

Aspirin, one of the oldest and most effective non-opioid analgesics has been largely abandoned in pediatric practice because of its possible role in Reye's syndrome, its effects on platelet function, and its gastric irritant properties. Despite these problems, a new salicylate product, choline - magnesium trisalicylate (Trilisate®) is increasingly being used in my pediatric pain management practice, particularly in the management of post - operative pain and in the child with cancer. Choline- magnesium trisalicylate is a unique aspirin-like compound that does not bind to platelets and therefore has minimal, if any effects on platelet function. It is a convenient drug to give to children because it is available in both a liquid and tablet form and is administered either twice a day or every 6 hours (table II). The association of salicylates with Reye syndrome will limit its use, even though the risk of developing this syndrome postoperatively or in cancer is extremely unlikely.

Table II. Dosage guidelines for commonly used nonsteroidal anti-inflamatory drugs (NSAIDs)

Generic Name	Brand Name®	Dose (mg/kg) Frequency	Maximum adult daily dose (mg)	Comments
Salicylates (aspirin)	Aspirin - many brands, e.g. Bayer, Bufferin, Anacin, Alka Seltzer	10 - 15 q 4 hours	4,000	Inhibits platelet aggregation, GI irritability, Reye Syndrome
Acetaminophen	Many brand names, e.g. Tylenol, "aspirin-free", Panadol, Tempra	10 - 15 q 4 hours	4,000	Lacks anti-inflammatory activity
Ibuprofen	Many brand names, e.g. Motrin, Advil, Medipren	8 - 12 q 6 - 8 hours	2,400	Available as an oral suspension
Naproxyn	Naprosyn	5 - 10 q 6 - 8 hours	1,000	Available as an oral suspension
Indomethacin	Indocid	0.3 - 1.0 q 6 hours	150	Commonly used in NICU to close PDA
Ketorolac	Toradol	IV or IM Load 0.5 Maint 0.2 - 0.5 q 6 hours	150	May be given orally. Maximun dose 60 mg. Causes GI upset and ulcer, discontinue after 72 hours
Choline-Manesium tri-salycilate	Trilisate	8 - 10 q 6 - 12 hours	3,000	Does not bind to platelets, see salicilate above

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Table III. Classification of opioid receptors

Receptor	Prototype agonist	CNS locations	Effects
μ	Morphine Fentanyl Meperidine Codeine Methadone	Brain: laminae III and IV of cortex, thalamus periaqueductal grey Spinal cord: substancia gelatinosa	μ1: supraspinal analgesia, dependence μ2: respiratory depression, inhibition of gastrointestinal mobility, bradycardia
κ	Ketocyclazocine Dinorphin ? Butorphanol	Brain: hypothalamus, periaqueductal grey Spinal cord: substancia gelatinosa	Spinal analgesia, sedation, miosis, inhibition of anti-diuretic hormone release
δ	Enkephalins DADL	Brain: pontine nucleus, amigdala, olfatory bulbs, deep cortex	Analgesia, euphoria
σ	N - allylnormetazocine Phencyclidine ? Ketamine		Dysphoria, hallucinations

The most commonly used non-opioid analgesic in pediatric practice remains acetaminophen. Unlike aspirin and the NSAIDs, acetaminophen has minimal, if any, anti-inflammatory activity. When administered in normal doses (10-15 mg/kg^{-1}, PO or PR), acetaminophen has very few serious side effects, is an antipyretic, and like all enterally administered NSAIDs, takes about 40-60 minutes to provide effective analgesia. Dosage guidelines for the most commonly used non-opioid analgesics are listed in table II. Recently Berde et al and Birmingham et al. have reported that acetaminophen should be administered rectally in significantly higher doses than current recommendations suggest. They recommend acetaminophen doses as high as 30-40 mg/kg^{-1} when the drug is administered rectally as a single (loading) dose.

TERMINOLOGY

Opioids

The terminology used to describe potent analgesic drugs is constantly changing. They are commonly referred to as "narcotics" (from the Greek "narco" - to deaden), "opiates" (from the Greek "opion"- poppy juice, for drugs derived from the poppy plant), "opioids" (for all drugs with morphine -like effects, whether synthetic or naturally occurring), or euphemistically as "strong analgesics" (when the physician is reluctant to tell the patient or the patient's family that narcotics are being used). Furthermore, the discovery of endogenous endorphins and opioid receptors has necessitated the reclassification of these drugs into agonists, antagonists, and mixed agonist - antagonists based on their receptor binding properties.

OPIOID RECEPTORS

Over the past twenty years multiple opioid receptors and subtypes have been identified and classified (table III). An understanding of the complex nature and organization of these multiple opioid receptors is essential for an adequate understanding of the response to, and control of, pain. In the central nervous system there are four receptor types, designated mu (μ), kappa (k), delta (d), and sigma (s). The mu (mu_1) is further subdivided into mu1 (supraspinal analgesia) and mu_2 (respiratory depression, inhibition of gastrointestinal motility, and spinal analgesia) subtypes. Other receptors and subtypes will surely be discovered as research in this area proceeds.

Organizationally, the distribution of the multiple opioid receptors may have significance in the modulation of pain (table III). Nociceptive impulses are transmitted from the periphery to the dorsal horn of the spinal cord where diverse synapses occur with essentially all incoming sensory input. In the substantia gelatinosa of the dorsal horn of the spinal cord, interneurons are activated and release substance P. an 11-amino acid peptide pain transmitter that facilitates nociceptive transmission. Descending fibers also synapse at the interneurons to inhibit or modulate sensory input about an injury as well, via the release of endogenous opioids and other neu-

Table IV. Commonly used μ agonist drugs

Agonist	Equipotent IV dose (mg/kg)	Duration (hr)	Bioavailability (%)	Comments
Morphine	0.1	3 - 4	20 - 40	"Gold standard", very inexpensive. Seizures in newborns. Histamine release, vasodilation →→ avoid in asthmatics and in circulatory compromise. MS - Contin® 8 - 12 h duration (pill), can not be crushed or given via gastric tube. Liquid morphine 2 - 20 mg/ml
Meperidine	1.0	3 - 4	40 - 60	Catastrophic interations with MAO inhibitors. Tachycardia, negative inotropism. Metabolite produces seizures. 0.25 mg/kg effectively treats shivering. Not recommend for routine use
Hydromorphone (Dilauid)	0.015	3 - 4	50 - 70	Less itching and nausea than morphine, commonly used when morphine produces too many of these systemic side effects.
Fentanyl	0.001	0.5 - 1.0		Very effective for short painful procedures. Chest wall rigidity (> 5 μg/kg rapid IV bolus). Rx: Naloxone or succinylcholine or pancuronium Oral transmucosal dose 10 - 15 μg/kg.
Methadone	0.1	4 - 24	70 - 100	Liquid preparation available. Long duration of action makes it ideal for cancer pain, wearing dependent patients, etc, wearing
Codeine	1.2	3 - 4	40 - 70	PO only. Prescribed with acetaminophen
Oxycodone (Tylox®)	0.1	3 - 4	60 -80	PO only. Usually prescribed with acetaminophen. Less nausea than codeine

ropeptides. If unblocked, nociceptive input is transmitted to the brain via the spinothalamic and spine reticular nerve pathways. Several areas within the brain may further modulate or abolish pain transmission including the brain stem's medial and lateral reticular formations, the medullary raphe nuclei, the periaqueductal gray, the thalamus and the cerebral cortex. Binding of either endogenous or pharmacologically administered opiates to receptors in these central locations initiates the modulation of pain transmission. Thus, the organization of opioid systems suggests that there may be a multiplicity of sites at which opioids might modify nociception.

