



Handbook of Acute Pain Management

Edited by
Jennifer A. Elliott
Howard S. Smith

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I would like to dedicate this book to my parents, David E. and Christel M. Elliott, and my husband, Michael J. Bell, who have provided much guidance, unconditional love and support, and the inspiration to complete this book.

I would also like to give thanks to the many contributors for their time and effort, as well as Dean Shepard for his assistance with creating many of the figures and tables in this book.

J.A.E.



Preface

Pain is a universal experience and is the most frequent reason people seek medical attention. Medical students and residents receive comprehensive guidance in the evaluation and diagnosis of the source of pain complaints, yet formal education on the topic of pain *symptom* management has not traditionally been offered in medical training, leaving many clinicians uncomfortable with providing treatment for pain. Pain can therefore become “painful” to the treating practitioner as well as the patient. This book is intended to assist clinicians who are called upon to treat the patient in acute pain by enhancing their knowledge of and comfort with pain therapies. The scope of providers who may be in a position to manage the acute pain patient is wide ranging, from medical students and residents to primary care providers, as well as anesthesiologists, neurologists, psychiatrists, and other specialists.

This book will provide the reader with background information on the anatomy and neurobiology of pain to lay a foundation for the understanding of pain pathophysiology. Pharmacologic approaches to acute pain management are thoroughly covered, including the use of local anesthetics, NSAIDs, opioids, and α_2 agonists. Patient-controlled analgesia options including patient-controlled epidural analgesia are also explored. Nonpharmacologic and interventional anesthetic techniques are covered, including the use of continuous catheter techniques for postoperative pain management. A chapter also reviews information about anticoagulation guidelines when considering the use of regional and neuraxial anesthetic techniques. Finally, a discussion of pain management issues in special populations such as pediatric, obstetric, trauma, opioid-tolerant, and elderly patients is provided.

The material in this book is intended to provide an up-to-date look at the emerging treatment strategies in the continuously expanding field of pain management and is accompanied by numerous figures and tables to give an at-a-glance review of important concepts discussed in the text. This text provides expanded information on topics such as opioids, including potential drug-drug and drug-disease interactions, which cannot readily be found in other similar texts currently on the market. It also highlights the evolution of new technologies such as “smart” patient-controlled analgesia devices along with associated safety innovations. Information on new developments in the field of regional anesthesia, especially the emergence of continuous catheter techniques, is included to bring the reader up to date on the latest available injection-based therapies.

My goal is that readers will find this book to be a user-friendly reference that addresses the most recent developments in the management of pain. I hope this will assist readers in the approach to the patient suffering acute pain and will enhance their level of comfort as well as that of their patients.

Jennifer A. Elliott

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INTRODUCTION

Postoperative pain or postsurgical pain can be considered a form of acute nociceptive pain with localized inflammatory responses resulting from surgical tissue damage (1). Pain is termed “nociceptive” when the clinical evaluation suggests that it is sustained primarily by the nociceptive system. Nociceptive pain is pain that is proportionate to the degree of actual tissue damage. This “good” pain serves a positive and protective function. Postoperative pain can be neuropathic or neurogenic and can become chronic if it involves inflammation or injury to a nerve, which can occur during surgical procedures such as amputation, hernia repair, hand surgery, or thoracotomy. It is estimated that about 80% of patients experience pain after surgery, of which 86% have moderate, severe, or extreme pain (2–4). In spite of considerable progress in postoperative analgesia, recent studies show that adequate pain relief remains elusive for a significant fraction of hospitalized surgical patients (5–7). It is important for health care professionals to have an understanding of the anatomy and physiology of postoperative pain to improve outcomes in managing postoperative pain.

ANATOMY OF POSTOPERATIVE PAIN

Understanding the physiology and pathophysiology of postoperative pain requires basic knowledge of the anatomy, such as pathways mediating the perception of somatosensory stimuli under normal physiological conditions.

The first step in the pain process involves the transduction of the sensory stimulus (e.g., mechanical, thermal, or chemical) into electrical pulses by primary afferent neurons whose cell bodies reside in the dorsal root ganglion (DRG). These neurons express specialized receptors at their distal ends, which respond to specific types of external (e.g., the skin) or internal (e.g., visceral organs) sensory stimuli by generating electrical pulses or action potentials, which propagate to the dorsal horn of the spinal cord. In general, DRG neurons can be classified as large, medium, and small, which are associated with A β -, A δ -, and C-fibers, respectively. Large-diameter DRG neurons possess large myelinated axons with rapid conduction velocities greater than 15 m/sec and generally transmit information about innocuous mechanosensation (touch, vibration, or pressure). Noxious stimulation is transmitted via small-diameter DRG neurons, which give rise to either thin myelinated A-fibers (which conduct impulses at 2–15 m/sec) or small unmyelinated C-fibers (with conduction velocities of <2 m/sec). Table 1.1 summarizes the properties and functions of three main primary afferent fibers in pain sensation under physiological and pathophysiological states.

The signals carried by primary sensory afferents are integrated by the synaptic network within the spinal dorsal horn, which consists of both local circuit interneurons and second-order projection neurons, which transmit electrical impulses from the spinal cord to higher brain areas predominantly via the

TABLE 1.1 Properties and Functions of Primary Afferent Fibers

Fiber type	Anatomy	Threshold	Main transmitters	Main receptors activated	Laminar level	Target spinal neurons	Normal function	Pathological function
C	Small unmyelinated	High	Peptides (SP, CGRP)	NK 1, 2	I–II, V	NS	Slow pain	Hyperalgesia
Aδ	Small myelinated	Low and high	EAA (glutamate)	NMDA AMPA mGlu	I–II, V	WDR	Fast pain	Allodynia
Aβ	Large myelinated	Low	EAA (glutamate)	AMPA	III–VI	LT WDR	Touch vibration Pressure	Mechanical allodynia

Abbreviations: AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CGRP, calcitonin-gene related peptide; EAA, excitatory amino acids; LT, low threshold; NK, neurokinin receptor; NMDA, *N*-methyl-*D*-aspartate; NS, nociceptive specific; SP, substance P; WDR, wide dynamic range.

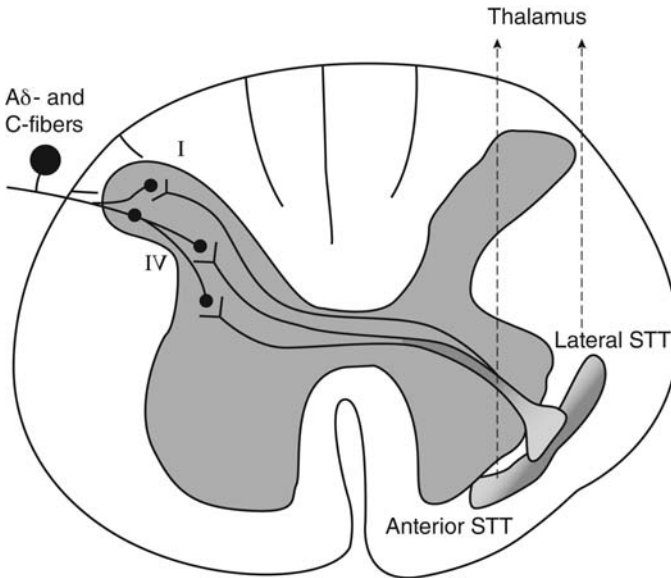


FIGURE 1.1 Pain pathway. *Abbreviation:* STT, spinothalamic tract.

spinothalamic tract (STT) (Fig. 1.1). The output of these STT neurons depends on the net balance between inhibitory and facilitatory mechanisms within the dorsal horn. For example, repetitive stimulation of tactile A β mechanoreceptive inputs can activate spinal interneurons and inhibit the response of STT neurons by decreasing the amount of glutamate released from the presynaptic terminals of nociceptive C-fibers. This is believed to underlie the effectiveness of both transcutaneous electrical nerve stimulation (TENS) and dorsal column stimulation (DCS) as clinically therapeutic interventions for patients with pain. In contrast, responses of STT neurons to nociceptive stimuli can be facilitated if they have been subjected to long-term excessive input from C-fiber nociceptive neurons, which can be caused by chronic inflammation or other chronic noxious stimulation of C-fibers. The excitability of STT neurons is also modulated by descending projections to the spinal cord from higher areas of the CNS, such as the rostral medulla, which can cause both facilitation and inhibition under different conditions.

The activation of third-order neurons in the thalamus by STT inputs allows the transmission of the noxious information to the cerebral cortex, where the perception of pain is generated. Evidence exists that many supraspinal control areas, such as the reticular formation, midbrain, thalamus, hypothalamus, the limbic system of the amygdala and the cingulate cortex, basal ganglia, and cerebral cortex, modulate the sensation of pain.

