

Chapter 13

PERIOPERATIVE PAIN MANAGEMENT

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INTRODUCTION

Pain control has become an integral part of the anesthesiologist's professional responsibilities. The physiological and humanitarian ramifications of inadequate pain relief can be catastrophic. Postinjury pain control in past wars has not always been optimal; in many instances, there has been none. Every war has its own descriptions of the suffering of untreated casualties, and it was the sound of casualties dying on the battlefield of Solferino in 1859 that motivated Henri Dunant to take the first steps that led to the formation of the International Red Cross:

The stillness of the night was broken by groans, by stifled sighs of anguish and suffering. Heart-rending voices kept calling for help. Who could ever describe the agonies of that fearful night!^{1(p41)}

More than humanitarian concerns are relevant to managing pain, however; postinjury or postoperative pain relief also blunts the trauma-induced neuroendocrine response that leads to detrimental metabolic, respiratory, and cardiovascular derangements. Thus, effective analgesia can both make the casualty more comfortable and decrease morbidity.

Although this chapter is oriented toward the management of pain in postoperative, hospitalized, combat casualties, military anesthesia providers need to know not only the full dimensions of providing analgesia to combat casualties but also what specifically can and should be done in the echelons below the corps level. The landmark battlefield study on pain in combat casualties was carried out by members of the U.S. Army Medical Corps in Italy in late 1943 and 1944.² The impetus for this study came from the observation that, at corps-level hospitals, increasing numbers of casualties were being seen who had obvious clinical signs and symptoms of morphine overdose and even lethal poisoning. This problem was soon shown to be due to the practice by field medical personnel of injecting morphine—in 30-mg increments, subcutaneously or intramuscularly—soon after the casualty had been wounded. Absorption of the morphine from the site of injection was sluggish because the weather was cold and many of the casualties were hypovolemic or even in shock. Thus, repeated doses were given to relieve pain. On arriving at the hospital level and with the initiation of resuscitation, the morphine that was deposited in peripheral

tissue was rapidly absorbed into the circulation—sometimes with fatal results.

By studying the prevalence of pain in combat casualties, the investigators set about determining how much morphine was really needed to obtain an acceptable degree of pain relief. On arriving at the corps hospital, casualties were asked to describe their pain, if any, using the following scale: none, slight, moderate, or severe. Casualties who admitted to pain of any degree were then asked if they wanted something to relieve it. Two hundred twenty-five casualties, representative of the more severely injured, were studied. Of these, 10 were subsequently excluded because their state of consciousness was altered. The remaining casualties were stratified into five groups according to the nature of their wounds: (1) fractures of extremity bone, (2) extensive soft-tissue injuries, (3) penetrating wounds of thorax, (4) penetrating wounds of abdomen, and (5) wounds of the head or brain or both (Figure 13-1 and Table 13-1). Ethical considerations precluded a study design in which one population would serve as an unmedicated control group; thus, most casualties had received morphine before reaching the hospital level.

Two striking findings emerged from this study. When seen at the hospital and evaluated for pain (7–14 h after their injuries, which was not a remarkably long time by World War II standards, and at least 5 h after last receiving morphine),

- approximately 75% of the casualties had no desire for medication for pain relief, and
- approximately 75% of the casualties had no pain or pain that was slight to moderate in intensity.

Because the amount of morphine administered was not different for those with or without pain and those who did or did not desire an analgesic, the investigators believed that the intensity of pain could not be explained on the basis of the amount of morphine administered. They concluded that

- most combat casualties do not need an analgesic prior to arrival at the hospital level, with the probable exception of casualties with abdominal wounds, in whom pain relief would appear to be usually indicated; and

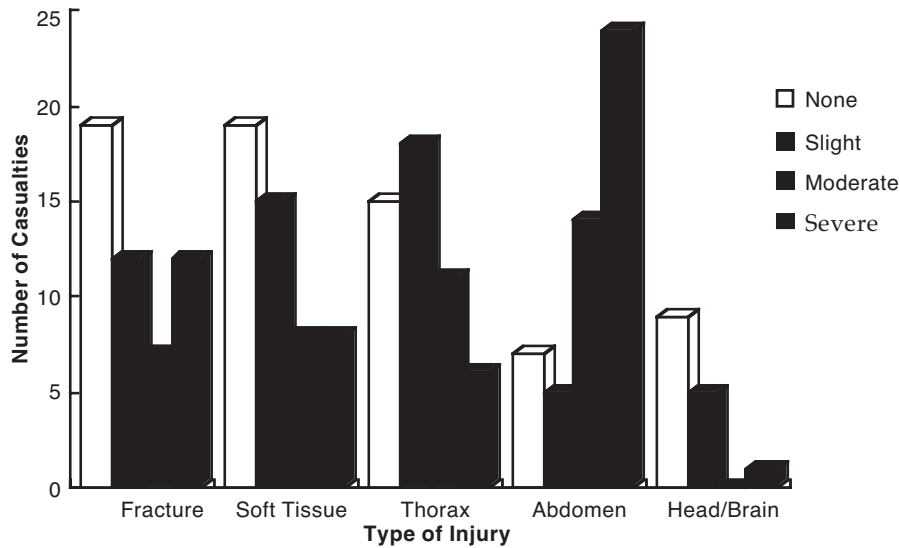


Fig. 13-1. When the nature of pain—assessed on admission to third-echelon hospitals—was studied in combat casualties who were wounded in Italy during World War II, the distribution of pain intensity could be plotted as a function of wound type. Most casualties with fractures, soft-tissue, and thoracic injuries reported little pain; most casualties with head wounds reported little or no pain. Only casualties with abdominal wounds demonstrated a great need for analgesia. Data source: Beecher HK. The control of pain in men wounded in battle. In: DeBaakey ME, ed. *General Surgery*. Vol 2. In: Coates JB Jr, ed. *Surgery in World War II*. Washington, DC: US Department of the Army, Medical Department, Office of The Surgeon General; 1955: 4–49.

- if morphine is required, it should be administered intravenously (which, of course, may not be practicable on the battlefield).

At the hospital level and especially following surgical intervention, a patient’s degree of pain is

often difficult to assess. The recovery room personnel’s assessment of the casualty’s pain is usually subjective. A patient’s communication skills and cultural background will influence the ability to express his or her level of discomfort. Several pain scores have been developed to help eliminate

TABLE 13-1
EPIDEMIOLOGICAL ASPECTS OF A WORLD WAR II COMBAT CASUALTY PAIN STUDY

Type of Injury	Time Since Injury (h) (m ± sd)	Total Dose of Morphine (mg) (m ± sd)	Time Since Last Dose (h) (m ± sd)	Request Further Pain Relief (%)
Fractured extremity bone (n = 50)	12.5 ± 1.3	27 ± 1.5	7.0 ± 0.8	22
Extensive soft-tissue extremity injury (n = 50)	11.4 ± 1.4	27 ± 2.7	7.2 ± 0.6	18
Penetrating, of thorax (n = 50)	9.8 ± 1.0	25.0 ± 1.8	6.5 ± 0.6	20
Penetrating, of abdomen (n = 50)	7.2 ± 0.7	29.0 ± 2.2	4.8 ± 0.7	54
Head and/or brain (n = 15)	7.9 ± 1.4	19.8 ± 4.2	6.2 ± 1.5	7

Adapted from Beecher HK. The control of pain in men wounded in battle. In: DeBaakey ME, ed. *General Surgery*. Vol 2. In: Coates JB Jr, ed. *Surgery in World War II*. Washington, DC: US Department of the Army, Medical Department, Office of The Surgeon General; 1955: 45.

the subjectivity in the assessment of acute pain, but these are much more useful in a research setting or a civilian hospital than on the battlefield.³

Fortunately for casualties of modern warfare, many techniques and drugs are now available that provide considerable analgesia. Some, such as patient-controlled analgesia (PCA), will allow the casualty more autonomy with respect to narcotics administration, which will simultaneously reduce the demand for nursing care.^{4,5} Administration of narcotics by the epidural or intrathecal routes will provide sustained pain relief far beyond that obtained with the more traditional intramuscular or intravenous routes.⁶ By employing dilute concentrations of local anesthetics, regional blocks can be used to provide pain relief with a minimal decrement of motor function.⁷ New nonsteroidal antiinflammatory drugs (NSAIDs), which are nearly

as effective as the narcotics used in prior wars but are not addictive, can be given intramuscularly or intravenously and act as an adjunct in the therapy of the injured soldier.⁸ By taking advantage of the newer techniques, military anesthesiologists can help soldiers who are injured on the battlefield to recover from surgery with minimal—or at least greatly reduced—discomfort.

Military trauma anesthesiologists must be able to meet the soldiers' postoperative pain requirements, have a sound working knowledge of the drugs at our disposal, and be adept in the use of the different modes of delivery and administration. The battlefield is not the ideal setting in which to treat patients. Therefore, we must be able to adapt to the situation and adequately treat the casualties as they present, using innovative ideas and combinations of treatment modalities to care for these soldiers.

PATHOPHYSIOLOGY OF PAIN

Visceral pain originates from organs of the abdominal cavity and thorax. The receptors cover large areas and the impulses travel through unmyelinated sympathetic fibers. These nerves respond to stretch, crush, ischemia, and displacement. The pain generated from these areas is dull, aching, and difficult to localize. The normal causes of visceral pain are distention of the viscera or renal pelvis secondary to obstruction. Somatic pain, in contrast, is transmitted in unmyelinated C fibers and small, myelinated, A-delta fibers, the impulse arising in receptors in skin, fasciae, bones, and joint spaces. These receptors innervate small discrete areas and are able to pinpoint noxious stimuli. Myelinated somatic nerve fibers, which are called A fibers, are the largest in diameter and conduct impulses the most rapidly. A fibers are further divided, by their progressively decreasing sizes, into alpha, beta, gamma, and delta fibers. The alpha and beta fibers convey motor and proprioception information. The gamma fibers control muscle spindle tone. The delta fibers, which are the A fibers with the smallest diameter, transmit messages concerning pain, temperature, and touch (Table 13-2).⁹

The thinly myelinated B fibers are smaller than the alpha fibers and have a preganglionic autonomic function for both sympathetic and parasympathetic systems.⁹ The unmyelinated C fibers are the smallest diameter nerve fibers. They have the lowest rate of impulse conduction velocity and contain postganglionic autonomic axons as well as axons conveying pain, temperature and touch information.¹⁰

Three major types of receptors are stimulated by nociceptive input: low-threshold mechanoreceptors, high-threshold mechanoreceptors, and polymodal nociceptors. Low-threshold mechanoreceptors respond to mechanical stimulation like pressure. These receptors are carried on A-delta fibers and transmit the stimuli at about 20 m/s.¹¹ As the input increases, the firing rate increases. High-threshold mechanoreceptors respond to noxious mechanical stimulation. As they are on low-threshold mechanoreceptors, impulses to high-threshold mechanoreceptors are carried on A-delta fibers. Polymodal nociceptors transmit impulses through unmyelinated C fibers. These receptors respond to many different kinds of nociceptive input including chemical, thermal, and mechanical. The receptive fields are larger than those of the A-delta fibers, and stimulation of these fibers lasts longer than with the other receptors.¹² The generally accepted paradigm for pain perception, modulators, and transmitters is shown in Figure 13-2.

Local Transmitters of Pain

The many different biochemical transmitters of pain include potassium and hydrogen ions, serotonin, histamine, bradykinin, substance P, and leukotrienes.¹³ When injected locally, all these substances either (a) are responsible for the transmission of noxious stimulation or (b) decrease the threshold of the pain transmission.¹⁴

Both potassium and hydrogen ions sensitize nerve endings and are usually released from cells when

TABLE 13-2
CLASSIFICATION OF NERVE FIBERS

Fiber Type	Diameter (μm)	Conduction Rate (m/s)	Anatomical Location	Function
A				
Alpha	12–20	100	Afferent to and efferent from muscles and joints	Large motor and proprioception
Beta	5–12	30–85	Afferent to and efferent from muscles and joints	Small motor, muscle tone, touch, pressure
Gamma	3–6	15–35	Efferent to muscle spindles	Muscle tone
Delta	2–5	3–25	Sensory roots and afferent peripheral nerves	Sharp pain, temperature, touch
B				
	3	3–15	Preganglionic autonomic	Vasomotor Visceromotor Suomotor Pilomotor
C				
sC	0.3–1.3	0.7–1.3	Postganglionic sympathetic	Vasomotor Visceromotor Suomotor Pilomotor
drC	0.4–1.2	0.1–2.0	Sensory roots and afferent peripheral nerves	Dull pain Temperature Touch

Data sources: (1) Raj P. *Practical Management of Pain*. 2nd ed. St. Louis, Mo: Mosby–Year Book; 1992: 139. (2) Barash PG, Cullen BF, Stoelting RK, eds. *Clinical Anesthesia*. Philadelphia, Pa: JB Lippincott; 1989: 374.

they are damaged during injury. Activity of peripheral pain receptors are regulated by, among other substances, serotonin and histamine. Serotonin is also a neurotransmitter for the descending inhibitory pathways. Bradykinin, a 9–amino acid peptide, is produced by enzymatic activity at the site of cell breakdown. Binding sites for bradykinins have also been found in the dorsal columns. Substance P, an 11–amino acid peptide, is synthesized in the dorsal root ganglia, from where it is transferred both centrally and peripherally along the nerve. In the peripheral locale—a nerve ending—substance P activates an enzyme that catalyzes the formation of arachidonic acid, which, in turn, serves as the substrate of the enzyme cyclooxygenase. This results in the production of prostaglandin E₂, an eicosanoid, that not only increases the sensitivity of nerve endings to chemical agents and mechanical injuries but also, by itself, causes hyperalgesia.¹⁵ Substance P is also indirectly responsible for the vasodilation associated with

local injury.¹⁶ The leukotrienes are also derivatives of arachidonic acid, but that reaction is catalyzed by lipoxygenase. There are many different leukotrienes, and most are associated with lowering the threshold of the nerves associated with the transmission of pain.