The differentiation of agonists and antagonists is fundamental to pharmacology. A neurotransmitter is defined as having agonist activity, while a drug that blocks the action of a neurotransmitter is an antagonist. By definition, receptor recognition of an agonist is "translated" into other cellular alterations (that is, the agonist initiates a pharmacologic effect), whereas an antagonist occupies the receptor without initiating the transduction step (it has no intrinsic activity or efficacy). The intrinsic activity of a drug defines the ability of the drug-receptor complex to initiate a pharmacologic effect. Drugs that produce less than a maximal response have a lowered intrinsic activity and are called partial agonists. Partial agonists also have antagonistic properties, because by binding the receptor site, they block access of full agonists to the receptor site. Morphine and related opiates are mu agonists and drugs that block the effects of opiates at the mu receptor, such as naloxone, are designated antagonists. The opioids most commonly used in anesthetic practice and in the management of pain are mu agonists (table IV). These include morphine, meperidine, methadone, and the fentanyl (s). Mixed agonist-antagonist drugs act as agonists or partial agonists at one receptor and antagonists at another receptor. Mixed (opioid) agonist - antagonist drugs include pentazocine, butorphanol, nalorphine, and nalbuphine. Most of these drugs are

Table V. Actions of opioids at receptor subtypes

Drug	μ	κ	σ
Morphine	Agonist	Agonist	
Naloxone	Antagonist	Antagonist	Antagonist
Naltrexone	Antagonist		
Pentazocine	Antagonist	Agonist	Agonist
Butorphanol		Agonist	Agonist
Nalbuphine	Antagonist	Partial agonist	Agonist

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agonists or partial agonists at the kappa and sigma receptors and antagonists at the mu receptor (table V).

The mu receptor and its sub species and the delta receptor produce analgesia, respiratory depression, euphoria, and physical dependence. Morphine is fifty to one hundred times weaker at the delta than at the mu receptor. By contrast, the endogenous opiate-like neurotransmitter peptides known as the enkephalins tend to be more potent at delta and kappa than mu receptors. The kappa receptor, located primarily in the spinal cord, produces spinal analgesia, miosis, and sedation with minimal associated respiratory depression. Indeed, this may have important clinical significance. As tolerance develops, increasing doses of morphine are required to produce effective analgesia. It is intriguing to speculate that at higher doses the analgesia produced by morphine occurs by its delta and kappa effects rather than by its mu agonist activity. Finally, the sigma receptor is responsible for the psychotomimetic effects observed with some opiate drugs particularly the mixed agonist- antagonist drugs. These effects include dysphoria and hallucinations.

A number of studies suggest that the respiratory depression and analgesia produced by mu agonists involve different receptor subtypes. These receptors change in number in an age-related fashion and can be blocked by naloxone. Pasternak et al. working with newborn rats, showed that 14- day - old rats are 40 times more sensitive to morphine analgesia than 2-day-old rats. Nevertheless, morphine depresses the respiratory rate in 2-day-old rats to a greater degree than in 14 - day - old rats. Thus, the newborn may be particularly sensitive to the respiratory depressant effects of the commonly administered opioids in what may be an age-related receptor phenomenon. Obviously this has important clinical implications for the use of narcotics in the newborn.

PHARMACOKINETICS

To relieve or prevent pain, the agonist must get to the receptor in the central nervous system. There are essentially two ways that this occurs, either via the blood stream (following intravenous, intramuscular, oral, nasal, transdermal or mucosal administration) or by direct application (intrathecal or epidural) into the cerebrospinal fluid (CSF). Agonists administered via the blood stream must cross the blood-brain barrier, a lipid membrane interface between the endothelial cells of the brain vasculature and the extracellular fluid of the brain, to reach the receptor. Normally, highly lipid soluble agonists, such as fentanyl, rapidly diffuse across the blood brain barrier, whereas, agonists with limited lipid solubility, such as morphine, have limited brain uptake. The blood brain barrier may be immature at birth and is known to be more permeable to morphine. Indeed, Way et al demonstrated that morphine concentrations were 2-4 times greater in the brains of younger rats than older rats despite equal blood concentrations.

Spinal administration, either intrathecally or epidurally, bypasses the blood and directly places an agonist into the CSF which bathes the receptor sites in the spinal cord (substantia gelatinosa) and brain. This "back door" to the r
reduces the amount of agonist need
After spinal administration, opioids are abso
the epidural veins and redistributed to the systemic circulation where they are metabolized and excreted. Hydrophilic agents, such as morphine, cross the dura more slowly than more lipid soluble agents such as fentanyl or meperidine. This phyisco-chemical property is responsible for the more prolonged duration of action of spinal morphine and its very slow onset of action following epidural administration.

Although it would be desirable to adjust opioid dosage based on the concentration of drug achieved at the receptor site, this is rarely feasible. The alternative is to measure blood or plasma concentrations and model how the body handles a drug. Pharmacokinetic studies thereby help the clinician select suitable routes, timing and dosing of drugs to maximize a drug's dynamic effects.

Following administration, the disposition of a drug is dependent on distribution ($t_{1/2}\alpha$) and elimination. The terminal half-life of elimination $t_{1/2}\beta$ is directly proportional to the volume of distribution (Vd) and inversely proportional to the total body clearance (Cl) by the following formula:

$$t_{1/2}\beta = 0.693 \times (Vd/Cl)$$

Thus, a prolongation of the $t_{1/2}\beta$ may be due to either an increase in a drug's volume of distribution or by a decrease in its clearance.

Morphine, meperidine, methadone, codeine, and fentanyl are biotransformed in the liver prior to excretion. Many of these reactions are catalyzed in the liver by microsomal mixed-function oxidases that require the cytochrome P_{450} system, NADPH, and

oxygen. The cytochrome P_{450} system is very immature at birth and does not reach adult levels until the first month or two of life. This immaturity of this hepatic enzyme system may explain the prolonged clearance or elimination of some opioids in the first few days to weeks of life. On the other hand, the P_{450} system can be induced by various drugs (phenobarbital) and substrates and matures regardless of gestational age. Thus, it is the age from birth, and not the duration of gestation, that determines how premature and full term infants metabolize drugs. Indeed, Greeley et al have demonstrated that sufentanil is more rapidly metabolized and eliminated in 2-3 week old infants than newborns less than a week of age. Finally, morphine is primarily glucuronidated into 2 forms, an inactive form, morphine-3-glucuronide and an active form, morphine-6-glucuronide. Both glucuronides are excreted by the kidney. In patients with renal failure, the morphine 6-glucuronide can accumulate and cause toxic side-effects including respiratory depression. This is important to consider not only when prescribing morphine but when administering other opioids that are metabolized into morphine such as methadone and codeine.

Whereas morphine and fentanyl are primarily glucuronidated into inactive forms that are excreted by the kidney, approximately 1/3 of meperidine is demethylated into normeperidine, a metabolite which is half as active as meperidine as an analgesic but twice as active as a convulsant. *Because of the propensity of normeperidine to produce seizures, I believe that meperidine should not be prescribed for either acute or chronic pain management.*

Fentanyl is highly lipid soluble and is rapidly distributed to tissues that are well perfused, such as the brain and the heart. Normally, the effect of a single dose of fentanyl is terminated by rapid redistribution, rather than by elimination, in a manner very much akin to thiopental. However, following multiple or large doses of fentanyl *(e.g.,* when it is used as a primary anesthetic agent), prolongation of effect will occur, because elimination and not distribution will determine the duration of effect (see below). This is particularly important in the newborn, where elimination may be further prolonged by abnormal or decreased liver blood flow following acute illness or abdominal surgery. Additionally, certain conditions that may raise intro-abdominal pressure may further decrease liver blood flow by shunting blood away from the liver via the still patent ductus venosus.