MECHANISMS OF POSTOPERATIVE PAIN

Like pain resulting from acute tissue injury, postoperative pain involves sensory, emotional, and cognitive components. This chapter focuses on the sensory changes contributing to the postoperative pain: peripheral and central sensitization. Since damage or inflammatory irritation of peripheral nerve endings near the surgical

site is considered the main cause of postoperative pain, we also discuss the neuropathic mechanisms in the pathogenesis of peripheral and central sensitization, and chronic postoperative pain.

Peripheral and Central Sensitization in Postoperative Pain

Surgical tissue damage results in the elevation of an enzyme, cyclooxygenase-2 (COX-2), in inflammatory cells (e.g., neutrophils and mast cells) and leads to the production and release of inflammatory mediators such as histamine, bradykinin, serotonin, and prostaglandins. In response to local chemical release, unmyelinated C-fibers and small myelinated A δ -fibers will be sensitized and generate electrical pulses at the nerve endings. This is referred to as "peripheral sensitization," in contrast to central sensitization, which occurs at the dorsal horn. Substance P may also be released peripherally with resultant increase in peripheral vasodilatation and further sensitization of the peripheral endings of C/A δ -fibers. Other chemical mediators, such as ATP and protons, can directly activate the ends of the peripheral nociceptors, signaling the presence of inflamed tissue and producing pain. Inflammatory cytokines released from damaged tissues, such as tumor necrosis factor α (TNF- α), may contribute to peripheral sensitization by direct activation of nociceptive fibers (8,9).

Following peripheral nerve lesion, strong sustained activation of nociceptive afferents, particularly C-fiber nociceptors, may lead to sensitization of dorsal horn neurons (i.e., "central sensitization"). This can result in the following alterations in the physiological properties of dorsal horn neurons: (i) increased size of the receptive field (i.e., the area of the body, which, when stimulated, evokes action potential firing in the cell); (ii) lower thresholds; neurons begin to fire in response to low-threshold afferent inputs that were previously too weak to evoke action potential discharge; (iii) increased magnitude of action potential discharge in response to nociceptive inputs; and (iv) increased spontaneous impulse activity. These alterations are thought to significantly contribute to the hyperalgesia, allodynia, and spontaneous pain that result from peripheral nerve injury.

Most research data on postoperative pain were obtained from basic research in animal models and human subjects (10). In a rat incisional pain model developed by Brennan et al., it was found that surgical incision in the plantar aspect of the rat hindpaw caused mechanical hyperalgesia to punctate and nonpunctate stimuli that closely parallels that seen in the patients during their postoperative course (11). Enhanced withdrawal response to punctate stimuli was observed in injured and uninjured tissues, suggesting that both primary and secondary hyperalgesia had developed. Further study discovered that *N*-methyl-D-aspartate (NMDA) receptor-mediated secondary hyperalgesia is short lasting in this model. Thus, on the basis of animal research, primary hyperalgesia is the most important mechanism in incisional pain. However, other research studies indicate that central sensitization may be important in the pathogenesis of viscerovisceral and viscerosomatic pain (12). Thus, it is likely that the underlying mechanisms of postoperative pain are associated with the types of surgical procedures performed.

Surgical Neuropathic Pain

Overall, surgery accounts for 10% to 30% of clinical neuropathic pain (13). Certain surgical procedures such as mastectomy, axillary clearance, thoracotomy, amputation, and herniorrhaphy have had higher prevalence rates varying between

TABLE 1.2 Comparison of Nociceptive and Neuropathic Pain

Nociceptive pain	Neuropathic pain
Pain caused by tissue injury	Pain caused by nerve injury
Stimulus evoked, high intensity	Spontaneous, evoked activity
Develops instantly	Develops in days or months
C-fiber mediated	A-fibers involved, low threshold
Opioid sensitive	Poorly opioid responsive

30% and 70% (14,15). Neuropathic pain is characterized by the factors listed in Table 1.2, and while it can be caused by injury to any component of the peripheral nervous system, it is most often associated with the peripheral nerve. It is a condition that develops after the original injury and is manifested by both spontaneous pain and evoked activity that is interpreted out of proportion to the intensity of the stimulus. In addition to C polymodal nociceptive fibers, it is apparently also mediated by low-threshold mechanosensitive A-fibers, since pain can be induced by light touch of the mechanoreceptors. Unlike nociceptive pain, neuropathic pain may respond poorly to traditional pain medications, including opioids. The well-established peripheral and central mechanisms of neuropathic pain can be briefly summarized as follows.

Ectopic Discharges and Ion Channel Alteration in Axotomized Sensory Neurons

Spontaneous activity is rarely observed in normal axons or DRG cells. However, this is a common phenomenon after the peripheral axons are injured. There is now compelling evidence that the expression of sodium channel subtypes (e.g., Nav1.3, Nav1.7, Nav1.8, and Nav1.9) is dramatically altered by nerve injury and may account for the increased excitability of DRG neurons after peripheral nerve injury. Recent works show that elevated chemokines, such as GRO/KC, in the DRG play a pivotal role in nerve injury-induced alteration of sodium channel expression (16).

A reduction in the density of potassium channels following axotomy may also increase the excitability of sensory neurons. This is supported by observations that mexiletine, which can lead to an attenuation of neuropathic pain, also facilitates K^+ currents in DRG neurons.

Previous work has also demonstrated that peripheral nerve injury causes alterations in voltage-sensitive Ca^{2+} channels in DRG neurons. Since these channels are involved in controlling the release of neurotransmitters from the terminals of sensory, central, and sympathetic neurons in the spinal cord, these alterations have significant implications on nociceptive processing under pathological conditions. In fact, the ability of anticonvulsants (e.g., carbamazepine and gabapentin) to reduce mechanical allodynia may involve, among other mechanisms, an interaction with Ca^{2+} channels localized on the injured DRG neurons.

Anatomical Changes in the Axotomized DRG:

Sympathetic Excitation of Injured Sensory Neurons

Complex regional pain syndrome (CRPS) is a neuropathic pain condition that can occur after surgery. The key symptom of CRPS is continuous, intense pain out of proportion to the severity of the injury, which gets worse rather than better over time. Typical features include dramatic changes in the color and temperature of the

skin over the affected limb or body part, accompanied by intense burning pain, skin sensitivity, sweating, and swelling. Although the mechanisms are not clear, in some cases the sympathetic nervous system plays an important role in sustaining the pain. Clinical observations and animal studies have shown that coupling of the activated sympathetic nervous system and the sensitized sensory nervous system is important for the development of sympathetically mediated pain (SMP). Under normal physiological conditions, the afferent sensory nervous system and the efferent sympathetic nervous system are anatomically separated and functionally independent of each other. There is evidence, however, that abnormally enhanced communication between these two systems may occur under pathological conditions. For example, sympathetic stimulation may excite sensory neurons in animals with inflamed peripheral tissue or following peripheral nerve injury. Extensive sympathetic sprouting occurs in the sensory ganglia after peripheral nerve injury. It has been reported that sprouted fibers may enwrap large and medium neurons and form basket-like structures (17,18). These observations suggest that increased activity of the sympathetic nervous system may be involved in the sensitization of sensory neurons toward the development of neuropathic pain. Clinically, it is found that chemical or surgical sympathectomy or sympathetic ganglionic blockade relieves allodynia and hyperalgesia and improves chronic pain in some human patients.

Long-Term Potentiation of Nociceptive Inputs in the Dorsal Horn

The repetitive activation of high-threshold C-fibers, as might occur at the time of surgery damaging a peripheral nerve, can result in a prolonged increase in the strength of their synaptic connections with dorsal horn neurons. The result is that a given impulse from the nociceptive fiber can produce a greater depolarization of second-order neurons in the spinal cord. Importantly, in lamina I of the dorsal horn, this potentiation of synaptic efficacy occurs selectively on spinal projection neurons (i.e., the output cells of the dorsal horn). Thus, strong activation of nociceptive sensory afferents can lead to a greater synaptic drive onto spinal projection neurons and a subsequent facilitation of pain transmission from the spinal cord to the brain.

The activation of the NMDA subtype of glutamate receptor is necessary to induce long-term potentiation in the superficial dorsal horn. Within lamina I of the spinal cord, activation of the substance P receptor NK1 is also required. Animal studies have confirmed that both NMDA and NK1 receptors are involved in the induction and maintenance of central sensitization produced by high-threshold nociceptive afferent inputs at the behavioral level. Because central sensitization is likely to contribute to postinjury pain hypersensitivity states in man, these data have a bearing on the potential importance of NMDA and NK1 antagonists for preemptive analgesia and the treatment of established pain states. However, it should be noted that other types of receptors such as metabotropic glutamate receptors and TrkB receptors are also capable of inducing synaptic plasticity in the dorsal horn.