Transmission of Pain

The events leading to the transmission of pain were first reported in 1927 and described as a triple response: intense vasodilation, local edema or wheal, and secondary vasodilation spreading to the local area.¹⁷ This response is mediated by the transmitters of pain and stimulates the nociceptor fibers to fire. These fibers then synapse in the dorsal column of the spinal cord. There, the impulses are modulated and transmitted to the contralateral spinothalamic tract up into the cerebral cortex. The spinothalamic tract is subdivided into subtracts, one of which, the *lateral* subtract (found

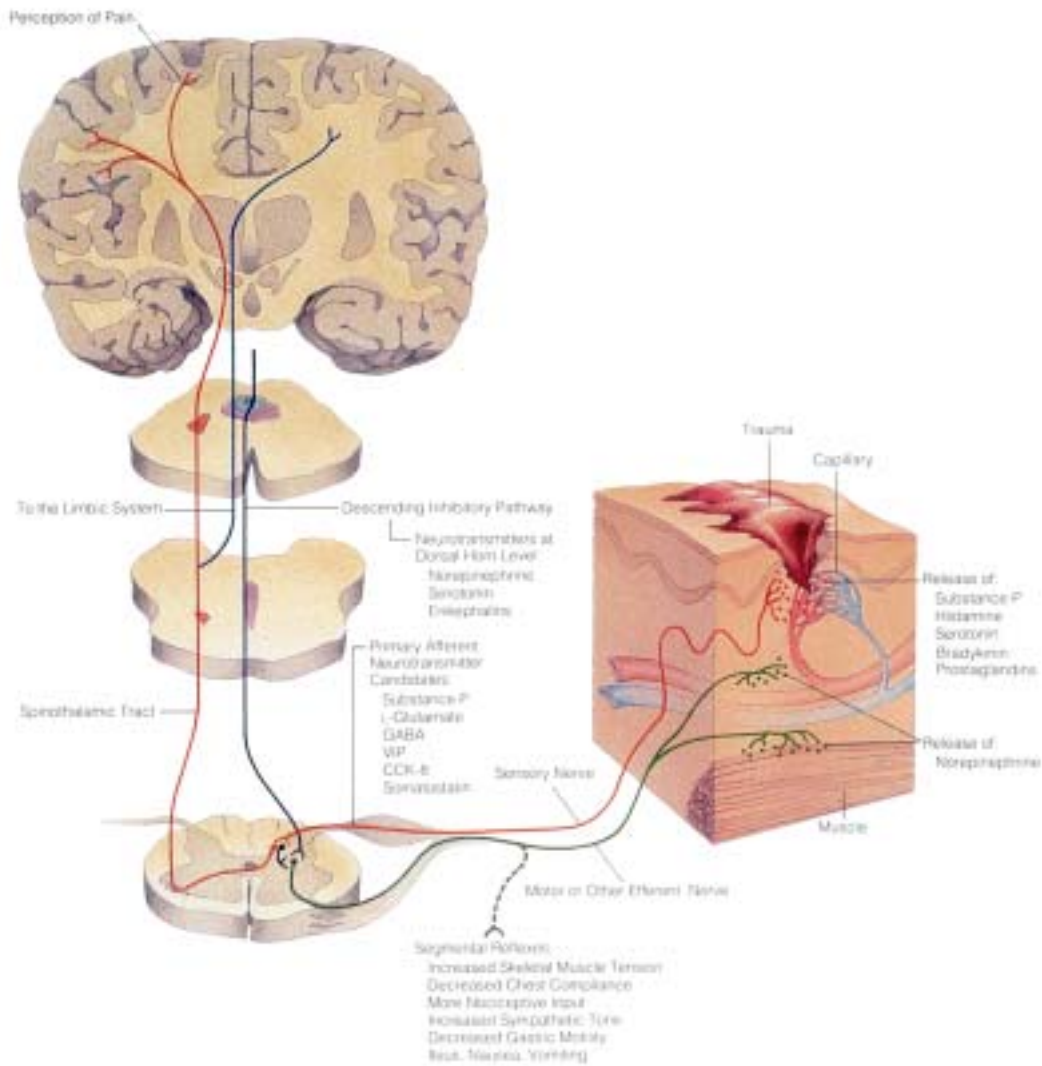


Fig. 13-2. Pain perception depends on the integrated function of three neurological pathways. First, peripheral nerves connect pain receptors in the injured tissue with neurons in the dorsal horn of the spinal cord. Second, nerve fibers pass from the dorsal horn neurons to the contralateral side of the cord, where they ascend to the cerebral cortex. The third component consists of tracts that arise in the upper brain stem and descend to the dorsal horn neurons, the function of which is thereby modulated. The ascending tract also has a component that passes to the limbic system and no doubt is important in modifying the emotional response to pain. A large number of transmitters are believed to be important in transmitting information about pain; several of these are discussed in text. GABA: γ -aminobutyric acid; VIP: vasoactive intestinal polypeptide; CCK-8: cholecystokinin-8. Reprinted with permission from Kehlet H. Postoperative pain. In: Wilmore DW, Brennan MF, Harken AH, Holcroft JW, Meakins JL, eds. *Critical Care*. Vol 1. In: *American College of Surgeons: Care of the Surgical Patient*. New York, NY: Scientific American, Inc; 1988–1993: II-12-10.

only in advanced primates), is probably responsible for the pinpoint perception of traumatic injury. As the impulses travel to the sensory tract of the cerebral cortex, they pass through the thalamus where they are again modulated. Once in the sensory cortex, the painful impulse is perceived and the body's response is determined. Thus, the major areas of the body in which pain is modulated are the

dorsal columns, the spinothalamic tract, the thalamus, and the sensory cortex. The treatment of pain needs to focus on these areas.

Descending inhibitory pathways originate in the sensory cortex and terminate in the dorsal horn. These pathways are responsible for down-regulation of painful stimuli by releasing serotonin, norepinephrine, and enkephalins, which inhibit the ac-

tivity of neurons that give rise to the fibers found in the spinothalamic tract. The release of substance P also causes the release of vasoactive substances (serotonin, bradykinin, histamine) at the site of injury. These substances stimulate both a hyperemic response and a hyperalgesic state at the injured site. Prostaglandins that are present in the cell membranes are also released in response to noxious stimuli. These substances do not themselves cause pain, but they do potentiate the noxious effects of the other substances that are present.¹⁸

The pharmacological treatment of pain is targeted to work on these sites of action. *Opioids* (ie, any natural or synthetic drug that has morphinelike pharmacological properties,¹⁹ including the natu-

rally occurring endorphins and enkephalins) activate both of the descending inhibitory pathways and bind presynaptically to the opioid receptors of the neurons in the dorsal horn. Opioids act to reduce the amount of substance P present.²⁰ Local anesthetics work by blocking the axonal transmission of pain.²¹ Antipsychotics work to increase the level of serotonin in the dorsal horn and thus down-regulate the pain transmissions.²² NSAIDs stop the production of prostaglandin E₂ from prostacyclin.²³ Alpha-2 adrenergic agonists inhibit substance P by stimulating presynaptic and postsynaptic spinal cord receptors, which, in turn, inhibit pain transmission with a mechanism of action that is different from that of narcotics.²⁴

SECONDARY MANIFESTATIONS OF ACUTE PAIN

The rationale for relieving pain transcends the anesthesiologist's professional mandate to alleviate suffering. Pain by itself has many deleterious effects, of which the inability to rest and sleep are the most obvious. Less obvious but of greater medical importance are such effects as pain-induced spasm of injured muscle, especially splinting of respiratory muscles; reflex stimulation of the autonomic nervous system, which causes hypertension and the release of catabolic hormones; and inhibition of the normal functions of the gut and urinary tract.

Respiratory System

The respiratory system is most often affected in injuries to the thoracic region or the upper abdomen. Casualties who remain in pain postoperatively splint when trying to breathe. This can cause decreased lung volumes and atelectasis, and can progress to lung collapse and pneumonia. The recognition of the importance of relieving pain in casualties with thoracic trauma was one of the most important advances in thoracic surgery during World War II:

[P]ain was an almost constant accompaniment of any wound of the chest. The relief of pain had a vital bearing on hastening recovery.... [U]ntil it had been accomplished, the patient was unwilling to breathe deeply or cough, because of the discomfort which followed both acts, and fluid substances therefore accumulated in the tracheobronchial tree, which led to wet lung.^{25(p244)}

Similar observations regarding pain in thoracic surgery have been made in civilian practice; pulmo-

nary function greatly improves when adequate analgesia is provided.²⁶

Cardiovascular System

Pain causes the amount of circulating catecholamines to increase. The effects of catecholamines on the cardiovascular system include increased (a) heart rate, (b) blood pressure, (c) cardiac output, and (d) systemic vascular resistance. Taken by itself, the increased heart rate, by limiting the time available for diastolic flow to occur, will cause a decrease in coronary blood flow. The usual concomitant increase in arterial pressure and coronary vasodilation caused by a catechol-mediated increase in cardiac metabolism negate the isolated effect of heart rate. Thus, coronary flow increases during tachycardia. Cardiac output may or may not change, depending on peripheral impedance. Increased systemic resistance will cause an increase in the workload for the heart. Together, these factors lead to increased myocardial oxygen consumption and, therefore, to an increased risk of myocardial ischemia in patients with limited cardiac reserve.²⁷ However, due to their age and physical condition, most injured soldiers should be able to tolerate this hemodynamic stress.

Gastrointestinal and Genitourinary Systems

Untreated pain will lead to decreased gastrointestinal motility with associated anorexia, nausea, and vomiting.²⁸ This places the patient at increased risk of pulmonary aspiration, and anastomotic and incisional dehiscence, and complicates the manage-

TABLE 13-3
NEUROENDOCRINE AND METABOLIC RESPONSES TO TRAUMA

Response	Effect	Cause
Endocrine	Catabolic	<i>Increased</i> ACTH, cortisol, ADH, GH, catecholamines, renin, angiotensin II, aldosterone, glucagon, interleukin-1
	Anabolic	<i>Decreased</i> insulin, testosterone
Metabolic		
Carbohydrate	Hyperglycemia, glucose intolerance, insulin resistance	<i>Increased</i> hepatic glycogenolysis (epinephrine, glucagon) <i>Increased</i> hepatic gluconeogenesis (cortisol, glucagon, growth hormone, epinephrine, free fatty acids) <i>Decreased</i> insulin secretion/ action
Protein	Muscle protein catabolism, increased synthesis of acute-phase proteins	<i>Increased</i> cortisol, epinephrine, glucagon, interleukin-1
Fat	Increased lipolysis and oxidation	<i>Increased</i> catecholamines, cortisol, glucagon, growth hormone
Water and Electrolyte Flux	Retention of H ₂ O and Na ⁺ , increased excretion of K ⁺ , decreased functional extracellular fluid with shifts to intracellular compartments	<i>Increased</i> catecholamines, aldosterone, ADH, cortisol, angiotensin II, prostaglandins, and other factors

ACTH: adrenocorticotropic hormone; ADH: antidiuretic hormone; GH: growth hormone. Adapted with permission from Cousins M. Acute and postoperative pain. In: Wall PD, Melzack R. *Textbook of Pain*. New York, NY: Churchill Livingstone; 1989: Chap 18: 294.

ment of the casualty who needs to be returned to the operating room for additional surgery. Furthermore, sluggish gastrointestinal function delays the resumption of enteral nutrition. Unrelieved pain has a similar effect on the function of the urinary tract: persistent bladder retention necessitating prolonged urinary catheterization.

Endocrine and Metabolic Systems

Increased pain causes a stress response that manifests as an increase in the release of endogenous catecholamines, cortisol, and other mediators of the sympathetic response that promote harmful pro-

tein catabolism, glucose intolerance, and insulin resistance.²⁹

An all-inclusive review of the endocrine response to postoperative pain is not within the scope of this chapter. Suffice it to say that the endocrine response to trauma—whether surgical or otherwise—is profound. Every system in the body is affected by these changes, most of which are secondary to circulating catecholamines released from the sympathetic nervous system (Table 13-3). Anabolism, catabolism, and substrate requirements all increase. The dual goals of postoperative pain control are the alleviation of pain and the subsequent decrease in the levels of circulating catecholamines.

CLINICAL PHARMACOLOGY OF OPIOID ANALGESICS

The opioids, of which morphine is the prototype, are the best known and most useful narcotic analgesics available. Morphine was first isolated from opium—the gum obtained by drying the milky juice made from the seedpod of the poppy plant *Papaver somniferum*—in 1803.¹⁹

Opioids act at two distinct anatomical sites: the supraspinal area and the spinal cord. In the supraspinal area, the drugs bind at receptor sites in the periventricular and periaqueductal gray area to modulate pain perception. In the spinal cord, the action is in the substantia gelatinosa of the dorsal

horn. Here, the drugs block the release of the mediators of pain by binding to presynaptic receptors of afferent nerve terminals.²⁰

Whether synthetic or derived from opium, these drugs are described by their effects at specific opioid receptors in the central nervous system (CNS). Four distinct opioid receptors have been identified in humans: mu, delta, kappa, and sigma.