Table VI. Morphine pharmacokinetics

	Premature (< 33 wks)	Full term	Adult
$t_{1/2}\beta$	7.4 ± 1.7	6.7 ± 4.6	3.0
Clearance (ml/kg/min)	9.6 ± 4.0	15.5 ± 10.0	3.2
D_v L/kg	5.18 ± 1.6	2.9 ± 2.1	15

The pharmacokinetics of morphine and fentanyl have been extensively studied in adults, older children, and in the premature and full term newborn. Following an intravenous bolus, 30% of morphine is protein bound in the adult v only 20% in the newborn. This increase in unbound ("free") morphine allows a greater proportion of active drug to penetrate the brain. This may explain, in part, the observation of Way et. al. of increased brain levels of morphine in the newborn and its more profound respiratory depressant effects. The elimination half life of morphine in adults and older children is 3-4 hours and is consistent with its duration of analgesic action (table VI). The trip is more than twice as long in newborns less than a week of age than older children and adults and is even longer in premature infants. Clearance is similarly decreased in the newborn compared to the older child and adult (table VI). Thus, infants less than one month of age will attain higher serum levels that will decline more slowly than older children and adults. This may also account for the increased respiratory depression associated with morphine in this age group.

Interestingly, the half-life of elimination and clearance of morphine in children older than two months of age is similar to adult values. Thus the hesitancy in prescribing and administering morphine in children less than 1 year of age may not be warranted. On the other hand, the use of any opioid in children less than 2 months of age most be limited to a monitored, intensive care unit setting.

Based on its relatively short half-life (3-4 h), one would expect older children and adults to require morphine supplementation every two to three hours when being treated for pain, particularly if the morphine is administered intravenously. This has led to the recent use of continuous infusion regimens of morphine and patient controlled analgesia (see below) which maximize pain-free periods. Alternatively longer acting agonists such as methadone may be used. Methadone is metabolized extremely

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slowly in children and has a very prolonged duration of action.

The $t_{1/2}\beta$ of methadone averages 19 hours and clearance averages 5.4 $ml/min^{-1}/kg^{-1}$.

Finally only about 30% of an orally administered dose of morphine reaches the systemic circulation. In the past, this led many to believe that morphine was ineffective was administered orally. This isn't true and was the result of failing to provide sufficient morphine. *When converting a patient's intravenous morphine requirements to oral maintenance, one needs to multiply the intravenous dose by* 3-4. Oral morphine is available as a liquid (20 mg/mL), tablet, and as a sustained release preparation (MS-Contin®). Because it so concentrated, the liquid is particularly easy to administer to children and severely debilitated patients. Indeed, in terminal patients who can not swallow, liquid morphine will provide analgesia even if it is simply dropped into the patients mouth. The sustained release tablet can not be crushed and therefore can not be given via a gastrostomy or naso-gastric tube.

Fentanyl and its structurally related relatives, sufentanil, alfentanil, and remifentanil are highly lipophilic drugs that rapidly penetrate all membranes including the blood brain barrier. Following an intravenous bolus, fentanyl is rapidly eliminated from plasma as the result of its extensive uptake by body tissues. The fentanyl is highly bound to alpha-1 acid glycoproteins in the plasma, which are reduced in the newborn. The fraction of free unbound sufentanil is significantly increased in neonates and children less than a year of age (19.5±2.7 and 11.5 ±3.2 percent respectively) compared to older children and adults (8.1 ± 1.4 and 7.8 ± 1.5 percent respectively) and this correlates to levels of alpha-1 acid glycoproteins in the blood.

Fentanyl pharmacokinetics differs between newborn infants, children and adults. The total body clearance of fentanyl is greater in infants 3-12 months of age than in children older than 1 year of age or adults (18.1 ± 1.4, 11.5 ± 4.2, and 10.0 ± 1.7 ml/kg-1/min-1, respectively) and the half life of elimination is longer (233 ± 137, 244 ± 79, and 129 ± 42 min respectively). The prolonged elimination half-life of fentanyl from plasma has important clinical implications. Repeated doses of fentanyl for maintenance of analgesic effects will lead to accumulation of fentanyl and its ventilatory depressant effects. Very large doses (0.05 - 0.10 mg kg-1 as used in anesthesia) may be expected to induce long-lasting effects because plasma fentanyl levels will not fall below the threshold level at which spontaneous ventilation occurs during the distribution phases. On the other hand, the greater clearance of fentanyl in infants greater than 3 months of age produces lower plasma concentrations of the drug and may allow these children to tolerate more drug without respiratory depression.

Remifentanil is a new μ-opioid receptor agonist with unique pharmacokinetic properties. The pharmacokinetics of remifentanil is characterized by small volumes, rapid clearances, and low variability compared to other intravenous anesthetic drugs. The drug has a rapid onset of action (half- time for equilibration between blood and the effect compartment = 1.3 min) and a short context- sensitive half-life (3-5 min). The latter property is attributable to hydrolytic metabolism of the compound by non-specific tissue and plasma esterases. Virtually all (99.8%) of an administered remifentanil dose is eliminated during the a half-life (0.9 minutes) and b half-life (6.3 minutes). The pharmacokinetics of remifentanil suggest that within 10 minutes of starting an infusion, remifentanil will nearly reach steady state. Thus, changing the infusion rate of remifentanil will produce rapid changes in drug effect. The rapid metabolism of remifentanil and its small volume of distribution mean that remifentanil will not accumulate. Discontinuing the drug rapidly terminates its effects. Finally, the primary metabolite has little biologic activity making it sate even in patients with renal disease. Remifentanil may have important applications intraoperatively and in acute pain management, particularly in patients with renal or liver disease.

CODEINE AND OXYCODONE

Codeine and oxycodone (the opioid in Tylox® and Percocet®) are opiates which are frequently used to treat pain in children and adults, particularly for less severe pain or when patients are being converted from parenteral narcotics to enteral ones. Although effective when administered either orally or parenterally, they are most commonly administered in the oral form, usually in combination with acetaminophen (Tylox®, Percocet®) or aspirin. In equipotent doses codeine's and oxycodone's efficacy as analgesics and respiratory depressants approaches that of morphine. In addition, codeine and oxycodone share with morphine and the other narcotics common effects on the central nervous system including sedation, respiratory depression, and stimulation of

the chemoreceptor trigger zone in the brain stem. Indeed, the latter is particularly true for codeine. Codeine is very nauseating and many patients claim they are "allergic" to it because it so commonly induces vomiting. There are much fewer nausea and vomiting problems with oxycodone. Indeed, because of this, oxycodone is now my preferred oral opioid (I rarely prescribe codeine). Both drugs delay gastric emptying and can increase biliary tract pressure. Finally, codeine like all mu-agonist opioids has potent antitussive properties and is commonly prescribed for this effect.

Codeine and oxycodone have a bioavailability of approximately 60 % following oral ingestion. The analgesic effects occur as early as 20 minutes following ingestion and reach a maximum at 60-120 minutes. The plasma half-life of elimination is 2.5 - 4 hours. Codeine undergoes nearly complete metabolism in the liver prior to its final excretion in urine. Approximately 10% of codeine is metabolized into morphine and it is this 10% that is responsible for codeine's analgesic effect. Interestingly, approximately 10% of the population can not metabolize codeine into morphine and in these patients codeine will have no analgesic effects (another reason why oxycodone may be the better oral opioid...).

Oral codeine and oxycodone are almost always prescribed in combination with either acetaminophen or aspirin (Tylenol and codeine elixir, Percocet, Tylox). If prescribing acetaminophen and codeine I recommend the combination compound for most children. When prescribed as a single agent, codeine is not readily available in liquid form at most pharmacies and is almost twice as expensive as the combined form. Furthermore, acetaminophen potentiates the analgesia produced by codeine and allows the practitioner to use less narcotic and yet achieve satisfactory analgesia. Progressive increases in dose are associated with a similar degree of respiratory depression, delayed gastric emptying, nausea and constipation as with other opioid drugs. Although it is an effective analgesic when administered parenterally, intramuscular codeine has no advantage over morphine or meperidine (despite 100 years of neurosurgical gospel). Intravenous administration of codeine is associated with serious complications including apnea and severe hypotension, probably secondary to histamine release. Therefore, I do not recommend the intravenous administration of this drug in children.