Spinal Glial Activation

There is now significant evidence showing that glial activation in the spinal cord appears to be important for both the initiation and maintenance of pathological pain (19). Spinal glia (e.g., astrocytes and microglia) are activated after peripheral nerve injury (20,21). Activation of spinal glia leads to the release of mediators that

then act on other glia and spinal neurons. The released chemicals, including proinflammatory cytokines (e.g., interleukin-1 and TNF- α), have been shown to be critical mediators of allodynia (19).

EFFECTIVENESS OF NERVE BLOCKADE AND STEROID ON POSTOPERATIVE PAIN INDUCED BY NERVE INJURY

There has been ample evidence supporting the efficacy of preemptive analgesia on postoperative pain. However, most studies have focused on skin infiltration of local anesthetics such as bupivacaine for acute postoperative pain (22–24). Data about whether ectopic discharges generated at the injury site contribute to the development of persistent pain is scarce. Recently, our laboratory has been assessing long-term effects of early nerve blockade and corticosteroid on nerve injury-induced neuropathic pain (25).

Using rat models of neuropathic pain, we show that local, temporary nerve blockade of afferent activity originating at the injured nerve permanently inhibits the subsequent development of both thermal hyperalgesia and mechanical allodynia. Timing is critical—the nerve blockade must last at least 3 to 5 days, and is effective if started immediately after nerve injury but not if started at 10 days after injury when neuropathic pain is already established (24). Nerve blockade proximal to the injury site of the sciatic nerve also reduced abnormal sympathetic sprouting in the axotomized DRG, a well-known phenomenon implicated in neuropathic pain (18). These results indicate that early spontaneous afferent fiber activity is the key trigger for the development of pain behaviors and suggest that spontaneous activity may be required for many of the later changes in the sensory neurons, spinal cord, and brain observed in neuropathic pain models. Many preclinical and clinical studies of preemptive analgesia have used much shorter duration of blockade or have not started immediately after the injury. Our results suggest that effective preemptive analgesia can be achieved only when nerve block is administered early after injury and lasts several days. Our studies suggest that local anesthetics with long-lasting effects should have a better impact on postoperative pain and possibly prevent the transition of acute pain to a persistent state.

In another study, we examined the effects of systemic administration of the corticosteroid triamcinolone acetonide (TA; Kenalog[®]) on mechanical pain behaviors and abnormal sympathetic sprouting in a rat model of neuropathic pain (26). TA was injected subcutaneously once per day for four days beginning on the day of surgery. It was found that early treatment with TA significantly decreased mechanical allodynia and sympathetic sprouting, with both effects lasting after cessation of steroid treatment. However, TA was without effect when given after mechanical pain behaviors were established. The observation that TA was effective when given starting at the time of injury, indicating the same effect as early nerve blockade, suggests that anti-inflammatory steroid treatment might alter the development of postoperative pain after certain surgical procedures that involve nerve injury.

CONCLUSION

Understanding the anatomy of acute and neuropathic postoperative pain requires knowledge of the underlying neuronal plasticity at the levels of the nociceptive neurons, spinal cord, and brain. Modulatory effects at the nociceptor, SMP, central sensitization, and alterations in ascending/descending CNS pathways are all involved in the perception of pain as well as the related pain motivations and

behaviors. Recent findings from laboratory experiments have provided encouraging information toward the clinical management of postoperative pain.

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INTRODUCTION

The onset of an acute pain event is distinctly characterized by a complex neurobiology involving multiple processes that go beyond the traditional understanding of neuroanatomic pathways (1–3). The most common definition of acute pain is the normal predicted physiological response to an adverse chemical, thermal or mechanical stimulus associated with surgery, trauma or acute illness (4). Yet, it is well recognized that patients' experiences, attitudes, beliefs, and personalities have a strong influence on how they respond to and perceive an acute pain event. Merskey and Bogduk noted that acute pain usually lasts less than a month, but could be evident up to six months following tissue injury (5). Despite the time differentiation noted in the literature between acute and chronic pain states, there is a growing body of evidence suggesting that the seeds of a chronic pain state are implanted very early on following the onset of acute pain (6,7). Therefore, acute pain should be considered as a potential cause of a persistent chronic pain state, if not corrected in a timely manner (4).

This chapter will not detail the neuroanatomy of the classic afferent pain pathways since this has been previously well documented in the literature. Instead, this chapter will concentrate on more recent developments emphasizing the pharmacological, immunohistochemical, and genetic factors that contribute to our understanding of how acute tissue injury (incision, inflammation, contusion, ischemia, or disease) causes afferent nociceptive signaling to the conscious brain. In addition, the mechanisms of chronic pain will not be addressed in detail, except in those areas where the impact of an acute pain signal could alter the neural environment that might initiate the development of a chronic pain state. A better understanding of these physiological, pharmacological, and genetic factors may help provide the basis for a more informed approach to the management of acute pain.

PAIN PHYSIOLOGY

The modern understanding of the mechanisms of acute pain has evolved from the classic work of Descartes in the 17th century, who thought that acute pain transmission occurred through anatomically distinct neural pathways from skin receptors to the spinal cord tracts. These spinal cord tracts, primarily the spinothalamic tract, would then conduct signals to the brain, where conscious perception of the noxious event is perceived. Presently, our understanding recognizes that the perception of acute noxious signaling involves a very dynamic process in both the peripheral and central nervous systems (CNS) in which the afferent signal can be augmented, diminished, or redirected to either the ventral horn of the spinal cord or to the sympathetic ganglia where autonomic and/or motor responses (reflexes) can be initiated. Clinical studies suggest that the intensity of the acute pain signal may be an important predictor of the development of a chronic pain state (8). In addition, intense nociceptive input from the periphery to the CNS can result in

central sensitization in which the nociceptive signaling may persist long after the primary insult to tissue has disappeared. This can result in hypersensitivity and hyperexcitability of the pain conducting pathways, both centrally and peripherally (1). The spinal circuitry appears to have the ability, under these conditions, to undergo considerable change. This has been referred to as dorsal horn plasticity, which is pivotal to the development of the hypersensitivity state (9). Also, acute pain can transition to a chronic pain state in which acute nociceptive stimuli can produce aberrant gene expression in the dorsal horn of the spinal cord (10). This gene expression has been noted in specialized dorsal horn neurons, primarily the wide-dynamic range (WDR) neurons. Although a number of genes appear to be involved in this process, the most studied genetic locus is the *c-fos* oncogene, which is thought to be a protein encoder for the neuropathic pain state (11).

The process of creating a painful stimulus is the result of a complex series of biochemical and electrical events summing in the conscious experience of pain. This process is the composite of four distinct subprocesses, which have been identified as: transduction, transmission, modulation, and perception (3). Beaulieu and Rice have previously described these four subprocesses in the following way: "Transduction or receptor activation, is the process by which external noxious energy is converted into electrophysiological activity in nociceptive primary afferent neurons. Transmission refers to the process by which this coded information is relayed to those structures of the CNS concerned with pain. The first stage of transmission is the conduction of impulses in primary afferent neurons to the dorsal horn of the spinal cord, from which a network of neurons ascends in the spinal cord to the brainstem and thalamus. Finally, reciprocal connections are made between the thalamus and the multiple higher areas of the brain concerned with the perceptive and affective responses associated with pain. However, nociceptive activity does not always result in pain perception (equally, pain may be perceived in the absence of tissue injury). Therefore, a process of signal modulation must be introduced into this system that is capable of interfering in this 'pathway.' The modulatory site about which most is known is the dorsal horn of the spinal cord. The final process is perception, in which the pain message is relayed to the brain, producing an unpleasant sensory experience, which has affective, defensive, and perceptive components (3)."

Acute nociceptive signals begin with tissue injury. Action potentials are created in afferent neurons that respond to a variety of noxious stimuli, such as mechanical, chemical or thermal action potentials. Nociceptive firing of afferent neurons increases following noxious stimulation. Although there is some specificity in terms of the response of the peripheral nociceptors, the majority of the nociceptors respond in a polymodal manner to a variety of painful inputs (12). In addition, the response of these polymodal nociceptors is in proportion to the logarithm of the stimulus applied. Once tissue injury occurs, a variety of tissue factors are released, which can cause tissue edema, vasodilatation, and the induction of an inflammatory state (13,14). These factors include potassium and prostaglandin (PG) from the injured tissue, cytokines and histamine from mast cells, tissue accumulation of serotonin (liberated from platelets), and bradykinin (plasma kininogen) from the vasculature. In addition, adenosine triphosphate (ATP) and nitric oxide (NO) are released. Endogenously produced PG, bradykinin, and a variety of cytokines are potent stimulants of the peripheral pain receptors (12). These compounds are released primarily as a result of the initiation of the arachidonic acid pathway (13). Of importance, the inflammatory mediators act to

modify the response of primary afferent neurons to subsequent stimuli resulting in a state of increased peripheral nerve sensitivity (13). Finally, C-fibers release substance P and calcitonin gene-related peptide (CGRP), which can sensitize both the local afferent neurons and their associated peripheral nociceptors. These mediators can sensitize nociceptors (lower the neuronal threshold) or activate dormant (silent) nociceptors, in addition to increasing the rate of neural discharge and the rate of spontaneous discharge (4,15).