The mu receptors are further subdivided into mu 1 and mu 2. Mu 1 receptors are located in the spinal cord and in the supraspinal area. Stimulation of these receptors produces analgesia. Morphine and beta-endorphin are agonists for this receptor. Mu 2 receptors cause ventilatory depression, decreased heart rate, euphoria, miosis, and physical dependence. Agonists of this group include fentanyl and meperidine.

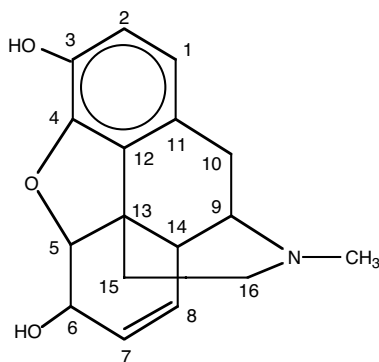
The delta receptors, which have no intrinsic function, function as modulators of the mu receptors. Leuenkephalin is an agonist in this group.

The kappa receptors are located in the cerebral cortex and their activation causes analgesia, sedation, miosis, and some depression of ventilation. Agonists of this group include nalbuphine and butorphanol.

The sigma receptors are the latest of the opioid receptors to be described. Activation of this receptor stimulates dysphoria, tachycardia, and tachypnea. This may be the site of ketamine's action. Naloxone is an antagonist for all the opioid receptors.³⁰

Opioid Agonists

Morphine



Morphine, the major phenanthrene alkaloid of opium, and codeine are the medically useful opioids derived from opium. Although codeine can be administered orally, it is not as potent as morphine and therefore will not be further discussed in this chapter.

An opioid agonist, morphine has demonstrated mu 1 activity in the periaqueductal gray matter. These receptors modulate noxious stimuli and send transmissions to the medullary nuclei. Spinal mu receptors also reduce the amount of substance P in the dorsal horn.

Morphine can be administered via the intravenous, intramuscular, epidural, and intrathecal routes. When delivered intravenously, morphine has a peak effect about 20 minutes after injection. Intramuscularly, an initial effect is seen in 15 to 30 minutes and the peak effect in 45 to 90 minutes. Orally administered morphine is not reliably absorbed. When given epidurally, the onset of pain relief tends to occur approximately 60 minutes later, and pain relief can last 16 to 24 hours. With intrathecal injections, the onset of pain relief tends to occur in approximately 10 to 15 minutes, which coincides with the peak level of drug in the cerebrospinal fluid.³⁰ Regardless of the mode of administration, the pain relief is relative to the concentration of the drug in the cerebrospinal fluid; pain relief is not always proportional to the blood levels.³¹ The drug is eliminated from the body primarily by conjugation with glucuronic acid at hepatic and extrahepatic sites. A small amount of the dose is excreted unchanged in urine. Only 7% to 10% of morphine is eliminated by biliary excretion; the rest is excreted by the kidneys.³⁰

Respiratory Side Effects. Mu 2 receptors in the pontine and medullary centers are responsible for respiratory depression.³² The agonists produce a dose-related depression of respiration, the evidence of which is increased P_{aCO_2} . When morphine is administered in small doses, the respiratory rate usually decreases, which is compensated for by an increase in the tidal volume. With increasing doses of morphine, however, the tidal volume will decrease. Maximal respiratory depression occurs approximately 7 minutes after intravenous administration, 30 minutes after intramuscular injection, 90 minutes after subcutaneous administration, and up to 16 hours after epidural or intrathecal administration.³⁰

Cardiovascular Side Effects. Morphine administration will decrease sympathetic outflow. No adverse effect will probably be seen in a supine, normovolemic patient, but a casualty who is standing or a supine casualty who is hypovolemic might suffer from hypotension. Morphine can also stimulate histamine release, causing peripheral vasodilation and hypotension. The histamine release can be attenuated by limiting the rate of infusion to less than 5 mg/min or by administering H_1 or H_2 block-

ing agents.³³ Morphine can also cause bradycardia, probably by stimulating the vagal nuclei in the medulla, and by exerting a depressing effect on the sinoatrial node. Although there are no known direct myocardial depressant effects of morphine, it causes a decrease in myocardial oxygen consumption. The mechanism is probably related to peripheral vasodilation and bradycardia. There is no direct effect on the cerebral circulation, but the secondary effect of the increased Paco_2 due to associated hypoventilation will cause cerebral vasodilation that could thereby increase intracranial pressure in the patient with neurotrauma.

Gastrointestinal Side Effects. Pain may cause decreased gastric emptying and motility. Morphine may enhance this dysmotility and lead to ileus. In addition, the tone of the ileocecal and anal sphincters is also increased. All these factors lead to decreased motility of and increased water absorption from the gut. Opioids will also cause spasm in the biliary smooth muscle (eg, the sphincter of Oddi). This spasm may mimic the pain of angina pectoris.

Nausea and vomiting are caused by direct stimulation of the chemoreceptor trigger zone of the medulla oblongata. This side effect can be treated with an antiemetic without reversing the analgesic effect of the morphine.

Genitourinary Side Effects. Morphine will cause increased peristalsis of the ureters, but the tone of the vesicle sphincter is also increased. The combination of these effects makes it more difficult for patients who are not catheterized to urinate. In some patients, morphine may also inhibit the urge to urinate.

Cutaneous Side Effects. Morphine will cause venodilation in the peripheral vessels of the extremities. The histamine release can also cause an erythema.

Pruritus, which is more pronounced in epidural and intrathecal use, can be pronounced and is secondary to a CNS effect of the drug. Pruritus can be reversed by titrating small amounts of an antagonist (eg, naloxone).³⁰

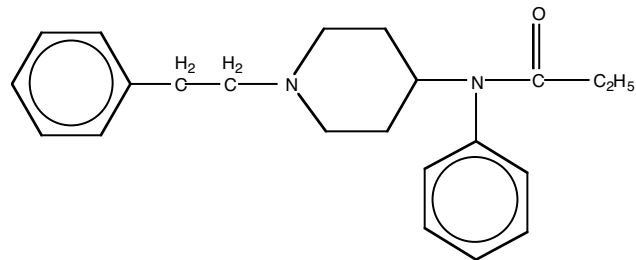
Physical Dependence. All opioids can cause physical dependence. This complication occurs more often with agonists than with drugs that have combined agonist-antagonist effects. Although it usually takes longer, dependence can occur after as few as 72 hours of use. However, the possibility of dependence should not be a factor in limiting the use of a narcotic in the acutely injured soldier.

Dosage and Administration. For postoperative pain control, morphine should be titrated for effect. For intravenous or intramuscular injections, 0.05 to

0.1 mg/kg should provide adequate analgesia. Following this dose, the patient should be monitored for adequacy of pain control, changes in blood pressure and pulse, and respiratory rate. If the patient's pain is not controlled, then more narcotic can be administered; again, the patient's vital signs should be observed. When used intravenously or intramuscularly, morphine should be given every 3 to 6 hours.³⁴ Strict adherence to dosing intervals is needed to maintain therapeutic drug levels.

Epidurally or intrathecally administered morphine can provide pain relief for 16 to 24 hours with a single dose. It is important to remember that morphine's respiratory depression might not manifest itself for up to 20 hours after an injection. For acute pain, the doses of epidural morphine are 0.05 to 0.07 mg/kg, and can be administered every 12 hours as needed.³⁵ The anesthesiologist must bear in mind that morphine delivered via the epidural route requires up to 1 hour before the onset of pain relief. Morphine can be continuously infused at a rate of 0.005 to 0.01 mg/kg/h. Intrathecal narcotics also have the benefit of extended pain relief from a single injection. The usual dose of intrathecal morphine is 0.3 to 1 mg. The onset of action is almost immediate and the duration of a single injection is 12 to 24 hours.^{6,35-37}

Fentanyl

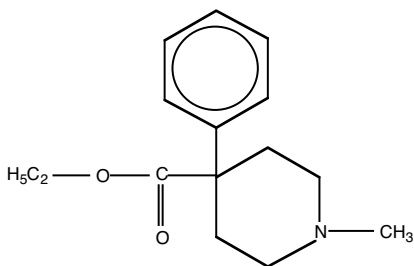


The opioid fentanyl is chemically similar to morphine. However, this synthetic narcotic is 75- to 125-fold more potent than morphine and, due to its high lipid solubility, it crosses the blood-brain barrier faster than morphine. The onset of action is approximately 30 seconds. The duration of action of the drug is also shorter than that of morphine, owing to fentanyl's rapid uptake by inactive tissue. Because of this uptake and subsequent release, when fentanyl has been given in repeated doses, its action can continue and be prolonged after the medication has been discontinued.³⁸ Fentanyl is metabolized by dealkylation, hydroxylation, and amide hydrolysis into inactive metabolites. The drug is excreted in the urine and feces.

Side Effects. The side effects of fentanyl are similar to those of morphine. Of note, less histamine is released than with morphine, but there is greater potential for physical dependence. Muscular rigidity, specifically of the chest wall, has also been associated with rapidly administered doses of fentanyl.³⁰

Dosage and Administration. For the postoperative patient with acute pain, 1 to 2 $\mu\text{g}/\text{kg}$ of fentanyl will give fast relief. Fentanyl's advantage over morphine is its speed of onset. However, the pain relief will not last as long as that from a dose of morphine, and fentanyl probably is not the best medication if prolonged use of intermittent boluses is anticipated. However, fentanyl can be given as an intravenous infusion to maintain pain relief. A starting dose of 1 to 2 $\mu\text{g}/\text{kg}/\text{h}$ is adequate, but can be titrated as necessary.³⁰ Epidural administration of fentanyl is another useful option. A single injection of 1 to 2 $\mu\text{g}/\text{kg}$ in the lumbar epidural space will give excellent relief from pain that originates in the abdomen or lower extremities. Long-term relief can be achieved with 10 $\mu\text{g}/\text{mL}$ of fentanyl infusing at a rate of 1 to 2 $\mu\text{g}/\text{kg}/\text{h}$.^{39,40} As with epidural administration of morphine, the patient's respiratory rate must be monitored throughout the duration of infusion, although the delayed respiratory depression seen with morphine has not been demonstrated with fentanyl. Intrathecal fentanyl can also be used for pain from the abdomen and lower extremities. A dose of 0.1 to 0.2 $\mu\text{g}/\text{kg}$ is adequate. The risk for respiratory depression lasts approximately 4 hours—approximately as long as the pain relief from a single dose.^{39,40}

Meperidine



Although it is structurally different from morphine, meperidine has many of the same properties. Meperidine is approximately one tenth the strength of morphine when given as an intravenous or intramuscular injection, but is much better absorbed by the gastrointestinal system. Analgesic effects are noted approximately 15 minutes after an oral dose and 10 minutes after an intramuscular injection.

The peak effect is usually seen within 2 hours after oral administration and 1 hour after an intramuscular injection. The effective length of analgesia is 2 to 4 hours. Meperidine is metabolized in the liver to normeperidine. The accumulation of the normeperidine is associated with increased CNS excitation. In large or frequently repeated doses, meperidine has caused seizures in humans. Normeperidine is excreted renally and will accumulate in patients with renal failure.³⁰

Side Effects. Meperidine's side effects, like fentanyl's, are similar to morphine's, but with some differences. Large doses exert a myocardial depressant effect that will decrease myocardial contractility and stroke volume. This will lead to increased left ventricular filling pressures.⁴¹ The incidence of nausea and vomiting associated with meperidine is equivalent to that of morphine, but patients who experience nausea and vomiting with morphine might not with meperidine.

Dosage and Administration. As mentioned above, meperidine is approximately one tenth as potent as morphine when given by intravenous or intramuscular injection. Thus, for acute postoperative pain relief, a starting dose of 0.25 to 0.5 mg/kg should be adequate. Also, owing to meperidine's better absorption, it is a good choice as an oral adjunct. The possibility for seizures exists with prolonged or high-dosage oral use of meperidine.³⁰

Opioid Agonist–Antagonists

Butorphanol

Butorphanol exerts its analgesic effect by being an agonist of both the kappa and sigma receptors. It is an antagonist of the mu receptors. A dose of 2 to 3 mg is equipotent to 10 mg of morphine. The onset, peak effect, and duration of action of butorphanol are similar to those of morphine. Therapeutic dosages produce increased pulmonary artery pressure, cardiac output, and systemic blood pressure.³⁴

Side Effects. In the low-dose, therapeutic range, the respiratory side effects of butorphanol are similar to those of morphine. The cardiovascular effects are the same as those described for meperidine. The drug will cause sedation, nausea, and diaphoresis in most people, and dysphoria in a small number of patients. Butorphanol will also antagonize mu agonists, thus making the choice of the proper dose of agonists difficult in the patient who is receiving butorphanol and will be returning to the operating room.

Dosage and Administration. Butorphanol is not available for enteral use. The suggested intravenous dose is 7 to 15 $\mu\text{g}/\text{kg}$, and the suggested intramuscular dose is 15 to 30 $\mu\text{g}/\text{kg}$. Butorphanol should be readministered every 3 to 4 hours.³⁴

Nalbuphine

Nalbuphine is an agonist at the kappa and sigma receptors and an antagonist at the mu receptors. A dose of 10 mg of nalbuphine is equipotent to 10 mg of morphine. Unlike butorphanol, nalbuphine does not increase cardiac output or blood pressure. One advantage of this drug is its *ceiling effect* on respiratory depression⁴²: the dose-related decrease in respiratory drive will not worsen with doses greater than 30 mg. Also, because nalbuphine is a mu antagonist, the drug can be used to reverse the respiratory depression of morphine or fentanyl without decreasing analgesia. The onset, peak effect, and duration of action are similar to those of morphine.