Codeine and oxycodone are available in liquid, tablet, and capsule form. Typically, codeine is prescribed in a dose of 0.5 - 1 mg/kg^{-1} and oxycodone is prescribed in a dose of 0.05 - 0.1 mg kg^{-1}. Both are usually prescribed in brand name (or generic) compounds that contain acetaminophen (or aspirin) as well. In tablet form oxycodone is commonly available as Tylox (500 mg acetaminophen + 5.0 mg oxycodone) and as Percocet (325 mg acetaminophen + 5.0 mg oxycodone). Codeine and acetaminophen are commonly prescribed as "numbered" tablets, e.g., Tylenol number 1,2, 3, or 4. This number refers to how much codeine is in each tablet. Tylenol number 4 has 15 mg of codeine, number 3 has 30 mg, number 2 has 60 mg. Acetaminophen and codeine elixirs are available in virtually every pharmacy and contain 120 mg acetaminophen and 12 mg codeine per teaspoon (5 mL). Oxycodone liquid is not available in many pharmacies. When it is it comes as 1 mg/mL.

PATIENT CONTROLLED ANALGESIA

Because of the enormous individual variations in pain perception and opioid metabolism, fixed

Table VII. Intravenous PCA treatment guidelines

Drug (concentration mg/ml)	Basal rate (mg/kg/hr)	Bolus rate range (mg/kg)	Lock out interval range (minutes)	Number of boluses/hr (range)
Morphine (1.0) In older patients or dependent patients, concentrations can be increased to 10 mg/ml	0.01 - 0.03 (10 - 30 mg; usually 20 mg)	0.01 - 0.03 (usually 0.02)	5 - 10 (usually 8 minutes)	2 - 6 (usually 5)
Fentanyl (0.01 in children < 20 kg; 0.05 in children > 50 kg)	0.0005 (0.5 mg)	0.0005 - 0.001 (0.5 - 1.0 mg)	5 - 10	1 - 6
Hydromorphone (0.2 in children < 50 kg; 0.5 - 1.0 in children > 50 kg)	0.003 - 0.005 (3 - 5 mg; usually 4 mg)	0.003 - 0.005 (3 - 5 mg; usually 0.004)	5 - 10 (usually 8 minutes)	2 - 6 (usually 5)

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("Harriet Lane") doses and time intervals make little sense. Based on the pharmacokinetics of the opioids, it should be clear that intravenous boluses of morphine or meperidine may need to be given at intervals of 1-2 hours in order to avoid marked fluctuations in plasma drug levels. Continuous intravenous infusions can provide steady analgesic levels and are preferable to intramuscular injections but are not a panacea because the perception and intensity of pain is not constant. Indeed, the most common method of opioid administration in adults and children is intramuscular injection. It is well known that children will suffer in silence and under report their level of pain, rather than ask for yet another painful stimulus, namely, the "shot". Thus, rational pain management requires some form of titration to effect whenever an opioid is administered. In order to give patients some measure of control over their pain therapy, demand analgesia or patient controlled analgesia (PCA) devices have been developed. These are microprocessor driven pumps with a button that the patient presses to self-administer a small dose of opioid.

PCA devices allow patients to administer small amounts of an analgesic whenever they feel a need for more pain relief. The opioid, usually morphine, is administered either intravenously or subcutaneously. The dosage of opioid, number of boluses per hour, and the time interval between boluses (the "lock-out period") are programmed into the equipment by the pain service physician to allow maximum patient flexibility and sense of control with minimal risk of overdosage (table VII). Generally, because patients know that if they have severe pain they can obtain relief immediately, many prefer dosing regimens that result in mild to moderate pain in exchange for fewer side effects such as nausea or pruritus. Typically, I initially prescribe morphine, 20 μg/kg per bolus, at a rate of 5 boluses/hour, with a 6-8 minute lock-out interval between each bolus (table VII). Variations include larger boluses (30-50 μg/kg shorter time intervals (5 min), etc. Hydromorphone has fewer side effects than morphine and is often used when pruritus and nausea complicate morphine PCA therapy. Because it is 5-7 times more potent than morphine the size of the bolus dose is reduced to 3-4 μg/kg. The PCA pump computer stores within its memory how many boluses the patient has received as well as how many attempts the patient has made at receiving boluses. This allows the physician to evaluate how well the patient understands the use of the pump and provides information to program the pump more efficiently.

Many PCA units allow low "background" continuous infusions (morphine, 20-30 μg/kg/hour, hydromorphone 3-4 μg/kg/hr) in addition to self-administered boluses. This is sometimes called "PCA-Plus". A continuous background infusion is particularly useful at night and often provides more restful sleep by preventing the patient from awakening in pain. It also increases the potential for overdosage. Although the literature on pain does not support the use of continuous background infusions, it has been my experience that continuous infusions are essential for both the patient and me (fewer phone calls, problems, etc.). Indeed, in my practice, I almost always use continuous background infusions when I prescribe IV (or epidural) PCA.

PCA requires a patient with enough intelligence and manual dexterity and strength to operate the pump. Thus, it was initially limited to adolescents and teenagers, but the lower age limit in whom this treatment modality can be used continues to fall. In fact, it has been my experience that any child able to play Nintendo® can operate a PCA pump (age 5-6). Furthermore, in my practice I empower nurses and parents to initiate PCA boluses and use this technology in children less than even a year of age. Difficulties with PCA include its increased costs, patient age limitations, and the bureaucratic (physician, nursing, and pharmacy) obstacles (protocols, education, storage arrangements) that must be overcome prior to its implementation. Contraindications include inability to push the bolus button (weakness, arm restraints), inability to understand how to use the machine, and a patient's desire not to assume responsibility for his/her own care.

INTRATHECAL/EPIDURAL OPIOID ANALGESIA

As mentioned previously, the presence of high concentrations of opioid receptors in the spinal cord makes it possible to achieve analgesia, in both acute and chronic pain, with small doses of opioids administered in either the subarachnoid or epidural spaces. By bypassing the blood and the blood- brain barrier, small doses of agonist are effective because they can reach the receptor by the "back- door". Indeed, CSF opioid levels, particularly for morphine, are several thousand times greater than those achieved by the parenteral route (see below).

It is these high levels that produce the profound and prolonged analgesia that accompanies intrathecal/epidural opioid administration.

The passage of epidurally administered agonists across the dura into the CSF is dependent on the lipid solubility of the drug. Additionally, once in the CSF, opioids must pass from the water phase of the CSF into the lipid phase of the underlying neuraxis to reach the receptor. This too is dependent on lipid solubility. Hydrophilic agents such as morphine will have a greater latency and duration of action than more lipid soluble agents such as fentanyl. On the other hand, the lipid soluble agonists (e.g., fentanyl) produce more segmental analgesia with less rostral spread than the less lipid soluble agonists.

Even when administered via the caudal route, epidural morphine has been shown to provide effective postoperative analgesia following abdominal, thoracic, and cardiac surgery. Krane et al. reported that 0.03 mg/kg of caudal-epidural morphine is equally effective as 0.1 mg/kg in providing post operative analgesia, although the higher dose provides a significantly longer duration of analgesia (13.3 ± 4.7 v 10.0 ± 3.3 hours, respectively). The incidence of side effects was the same in both groups, although one patient receiving 0.1 mg/kg developed late respiratory depression. Therefore, these investigators suggest starting with the lower dose when using this technique. Whether even lower doses would be effective is unknown.