Once the peripheral nociceptors have been activated, afferent transmission of the nociceptive signal occurs via three primary somatosensory afferent neural pathways, which have been classified as A β -, A δ -, and C-fibers (16). Each of these fiber types responds differently, and they synapse in the spinal cord at different locations (16).

The thickly myelinated A β -fibers transmit nonnoxious, low-intensity mechanical signals from specialized encapsulated receptors on their peripheral nerve endings at a rate of approximately 7 to 75 m/sec. These fibers terminate in the deeper layers of the dorsal horn, primarily in laminae III, IV, and V before their signals are projected to the brain, primarily via the spinothalamic tract. Of note, A β -fibers synapse on WDR neurons, which are located in lamina V, potentially modulating the output of the WDR neurons.

The A δ -fibers, which are less heavily myelinated, conduct both nonnoxious and noxious (thermal and/or mechanical) signals at a slower conduction velocity of 2 to 7 m/sec. In addition, the A δ -fibers receive afferent nociceptive signals from high-threshold mechanoreceptors. They distribute these signals to not only the deeper portions of the spinal cord (similar to the A β -fibers in lamina V), but they also synapse in the more superficial layers of the dorsal horn (similar to the C-fibers in lamina I).

The C-fiber is the smallest and slowest conducting of the three fiber types, transmitting at a rate of 0.5 to 1.5 m/sec. C-fibers are specialized in that they conduct polymodal (i.e., respond to a full range of mechanical, thermal, and chemical stimuli) noxious signals from free peripheral nerve endings and are the most numerous of the somatic nociceptors (3,16). Furthermore, from a histochemical perspective, the C-fibers are further divided into IB4-positive (plant derived isolectin) and tyrosine kinase receptor (TrkA)-positive [nerve growth factor (NGF)] types (16). C-fibers terminate on second order neurons located primarily in the superficial layers of the spinal cord, lamina I (marginal zone) and lamina II (substantia gelatinosa). From these superficial connections, second order neurons transmit C-fiber input to the deeper layers of the cord, primarily to the WDR neurons in lamina V.

The WDR neurons receive afferent input from many different first order neurons in the dorsal horn. This is referred to as convergence, which allows the WDR neuron to fire more action potentials in response to noxious stimuli. The majority of nociceptive signaling, however, occurs via A δ - and C-fibers. At the same time, not all A δ - and C-fiber transmission encodes for a painful stimulus. Some signaling from these peripheral neurons may encode for innocuous temperature, itch, and touch sensations (12). In addition to the primary afferents, signaling may occur via specialized afferent fibers, which have been referred to as "silent" neurons. They were first identified in joint tissue and later found in visceral and cutaneous tissue (11). They are activated only when there has been significant tissue injury (12).

Nociception of viscerally mediated pain is not as well understood. Thermal and mechanical stimuli, which are potent stimulants of somatically mediated pain,

do not appear to initiate pain from visceral organs. However, pathological distension or contraction of visceral structures, such as obstruction of the intestines, induces a painful reaction. The question that has been raised is whether there are specialized visceral nociceptors that respond to pressure changes in the walls of visceral organs. There is some evidence to suggest that there may be either pressure sensitive receptors in the muscular walls of visceral organs or specialized neurons that respond to high-intensity stimuli (3). In addition, visceral afferent signaling may have monosynaptic input to the central canal of the spinal cord (lamina X) (12). New models for studying visceral pain have been recently introduced, which may help delineate this issue in the future (17).

Following first order synaptic transmission in the spinal cord, the afferent signal is processed by three different neuronal cells. These neuronal cells consist of projection neurons, inhibitory, or excitatory interneurons. They conduct the afferent signals via spinal tracts that ascend anterolaterally in the contralateral spinal cord to the thalamus (3). Signals coming from the body are transmitted through the brainstem to the thalamus, while those coming from the head enter the thalamus via the midbrain. Signals may also connect to the ventral horn neurons, facilitating motor reflex responses and/or sympathetic responses via the spinal sympathetic ganglion. The dorsal horn of the spinal cord thus acts as a master integrator of nociceptive signals (18). Pain transmission can be directed to the autonomic centers of the brain, which regulate the cardiovascular and respiratory functions of the body, or to the limbic system, where affect and emotion are imprinted into the pain signaling process. Nociceptive information is then processed into consciousness (2,12).

Pain transmission may occur via ipsilateral projecting neural systems such as uncrossed components of the spinothalamic, spinoreticular, and spinomesencephalic tracts (19). The dorsal horn neurons act to direct, reduce, and amplify nociceptive signaling utilizing multiple mechanisms. These include neural inhibitory neurons (descending posterior column), sometimes referred to as diffuse noxious inhibitory controls, and the WDR neurons located in lamina V (4).

In addition, acute nociceptive transmission to the CNS results in a neuroendocrine stress response, which includes the release of not only local inflammatory mediators (cytokines, PG, leukotrienes) but also systemic mediators of the stress response such as cortisol, adrenocorticotrophic hormone (ACTH), antidiuretic hormone (ADH), glucagon, aldosterone, renin, catecholamines, and angiotensin II (20). The stress response may trigger additional unwanted events, such as hypercoagulability, inhibition of fibrinolysis, increased platelet activity, and may potentiate postoperative immunosuppression (21,22).

NEURONAL PLASTICITY AND PAIN

A greater understanding of the biochemical changes that occur in the dorsal horn following nociceptive signaling has been achieved in recent years (13,23,24). A diverse group of membrane-bound ionotropic and metabotropic glutamate receptors are located throughout the CNS. The former is divided into three major subclasses: AMPA, kainite, and NMDA receptors (25). With nontissue damage-related nociceptive signaling, the excitatory amino acid receptor AMPA (α -amino-3-hydroxy-5-methylisoxazole acid) is stimulated in the neural cell membrane of the dorsal horn. However, with more repetitive stimulation, such as resulting from tissue damage, a second excitatory amino acid receptor also located on the neural

cell wall, the NMDA receptor (*N*-methyl-D-aspartate), is stimulated (13). The major excitatory neurotransmitter that activates these receptors is glutamate. Glutamate produces a fast response depolarization in the dorsal horn neurons primarily via the NMDA receptor. In addition, it can activate the metabotropic glutamate receptors (mGluRs) which are linked to intracellular G proteins (23). Activation of the NMDA receptor leads to increased excitability of dorsal horn neurons and increased calcium flux (12). Intracellularly, activation of G α q protein-coupled group 1 mGluRs induces calcium release from stores found in the endoplasmic reticulum, as well as activation of protein kinase C (PKC). PKC phosphorylates the NMDA receptor, releasing the magnesium (Mg²⁺) plug within the NMDA channel, allowing cell membrane depolarization to occur (13). Calcium is also involved in a number of other intracellular cascades such as the activation of a variety of enzymes and protein kinases (12). This intracellular process is significantly more complicated than described, and therefore, the reader is referred to a more in depth discussion of this intracellular cascade (23). In addition, NMDA receptors have been identified on unmyelinated and myelinated axons in peripheral somatic tissue, suggesting that they have not only a central role in nociceptive signaling, but also a peripheral role (26). They also appear to play an important, if not a pivotal role, in the development of spinally mediated hyperexcitability and the development of chronic pain (27). The development of a hyperexcitable state may result from changes that occur in the NMDA receptor mRNA expression pattern following peripheral stimulation (25). A more detailed description of the role of mRNA expression can be found in the work of Petrenko and coworkers (27).

RECEPTORS AND NEUROTRANSMITTERS INVOLVED IN PAIN SIGNALING

In addition to the more widely known AMPA, kainate, and NMDA receptors, a series of ion channel-linked receptors related to sensory transduction of noxious stimuli have recently been described (13,24,28). Three types of receptors have been defined and include the vanilloid receptor (VR)-1, the acid-sensing receptor, and the purinergic receptor. The VR-1 is primarily distributed in small diameter afferent neurons throughout the CNS. It is sensitive to capsaicin and to moderate thermal stimuli. The acid-sensing receptor is part of a group of ion channels that are selectively activated by protons, are found throughout the CNS, and appear to be activated by inflamed tissue, arthritic joints, and ischemia (29). The purinergic receptors are phosphate derivatives of AMP, ADP, and ATP (13). They mediate fast synaptic transmission via extracellular ATP, which is released by the somatic cell following tissue injury, or in the presence of tumors, inflammation, migraine headaches and visceral distension. Purines appear to cause pain by initiating the release of other inflammatory mediators. ATP acts extracellularly at two P2 purinergic receptors, either the P2X (ligand-activated cationic channel) receptor or the P2Y (G protein-coupled) receptor (30).