For postoperative pain relief, nalbuphine should be titrated for effect. For intravenous or intramuscular injections, 0.05 to 0.1 mg/kg should provide adequate analgesia. Whether administered via the intravenous or intramuscular route, nalbuphine should be given every 3 to 6 hours for pain control.³⁰

Mixed Agonists

Dezocine

Dezocine is a new, mixed agonist with activity at the mu, kappa, and delta receptors. Its affinity for the mu receptors is 10-fold greater than for the delta receptors, and 40-fold greater than for the kappa receptors. This drug's advantage over other opioids is its ceiling effect on respiratory depression. Additionally, it is not a *scheduled* drug (ie, a federal narcotics license is not required). Its physical dependence has not been described. The hemodynamic effects are equivalent to those of morphine. The onset, peak effect, and duration of action are also similar to those of morphine.⁴³ Minimal side effects have been found in the clinical studies so far

reported, but the number of patients reported is small.

The recommended dose for dezocine is 70 to 150 $\mu\text{g}/\text{kg}$ intravenously and 70 to 200 $\mu\text{g}/\text{kg}$ intramuscularly. It is suggested that dezocine be readministered every 3 to 4 hours.⁴³

Naloxone

Naloxone is a competitive inhibitor of the mu, delta, kappa, and sigma receptors. After an intravenous injection, the onset of action is 1 to 2 minutes. The duration of action is 1 to 4 hours but is dose dependent. Naloxone can reverse the effects of *all* opioid agonists. It can also cause increased heart rate and systolic blood pressure. Acute pulmonary edema has been associated with narcotic reversal with naloxone, although this is a relatively rare complication. The case reports of pulmonary edema following naloxone administration have been in young healthy patients, and the reported doses have been as low as 80 μg .^{44,45}

The recommended dose is 0.5 to 1 $\mu\text{g}/\text{kg}$, with doses being repeated until the desired effect is achieved. If the opioid being reversed has a longer half-life than naloxone, then it is important to start a naloxone infusion. The recommended rate of infusion is 5 to 10 $\mu\text{g}/\text{kg}/\text{h}$, but this rate can be titrated for effect.^{46,47}

Adjunct Medications

Promethazine is an H_1 receptor antagonist that has been used in conjunction with narcotics to reduce the narcotic-associated nausea. The recommended dose to control nausea in patients is 12.5 to 25 mg every 4 to 6 hours. The dose is given as an intramuscular injection.

Droperidol is a powerful antiemetic owing to its inhibition of the dopaminergic receptors in the chemoreceptor trigger zone of the medulla. A dose of 0.625 to 1.25 mg given to a 70-kg adult is considered adequate to prevent nausea. Side effects of the drug include drowsiness and, in a small number of patients, extrapyramidal reactions. Droperidol may also cause increased sedation in the patient emerging from anesthesia.

CLINICAL PHARMACOLOGY OF NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Nonsteroidal antiinflammatory drugs (NSAIDs) act by interrupting the inflammatory response.⁴⁸ This interruption is thought to be due to their inhibition of prostaglandin biosynthesis. Aspirin (ace-

tylsalicylic acid) is the prototype of the nonopioid analgesic, antipyretic, and antiinflammatory drugs.⁴⁹

NSAIDs are most often used

TABLE 13-4
SPECIFIC NONSTEROIDAL ANTIINFLAMMATORY AGENTS BY CLASS

Generic Name	Trade Name	Common Adult Dose for Pain
<i>Salicylates</i>		
Aspirin		325–650 mg/4 h PO
Choline/magnesium trisalicylate	Trilisate	1,000 mg, PO bid
Diflunisal	Dolobid	500 mg PO q 12 h
Salsalate	Disalcid	3,000 mg/d total dose divided as tid or bid
<i>Propionic Acid Derivatives</i>		
Fenoprofen	Nalfon)	200 mg qid or tid
Flurbiprofen	Ansaid	200–300 mg total daily dose divided bid, tid, or qid
Ibuprofen	Advil, Medipren, Midol, Nuprin, Motrin	300–800 mg tid to qid PO
Ketoprofen	Orudis	25–50 mg tid to qid PO
Naproxen	Naprosyn	250 mg tid to qid PO
Naproxen sodium	Anaprox	275 mg tid to qid
<i>Indoles/Pyrrroles</i>		
Indomethacin	Indocin	25–50 mg bid to tid
Sulindac	Clinoril	150 mg bid
Tolmetin	Tolectin	400 mg tid
Ketorolac	Toradol	30–60 mg IM loading dose, then 15–30 mg IM qid
<i>Oxicams</i>		
Piroxicam	Feldene	20 mg qid
<i>Anthranilic Acid Derivatives</i>		
Meclofenamate sodium	Meclomen	50 mg tid to qid
Mefenamic acid	Ponstel	250 mg qid
<i>Phenylacetic Acid Derivatives</i>		
Diclofenac sodium	Voltaren	50 mg tid or qid or 75 mg bid
<i>Pyrazolone Derivatives</i>		
Phenylbutazone	Butazolidin	100 mg qid

IM: intramuscularly; PO: by mouth; bid: twice daily; tid: three times daily; qid: four times daily

Data sources: (1) *Physicians' Desk Reference*. 48th ed. Montvale, NJ: Medical Economics Data; 1994. (2) DiGregorio G. *Handbook of Pain Management*. 3rd ed. West Chester, Pa: Medical Surveillance Inc; 1991.

- as analgesics, to provide symptomatic relief of low-intensity pain associated with headache and musculoskeletal disorders (eg, osteoarthritis and rheumatoid arthritis),
- as antipyretics,
- to inhibit platelet aggregation in patients vulnerable to vascular obstruction from emboli,
- to inhibit synthesis of prostaglandins in neo-

nates to evoke closure of the ductus arteriosus, and

- to treat excessive production of prostaglandins (eg, in Bartter's syndrome).⁴⁹

Important information regarding generic names, trade names, and adult dosages of selected NSAIDs is summarized in Table 13-4; pharmacokinetic data are presented in Table 13-5.

TABLE 13-5
PHARMACOKINETIC DATA OF SELECTED NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Name	Time to Peak Plasma Concentration (h)	Elimination Half-life (h)	Duration of Action (h)	Effective Plasma Concentration (µg/mL)
Aspirin	0.5–1	0.25–0.35	4–6	20
Choline/magnesium	1–2	9–17	12	150–300
Ibuprofen	1–2	2	4–6	—*
Indomethacin	2	2–3	4–6	0.3–1.0
Ketorolac	0.5	4–6	4–6	—
Sulindac	2	7–18	8–12	—
Piroxicam	3–5	30–80	48–72	1.5–2
Meclofenamate sodium	0.5–1	2	2	—
Diclofenac sodium	1–4	2	2	1–2
Phenylbutazone	1–3	60–100	80	50–150
Naproxen	1–2	10–17	8–12	25–75

*[—] Indicates data not available

Adapted with permission from Digregorio GJ, Barbieri EJ, Sterling GH, Camp JF, Prout MF. *Handbook of Pain Management*. 3rd ed. West Chester, Pa: Medical Surveillance Inc; 1991: 129.

Mechanisms of Action

The primary actions of NSAIDs—producing analgesia, acting as an antipyretic, and exerting an antiinflammatory effect—result from different mechanisms. These actions and mechanisms are discussed below.

Analgesia

NSAIDs produce analgesia by inhibiting the activity of cyclooxygenase (prostaglandin synthetase), an enzyme that leads to a decrease in the synthesis and release of prostaglandins from cells. Individual classes of NSAIDs have different methods of inhibiting the cyclooxygenase enzyme.⁴⁹ Prostaglandins enhance the potency of algescic substances such as bradykinin or substance P, which may stimulate nerve endings of unmyelinated C fibers and small-diameter A-delta fibers to elicit noxious afferent input. Bradykinin stimulates formation and release of more prostaglandins.⁵⁰ NSAIDs appear to reduce this potentiation of algescic activity of prostaglandins by blocking their synthesis.

In contrast to that produced by opioids, which act centrally, the analgesia produced by aspirinlike drugs is a peripheral phenomenon. Pain is pro-

duced when prostaglandins are produced locally around sensitive nerve endings, as seen with inflammation. NSAIDs are effective in relieving this pain by blocking prostaglandin synthesis. NSAIDs are not effective as analgesics when inflammation is not present (ie, there is no increase in prostaglandin synthesis in the area) or for the sharp, stabbing pain that is caused by direct stimulation of sensory nerves (ie, visceral pain).⁴⁹

Antipyresis

NSAIDs exert an antipyretic action via a CNS mechanism. Fever is thought to occur because endogenous pyrogens cause a shift in the temperature-regulating system in the preoptic hypothalamus. NSAIDs are postulated to reduce the effect of endogenous pyrogens on the hypothalamus. In therapeutic doses, NSAIDs do not affect either normal body temperature or an increase in temperature associated with exercise, drugs, or hypothalamic lesions to which pyrogen does not contribute. Salicylates, acetaminophen, and ibuprofen are the only drugs approved in the United States as antipyretics, although indomethacin and naproxen have been recommended as drugs to lower fever of neoplastic disease that is uncontrolled by other antipyretics.⁵⁰

Antiinflammatory Effect

Since prostaglandins induce symptoms of inflammation and enhance the effects of bradykinin and histamine, a reduction of prostaglandins at sites of inflammation is thought to decrease the inflammatory response. In arthritic diseases, NSAIDs reduce inflammation and swelling, thereby providing relief.⁵⁰

Side Effects

Gastrointestinal System

All NSAIDs can cause gastrointestinal pathology, including gastritis, nausea, vomiting, diarrhea, constipation, and occult blood in the stool.^{48,49} Gastrointestinal problems are more common with aspirin, indomethacin, and mefenamic acid⁴⁹ although nonacetylated salicylates may be less irritating.⁵⁰ Alcohol ingestion increases the likelihood that gastrointestinal side effects will occur.⁴⁹ The United States Pharmacopeia recommends that all NSAIDs be taken with a full glass of water.⁴⁹ NSAID-associated gastropathy has been proposed as the most frequent, serious, adverse drug effect in the United States; the risk of gastrointestinal problems is greater in elderly and debilitated patients.⁵⁰

Aspirin should be avoided by patients with a history of ulcers and should not be used with agents that promote ulcer formation (eg, alcohol). The mechanisms of gastrointestinal bleeding and NSAID-induced ulceration are due in part to irritation from direct contact with mucosal cells and cyclooxygenase inhibition after absorption, which weakens the gastric-acid barrier. Chronic inhibition of prostaglandin synthesis appears to decrease mucosal cytoprotection. It is likely that aspirin-induced bleeding is aggravated by its effect on platelet aggregation.⁵⁰

Renal System

Renal prostaglandins are important to ensure adequate renal perfusion and function in certain disease states, including congestive heart failure, cirrhosis with ascites, nephrotic syndrome, and dehydration. In these patient groups, NSAIDs may precipitate acute renal failure. Long-term use of high-dose NSAIDs may cause renal medullary ischemia and papillary necrosis. This was more common when phenacetin was used, especially in combination with aspirin, caffeine, and acetami-

nophen. Phenacetin has been replaced with acetaminophen, which may also be a risk factor for papillary necrosis. Renal prostaglandins inhibit tubular reabsorption of Na⁺ and water, and inhibit renin secretion. In patients with poor renal perfusion states, NSAIDs may cause fluid retention, impaired responsiveness to diuretic therapy, and hyperkalemia.⁵⁰

Respiratory System

Inhibition of bronchodilator prostaglandins by NSAIDs may leave the leukotriene pathway uncontested and lead to bronchospasm.⁴⁹ This may be a consideration in susceptible patients such as asthmatics. Full therapeutic doses of salicylates increase oxygen consumption and carbon dioxide production in skeletal muscle. Higher doses result in medullary stimulation, causing hyperventilation with a respiratory alkalosis. This is compensated for by excretion of bicarbonate by the kidneys, which leads to a compensated respiratory alkalosis. Toxic doses of salicylate depress the medulla, leading to an uncompensated respiratory acidosis in a patient with high renal bicarbonate excretion, which, in turn, leads to a coexisting metabolic acidosis.⁴⁸

Hematological Effects

NSAIDs inhibit both thromboxane A₂ synthesis within platelets and prostacyclin synthesis within endothelial cells. Thromboxane A₂, a potent vasoconstrictor, stimulates platelet aggregation, which promotes clotting. Prostacyclin, a potent vasodilator, inhibits platelet aggregation, which promotes bleeding. NSAIDs inhibit the synthesis of both thromboxane A₂ and prostaglandin I₂. The net balance determines the tendency towards bleeding or clotting.⁵¹

Aspirin irreversibly inhibits platelet cyclooxygenase which prevents the formation of thromboxane A₂, thereby inhibiting platelet aggregation. The bleeding time is prolonged for the lifetime of the platelet. All other NSAIDs reversibly inhibit platelet cyclooxygenase, so that five half-lives are required to clear all the drug from the body and restore normal platelet function.⁵¹

Reye's Syndrome

Reye's syndrome, a childhood illness that develops after recovery from influenza or chickenpox, is characterized by vomiting, liver abnormalities, and encephalopathy. Nearly all victims of Reye's syn-

drome had received salicylates for management of the viral illness. If an analgesic antipyretic is required for use in children with acute viral illness,

acetaminophen should be used, as there is no evidence of an association between acetaminophen and Reye's syndrome.⁵⁰

CLINICAL PHARMACOLOGY OF LOCAL ANESTHETICS

Since prehistoric times, the natives of Peru have chewed the leaves of the indigenous plant *Erythroxylon coca*, the source of cocaine, to obtain a feeling of well-being and to reduce fatigue.^{9,52} Chewing of the coca leaves caused a reversible perioral numbness, and subsequent investigation of the coca leaf allowed the identification of cocaine, the active ingredient. Cocaine was used as a topical ocular anesthesia and for nerve blocks during the latter 18th century.⁴⁹ Addictive properties and toxicity limited the use of cocaine for local anesthesia, but this finding stimulated research for more ideal local anesthetic agents. Einhorn introduced the esters procaine in 1905 and tetracaine in 1932, and Lofgren introduced lidocaine, an amide, in 1932.⁹

Local anesthetics are important adjuncts to the management of postoperative pain; they significantly reduce the amount of narcotics necessary to maintain a pain-free state in the postoperative patient.⁷ A simple system governs the naming of local anesthetic drugs: those spelled with one *i* in the name are esters (eg, procaine, 2-chloroprocaine, tetracaine); those with two are amides (eg, lidocaine, mepivacaine, bupivacaine). Among the amides, stereoisomers of etidocaine, mepivacaine, bupivacaine, prilocaine, and ropivacaine have been recognized. Although the *S* forms of these molecules are generally less toxic and have a longer duration of action,⁵³ the chiral forms of local anesthetics are not discussed in this chapter.