Spinal opiates produce analgesia without altering autonomic or neuromuscular function. Additionally both light touch and propioception are preserved. Thus, unlike local anesthetics, spinal opioids allow patients to ambulate without orthostatic hypotension. Common side effects of intrathecal/epidural narcotics include facial or segmental pruritus, urinary retention, nausea and vomiting, and respiratory depression. These side effects occur with greater frequency when opioids are administered intrathecally as opposed to epidurally. Except for urinary retention, reversal of adverse side effects, with maintenance of adequate analgesia, can be achieved through the use of a low dose (0.001-0.002 $mg.kg^{-1}$) naloxone infusion. Pruritus and nausea can also be treated with intravenous or oral diphenhydramine (Benadryl®), 0.5-1.0 mg/kg or hydroxyzine (Vistaril®, Atarax®) 0.5-1.0 mg/kg, or intravenous butorphanol (Stadol) (a mixed opioid agonist/antagonist) 0.03-0.05 mg/kg. Urinary retention has not been a reported complication in children because in the majority of pediatric patients studied to date, all patients have had bladder catheters as part of their post-operative management regimen.

Although rare, respiratory depression is a major risk when utilizing intrathecal/epidural opioids. Attia et al. demonstrated that the ventilatory response to CO_2 is depressed for as long as 22 hours following the administration of 0.05 mg/kg^{-1} of morphine epidurally. Following intrathecal morphine administration (0.02 mg/kg), Nichols et al demonstrated, in children varying between 3 month and 15 years, significant depression of the ventilatory response to carbon dioxide for up to 18 hours. The greatest respiratory depression correlated with the highest CSF morphine levels (2,863 ± 542 ng/mL) which occurred 6 hours after administration. This depression persisted despite a fall in CSF morphine levels 12 (641 ± 219 ng/mL) to 18 (223 ± 152 ng/mL) hours later.

This confirms the clinical impression that respiratory depression usually occurs within the first six hours after the administration of epidural or intrathecal morphine but may occur as long as 18 hours afterward.

In clinical practice, respiratory depression most commonly occurs when intravenous or intramuscular narcotics have been administered to supplement the intrathecal opioid. The risk of respiratory depression can be minimized if smaller doses of supplemental narcotics are used, or through the epidural use of shorter acting, more lipid soluble agents (fentanyl, sufentanil), which produce more segmental analgesia, with little rostral spread.

On the other hand, because of its shorter duration of action, fentanyl and sufentanil are increasingly being administered by continuous epidural infusion, either alone or in combination with very dilute (1/16%, [0.0625 mg/mL] or 0.1% [1.0 mg/mL]) bupivacaine or lidocaine (1-5 mg/mL) concentrations. Typically, the epidural solution contains 1-5 μg/mL of fentanyl, with or without bupivacaine or lidocaine, and is administered at rates ranging between 0.5 and 1.0 μg/kg/hr . This provides effective analgesia for both post-operative and chronic cancer pain. In my experience, fentanyl doses higher than 0.75-1.0 μg/kg/hr inevitably result in pruritus.

Regardless of the opioid and route of administration a regular system of monitoring for respiratory depression is required. Clinical signs that predict impending respiratory depression include somnolence, small pupils, and small tidal volumes. I also insist on the use of oxyhemoglobin saturation moni-

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toring ("pulse oximetry"), particularly in the first 24 hours of instituting this therapy.

TRANSDERMAL AND TRANSMUCOSAL FENTANYL

Because fentanyl is extremely lipophilic it can be readily absorbed across any biologic membrane including the skin. Thus, it can be given painlessly by new, non-intravenous routes of drug administration including the transmucosal (nose and mouth) and transdermal routes. The transdermal route is frequently used to administer many drugs chronically including scopolamine, clonidine, and nitroglycerin. A selective semipermeable membrane patch with a reservoir of drug allows for the slow, steady state absorption of drug across the skin. Transdermal fentanyl is contraindicated for acute pain management and is applicable only for patients with chronic pain (e.g., cancer) or in dependent patients. The use of this drug delivery system for acute pain has resulted in the death of an otherwise healthy patient. Additionally, the safety of this drug delivery system is compromised even further, because fentanyl will continue to be absorbed from the subcutaneous fat for almost 24 hours after the patch is removed.

On the other hand, the transmucosal route of fentanyl administration is extremely effective for acute pain relief and heralds a new era in the management of acute pain management in children. In this novel delivery technique, fentanyl is manufactured in a candy matrix (Fentanyl Oralet®) attached to a plastic applicator (it looks like a lollipop); as the child sucks on the candy, fentanyl is absorbed across the buccal mucosa and is rapidly (10-20 min) absorbed into the systemic circulation. If excessive sedation occurs, the fentanyl is removed from the child's mouth by the applicator. The Fentanyl Oralet® has been approved by the FDA for use in children for premedication prior to surgery and for procedure related pain (lumbar puncture, bone marrow aspiration, etc.). When administered by this route, fentanyl is given in doses of 10-15 µg/kg 10-15 µg/kg is effective within 20 minutes, and lasts approximately 2 hours. Approximately 25-33% of the given dose is absorbed. Thus, when administered in doses of 10-15 µg/kg blood levels equivalent to 3-5 µg/kg IV fentanyl are achieved.

The major side-effect, nausea and vomiting, occurs in approximately 20-33% of patients who receive it. This product is only available in hospital (and Surgicenter) pharmacies and will, like all sedative/analgesics, require vigilant patient monitoring.

LOCAL ANESTHETICS

The use of local anesthetics in pediatric practice has recently undergone a revolutionary metamorphosis. For decades children were considered poor candidates for regional anesthetic techniques because of their overwhelming fear of needles. However, once it was recognized that regional anesthesia could be used as an adjunct, and not a replacement for general anesthesia, its use has increased exponentially. Furthermore, since catheters placed in the epidural, pleural, and other spaces can be used for days or months, local anesthetics are increasingly being used for postoperative, neuropathic, and terminal pain relief. To be used safely, a working knowledge of the differences in how local anesthetics are metabolized in infants and children is necessary (tables VIII-X).

The ester local anesthetics are metabolized by plasma cholinesterase. Neonates and infants up to six months of age have less than half of the adult levels of this plasma enzyme. Clearance may thereby be reduced and the effects of ester local anesthetics prolonged. Amides, on the other hand, are metabolized in the liver and bound by plasma proteins. Neonates and young infants (less than 3 months of age) have reduced liver blood flow and immature metabolic degradation pathways. Thus, larger fractions of local anesthetics are unmetabolized and remain active in the plasma than in the adult. More local anesthetic is excreted in the urine unchanged. Furthermore, neonates and infants may be at increased risk for the toxic effects of amide local anesthetics because of lower levels of albumin and alpha-1 acid

Table VIII. Comparative pharmacology of local anesthetics

Classification	Potency	Onset	infiltration (min)
Esters			
Procaine	1	slow	45 - 60
Chloroprocaine	4	rapid	30 - 45
Tetracaine	16	slow	60 - 180
Amides			
Lidocaine	1	rapid	60 - 120
Mepivacaine	1 - 2	slow	90 - 180
Bupivacaine	4 - 8	slow	240 - 480
Etidocaine	4 - 8	slow	240 - 480
Prilocaine	1	slow	60 -120

Table IX. Suggested maximal doses of local anesthetics (mg/kg)*

Drug (Concentration)[&]	Spinal	Caudal/Lumbar/ Epidural	Peripheral[†]	Subcutaneous[†]
Esters				
Cloroprocaine (1.0% infiltration) (2 - 3% epidural)	NR	8 - 10[§]	8 - 10[§]	8 - 10[§]
Procaine	NR	NR	8 - 10[§]	8 - 10[§]
Tetracaine (0.5% - 1.0%)	0.2 - 0.6[‡]	NR	NR	NR
Amides				
Lidocaine (0.5% - 1.0% infiltration) (1 - 2% peripheral, epidural, subcutaneous) (5% spinal)	1 - 2.5	5 - 7[§]	5 - 7[§]	5 - 7[§]
Bupivacaine (0.625 - =.5%) (0.125 - 0.5% infiltration) (0.25 - 0.5% peripheral, epidural, subcutaneous)	0.3 - 0.5	2 - 3[§]	2 - 3[§]	2 - 3[§]
Etidocaine (0.5 - 1.0%)	NR	3 - 4[§]	3 - 4[§]	3 - 4[§]
Prilocaine (0.5 - 1.0% infiltration) (1 - 1.5% peripheral) (2 - 3% epidural)	NR	5 - 7[§#]	5 - 7[§#]	5 - 7[§#]