Various voltage-gated ion channels, which are membrane proteins forming temporary permeable pores between the extra- and intracellular spaces, have been noted to play an important role in nociceptive transmission (13). The two most important ion channels appear to be the sodium and calcium channels. The sodium channels have been classified into two types on the basis of their sensitivity to tetrodotoxin (TTX): TTX-resistant (TTX-R) and TTX-sensitive (TTX-S) channels. Large diameter afferent fibers express only TTX-S sodium channels, while the small

diameter afferent fibers express both TTX-R and TTX-S sodium channels (13). During different types of nerve injury, the response of the sodium channels may differ. For example, during acute nerve injury it appears that there is a decrease in the expression of TTX-R channels and an increase in TTX-S channels. However, following an inflammatory pain event there is an increase in the expression of TTX-R channels and a reduction in the expression of TTX-S channels (31). The variable response of the TTX-R and the TTX-S channels to different nociceptive stimuli may explain why there is variability in patient responses to the use of local anesthetics and anticonvulsants for the treatment of pain. These agents work by blocking sodium channels and thus offer a potentially attractive opportunity to control pain transmission at the cellular level. Calcium channels also play a role in transmission of afferent signaling; however, the therapeutic benefit of blocking their function in acute pain states has not been fully elucidated. The N-type calcium channel, which is found specifically on neuronal membranes, appears to have potential for therapeutic channel blockade (32). This is the mechanism by which the conotoxin, ziconotide, is presumed to relieve pain.

Substance P has been known for some time to be an important transmitter of nociceptive signaling (10). It is synthesized in the small diameter afferent fibers and is transported to the CNS, where it is stored in vesicles in the cell bodies of the afferent fibers. Substance P is a member of a family of tachykinins, which include neurokinin (NK)-A and NK-B. These peptides target specific tachykinin receptors: NK-1, NK-2, and NK-3 receptors, which are found in the dorsal horn neurons (1). During an acute noxious stimulus, it appears that substance P acts only in the region of lamina I and II rather than throughout the entire dorsal horn, however it can stimulate the WDR neuron via dorsal horn interneurons (1). This peptide causes the degranulation of mast cells with resultant release of histamine. Vasodilatation and plasma extravasation can result, causing the release of bradykinin and serotonin, both of which are powerful inflammatory and nociceptive mediators (11). In addition, substance P can induce the production of NO, which is another powerful vasodilator released from the endothelium of the vasculature. Intracellularly, substance P activates phospholipase C (PLC), which increases inositol 1,4,5-triphosphate (IP) and diacylglycerol (DAG), resulting in an increase in intracellular calcium. The rise in intracellular calcium alters phosphorylation and gene expression of proteins and induces cellular depolarization, which in turn are implicated in the regulation of nociceptive transmission (23).

Another nociceptive substance released during tissue/nerve damage is nerve growth factor (NGF), which is not only important in the development of sensory and autonomic nerves, but appears to play a role in the process of nociception (33). It is released in the periphery by Schwann cells and fibroblasts and can in turn increase excitability of the peripheral nociceptors on primary sensory nerve terminals to promote thermal hypersensitivity. NGF selectively interacts with its receptor, TrkA, and has the ability to sensitize both cutaneous and visceral primary afferent nociceptors and recruit the silent nociceptors (23). Also, NGF not only has an impact on the primary nociceptive afferent, but can stimulate mast cells and sympathetic efferent nerves. NGF regulates the responsiveness of nociceptors to bradykinin and the sensitivity of the sodium channels located on sympathetic neurons (23).

The PGs are weak in their ability to stimulate nociceptive neurons; however, they appear to be important in the process of sensitizing nociceptive receptors to other compounds (11). Following tissue injury, arachidonic acid is formed from phospholipase, which results in the transformation to three other compounds:

thromboxane, prostacyclins, and PGs. The PGs, particularly from the E and F series, act on specific PG receptors to increase the amount of neurotransmitter released, thus magnifying the transmitted response (12,34). All PG receptors are G protein coupled and when activated trigger intracellular changes in calcium, cAMP, and phosphoinositol concentrations (34). In addition, these receptors show large differences in affinity for and reactivity under various ligands. When PGs are given to test animals intrathecally, the animals demonstrate two types of responses. The first is an increase in response to noxious stimuli (hyperalgesia) and the second is the response of allodynia (touch-evoked pain). This response occurs within minutes of the administration of PG and the dose response curve appears to be bell shaped (34). For a more in depth review of the role of PGs in nociceptive transmission, the reader is referred to an article by Vanegas and Schaible (34).

INHIBITORY COMPONENTS IN PAIN TRANSMISSION

Up to this point, the discussion of the nociceptive system has been related to the afferent excitatory component. There is, however, a powerful inhibitory component to the nociceptive signaling system. The raphe nuclei, periaqueductal gray and the nucleus gigantocellularis exert inhibitory actions on spinal processing of afferent nociceptive signaling (23). These brainstem nuclei form the basis of the descending inhibitory system, which travels caudally to the spinal cord via the posterior descending columns and links to the afferent neurons and interneurons in the dorsal horn. This linkage is referred to as presynaptic inhibition and is thought to reduce the probability of action potentials or inhibit neurotransmitter release by restricting the calcium influx into nerve terminals (23). Second order neurons in the dorsal horn also can receive synaptic connection with the descending fibers, which is referred to as postsynaptic inhibition. This inhibitory system depends on inhibitory neurotransmitters such as γ -aminobutyric acid (GABA), catecholamines, glycine and serotonin, as well as the endogenous opioid system. GABA and glycine are thought to exert inhibitory control over the A β primary afferents and the second order neurons in the dorsal horn (35). The GABA receptor exists in two forms, GABA-A and GABA-B. Both have different functions in the spinal cord, as they respond to different agonists. For example, GABA-A will respond to the benzodiazepines while GABA-B will respond to baclofen, a non-benzodiazepine compound. There is some evidence that following nerve injury there is a loss of GABAergic function, which may explain the loss of inhibitory control noted in neuropathic pain states (36).

Finally, recent findings suggest that inflammatory induced nociceptive signaling to the dorsal horn evokes synaptic rearrangement, which may actually strengthen the nociceptive neural connections that result in a chronic pain state (23). In addition, posttranslational and transcriptional changes appear to occur in second order neurons in the spinal cord. These changes lead to an increase in excitability. By inducing the activity of primarily the NMDA receptor, IP is activated intracellularly, which increases the activity of calcium and calcium-sensitive signaling pathways.

The transcriptional system is then initiated, allowing the inducible expression of proto-oncogenes to occur (23). The end result is the protein encoding of a hypersensitivity state and the potential for the development of a long lasting chronic pain state (24).

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3

Local anesthetics in the management of acute postoperative pain

Gary McCleane

INTRODUCTION

Conventional treatment of postoperative pain revolves around the use of opioids, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and local anesthetics. Utilization of such drugs has been accepted for many years, and yet we still have not optimized our use of them. When specifically considering local anesthetics, novel formulations, and new uses of currently available preparations give the prospect of increasing the quality of postoperative pain relief. It is therefore possible that with imaginative use of these drugs, even though they have been available for many years, increased levels of postoperative pain relief may be produced while the need for other systemically active compounds may be reduced. When considering postoperative pain, and indeed any acute pain, a nociceptive stimulus (e.g., surgical incision, tissue reaction to trauma) precipitates a nociceptive stimulus from periphery to spinal cord and hence to the brain. This structure responds by adding an affective component and by initiating descending inhibitory and facilitatory drives. With the local anesthetics we have an opportunity to intervene at the periphery, along the peripheral nerves, and even at the cord level in an attempt to block this nociceptive process.

When we consider local anesthetics, we have certain drugs in mind. Lidocaine and bupivacaine are good examples. By implication, we are talking about drugs with sodium channel blocking effects and, from a clinical perspective, drugs that have numbing or freezing effects when applied locally. A number of other drugs also possess these local anesthetic effects by virtue of their sodium channel effects, and are yet not conventionally classified as local anesthetics. For example, tricyclic antidepressants and a number of the antiepileptic drugs have known sodium channel effects. In this chapter, we will confine our attention to those drugs conventionally referred to as local anesthetics.

MODE OF ACTION OF LOCAL ANESTHETICS

The intimate relationship between the activity of the membrane bound enzyme, $\text{Na}^+\text{-K}^+$ ATPase, and propagation of nerve impulses is firmly established. The ionic disequilibrium across the semipermeable membrane in a nerve produces the potential energy for an action potential with the disequilibrium being rectified by the activity of $\text{Na}^+\text{-K}^+$ ATPase. Local anesthetics block impulses by inhibiting individual Na^+ channels, and thereby reducing the aggregate inward sodium current (1–3). When used at sufficient concentration, local anesthetics can cause complete neural blockade with obvious consequences on motor and sensory function of the nerve involved. However, when agents such as lidocaine are administered systemically at lower doses, no effect is apparent on the conduction of action potentials in normal A β , A δ , or C primary afferents (4). In contrast, systemic lidocaine significantly suppresses the C-fiber evoked polysynaptic reflex generated by nerve stimulation. At concentrations of 1 to 20 $\mu\text{g}/\text{mL}$, lidocaine

reversibly suppresses the tonic action potential discharge of acutely injured nerves and axotomized dorsal root ganglion cells (5–7).