Very dilute solutions of a local anesthetic combined with an opiate produce anesthesia comparable to that produced by more-concentrated solutions of plain local anesthetics. Use of dilute solution of local anesthetic causes less motor blockade, which facilitates postoperative ambulation. The interaction of opiates and local anesthetics is postulated to be due to a synergistic action of the drugs (administered epidurally) acting in two or more different sites to decrease sensory input. The local anesthetics act at the dorsal root ganglion while the opiates act on the dorsal horn of the spinal cord.⁵³

Chemical and Physical Properties

The potency, onset of action, and duration of local anesthetic action are directly related to the physical properties of lipid solubility, pKa (ie, ion-

ization), and protein binding (Figure 13-3).⁵³ Local anesthetics consist of a lipophilic, unsaturated, benzene-ring aromatic group; and a hydrophilic, tertiary amine separated by a hydrocarbon connecting chain (Figure 13-4). Clinically useful local anesthetic agents fall into two chemically distinct groups, based on the linkage between the aromatic portion and the intermediate chain.⁵² This linkage can be via an ester (–CO–) or an amide (–HNC–) bond. The ester and amide compounds differ in their chemical stability, metabolic cycles, and allergic potentials.

In general, the greater the length of the connecting group and the more complicated the aromatic and amine structures, the greater the potency and the toxicity of the local anesthetic.⁴⁸ The addition of more complicated side chains to local anesthetics causes an increase in their tissue-protein binding ability and also makes the drug more fat soluble, thereby increasing the duration of action.⁴⁹

Lipid Solubility

The aromatic group (ie, the benzene ring) that is present at one end of the molecule is the major determinant of the lipid solubility of local anesthetic drugs. The more-lipid-soluble drugs are the more-potent local anesthetics, probably because the lipid-soluble uncharged base form can pass through the lipid-containing nerve membrane to reach its site of action.⁵³

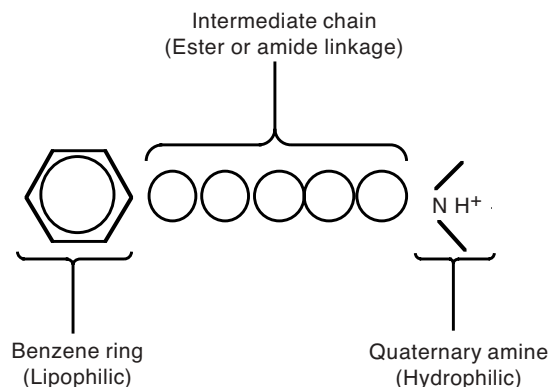


Fig. 13-3. The general structure of a local anesthetic molecule.

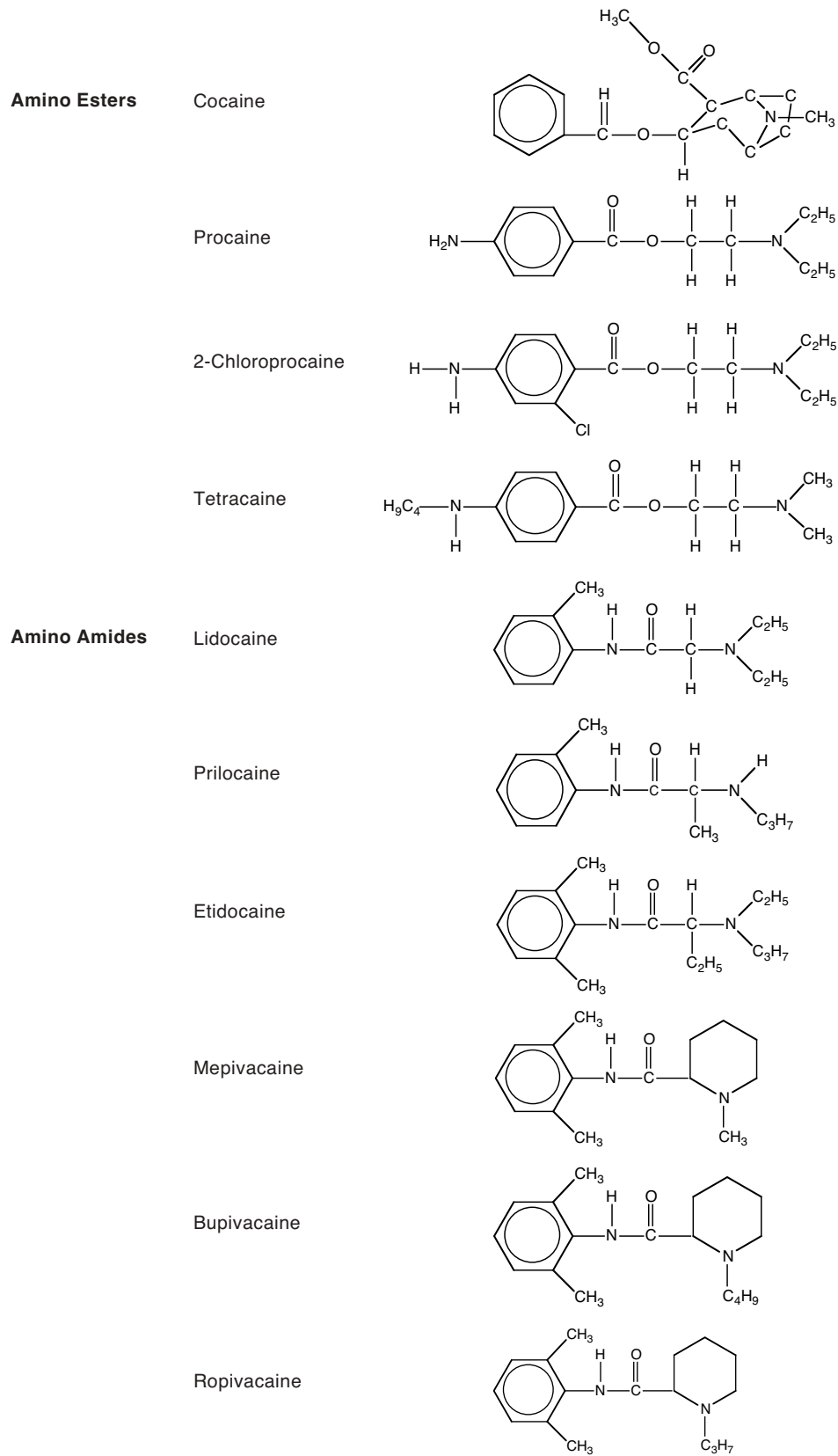


Fig. 13-4. Chemical structures of commonly used local anesthetics.

Ionization

Local anesthetic molecules contain an amino group, which determines the hydrophilic activity and ionization of the molecule. The amino group is capable of accepting a hydrogen ion, which converts the nonionized base form of the drug into the cationic (ie, charged) form. The proportion of each form (nonionized base and cation) present is determined by the pKa of the drug and the pH of the solution (pKa is defined as the pH at which 50% of the drug is ionized and 50% is present as the free base). The nonionized (free base) form penetrates the nerve membrane and the ionized (cationic) form produces blockade of the sodium channel. With many local anesthetics, the speed of onset can be related to the degree of difference between the pKa of the drug and the pH of the normal human body.⁵³

As a general rule, the lower the pKa of the local anesthetic, the shorter the onset time for induction of anesthesia. The closer the pH of the injected solution of local anesthetic is to body pH, the shorter the onset time. Commercial preparations of local anesthetics are made more acidic to enhance stability, which favors the formation of the cationic form (Figure 13-5).⁵³

Protein Binding

Anesthetics are not pharmacologically active while in their protein-bound form. In the plasma, local anesthetics bind to albumin (a low-affinity, high-capacity binding) and to α_1 -acid glycoprotein (a high-affinity, low-capacity binding). The binding of local anesthetics to proteins is concentration-dependent and decreases in a curvilinear manner as the local anesthetic concentration in plasma increases. So the potential for toxicity increases disproportionately with increases in plasma concentration.⁵³

Protein binding of local anesthetics is influenced by the pH of the plasma. The percentage of bound drug decreases as the pH decreases. Therefore, acidosis potentiates the toxicity of local anesthetics by increasing the fraction of the active form of the drug—both in the circulation and at the active site.⁵³ Protein binding of local anesthetics, which is decreased in newborns and pregnant women, causes an increase in the free fraction of local anesthetic.⁵³ α_1 -Acid glycoprotein is decreased in elderly individuals, pregnant women, and newborns. Premature infants have approximately one half the α_1 -acid glycoprotein that is present in newborns.⁵³ The fraction of drug that is bound to protein in

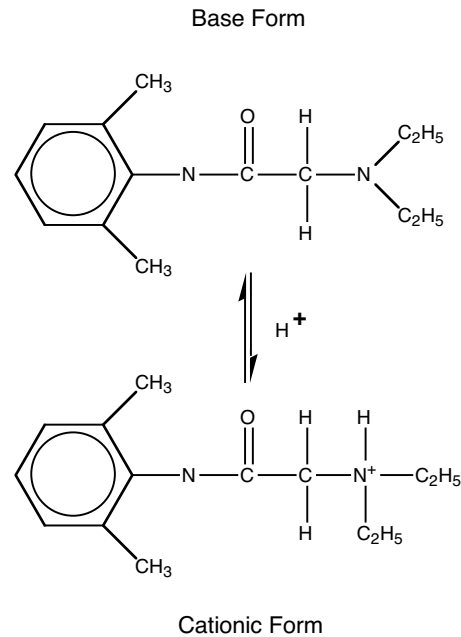


Fig. 13-5. Equilibrium between the base and the cationic forms of a local anesthetic.

plasma correlates with the duration of activity of the local anesthetic. Bupivacaine and etidocaine are 95% protein bound. These drugs last longer than lidocaine, which is 65% protein bound. Recently, researchers have speculated that there may be a similarity between the binding of the local anesthetic molecule to plasma protein and the binding to the receptor protein in the sodium channel.⁵⁴

Mode of Action

The local anesthetics in clinical use today are sodium channel-blocking agents. They exert their effect by inhibiting the influx of Na^+ across the neuronal cell membrane. This produces a conduction blockade of nerve impulses by preventing increases in permeability of nerve membranes to Na^+ . If the permeability to Na^+ fails to increase, the rate of depolarization will slow such that the threshold potential is not reached and an action potential is not propagated. The ionic gradients and the resting-membrane potential of the nerve are unchanged, but the increase in Na^+ permeability that is associated with the nerve impulse is inhibited. Local anesthetics do not alter the resting transmembrane potential or the threshold potential.⁵²

The theories of the mechanism of action include (a) the displacement of Ca^{++} from a membrane site

that controls Na^+ permeability, (b) the Meyer-Overton rule of anesthesia, (c) a change in surface charge, and (d) the specific-receptor theory.

Displacement of Calcium

A low calcium concentration outside the neuron enhances local anesthetic activity, while an increasing external calcium concentration antagonizes local anesthetic activity. However, the direct actions of calcium and local anesthetic appear to be independent of each other.⁹

Meyer-Overton Rule

The Meyer-Overton rule of anesthesia postulates that diffusion of the relatively lipophilic anesthetic molecules into the lipid component of the neuronal membrane expands the membrane to a critical volume and interferes with sodium conductance. Local anesthetics have been shown to increase the volume of lipid membranes and increase their degree of disorder. High-pressure antagonism of the anesthetic activity of certain uncharged local-anesthetic molecules such as benzyl alcohol and benzocaine has been seen. Pressure reversal has not been shown to occur in the case of charged local anesthetics. These findings indicate charged and uncharged local anesthetics may have separate sites of action.^{9,55}

Change in Surface Charge

A third proposal for the mechanism of action of local anesthetics involves the induction of alterations in the membrane surface charge. The cationic molecule neutralizes, to a variable degree, the fixed negative charges on the inside membrane surface, altering the transmembrane potential. If the molecule of local anesthetic is absorbed into the extracellular side of the axonal membrane, the extra positive charges add to the already relatively positive extracellular charge and hyperpolarize the membrane. This hyperpolarization makes it harder for a nerve impulse to raise the transmembrane potential to the depolarization threshold. If the local anesthetic is absorbed into the intracellular side of the axonal membrane, the increase in positive charge could prevent sufficient repolarization of the membrane interior to allow reactivation of the sodium channels that were inactivated by a previous action potential. The surface-charge theory could account for the antagonism between divalent cations such as calcium and local anesthetics.⁹

Specific-Receptor Theory

The specific-receptor theory postulates that local anesthetics interact directly with specific receptors in the neuronal membrane. This interaction affects specific ion channels of the neuronal membrane in such a fashion that the ionic flux needed for initiation and propagation of the action potential is inhibited. The structure of the sodium channel is that of a lipoglycoprotein that spans the neuronal membrane and contains an aqueous pore that is able to discriminate between sodium and other ions, being selectively more permeable to sodium.⁹ Intrinsic electrical properties of the macromolecules that compose the channel allow it to change configuration in response to changes in the membrane potential, thus determining the conductance of sodium ions across the axolemma.