* These are suggested safe upper limits; direct intraarterial or intravenous injection of even a fraction of these doses may result in systemic alteration or death. [†]Epinephrine should never be added to local anesthetic solution administered in area of an artery (e.g., penile nerve block); [‡] The minimal effective dose in children < 10 kg is 1.2 - 2 mg. [§] The higher dose is recommended only with the concomitant use of epinephrine 1:200,000. [#] Total adult dose should not exceed 600 mg. NR: Not recomended. [&] Concentrations are in mg percent. For example a 1% solution contains 10 mg/ml.

glycoproteins which are proteins essential for drug binding. This leads to increased concentrations of free drug and potential toxicity, particularly with bupivacaine. On the other hand, the larger volume of distribution at steady state seen in the neonate for these (and other) drugs may confer some clinical protection by lowering plasma drug levels.

Table X. Use of local anesthesia to produce regional anesthesia

Classification	Topical	Local Infiltration	Peripheral Nerve Block	Intravenous Regional (Bier)	Epidural	Spinal
Esters						
Procaine	No	Yes	Yes	No	No	No
Chloroprocaine	No	Yes	Yes	No	Yes	No
Tetracaine	Yes	No	No	No	No	Yes
Amides						
Lidocaine	Yes	Yes	Yes	Yes	Yes	Yes
Mepivacaine	No	Yes	Yes	No	No	No
Bupivacaine	No	Yes	Yes	No	No	Yes
Etidocaine	No	Yes	Yes	No	No	No
Prilocaine	No	Yes	Yes	Yes	Yes	No

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The metabolism of the amide local anesthetic prilocaine is unique in that it results in the production of oxidants that can lead to the development of methemoglobinemia. This occurs in adults with doses of prilocaine greater than 600 mg. Because premature and full term infants have decreased levels of methemoglobin reductase, they are more susceptible to developing methemoglobinemia. An additional factor rendering newborns more susceptible to methemoglobinemia is the relative ease by which fetal hemoglobin is oxidized compared to adult hemoglobin. Because of this, prilocaine can not be recommended for routine use in neonates. Unfortunately, this may limit the use of an exciting new topical local anesthetic, EMLA (eutectic mixture of local anesthetics), in the newborn..Nevertheless, a single dose, is safe and has been shown to be extremely effective in the management of newborn circumcision.

Fortunately, cardiovascular and central nervous system toxicity have rarely been observed in children following local anesthetic administration, although they do occur.

The hemodynamic response to regional anesthesia, even after fairly extensive epidural blockade (cutaneous analgesia below T4-T5), is minimal in children compared to adults. Convulsions have rarely been noted to date, probably because they may be masked or the seizure threshold may be increased by the concomitant use of sedatives, particularly the benzodiazepines. Local anesthetic toxicity can be limited by careful attention to dose, route of administration, and rapidity of absorption of local anesthetic into the systemic circulation.

EMLA

EMLA (eutectic mixture of local anesthetics) cream, a topical emulsion composed of prilocaine and lidocaine, produces complete anesthesia of intact skin following application. Unfortunately, for best effect, EMLA cream must be applied and covered with an occlusive dressing (such as Sagan® wrap or Tegaderm®) for 60 minutes prior to performing a procedure. This limits its use in the emergency room or office to situations in which the site can be prepared well in advance of anticipated use. Furthermore, if the procedure is a venipuncture, multiple sites must be prepared, in case one's initial attempt is unsuccessful.

Unfortunately, the effectiveness of EMLA cream (like all other methods) at reducing pain is dependent on who makes the assessment. Soliman et al. studied the efficacy of EMLA cream compared to injected lidocaine at reducing the pain associated with venipuncture. Both an observer and a physician performing the procedure judged pain relief to be virtually complete in both groups. The children involved in the study were not so sanguine and wore equally dissatisfied with both methods, particularly if the needle used for venipuncture was visible to them. Thus, despite the fact that two observers felt that the child was pain free, the child's cooperation with venipuncture did not improve. Therefore it is not clear whether the delay which is involved in the use of EMLA (30-60 minute wait for effect) is justified. On the other hand, EMLA may be more effective in children accustomed to frequent medical procedures (e.g. oncology patients) or for procedures in which the child cannot see the needle such as lumbar puncture or bone marrow aspiration (although there is little evidence to support the effectiveness of EMLA even in these situations). Finally, as discussed above, it appears to be both safe and effective in the treatment of newborn circumcision.

CONTINUOUS EPIDURAL ANALGESIA

Continuous or intermittent epidural analgesia using local anesthetics administered either alone or in combination with opioids block nociceptive impulses from entering the central nervous system and thereby provides profound analgesia without producing systemic sedation or hemodynamic changes (hypotension). Epidural analgesia has become the most commonly performed regional anesthetic technique for the intra- and post - operative management of patients with urologic, orthopedic, and general surgical procedures below the T_4 dermatomal level in children. It has been used to provide continuous sympathetic blockade in children with vascular insufficiency secondary to intense vasoconstriction (e.g., purpura fulminans), in patients with cancer unresponsive to parenteral and enteral opioids, and in the management of sickle cell vase-occlusive crisis.

Epidural catheters can be inserted at the caudal, lumbar, or thoracic level. Obviously, the closer the tip of the catheter lies to the dermatome to be blocked the smaller the amount of drug needed to produce neural blockade. Since local anesthetic toxicity is directly related to the total amount of drug infused catheter placement plays a very important role in the overall safety of this technique. Epidural placement via the caudal and lumbar approach is most common. Indeed, because the epidural space

of young children is filled with loosely packed fat and blood vessels (compared to adults), it is possible to advance a caudally (or lumbar) placed catheter as far as the thorax. Bosenberg et al. first reported the use of the caudal approach for thoracic placement of an epidural catheter in children less than 2 years of age. Gunter et al extended this observation to older children as well. Indeed, in my own practice, caudal insertion and threading 8-10 cm catheter is the preferred epidural technique for most surgery below T4 in children less than 8-10 years of age.

Continuous infusions provide pain relief during the entire period of infusion. This makes it very attractive for post-operative pain management and pain management where conventional therapy has proven ineffective (e.g., cancer, sickle cell crisis). Initially, high doses of local anesthetics, similar to those used intro-operatively, were used post- operatively and this resulted in local anesthetic toxicity. Dilute concentrations given at much lower doses turned out to provide sensory and autonomic blockade without risking local anesthetic toxicity. As an added benefit, the lower concentrations of local anesthetics do not produce motor blockade, a side effect of local anesthetic administration that is disliked by patients, parents, and surgeons alike. Very dilute concentrations of local anesthetics (0.625-1.25 mg/mL bupivacaine, 1.0-5.0 mg/mL lidocaine) were found to be effective when they were combined with opioids.