Even when given in doses sufficient to cause significant cardiovascular side effects, lidocaine reduces the conduction in uninjured A δ -fibers by less than 5%, and in C-fibers by under 50%, demonstrating that when lidocaine is administered systemically at reasonable dose levels, “normal” neural function is essentially uninterrupted, while a measurable effect is observed in damaged neural tissue (8,9).

It has also recently been shown that when lidocaine is administered systemically in animal models, sympathetic noradrenergic sprouting from damaged dorsal root ganglia is significantly reduced when compared with control animals. Of particular note is that this effect persists for more than seven days after the cessation of lidocaine administration. This persistence of effect from systemic lidocaine is again seen when frog sciatic nerves are treated with this drug, causing a rapid, concentration-dependent decrease in the action potential plateau with this effect lasting for over one hour after washout of lidocaine (10).

CLASSIFICATION OF LOCAL ANESTHETICS

Ester-Linked Local Anesthetics

- Cocaine
- Procaine (Novocain[®])

Procaine Analogs

- Tetracaine (Pontacaine[®], Amethocaine[®])
- Benzocaine (Hurricane[®], Solarcaine[®], Dermoplast[®])
- 2-Chloroprocaine (Nesacaine[®])

Amide-Linked Local Anesthetics

Aminoacyl Amides

Aminoalkyl xylidide family.

- Lidocaine (Xylocaine[®])
- Prilocaine (Cintanest[®])
- Etidocaine

Pipicolyl xylidide family.

- Mepivacaine (Polocaine[®], Carbocaine[®])
- Bupivacaine (Marcaine[®], Sensorcaine[®])
- Ropivacaine (Naropin[®])

Aminoalkyl Family

- Procainamide
- Dibucaine

CLINICAL USES OF LOCAL ANESTHETICS

Topical

Gels/Creams

Several topical local anesthetic preparations are available in gel, cream, and patch form. Tetracaine is available as a gel, and lidocaine/prilocaine are presented in a eutectic mixture as EMLA[®] cream. EMLA cream use has become established in the

anesthetizing of skin prior to cannula insertion. It also has demonstrable benefit in reducing the pain of other procedures including lumbar puncture, intramuscular injections, and circumcision (11). Caution should be used with long-term use of this preparation, as prilocaine use has been associated with the onset of methaemoglobinemia.

Patches

Lidocaine is available in a topically applied patch in a 5% strength (Lidoderm[®]). In the United States, lidocaine 5% is approved by the FDA for the treatment of postherpetic neuralgia (PHN). Its efficacy in this pain condition is supported by several trials, which also confirm that it is well tolerated (12–15). Not only can pain levels in patients with PHN be reduced, but measures of quality of life show improvement. In one study of patients with PHN, 66% of subjects reported reduced pain intensity when up to three lidocaine 5% patches were used for 12 hours each day (16).

While lidocaine 5% has an indication for use in PHN, it may also be efficacious in other pain conditions. When used in the treatment of focal neuropathic pain conditions, such as mononeuropathies, and intercostal or ilioinguinal neuralgia, one controlled study has confirmed a pain reducing effect (17,18). In an open-label study of 16 patients with “refractory” neuropathic pain (including patients with postthoracotomy pain, complex regional pain syndrome, postamputation pain, neuroma pain, painful diabetic neuropathy, meralgia paresthetica, and postmastectomy pain), 81% of subjects experienced pain relief. In this report, refractory was used to describe those patients who had either failed to gain pain relief, or those who experienced unacceptable side effects with opiates, anticonvulsants, antidepressants or antiarrhythmics agents.

It is intriguing to speculate what pain relieving effect topical application of lidocaine 5% patch might have on postoperative pain. If it were prepared in a sterile form, then it could be applied directly over a wound site and changed on a daily basis. Where pain would be expected to be largely local and of body wall in origin, such as in the case of inguinal hernia repair or after mastectomy, then it is reasonably likely that it may reduce pain. Suitable studies are needed to verify or refute this speculation.

Infiltration

Infiltration of local anesthetic around a surgical wound is now accepted practice. A variety of local anesthetics can be used, always remembering the potential for them to cause systemic toxicity if used in excessive doses. In the case of lidocaine, which can cause vasodilatation, the maximum safely administered dose can be increased and its duration of effect lengthened by the addition of epinephrine. In the case of other local anesthetics such as levobupivacaine, bupivacaine, and ropivacaine, the addition of epinephrine has little to no influence on the maximum dose to be administered or on duration of effect. When epinephrine is considered, it should not be injected into any area adjacent to an end artery, or peripheral ischemia may result.

While local infiltration offers significant analgesic benefit, the commonly utilized local anesthetics have finite durations of action, and so at some stage, pain is expected to return. Currently, investigation is ongoing into extended duration of effect of local anesthetics with which duration of effect may be measured in days rather than hours.

Perineural Injection

Widespread use is made of perineural local anesthetics in anesthesiology practice. Epidural and spinal anesthetics are used to enable surgical procedures to be carried out, while epidural techniques are also used to provide relief of postoperative pain, trauma related pain (as in patients who have sustained rib fractures), and analgesia during childbirth.

When spinal and epidural techniques are used, it is commonplace for an opioid to be added to the local anesthetic, both to enhance the quality and duration of the subsequent block, and to allow a reduction in the concentration of local anesthetic used. By doing this, it is possible to block pain while retaining a degree of motor function. In some circumstances, long-term intrathecal delivery of drugs is appropriate, including occasionally the use of low doses of local anesthetic.

Nerve blocks can be used to treat acute pain, chronic pain, and to define what nerve or group of nerves is involved in a pain process. When used in the postoperative situation, a local anesthetic, such as bupivacaine, is often used on its own. The duration of relief is then equivalent to the duration of effect of the local anesthetic. When longer relief is desired, a catheter can be inserted adjacent to the nerve, allowing for continuous infusion or intermittent bolus injection of local anesthetic via the cannula.

In chronic pain treatments, it seems that addition of a corticosteroid, usually a depot preparation such as triamcinolone acetonide, is done in an attempt to prolong pain relief. While this is well established in clinical practice, there is no great base of evidence to support the use of steroid. The effect of steroid in prolonging the action of local anesthetic may be related to its effects as an anti-inflammatory, as well as its membrane-stabilizing effects and its action on dorsal root ganglia.

In practice, the only limiting factor for nerve blockade is the accessibility of individual nerves. If located adjacent to fixed landmarks, there can be more confidence in determining their location. Further reassurance can be gained by using a nerve stimulator. The exact methods of performing nerve blocks are beyond the scope of this chapter, and the practicalities of performing these procedures are covered elsewhere in this book.

Parenteral

Animal Pain Models

The use of spinal nerve root ligation in rats is a conventional method for producing allodynia, a cardinal feature of neuropathic pain, and allows the efficacy of pharmacological entities to be assessed as potential antineuropathic pain agents. When low doses of lidocaine are systemically infused for a defined period of time in rats with surgically induced allodynia, paw withdrawal thresholds, a measure of allodynia, are increased for the period of infusion (19,20). When larger doses are given, the reduction in allodynia persists well beyond the period of infusion (21). It has been noted that in some animals, a dramatic reduction in allodynia is observed, while in others, absolutely no effect is generated at all. This parallels human clinical practice closely. An alternative model involves the creation of neuromas in rat sciatic nerves. Electrophysiological measurements can then be made to quantify the amount of spontaneous electrical activity that emanates from the neuroma. Systemic lidocaine almost completely abolishes the spontaneous activity of these neuromas in the absence of nerve conduction blockade (22).

When given at the right concentrations, systemic lidocaine given to rats prior to the ligation of a sciatic nerve prevents the onset of thermal hyperalgesia. If the lidocaine is given 24 hours after the nerve ligation, then the thermal hyperalgesia already present is significantly reduced (23–25). In rats with induced allodynia, systemic lidocaine administration resulted in up to 66% reduction in tactile allodynia. Remarkably, 21 days after the infusion period, 30% to 40% of the maximal possible effect on tactile allodynia persisted (26).

The effect of intravenous lidocaine on allodynia, at least in animal models, seems to fall into three distinct phases. The first is a marked antiallodynic effect during infusion that decreases in the 30 to 60 minutes after cessation of the infusion. The second is a transient reduction that occurs in the hours after infusion. The third is a sustained reduction developing in the 24 hours after infusion and maintained over the next 21 days.