The sodium channel can exist in three states: closed (ie, resting), open, and inactivated.¹⁰ When a nerve impulse occurs and the sodium channel goes through the open to the inactivated state, it carries another impulse until it repolarizes and returns to the resting state. Immediately following an action potential, many of the sodium channels are in the inactivated state and cannot be reopened by a subsequent voltage change. So once an excitable membrane has been depolarized by an action potential, it cannot conduct a second impulse until it has first repolarized and allowed inactivated sodium channels to return to their resting state. If an adequate number of sodium channels are not present in the resting state, sodium current sufficient for a second action potential cannot be generated.^{9,10}

Frequency-Dependent Blockade

The property of frequency-dependent blockade (ie, use-dependent blockade), in which neuronal blockade by charged local anesthetic molecules increases with repetitive, brief, membrane depolarizations, is one phenomenon that suggests direct interaction between sodium channel receptors and the charged local anesthetic molecules. It is postulated that frequency-dependent blockade develops because charged, hydrophobic, anesthetic molecules inhibit Na^+ conductance through the sodium channel by gaining access to a channel receptor located within the channel itself, while the pore of the sodium channel is open. For this reason, selective conduction blockade of nerve fibers by local anesthetics may be related to the nerve's characteristic frequencies of activity (ie, selective conduction blockade occurs more readily in a rapidly firing

nerve).^{9,10} Reversal of the inhibitory effect of the local anesthetic also requires an open channel pore to facilitate the dissociation of the molecule of local anesthetic. Consequently, a closed channel containing a local anesthetic molecule would be slow to return to its uninhibited state.^{9,10}

In contrast to charged anesthetics, neutral anesthetics exhibit much less frequency-dependent blockade; this may be because they are not restricted to the aqueous phase and can gain access through the lipid milieu of the membrane interior. Local anesthetics may also shift the sodium channel population to a nonconducting state by binding channels that have already been inactivated, preventing their return to the resting depolarization-susceptible configuration. A weak tonic (ie, resting) block may be induced by binding with channels in the resting (closed) state to prevent their voltage-induced activation.

The discovery that the blocking potency of local anesthetic molecules is much greater when the interaction is with receptors of open and inactivated channels, as compared to those of closed channels, has led to the modulated-receptor hypothesis of local anesthetic receptor binding. According to the modulated-receptor hypothesis, local anesthetics have a higher affinity for open and inactivated sodium channels than for closed channels. During stimulation, channels that are open and inactivated bind local anesthetics more tightly. This binding stabilizes the channels in a nonconducting state, and increasingly so with each stimulating pulse.⁹ The variable state of the local anesthetic receptor determines the strength of its interaction with the local anesthetic molecule. An excitable membrane with a higher depolarization frequency will be more sensitive to the blocking effects of local anesthetics. This theory offers an explanation for frequency-dependent blockade.

Receptor Sites in the Sodium Channel

It is uncertain as to exactly where in the sodium channel the local-anesthetic receptors are located. Three sites of binding are postulated^{9,10}:

1. near the interior opening; this area has an affinity for charged local anesthetic molecules;
2. at the interface between the channel and membrane lipid; this area has an affinity for uncharged molecules; and
3. at the outer aspect of the sodium channel; this area is the site of actions of toxins such as tetrodotoxin.

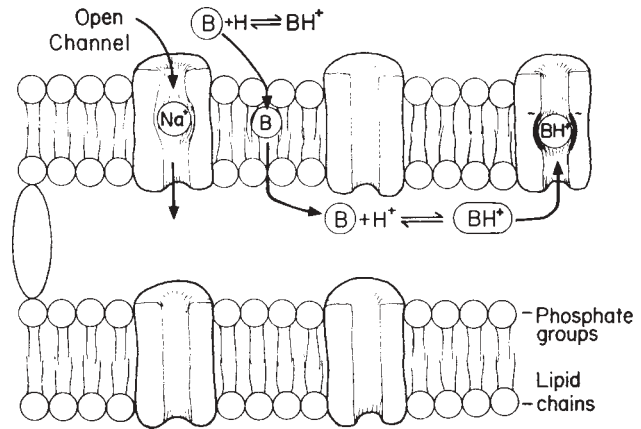


Fig. 13-6. A molecule of local anesthetic moves through a lipid bilayer and enters the sodium channel. On the drawing, B represents the base form of a local anesthetic and BH⁺ represents the cationic form. Reprinted with permission from DiFazio CA, Woods AM. Drugs commonly used for nerve blocking. Pharmacology of local anesthetics. In: Raj PP, ed. *Practical Management of Pain*. St. Louis, Mo: Mosby-Year Book; 1992: 690.

Figure 13-6 shows the nonionized base form of the local anesthetic molecule diffusing through the neural lipid bilayer. Inside the nerve, the equilibrium is established between the free base and cationic forms of the local anesthetic. The ionized cationic form enters the sodium channel from the intracellular side of the nerve membrane, binding to an anionic site, which blocks the sodium channel.⁵³

Actions of Local Anesthetics on Nerve Fibers

Actions of local anesthetics on nerve fibers generally depend on the diameter of the fiber and the length of the fiber exposed to the agent. These two related characteristics are discussed below.

Minimum Length of Exposed Nerve

A minimum length of myelinated nerve fiber must be exposed to an adequate concentration of local anesthetic for nerve block to occur. Conduction blockade is predictably present if at least three successive nodes of Ranvier are exposed to adequate concentration of local anesthetic.⁴⁹ Both types of pain-conducting fibers (ie, myelinated type A-delta and nonmyelinated type C fibers) are blocked by similar concentrations of local anesthetics despite their differences in diameter. Pregangli-

onic type B fibers are more readily blocked by local anesthetics than any other fiber, even though these fibers are larger in diameter than type C fibers (type B fibers are myelinated; type C are not).

Differential Blockade

It has long been a clinical observation that all neuronal functions are not affected equally by local anesthetics. Blockade of the components of a peripheral nerve may proceed at different rates, with loss of sympathetic function first, followed by pinprick sensation, touch and temperature, and, lastly, motor function. Or there may be relative sparing of one neuronal function over another (eg, low-dose bupivacaine labor epidural, with its relatively intact motor tone). There are several potential explanations for differential blockade:

1. The fiber's diameter is inversely proportional to the fiber's susceptibility to local anesthetic blockade.
2. Internodal distance is proportional to the axon diameter, so the equivalent spread of local anesthetic may produce conduction blockade of a thin axon but not of the adjacent thick axon (Figure 13-7).
3. C fibers may be blocked faster, owing to the relatively unimpeded local anesthetic access to the axon.
4. The slower local anesthetic block of A fibers depends on the pKa and the lipid partition coefficient of the local anesthetic molecule.

The lower the pKa (the greater the percentage of lipophilic uncharged molecules at physiological pH) and the greater the lipid partition coefficient of the local anesthetic molecule, the more rapid the onset of block in A fibers. In high concentrations, even a relatively hydrophilic local anesthetic can produce a rapid block of A fibers because of the greater diffusion gradient, causing a rapid transit across the myelin sheath. Thus, the use of a less-lipid-soluble local anesthetic would most likely result in differential block of A-delta and C fibers at the onset of the nerve block. The differential block seen with bupivacaine is believed to be due to the relatively high pKa of this agent, such that fewer uncharged molecules are available to penetrate the diffusion barriers surrounding large A fibers. Differential blockade may be the manifestation of a frequency-dependent process with more-rapid-firing axons being sensory and slower-firing axons being somatic motor efferents.

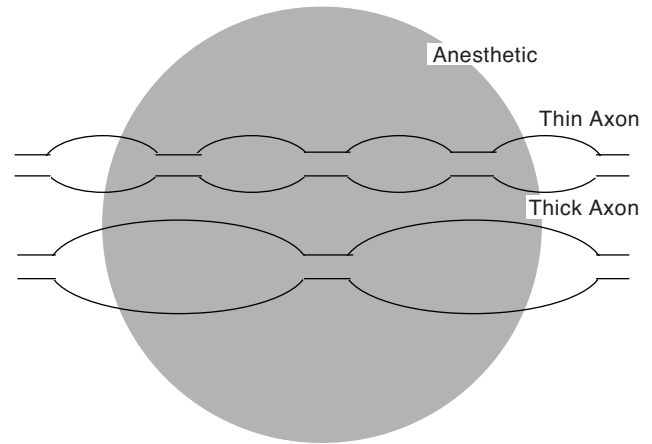


Fig. 13-7. Differential blockade of myelinated nerve fibers of different diameters. Internodal distance is proportional to axon diameter. Conduction blockade occurs when at least three adjacent nodes of Ranvier are blocked. This drawing shows the blockade of a thin myelinated axon occurring before a block will be established in a thicker myelinated fiber. Adapted with permission from Franz DN, Perry RS. Mechanisms for differential block among single myelinated and non-myelinated axons by procaine. *J Physiol.* 1974;236:207.

Differential block may also be a reflection of the geographical arrangement of the nerve fibers within the peripheral nerve, with the outermost fibers being blocked preferentially if the local anesthetic solution is dilute. The local anesthetic diffuses from the outer surface (ie, the mantle) toward the center (the core) along a concentration gradient. The mantle is blocked first. These are the more proximal structures. The core is the more distal structure. Skeletal muscle paralysis may precede the onset of sensory blockade if motor nerve fibers are distributed peripheral to sensory fibers in the mixed peripheral nerve (Figure 13-8).

Pharmacokinetics

Pharmacokinetics denotes the movement of a drug through the body: movement into the bloodstream, movement from blood into tissues, and movement out of the body by metabolism and excretion. When regional anesthesia is sought, the local anesthetic is injected in close proximity to the site of desired effect so that local, physical factors become more important than systemic pharmacokinetic factors for predicting the desired pharmacodynamic effects. The concentration of local anesthetic that develops in neural tissue is affected by the proximity of the injected anesthetic to the nerve, the flow of anesthetic around the nerve tissue, diffusion across

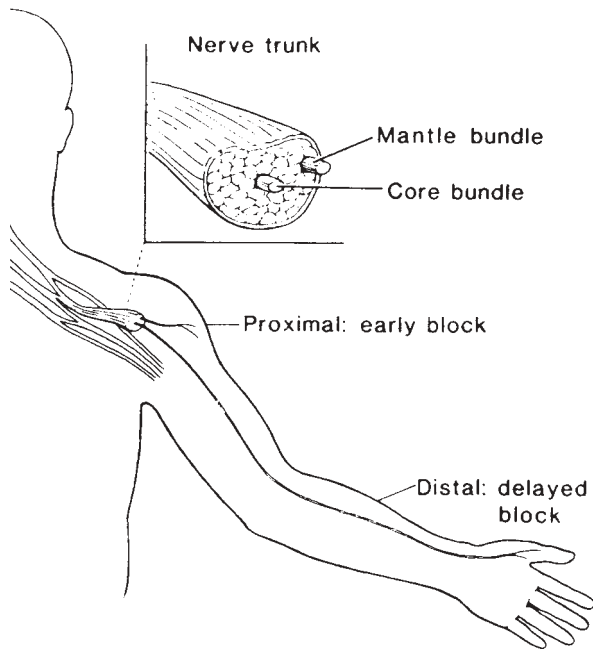


Fig. 13-8. Somatotropic arrangement of fibers in a neuron. Local anesthetics diffuse along a concentration gradient to block the mantle fibers before the core bundle. This is the explanation for anesthesia occurring in more proximal areas of the extremity first. Reprinted with permission from Stoelting R, Miller R. *Basics of Anesthesia*. 2nd ed. Philadelphia, Pa; JB Lippincott; 1989: 84.

the tissue barriers and into the nerve, binding to nonneural tissues, and absorption into the vascular and lymph system.

Both local carbon dioxide partial pressure and temperature are determinants of the pharmacokinetics of local anesthetics. Making local anesthetics from the carbonate salt rather than the hydrochloride salt and adding carbon dioxide to the solution yields a better-quality neural blockade. This approach both shortens the time of onset and improves the neural blockade. This effect may be due to (1) elevated carbon dioxide, which causes a direct neural blockade, and (2) increased carbon dioxide in the axoplasm, which causes an increase in ion trapping of the local anesthetic in the axoplasm by favoring the shift of nonionized free base form to the impermeable ionized form of local anesthetic.⁵³ Warming the local anesthetic solution increases the pKa of the local anesthetic so that at a constant pH, warming results in an increase in the fraction of free base available. Warming the local anesthetic solution causes a consistently faster onset of action.⁵³

Bulk Flow

A large volume of local anesthetic solution will spread by bulk flow to a greater extent and produce a greater spread of nerve block. Concentration (or total mass of drug) also affects the spread, probably by influencing diffusion gradients. Separating the effects of volume, concentration, and mass is difficult. A minimum volume is probably necessary to provide adequate spread around the nerve. A minimum concentration is necessary to provide an adequate diffusion gradient to penetrate the nerve. Once these minimum values have been attained, the total mass of drug becomes important.