In North America, the most commonly used local anesthetic in continuous epidural blockade is bupivacaine. Bupivacaine is administered in concentrations ranging from 0.625 mg/mL ($1/16^{th}$ % solution) to as high as 2.5 mg/mL (0.25 % solution). Concentrations above 1.25 mg/mL (1/8 % solution) are rarely required for post-operative or medical analgesia and significantly increase the risk of toxicity and unwanted side-effects (sensory, motor, autonomic dysfunction, urinary retention, and an inability to walk). Berde in the editorial accompanying the McCloskey's report of bupivacaine toxicity in children recommended that bupivacaine infusions be kept below 0.4 mg/mL/hr . This has become the accepted standard. The most commonly used (and easiest) epidural concentration of bupivacaine is 0.1% (1.0 mg/mL). Fentanyl 2-2.5 μg/mL or hydromorphone (Dilaudid) 10 μg/mL or morphine (Duramorph) 20-30 μg/mL is almost always added to this dilute epidural solution because in concentrations of 1.0 mg/mL bupivacaine does not provide adequate analgesia. Which opioid to use is based on one's experience and, to some degree, on the site of the surgical procedure? For surgical procedures performed above the umbilicus (e.g. Nissen fundoplication, thoracotomy) many people prefer hydromorphone or morphine, because it is slightly less lipophilic than fentanyl and may have better rostral spread.

For pain below the umbilicus, the initial starting infusion is 0.2 mL/kg/hr (0.2 mg/kg/hr bupivacaine; 0.4-0.5 μg/kg/hr fentanyl, or 2 μg/kg/hr hydromorphone, or morphine 6 μg/kg/hr); for pain above the umbilicus the initial starting epidural infusion is 0.3 mL/kg/hr (0.3 mg/kg/hr bupivacaine; 0.6-0.75 μg/kg/hr fentanyl or 3 μg/kg/hr hydromorphone, or morphine 9 μg/kg/hr). Maximum dose: 14-16 mL/hr .

If bupivacaine is used in older children for epidural PCA I use a solution that contains 1.0 mg/mL bupivacaine and either 2.0-2.5 μg/mL of fentanyl or 10 μg/mL hydromorphone or morphine 20-30 μg/mL. The basal solution is administered at a rate that provides 0.2 mg/kg/hr bupivacaine and either 0.4-0.5 μg/kg/hr of fentanyl or 2.0 μg/kg/hr hydromorphone or 4-6 μg/kg/hr morphine. Half of the basal rate is given as a bolus (0.1 mg/kg/bolus bupivacaine, and either 0.2-0.25 μg/kg/bolus fentanyl or 1.0 μg/kg/bolus hydromorphone or 2-3 μg/kg/bolus morphine), with a lockout period of 15 minutes. A maximum of 2 boluses are allowed per hour. This will provide a maximum of 0.4 mg/kg/hr bupivacaine and either 0.8-1.0 μg/kg/hr fentanyl or 4.0 μg/kg/hr hydromorphone or 8-12 μg/kg/hr morphine.

Cardiovascular toxicity due to bupivacaine is the most feared complication of local anesthetic administration, whether it is administered acutely (intermittent dosing) or continuously, because it presents as ventricular dysrhythmias that may be refractory to treatment. Neonates may be at increased risk for bupivacaine toxicity. First, young infants (less than 3 months of age) have reduced liver blood flow and immature metabolic pathways. Thus, larger fractions of amide local anesthetics are unmetabolized and remain active in the plasma. Second, neonates have lower levels of albumin and alpha1-acid glycoproteins, leading to increased concentrations of unbound drug. The larger volume of distribution at steady state in the neonate may confer some clinical protection by lowering plasma drug levels with bolus administration.

The mechanism of action of bupivacaine, blockade of fast Na^+ channels in the plasma membrane, results in both its therapeutic and toxic effects. It

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has a longer duration of action in both the nerve cell membrane and the entire cardiac conducting system than lidocaine because of its greater affinity for sodium channels. In addition, bupivacaine dissociates from the cardiac sodium channel much more slowly than lidocaine resulting in slowing of cardiac conduction. Slowing of the action potential in the Purkinje system leads to prolonged QRS and QT duration which increases the likelihood of reentrant rhythm which may be either ventricular or supraventricular with aberrant conduction (both "wide - complex"). High resolution ventricular epicardial mapping in rabbit hearts has provided the first direct evidence of reentrant ventricular dysrrhythmias via prolongation of ventricular effective refractory period and slowed conduction velocity in a dose and use-dependent manner.

We recently reported the first successful use of phenytoin for the treatment of bupivacaine- induced dysrhythmias. Other therapies including bretylium, prolonged CPR, and even extracorporeal oxygenation and circulatory assist have been suggested in the literature and have had only questionable success. Because lidocaine can be easily measured in most hospital clinical laboratories and it is less cardiotoxic than bupivacaine, I now preferentially use it for continuous local anesthetic infusions and/or for "top up" doses in neonates and young infants in the operating room.

Lidocaine can be administered epidurally by continuous infusion quite easily. Its shorter duration of action, when compared to bupivacaine, is irrelevant if it is administered by continuous infusion. In neonates I use lidocaine in 1.0 mg/mL concentrations administered at a rate of 1.0 mg/kg/hr . Blood levels (50 µL) are measured every 12 hours and the infusion is titrated downward if the lidocaine blood levels are greater than 4 mg/L. In children older than 2 months of age I've found that lidocaine administered in doses of 1.5 mg/kg/hr (lidocaine concentrations of 3-5 mg/mL) is safe and effective. At these doses, lidocaine plasma levels are below 5.0 mg/L in more than 95 % of patients. Nevertheless, there are patients (approximately 2- 5 %) in whom even at these doses blood levels are in the toxic range. Thus vigilance is mandatory. I routinely measure lidocaine levels once a day in all of my patients receiving epidural lidocaine infusions. (Because of their increased risk and relatively poor ability to metabolize the drug, lidocaine levels are measured twice a day in neonates.)

In children who are older than 2 month s and who weigh less than 20 kg, I use lidocaine in 3.0 mg/mL solutions to which fentanyl 1.0 µg/mL is added. The solution is administered at a rate that provides 1.5 mg/kg/hr lidocaine and 0.5 µ/kg/hr of fentanyl. Conveniently the weight in kg divided by 2 of the mixture described provides the right dose in mL/hr (weight in kg * 1.5/ 3, the concentration of lidocaine... which equals weight in kg * 0.5 or the weight divided by 2). In older children weighing more than 20 kg I use a solution that contains 5.0 mg/mL lidocaine and 1.5 µg/mL of fentanyl. The solution is administered at a rate that provides 1.5 mg/kg/hr lidocaine and approximately 0.5 µg/kg/hr of fentanyl (see example below). Conveniently the weight in kg * 0.3 of the mixture described provides the right dose in mL/hr (weight in kg * 1.5/ 5, the concentration of lidocaine...which equals weight in kg * 0.3). The maximum hourly dose is 14-16 mL/hr .

Finally, if lidocaine is used in older children for epidural PCA I use a solution that contains 5.0 mg/mL lidocaine and 2.5 µg/mL of fentanyl. The solution is administered at a rate that provides 1.0 mg/kg/hr lidocaine and 0.5 µg/kg/hr of fentanyl (see example below). Note that in PCA we give lidocaine 1.0 mg/kg/hr and in continuous infusions without PCA we use 1.5 mg/kg/hr .

I've found that when lidocaine is administered in doses greater than 2.0 mg/kg/hr , toxic levels occur much too frequently...) Conveniently if you use the mixture described the basal rate can be calculated by dividing the patient's weight in kg by 5. This provides the right dose in mL/hr (weight in kg * 1.0/ 5, the concentration of lidocaine equals the weight in kg * 0.2 or weight in kg/5). Half of the basal rate is given as a bolus (0.5 mg/kg/bolus lidocaine, 0.25 µg/kg/bolus fentanyl), with a lockout period of 15 minutes. A maximum of 2 boluses are allowed per hour. This will provide a maximum of 2.0 µg/kg/hr lidocaine and 1.0 µ/kg/hr fentanyl.

EXAMPLES

Case 1: a 10 kg, ASA PS 1, I year old who underwent bilateral ureteral reimplantation presents Jar post-operative analgesic management. An epidural catheter was placed intraoperatively.