It may be that intravenous lidocaine has effects other than just on the features of neuropathic pain. When used in animals undergoing colorectal distension, electrophysiological responses indicate that there is a dose-dependent inhibition of visceromotor and cardiovascular reflexes evoked by colorectal distension, suggesting a potentially beneficial effect on visceral pain.

It would seem fair to propose that the animal evidence is in support of the contention that intravenous lidocaine can have a pain relieving effect, with the evidence being most robust in the case of neuropathic pain, but with the implication that a similar effect may be apparent in the case of visceral pain. Of particular note is that the effect of infusion in animal models can most definitely far exceed the duration of infusion and the half-life of the drug, suggesting that the human clinical observation of prolonged relief has a scientific foundation and is not just a form of placebo response.

Human Experimental Pain

A small number of studies have examined the effect of intravenous lidocaine on human experimental pain. Two such experimental paradigms are the subcutaneous injection of capsaicin, which causes an acute sensitization of the skin, and the application of a heat stimulus. When these stimuli are applied and intravenous lidocaine is administered, the area of secondary hyperalgesia as detected by brush strokes (but not that detected by filament application) is reduced. In an attempt to define if the effect of lidocaine is primarily peripheral or central, the effects of systemic intravenous and regional intravenous (isolating the reference limb with a cuff) lidocaine have been examined. After capsaicin application, both systemic and regional lidocaine reduced the capsaicin related pain (27). The area of pinprick hyperalgesia is significantly reduced after systemic, but not regional lidocaine treatment, suggesting that the effect of intravenous lidocaine is mediated centrally and not peripherally.

One other experimental model that has been utilized is that of experimental skin burn in healthy volunteers. When such an injury is inflicted, those volunteers who received lidocaine had significantly faster resolution of residual erythema compared with controls 12 hours after the burn. This suggests that lidocaine may have an effect on the long-term inflammation-induced tissue responses to thermal trauma (28).

Human Use

Historically, the postoperative setting was among the first in reports of pain relief with intravenous local anesthetics. As long ago as 1951, Keats and colleagues reported marked relief of postoperative pain when intravenous procaine was

administered (29). In 1961, Bartlett and Hutaserani reported that of 302 patients who received intravenous lidocaine during surgery, 83% experienced either little or no pain in the first three days after surgery as opposed to 25% of the 302 controls (30). More recently, several studies have shown that when lidocaine is given intravenously during major abdominal surgery, postoperative morphine consumption is significantly reduced, as is movement pain and time to first bowel movement. The effects of intraoperative lidocaine persisted for three days after treatment (31,32). In addition, the release of cytokines during the trauma of surgery is reduced by intraoperative lidocaine use (33).

It is accepted that the body of evidence that supports the use of intravenous lidocaine in postoperative pain management is limited. Significantly more evidence of effect is available for other pain situations, and in particular that of neuropathic pain. Three recent systematic reviews have considered the available evidence of analgesic effect when lidocaine is administered intravenously.

Challapalli and colleagues (2005) conclude

Lidocaine and oral analogs were safe drugs in controlled clinical trials for neuropathic pain, were better than placebo, and were as effective as other analgesics. (34)

Tremont-Lukats and colleagues (2005) conclude

Lidocaine and mexiletine produced no major adverse events in controlled clinical trials, were superior to placebo to relieve neuropathic pain, and were as effective as other analgesics used for this condition. (35)

Kalso and Colleagues concluded in relationship to intravenous lidocaine (1998) that:

Local anesthetic-type drugs are effective in pain due to nerve damage (36)

Clearly, the most significant anxiety relating to use of intravenous lidocaine is the fear of cardiovascular side effects. Several studies on animals suggest that intravenous lidocaine has a negative inotropic effect mediated by an effect on sodium channels and calcium handling (37,38). However, in a human study of noncardiac patients given up to 2 mg/kg of intravenous lidocaine, Matos and colleagues have shown that lidocaine had no effect on the strength of myocardial contraction (39). When it is given to dogs with induced coronary artery occlusion, the myocardial acidosis that normally occurs is reduced (40). This may be mediated by a coronary artery dilating effect of lidocaine (41). As well as these effects, lidocaine increases the ventricular fibrillation threshold by a direct effect on ventricular cells (42-44).

This leaves a somewhat unsatisfactory situation. Extensive clinical experience suggests that intravenous lidocaine is a safe form of treatment, and yet hard scientific evidence of such safety is missing. Conversely, hard scientific evidence of lack of safety is also absent. Perhaps if work could be done to define the cardiovascular effects of intravenous lidocaine in noncardiac patients at the doses used in pain management, then anxieties about the use of this treatment could be reduced.

CONCLUSION

The local anesthetic group of drugs is an important tool in our management of postoperative pain. Their use in postoperative wound infiltration and epidural and spinal anesthesia are widespread and well accepted. Their use as nerve blocking

agents is common, although not universally applicable. To date, their topical use has been confined largely to very minor surgery and as a method of achieving skin anesthesia prior to intravenous cannula insertion. With increasing availability of topical local anesthetic preparations, the potential exists for their use in the postoperative phase as analgesics. In a wider sense, if the current work in development of longer acting local anesthetics comes to fruition, then one could be confident that our ability to provide good quality postoperative pain relief with local anesthetics will be increased.

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs in the world. They are utilized in the management of a wide variety of pain syndromes, both acute and chronic. Most of us will take NSAIDs on at least an occasional basis during our lifetimes. In the United States, more than 70 million prescriptions for NSAIDs are issued per year, and over 30 billion over-the-counter NSAID tablets are purchased annually (1). As of late 2010, the Centers for Disease Control and Prevention estimated that 49.9 million American adults (22.2% of the adult population) had self-reported or doctor diagnosed arthritis, with even higher rates noted among the obese (29.6%) (2). As the population ages and with the increasing prevalence of obesity, the incidence of arthritis and associated NSAID use will likely continue to increase.

In addition to their use for chronic arthritic conditions, NSAIDs are an important component of perioperative multimodal analgesic therapy and may help to prevent the onset of central sensitization that can contribute to the progression from acute to chronic pain. Though these agents are often perceived to be very safe, especially since several of them are available over the counter, NSAIDs have been associated with significant morbidity and mortality. It is, therefore, important for prescribers of these drugs to understand the physiologic effects of NSAID administration and evaluate patients for evidence of associated adverse effects. The elderly and patients with certain medical conditions may be at higher risk for complications associated with NSAID use. Such conditions may include congestive heart failure, hypertension, renal dysfunction, and use of various pharmacologic agents that may negatively interact with NSAIDs. Clinically significant adverse events associated with NSAID use include possible gastrointestinal (GI) bleeding, acute renal failure, precipitation of congestive heart failure, hypertension, and cognitive impairment. When used perioperatively, excessive bleeding and delayed bone healing may constitute additional hazards of NSAID use. Selective cyclooxygenase-2 (COX-2) inhibitors may help mitigate some of the adverse effects commonly seen with traditional NSAIDs, but problems such as an increased incidence of myocardial infarctions and cerebrovascular events observed during clinical trials utilizing these agents further underscore concerns about the risks associated with NSAID use. NSAIDs can be a valuable component of multimodal analgesia for acute pain management, but prescribers of these drugs must remain cognizant of their potential undesirable effects and must exercise caution especially when their use is considered in patients at highest risk.

MECHANISM OF ACTION OF NSAIDS

Acute pain often accompanies tissue injury, and its occurrence is the result of a nociceptive process that can be divided into four stages: transduction, transmission, modulation, and perception. Transduction begins following noxious

stimulation of peripheral afferent nociceptors. Nociceptor activation can be triggered by thermal, chemical, or mechanical stimuli. The physiologic response to nociceptor activation involves the release of multiple excitatory neurotransmitters that convey the pain signal along afferent nociceptive pathways to the dorsal horn of the spinal cord. Other neurotransmitters are released within the spinal cord to modulate the nociceptive signal and convey it to the brain, where pain is perceived on both a sensory and an emotional level. While this process can be delineated in simple terms, the process itself is quite complex.

Tissue injury causes disruption of cell membranes, leading to an influx of calcium ions. Phospholipids that were previously sequestered are also exposed to phospholipase A₂, resulting in the release of arachidonic acid (3). Arachidonic acid is converted to a variety of eicosanoids, which are local signaling molecules found throughout the body in nearly every tissue and fluid (3,4). Eicosanoids include the prostaglandins, prostacyclins, thromboxanes, and the leukotrienes. One of the families of eicosanoids formed from the conversion of arachidonic acid is the prostaglandins. Prostaglandins have multiple and varied effects on several body systems and often play a role in the stimulation of afferent nociceptors, resulting in the experience of pain. Prostaglandin E₂ (PGE₂) and prostaglandin I₂ (PGI₂) promote blood flow to the injured area resulting in enhanced edema and leukocyte infiltration, and sensitization of afferent nerve endings to mechanical and chemical stimulation by decreasing nociceptor pain thresholds (3,5).