Diffusion and Binding

The rapidity and extent of diffusion depends to largest extent on the pKa of the local anesthetic, the concentration injected, and the lipid solubility. The ionized form of the drug diffuses poorly, whereas, the nonionized free base is freely diffusible. Alkalinization of the injected solution will increase the proportion of nonionized drug and should facilitate diffusion. Acidosis from local infection will retard diffusion of local anesthetic because of increased ionization. Local anesthetics with high lipid solubility can penetrate neural membranes more readily but they also have more nonspecific binding, which can impede diffusion to the specific site of action.

Systemic Absorption

The most important factors affecting peak blood level (C_{max}) are (a) the total dose of local anesthetic, which is almost a linear relationship, and (b) the site of injection (see Chapter 12, Regional Anesthesia, Figure 12-2), in the following relationship:

intercostal > caudal > epidural >
brachial plexus > sciatic or femoral

When a 1 mg/kg dose of local anesthetic is given as an epidural or caudal injection, a peak blood level of approximately 1 µg/mL results. When a 1 mg/kg dose of local anesthetic is given in a less-vascular area (eg, the brachial plexus) or as a subcutaneous infiltration, a peak blood level of approximately 0.5 µg/mL is seen. During an intercostal block, a peak blood level of 1.5 µg/mL occurs. Peak blood levels may be seen 10 to 30 minutes after injection.⁵³

The peak blood levels that are seen after injection are affected by the rate of local anesthetic biotransformation and elimination. For amides, this effect is small. For example, 70% of the lidocaine presented to the liver undergoes hepatic extraction. This is limited by hepatic blood flow and the low concentration of local anesthetic in the plasma after a nerve block is performed.⁵³ Biotransformation is the primary determinant of the very low plasma levels that occur after a nerve block by an ester local anesthetic. Due to their metabolism by plasma cholinesterase, esters such as 2-chloroprocaine have a plasma half-life of approximately 45 seconds.⁵³

Distribution, Metabolism, and Elimination

Once a local anesthetic is absorbed into the blood, it is distributed first to the lung, where local anesthetics have a high solubility. On reaching the systemic circulation, distribution is determined by tissue blood flow. The local anesthetics go first to vessel-rich groups and then are redistributed into tissues with lower relative perfusions.

The amide local anesthetics are extremely stable agents; esters are relatively unstable in solution. Amino esters are hydrolyzed in plasma by plasma cholinesterase. Patients with atypical plasma cholinesterase may be at increased risk for developing excessive plasma concentrations of ester local anesthetics. Amide compounds undergo hepatic microsomal metabolism. Hepatic disease or reductions in hepatic blood flow—such as those that occur with congestive heart failure or during general anesthesia—can reduce the rate of local clearance of amide local anesthetics.

If a patient develops seizures and becomes acidotic, the local anesthetic that has accumulated in the brain will be more ionized and unable to cross the lipid blood-brain barrier for redistribution. Acidosis also modifies the pharmacokinetics of local anesthetics in the fetus. When a fetus is depressed and more acidotic, the uncharged, absorbed local anesthetic that crosses the placenta will become ionized and be trapped in the fetus.⁴⁹

Expedited Onset and Prolongation of Action

Expedited Onset. Onset of local anesthesia can be expedited by increasing the nonionized lipid-soluble form of local anesthetic. As discussed previously, this is the form of local anesthetic that can penetrate the nerve membrane. The fraction of the free base (nonionized) form and the cationic (ion-

ized) form is determined by the pKa of the drug and the pH of the drug solution, and the pH of the tissue in which the drug is injected.⁵³ Adjustment of the pH by alkalinizing the injectate shifts the equilibrium towards the nonionized free-base form of the local anesthetic, so that more molecules are available to penetrate the nerve membrane. Increases in the amount of free base in solution are limited by the solubility of the free base in solution. After a saturated solution of free base is achieved, further alkalinization will result in precipitation of the drug.⁵³ Local anesthetics often fail to work in areas of local acidosis (eg, an abscess). In these areas, the equilibrium between charged and uncharged forms of the anesthetic is shifted in favor of the charged form as a result of the abundance of hydrogen ions. This decreases the amount of uncharged local anesthetic available to diffuse through the neural membrane to initiate anesthesia.⁴⁹

Prolongation of Action with Epinephrine. The addition of epinephrine (1:200,000, 5 µg/mL) or phenylephrine (2 mg) to local anesthetic solutions that are to be injected produces local tissue vasoconstriction, which limits systemic absorption, and prolongs the duration of action by keeping the local anesthetic in contact with nerve fibers.⁵²

In the presence of volatile anesthetics, systemic absorption of epinephrine may contribute to cardiac dysrhythmias, or accentuate hypertension in selected patients (eg, those with preeclampsia or thyrotoxicosis). Addition of epinephrine is not recommended⁵² in patients with

- unstable angina pectoris,
- cardiac dysrhythmias,
- uncontrolled hypertension,
- uteroplacental insufficiency,
- peripheral nerve block in areas lacking collateral blood flow (eg, the digits, penis, nose), or
- those receiving intravenous regional anesthesia.

Commercially prepared local anesthetic solutions with epinephrine are pH-adjusted to a more acidic environment, which creates stability for the epinephrine (see Table 12-2 for appropriate doses of commonly used local anesthetics).⁵³ Alkalinization of these solutions improves onset time for anesthesia. If epinephrine is added to plain local anesthetic solution, the onset time is improved because the pH of the plain solution is higher (pH 6.5) than the pH of the commercially prepared, pH-adjusted, epinephrine-containing local anesthetic solution (pH 4.5).⁵³

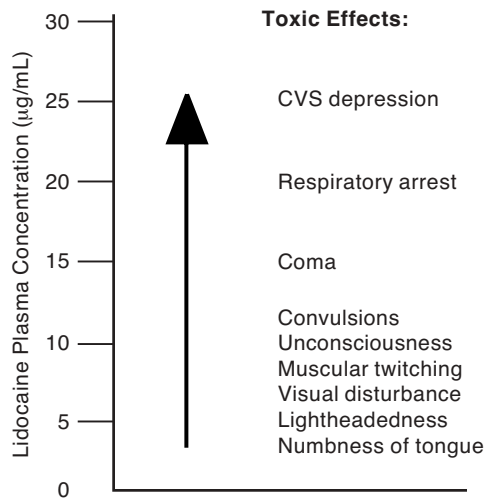


Fig. 13-9. Toxic effects of local anesthetics produced by increasing lidocaine plasma levels. CVS: cardiovascular system. Reprinted with permission from Carpenter RL, Mackey DC. Local anesthetics. In: Barash PG, Cullen BF, Stoelting RK, eds. *Clinical Anesthesia*. Philadelphia, Pa: JB Lippincott; 1989: 389.

Toxicity

Central nervous system (CNS) toxicity in the form of seizures occurs at a lower blood level than cardiac toxicity (Figure 13-9). Excessively high blood levels of local anesthetic can result from various mishaps, including the following:

- accidental intravascular injection of a large amount of local anesthetic,
- premature release of a tourniquet during a Bier block,
- administration of an improper dose for the site of administration (absorption into the bloodstream depends on the site of administration), and
- administration of a local anesthetic to a patient with an allergy to the drug.

Toxicity should be prevented by the means described in Exhibit 13-1. Table 13-6 compares safe doses (in mg/kg) of local anesthetics between various agents and areas of injection. Peripheral blocks are slowly absorbed, which allows administration of a higher dose, compared with an intercostal block, which is rapidly absorbed.

Blood levels of lidocaine of 1 to 5 µg/mL are therapeutic for treating cardiac arrhythmias and as a supplement to general anesthesia. With levels of 3 to 5 µg/mL, systemic symptoms such as circumoral

numbness and buzzing or ringing in the ears may be seen. With levels of 10 to 12 µg/kg, seizures are seen, which are due to selective blockade of inhibitory pathways in the brain, leaving facilitatory neurons unopposed. Before the onset of seizures, patients have slow speech, jerky movements, tremors, and hallucinations. Cardiac toxicity is seen with levels of 20 to 25 µg/kg.⁵³

Bupivacaine blood levels of 4 µg/mL causes seizures, while with higher doses (6 µg/mL), cardiac toxicity is seen.⁵³

Central Nervous System Toxicity

CNS toxicity manifests as seizure activity. If seizure activity is not rapidly stopped, acidosis progresses due to anoxia, which decreases protein binding of the local anesthetic, creating more free (unbound) active drug. This is treated primarily by preventing the detrimental effects of hypoxia and is accomplished by the following protocol⁵³:

- Ventilate with 100% oxygen.
- Suppress the seizures by raising the seizure threshold of the CNS with intravenous thiopental (50–100 mg if myocardial function is not depressed), midazolam (1–2 mg), or diazepam (5–10 mg).
- Patients with severe toxicity should be intubated. Succinylcholine may be used to facilitate intubation.
- Termination of the tonic clonic muscle activity with muscle paralysis will prevent further acidosis due to increased muscle activity.

Cardiotoxicity

All local anesthetics cause a dose-dependent depression of contractility of cardiac muscle. This cardiodepressant effect on contractility parallels the anesthetic potency of local anesthetics in blocking peripheral nerves (bupivacaine has 4-fold more cardiac toxicity than lidocaine).⁵³

Progressive prolongation of ventricular conduction predisposes to reentrant phenomena. Widened QRS is followed by a sudden onset of ventricular fibrillation. All local anesthetics produce a dose-dependent depression of conduction velocity in cardiac tissue, including intraatrial, AV nodal, His-Purkinje, and intraventricular pathways.⁵³

Bupivacaine is 4-fold more cardiotoxic than lidocaine, perhaps because with depolarization of the cardiac sodium and calcium channels, lidocaine

EXHIBIT 13-1

PREVENTION OF LOCAL ANESTHETIC-INDUCED TOXICITY

1. Be familiar with the local anesthetic agent being used.
2. Select a dose that should be associated with clinically safe blood levels at the site of injection.
3. Administer the drug in a manner that identifies an unintended intravascular injection:
 - Fractionate the dose by injecting 3- to 5-mL increments of local anesthetic so that an intravenous or intrathecal injection can be identified before a large amount of drug has been administered.
 - Aspirate frequently during injection to identify intravenous or intrathecal injections.
 - Maintain verbal contact with the patient to identify early subjective sensations such as circumoral tingling and ringing in the ears.
 - Inject a small test dose of epinephrine in a 1:200,000 concentration to elicit an increase in heart rate with inadvertent intravascular injection.
 - Injecting a small amount of air before injecting local anesthetic, combined with precordial Doppler monitoring, may detect intravenous injections.
 - Have resuscitation equipment available when local or regional anesthesia is performed.
4. Have a knowledge of the patient's medical history (hepatic/renal disease or allergy to *p*-aminobenzoic acid).

Data source: Warfield D. *Manual of Pain Management*. Philadelphia, Pa: JB Lippincott; 1991.

rapidly enters and leaves the open channels (ie, the fast-in, fast-out effect). Bupivacaine, on the other hand, rapidly enters the channels but binds the proteins in the channel causing a fast-in, slow-out

effect, which strongly blocks inactivated open cardiac channels. This prevents the channels from recovering during diastole, leading to increased susceptibility to reentrant dysrhythmias.⁵³

TABLE 13-6
COMPARABLE SAFE DOSES OF LOCAL ANESTHETICS (MG/KG)*

Drugs	Peripheral Blocks [‡]	Areas Injected		Intercostal Blocks [§] with Epi 1:200,000
		Plain	Central Blocks [†] With Epi 1:200,000	
2-Chloroprocaine	—	20	25	—
Procaine	—	14	18	—
Lidocaine	20	7	9	6
Mepivacaine	20	7	9	6
Bupivacaine	5	2	2	2
Tetracaine	—	2	2	—

*Estimated to produce peak plasma levels that are less than half the plasma levels at which seizures could occur

[†]Areas of moderate vascularity (ie, caudal epidural blocks)

[‡]Areas of low vascularity (ie, axillary blocks using local anesthetic solutions containing 1:200,000 epi)

[§]Areas of high vascularity (ie, intercostal blocks using local anesthetic solutions containing 1:200,000 epi)

Epi: epinephrine

Reprinted with permission from DiFazio CA, Woods AM. Drugs commonly used for nerve blocking. Pharmacology of local anesthetics. In: Raj PP, ed. *Practical Management of Pain*. St. Louis, Mo: Mosby-Year Book; 1992: 695.

Acidosis increases cardiotoxicity of local anesthetics by decreasing protein binding, which increases the free (active) fraction of the drug. Acidosis also increases the ionized form of the local anesthetic, which is the active form in blocking cardiac channels.⁵³

Therapy for local anesthetic-induced cardiotoxicity employs the following protocol:

- Institute adequate ventilation.
- Terminate the seizures.
- Support blood pressure with fluids, vasopressors, or cardiopulmonary resuscitation.
- Institute antiarrhythmia therapy with bretylium or magnesium sulfate.
- In some cases, remove the offending agent by means of iontophoresis.

SELECTION OF LOCAL ANESTHETICS

Local anesthetics are selected based on (a) the duration of anesthesia needed, (b) the need for motor blockade, and (c) the speed of their onset of action.⁵³

Esters

Procaine

Procaine, the first synthetic local anesthetic, is characterized by slow onset and short duration of action. It penetrates tissue barriers poorly. Procaine is metabolized to *p*-aminobenzoic acid, which has allergenic potential.