I would use a continuous infusion of lidocaine plus fentanyl. I want to provide 1.5 mg/kg/hr lidocaine and 0.5 µg/kg/hr fentanyl. I have the pharmacist make a 500 mL bag (3 day solution) of lidocaine 3.0 mg/mL and fentanyl 1.0 µg/mL.

Step 1: 1.5 (mg lidocaine per hour) X 10 kg = 15 mg lidocaine that will be infused per hour

Step 2: 15 mg divided by 3 mg (the concentration of lidocaine

in the epidural solution) = 5 which is the mL/hr to be ordered

Step 3: 5 mL of this solution contains 5 µg of fentanyl which will provide 0.5 µg/kg/hr of fentanyl (5 µg divided by 10 kg)

Step 4: Obtain once a day blood level. If the level is high reduce the infusion. If analgesia is inadequate and the level is low titrate upward.

NOTE: In children less than 20 kg, 0.5 mL/kg of an epidural solution containing lidocaine 3.0 mg/mL and fentanyl 1.0 µg/mL will always produce the desired drug dosing, that is lidocaine 1.5 mg/kg and fentanyl 0.5 µg/kg.

Case 2: a 20 kg, ASA PS 1, 4 year old who underwent bilateral ureteral reimplantation presents for post-operative analgesic management. An epidural catheter was placed intraoperatively.

I would use a continuous infusion of lidocaine plus fentanyl. I want to provide 1.5 mg/kg/hr lidocaine and 0.5 µg/kg/hr fentanyl. I have the pharmacist make a 500 mL bag (3 day solution) of lidocaine 5.0 mg/mL and fentanyl 1.5 µg/mL.

Step 1: 1.5 (mg lidocaine per hour) X 20 kg = 30 mg lidocaine that will be infused per hour

Step 2: 30 mg divided by 5 mg (the concentration of lidocaine in the epidural solution) = 6 which is the mL/hr to be ordered

Step 3: 6 mL of this solution contains 9 µg of fentanyl (6 X 1.5) which will provide 0.45 µg/kg/hr of fentanyl (9, µg divided by 20 kg)

Step 4: Obtain once a day blood level. If the level is high reduce the infusion. If analgesia is inadequate and the level is low titrate upward.

NOTE: In children greater than 20 kg, 0.3 times the weight in kg of an epidural solution containing lidocaine 5.0 mg/mL and fentanyl 1.5 µg/mL will always produce the desired drug dosing, that is lidocaine 1.5 mg/kg and fentanyl 0.5 µg/kg.

Case 3: a 30 kg, ASA PS 1, 10 year old who underwent bilateral ureteral reimplantation presents far post-operative analgesic management. An epidural catheter was placed intraoperatively.

I would use epidural PCA with a continuous infusion of lidocaine plus fentanyl as well as boluses. I want to provide 1.0 mg/kg/hr lidocaine and 0.5 µg/kg/hr fentanyl as a basal infusion. I want to provide 0.5 mg/kg lidocaine and 0.25 µg/kg fentanyl with each bolus. I have the pharmacist make a 500-1,000 mL bag (3 day solution) of lidocaine 5.0 mg/mL and fentanyl 2.5 µg/mL.

Step 1: 1.0 (mg lidocaine per hour) X 30 kg = 30 mg lidocaine that will be infused per hour

Step 2: 30 mg divided by 5 mg (the concentration of lidocaine in the epidural solution) = 6 which is the mL/hr to be ordered as the basal rate

Step 3: 6 mL of this solution contains 15 µg of fentanyl (6 X 2.5) which will provide 0.5 µg/kg/hr of fentanyl (15 µg divided by 30 kg)

Step 4: Order half the basal rate (step 2) as the bolus dose. This will provide 0.5 mg/kg lidocaine and 0.25 µg/kg fentanyl. (Do the math: In this example 3 mL = 15 mg lidocaine and 7.5 µg fentanyl)

Stop 5: Obtain once a day blood level. If the level is high reduce the basal infusion and/or limit the number of boluses per hour.

NOTE: Dividing the weight by 5 of an epidural solution containing lidocaine 5.0 mg/mL and fentanyl 2.5 µg/mL will always produce the desired basal drug dosing, that is lidocaine 1.0 mg/kg and fentanyl 0.5 µg/kg. Half of the basal rate is the bolus dose.

Case 4: a 20 kg, ASA PS 1, 4 year old who underwent bilateral ureteral reimplantation presents for post-operative analgesic management. An epidural catheter was placed intraoperatively.

As I said earlier, I prefer lidocaine. However, for teaching purposes let's set this up as a continuous infusion of bupivacaine plus fentanyl. Because the surgical procedure is below the umbilicus I'll start at 0.2 mg/kg/hr bupivacaine. This is an effective dose and is well below the maximum of 0.4 mg/kg/hr bupivacaine. I have the pharmacist make a 500 mL bag (3 day supply) of bupivacaine 1.0 mg/mL and fentanyl 2.5 µg/mL.

Step 1: 0.2 (mg bupivacaine per hour) X 20 kg = 4 mg bupivacaine that will be infused per hour = 4 mL/hr (each mL equals 1 mg bupivacaine). This will also provide 10 µg of fentanyl (4 * 2.5, the concentration of fentanyl in each mL) which equals 0.5 µ/kg/hr (10 µ/g20 kg)

Step 2: If analgesia is inadequate increase the basal rate (to a maximum of 8 mL = 0.4 mg/kg/hr bupivacaine and 1.0 µg/kg/hr fentanyl.

NOTE: Multiplying the patient's weight by 0.2 of an epidural solution containing bupivacaine 1.0 mg/mL and fentanyl 2.5 µg/mL will always produce the desired basal drug dosing, that is bupivacaine 0.2 mg/kg and fentanyl 0.5 µg/kg.

Case 5: a 30 kg, ASA PS 3, 10 year old underwent a Nissen Fundoplication and presents for post-operative analgesic management. An epidural catheter was placed intraoperatively.

As I said previously, I prefer lidocaine, but for teaching purposes let's set this up for bupivacaine. I would use epidural PCA with a continuous infusion of bupivacaine plus hydromorphone as well as boluses.

In this situation hydromorphone may be better than fentanyl because it may have better rostral spread than fentanyl. I want to provide 0.2 mg/kg/hr bupivacaine and 2.0 µg/kg/hr hydromorphone as a basal infusion. I want to provide 0.1 mg/kg bupivacaine and 1.0 µg/kg hydromorphone with each bolus and I'11 prescribe 2 boluses/hr . I have the pharmacist make a 500-1,000 mL bag (3 day solution) of bupivacaine 1.0 mg/mL and hydromorphone 10 µg/mL.

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Step 1: 0.2 mg bupivacaine per hour X 30 kg = 6 mg bupivacaine that will be infused per hour = 6 mL because each mL of solution has 1 mg of bupivacaine.

Step 2: 6 mL of this solution contains 60 µg of hydromorphone (6 X 10) which will provide 2.0 µg/kg/hr of hydromorphone (60 µg divided by 30 kg)

Step 3: Order half the basal rate (step 2) as the bolus dose. This will provide 0.1 mg/kg bupivacaine and 1.0 µg/kg hydromorphone with each bolus. In this case we would order 3 mL.

NOTE: Multiplying the weight by 0.2 of an epidural solution containing bupivacaine 1.0 mg/ml and hydromorphone in µg/mL will always produce the desired basal drug dosing, that is bupivacaine 0.2 mg/kg/hr and hydromorphone 2 µg/kg/hr . Half of the basal rate (0.1 * weight in kg) is the bolus dose. Prescribe a 15 minute lockout and 2 boluses/hour. Thus, the maximum dose a patient can receive per hour is 0.4 mg/kg (0.2 + 0.1 + 0.1) bupivacaine and 4.0 µg/kg (2 + 1 + 1) hydromorphone.

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