2-Chloroprocaine

The 2-chloro- derivative of procaine, 2-chloroprocaine has a rapid onset of action and a short (30–60 min) duration of activity. Its half-life is 45 seconds in the plasma. 2-chloroprocaine has a low potential for systemic toxicity owing to its rapid breakdown. Sensory deficits have occurred with inadvertent intrathecal administration due to bisulfite, the preservative that was added. Bisulfite is an acidic solution that releases sulfur dioxide, forming neurotoxic sulfurous acid. Bisulfite has been removed from the preparation and ethyl-enediaminetetraacetic acid (EDTA) substituted. EDTA may cause spasm of back muscles after epidural administration owing to EDTA's binding of calcium in the paraspinal muscles.⁵³

Cardiotoxicity of the long-acting local anesthetics may be increased in the patient who is pregnant. Lower doses of bupivacaine are required to produce cardiotoxicity in pregnant ewes compared to nonpregnant controls.⁵³ This may be due, in part, to the fact that protein binding is decreased during pregnancy, causing an increased fraction of free drug.

Allergy to Local Anesthetics

p-Aminobenzoic acid is one of the metabolites of esters and related compounds that can induce allergic reactions in some patients. Amino amides, on the other hand, are not metabolized to *p*-aminobenzoic acid, and reports of allergic reactions to these agents are extremely rare.

Tetracaine

Tetracaine, the butyl aminobenzoic acid derivative of procaine, is potent and long acting. This drug is usually used for spinal analgesia in a dose of 6 to 15 mg. The high degree of motor block tetracaine produces may outlast the sensory blockade.

Cocaine

Cocaine is an ester of benzoic acid. It produces topical anesthesia and vasoconstriction. In addition to its local anesthetic activity, cocaine causes CNS stimulation that manifests initially as euphoria and sometimes dysphoria. This is followed by poststimulatory depression. Cocaine's cardiovascular effects are caused by the drug's blocking the uptake of catecholamines at adrenergic nerve terminals. This block can cause sympathetically mediated tachycardia, vasoconstriction leading to hypertension, myocardial ischemia, and dysrhythmias. Administration of epinephrine or volatile anesthetics may sensitize the myocardium to the effects of cocaine. Cocaine is metabolized by plasma cholinesterase.

Preparations of this drug consist of 4% to 10% concentrations for topical anesthesia of the nose, pharynx, and tracheobronchial tree.⁴⁸ The usual topical dose is 1 to 3 mg/kg.¹⁰

The fatal dose of cocaine has been approximated at 1.2 g, although severe toxic effects have been reported from doses as low as 20 mg.⁵⁶ In well-premedicated, extensively monitored, anesthetized

patients presenting for cardiac surgery, no sympathomimetic effect was seen due to nasal topical cocaine (1.5 mg/kg).⁵⁷ Treatment of toxicity from cocaine consists of the following protocol:

- Cardiotoxicity may be treated with esmolol to control the heart rate.
- Labetalol offers hypertension control with alpha and beta blockade.⁵⁷
- Seizures from cocaine may respond to benzodiazepines.⁵²

Amides

Lidocaine

Lidocaine was the first amide-derived local anesthetic. It has excellent tissue penetration, a rapid onset, and intermediate duration (1–2 h). The addition of epinephrine improves the quality of the block and decreases absorption from the site of injection while also prolonging the duration of anesthesia.

Mepivacaine

Mepivacaine is similar to lidocaine in activity and toxicity, and has an intermediate duration of action. This drug is poorly metabolized by the fetal liver, so therefore is infrequently used for obstetric anesthesia. It is not effective topically.

Prilocaine

Prilocaine in doses higher than 600 mg may result in accumulation of the metabolite *o*-toluidine,

an oxidizing compound that converts hemoglobin to methemoglobin. This methemoglobin production is reversed with methylene blue 1 to 2 mg/kg administered intravenously.

Bupivacaine

Bupivacaine was developed from mepivacaine. It has good separation of motor and sensory anesthesia. Bupivacaine has a slow onset, with a long (3 h) duration of action. It is often used for postoperative analgesia because of the motor–sensory separation. Hepatic enzymes for bupivacaine metabolism are present in the fetus, so it may be used in obstetrical anesthesia. Bupivacaine is commonly used for subarachnoid anesthesia in hyperbaric (0.75% bupivacaine with glucose) or isobaric (0.5% bupivacaine) forms.

Etidocaine

Etidocaine is structurally similar to lidocaine. It has a rapid onset of action and a prolonged duration. Its motor block may outlast its sensory block.

Ropivacaine

Ropivacaine is currently undergoing clinical trials. It has properties similar to bupivacaine but may have less cardiotoxicity. Ropivacaine has a similar pKa and protein-binding characteristics as bupivacaine. It is less lipid soluble than bupivacaine, with similar onset and duration. It comes as 0.75% to 1% concentrations. Ropivacaine has good separation of sensory and motor block.

MODE OF ADMINISTRATION OF ANALGESIC DRUGS

Under battlefield conditions, the postoperative care of casualties should be as simple as possible. Whenever possible, casualties should take an active role in their own care, thus limiting the amount of support services needed. Monitored recovery areas are small in wartime, compared with the number of patients who will need operations. The task of the recovery-area staff is to provide safe, adequate pain relief that allows the casualty to be returned to an unmonitored setting as quickly as possible.

Intramuscular and Intravenous Routes

The mainstay of postoperative pain relief will

probably be narcotics administered via the intravenous and intramuscular routes. Their mechanisms of actions are well defined, they are easily administered, they are effective for acute pain, and their effects can easily be reversed with an antagonist like naloxone. Morphine and meperidine in particular are well-known drugs and most medical personnel are familiar with the dosing regimens (Tables 13-7 and 13-8).

Intravenous narcotics can also be delivered via a PCA pump. The pump can be loaded with a supply of narcotics that will last many hours, and, within preset time limits (during which time the patient is effectively locked out of the system), the patient can

TABLE 13-7
INTRAMUSCULAR MEDICATIONS

Drug	Dose (mg/kg)	Peak Onset (min)	Duration (h)
Narcotics			
Morphine	0.05–0.10	45–90	3–6
Meperidine	0.25–0.50	60	2–4
Agonist–Antagonists			
Butorphanol	0.015–0.030	45–90	3–4
Nalbuphine	0.05–0.10	45–90	3–6
Mixed Agonists			
Dezocine	0.070–0.20	45–90	3–6
Nonsteroidal Antiinflammatory Drugs			
Ketorolac	30–60 mg	90	6–12

control the administration. Many authorities^{4,5,58,59} consider the pain relief from the pump to be superior to other forms of narcotics administration. The added advantage of the PCA pump is that the patient feels a sense of control over his or her own care.⁴ This administration technique would be very useful in a field hospital. The drugs commonly used in PCA pump are meperidine and morphine, both in standard concentrations. Once the patient's PCA pump is programmed, it needs only to be checked every 8 hours. The patient needs to be observed every hour to check respiratory rate only.

This means that the personnel monitoring these patients will have more time to function in other capacities. For an adult, the starting dose can be 1 mg per dose for morphine and 5 mg per dose for meperidine. The lockout interval should be 8 to 12 minutes. The dose can be increased as needed according to the patient's needs. If the clinical picture mandates, a continuous infusion of narcotics can also be considered.

The usefulness of agonist–antagonists in the field is limited. The major disadvantage of these medications is that the dose–response curves are usually

TABLE 13-8
INTRAVENOUS MEDICATIONS

Drug	Dose (mg/kg)	Peak Onset (min)	Duration (h)
Narcotics			
Morphine	0.05–0.10	20	3–6
Fentanyl	0.001–0.002	10	1–3
Meperidine	0.25–0.50	20–30	2–4
Agonist–Antagonists			
Butorphanol	0.007–0.015	20–30	3–4
Nalbuphine	0.05–0.10	20–30	3–6
Mixed Agonists			
Dezocine	0.070–0.15	20–30	3–6

shaped like an inverted U: the pain relief reaches a plateau, then decreases with higher doses. With lower doses, the agonist effects of the drugs predominate and the patient will obtain pain relief. However, if the pain is intense and the patient needs large doses of narcotic, the antagonist effect of the drug tends to predominate and the patient will not obtain relief.³⁰ The next dilemma that the medical officer encounters is that the agonist-antagonist opioid will also inhibit the activity of other narcotics that would be used to alleviate the patient's pain. Thus, it would be very difficult to give the correct amount of narcotics. Because of these problems, agonist-antagonist drugs would have limited usefulness in the field for intravenous or intramuscular administration.

Another drug that could have a useful postoperative role in field hospitals is ketorolac, administered intramuscularly. This drug has been used successfully for acute postoperative pain.⁶⁰ Its advantages are that it is not a controlled substance and it can be administered in conjunction with narcotics for additive pain relief without additive side effects. Ketorolac would be a good adjunct to the therapy of patients whose pain cannot be controlled with large doses of narcotics. Once the patients are tolerating oral intake, they can be switched to an oral NSAID.

Epidural and Intrathecal Routes

Intrathecal or epidural delivery of narcotics should be considered whenever possible. The advantage of these modes of administration is the small amount of observation necessary for the maintenance of good postoperative pain relief. The prolonged and profound pain relief obtained from medication delivered via these modes makes them ideal for use in field hospitals. After epidural or intrathecal administration, patient care includes observation for respiratory depression and side

effects common to narcotics. Depending on the type of injury, catheters can be placed in the epidural space for long-term narcotic administration. Not only will the patient be able to obtain narcotics for pain relief, but if the patient needs to be returned to the operating suite, the catheter can be used to provide anesthesia for subsequent operations.

After the narcotics have been administered, the patient can return to a minimally monitored setting for continued postoperative care. The patient can receive either intermittent boluses of a long-acting narcotic, or a continuous infusion of a shorter-acting substance (Table 13-9). The side effects of narcotics have been described above. The most dangerous side effect is respiratory depression but its true incidence is difficult to determine. Current studies indicate that it ranges from 1:32 to 1:260, depending on the dose.⁶ The predisposing factors to respiratory depression are advanced age, CNS depression or concomitant systemic narcotic use, increased intrathoracic pressure, and thoracic extradural administration.^{6,36,37} The healthy, young adults who comprise most of the military patient population are at less potential risk for respiratory depression. A well-tolerated treatment of narcotic side effects is a naloxone infusion: the effects of respiratory depression and the other side effects can be reversed without also reversing the analgesic effects of the narcotics.

If the need for an epidural catheter is anticipated for postoperative pain relief, and if the patient is to remain at relative bed rest, then epidurally administered local anesthetics can be considered. Administering 0.125% to 0.25% solutions of bupivacaine will not only increase the pain relief to the prescribed area, but will also increase the blood flow. However, for this route to be of use, injury has to be located in a nerve distribution that can be blocked safely by an infusion of local anesthetic through an epidural catheter.⁷

TABLE 13-9
POSTOPERATIVE OPIOID DOSES

Drug	Intravenous Dose (mg)	Epidural Dose (mg)	Subarachnoid Dose (mg)
Morphine	5-10	2-5	0.20-0.50
Meperidine	50-100	30-50	10-20
Fentanyl	0.10-0.15	0.10-0.20	0.075-0.15

SUMMARY

Eliminating perioperative pain is justified not only by medical ethics—the imperative to relieve pain and alleviate suffering—but also because severe and unremitting pain can accentuate the potentially dangerous alterations in metabolism and the function of various organs that are caused by severe trauma. Foremost among the metabolic effects is hypermetabolism, leading to catabolism of muscle protein and decreased lean body mass. Similarly, unrelieved pain from thoracic or upper-abdominal trauma may, by causing splinting of respiratory muscles, prevent normal pulmonary gas exchange and clearance of tracheobronchial secretions. Thus, morbidity may be reduced by eliminating pain.

The neurological pathway by which we are made aware of painful stimuli arising in peripheral tissue begins in peripheral pain receptors, which connect via peripheral nerves with ascending pathways that arise in the dorsal horn cells of the spinal cord. From here, information travels in the anterolateral portion of the spinal cord through the brain stem and hypothalamus to the cerebral cortex. The activity of the ascending tracts is modified by impulses that descend from higher centers via descending tracts that synapse with neurons in the dorsal horn. Neurotransmitters are found along the neurological pathway—from substance P and histamine at the peripheral pain receptors to serotonin and enkephalins in the CNS.

Therapeutic interventions that are likely to be useful in treating combat casualties with painful trauma are of two classes: those such as local anesthetics, which prevent transmission of impulses along nerves either in the periphery or in proximity to the spinal cord; and those that either interfere with the synthesis and function of neurotransmitters or directly inhibit neurons in the CNS, which transmit painful stimuli from the periphery. The NSAIDs are examples of substances that alter neurotransmitter activity, while morphine and other opiates, by acting on cells in the spinal cord, decrease traffic passing up the ascending tracts. Opiates also activate the descending inhibitor tracts and act at sites along the neurological pathways for pain in the brain stem and cerebrum.

The spectrum of pain-relieving interventions that are available to military anesthesia providers ranges from orally administered NSAIDs, through intravenous morphine, through regional or epidural blocks with local anesthetics, to epidural analgesia with opioids. Opioids have the advantage of being both potent and, by not blocking sympathetic and motor pathways, selective. There is, however, a risk of respiratory depression. Epidural block with a local anesthetic stops all afferent nerve traffic, one consequence of which is peripheral vasodilation in the affected body parts, which may give rise to potentially dangerous hypotension.

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