In addition to the production of prostaglandins, tissue injury causes release of other biochemical substances such as cytokines, excitatory amino acids, tachykinins, noradrenalin, neurotrophins, and bradykinin (6). Sensory nerve endings are, therefore, immediately bathed in what has been coined "inflammatory soup." Afferent nociceptors have receptors that are specific for these excitatory neurotransmitters, which, when stimulated, results in a message being sent to the central nervous system (CNS) (6). Prostaglandins potentiate the excitatory effects of bradykinin on primary sensory neurons. Bradykinin exerts powerful local inflammatory and pain-provoking activity via the release of substance P, neurokinin A, and calcitonin G-related peptide. This ultimately results in intense burning pain, vasodilation, increased vascular permeability, and synthesis of prostaglandins (7). Bradykinin-1 receptors on inflammatory cells such as macrophages can elicit production of inflammatory mediators such as interleukin-1 and tumor necrosis factor (TNF). Though the pain-provoking effects of PGE₂ are not as immediate or intense as those of bradykinin or histamine, they are of longer duration (3). Prostaglandins also play a key role in the amplification of the pain response referred to as hyperalgesia.

COX is the first enzyme in the prostaglandin synthesis pathway and is responsible for the conversion of arachidonic acid to the short-lived, unstable endoperoxides prostaglandin G₂ (PPG₂) and prostaglandin H₂ (PGH₂). Other prostaglandins are derived from these prostaglandin intermediates (Fig. 4.1). COX has two forms COX-1 and COX-2. COX-1 is a constitutively expressed enzyme that plays a role in platelet aggregation and hemostasis as well as protection of the gastric mucosa. It is necessary for many physiological functions and is present in most cells. COX-2 is an enzyme that is induced by cytokines and other inflammatory mediators and is crucial in the mediation of pain, inflammation, and fever (5,9). In addition, COX-2 is constitutively expressed in a

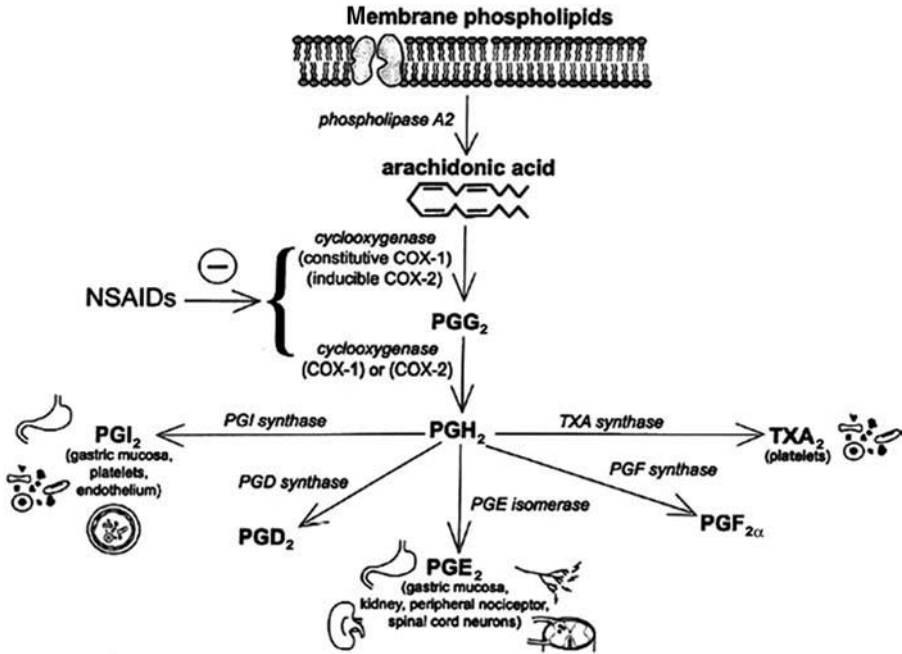


FIGURE 4.1 The role of COX in prostaglandin synthesis. Arachidonic acid, once liberated from membrane phospholipids by phospholipase A2, is converted to intermediate prostaglandins by the actions of the cyclooxygenases (COX-1 and COX-2). These intermediate prostaglandins are then transformed into a variety of final products such as thromboxane A2 (TXA2) and prostaglandins E2 and I2 (PGE2 and PGI2). NSAIDs prevent the production of prostaglandins via inhibition of cyclooxygenase. *Source:* Adapted from Ref. 8; courtesy of American Society of Anesthesiologists, copyright 2003, by Lippincott Williams & Wilkins.

number of tissues including the brain, testes, and kidneys, and plays a key role in the response of central neurons to inflammation (9,10).

The therapeutic action of the class of drugs, known as NSAIDs, relates to their ability to block the formation of certain eicosanoids, particularly prostaglandins, via inhibition of COX (3). Most NSAIDs dually inhibit COX-1 and COX-2, but with a general tendency toward COX-1 inhibition (11,12). Agents that are more selective for COX-2 inhibition have been developed in efforts to decrease the negative consequences of COX-1 inhibition, such as GI toxicity. However, even though the development of the COX-2 inhibitors may have improved the risk profile of NSAIDs in some areas, newer concerns about NSAID safety have arisen during clinical trials of these agents (see the section on COX-2-specific concerns for more information). PGE₂ is the prostaglandin synthesized primarily by COX-2. PGE₂ is an inflammatory mediator involved in the pain response. NSAIDs designed to specifically interrupt the COX-2 pathway disrupt the formation of PGE₂ (13). Depending on the COX affinity of each NSAID, this class of drugs can be very beneficial in reducing pain and/or inflammation. Although NSAIDs have been understood to promote analgesia by blocking the production of prostaglandins peripherally, there is now

evidence to suggest that NSAIDs also modulate pain centrally by inducing inhibition of prostaglandin synthesis in the spinal cord (14).

ROLE OF NSAIDs IN MULTIMODAL AND PREEMPTIVE ANALGESIA

In the early 1980s, the concept of central sensitization of spinal and presumably brain neurons following peripheral injury was elucidated by Woolf (15). However, the original construct of preemptive analgesia was first described by Crile, who suggested the use of regional blocks in addition to general anesthesia to prevent pain and the formation of painful scarring (16). The importance of Woolf's discovery is that the CNS is not hard-wired but has the capacity to respond differently to different stimuli, or, in other words, it can be "plastic" in its response. In terms of the painful stimulus, the increased excitability ("spinal wind-up") that can be triggered in the spinal cord following a noxious stimulus can result in an exaggerated response, which is thought to be due to N-methyl-D-aspartate (NMDA) glutamate receptor activation (17). When peripheral inflammation and injury occur, postsynaptic changes result in the release of neuromodulators such as prostaglandin E_2 (18). In addition, there is a reduction in the threshold of the afferent peripheral nociceptors and an increase in the excitability of spinal neurons (19). These changes can ultimately lead to the development of pain hypersensitivity in the postoperative period. Since central sensitization can result in a patient experiencing persistent pain, treatment strategies aimed at reducing the potential for this to occur, particularly following trauma or surgery, seem to make rational sense. In addition, the recognition that increased pain can occur in the postoperative period is important since patients continue to report moderate (47%) to severe pain (31%) postoperatively (20).

Definition of Preemption

In 2000, Kissin provided three different definitions of preemption based on what had been used in various clinical trials: (i) it starts before surgery; (ii) it prevents the establishment of central sensitization caused by incisional injury (covers only the period of surgery); and (iii) it prevents the establishment of central sensitization caused by incisional and inflammatory injuries (covers the period of surgery and the initial postoperative period) (21). It appears that various authors have used different definitions of preemptive analgesia, and therefore the evaluation of study results can be confusing and difficult. What appears to be important is to be able to distinguish between (i) the relief of physiologic pain that can be controlled with conventional therapy (e.g. opioids) and (ii) the prevention or reversal of central and peripheral neural sensitization. The latter mechanism can potentially cause severe and continued pain despite the absence of an inflammatory response or tissue damage. The lack of a uniform definition might explain the differences in preemptive analgesic results seen in the literature (21). For the sake of this chapter, the latter definition of preemptive analgesia will be used. It should also be noted that Kissin recommended that two most important conditions for establishing and evaluating a clinical study on preemption are as follows: (i) providing effective suppression of the afferent input with sufficient duration of such treatment that also covers the initial postoperative period and (ii) combined treatment approaches be aimed at preemptive treatment, maintenance of the obtained effect, and reversal of central

sensitization (21). Later, Kissin further modified the definition of preemptive analgesia to be "a treatment that prevents the establishment of the altered sensory processing that amplifies postoperative pain (22)."

Physiologic Rationale for Preemption

The goal of preemption is to intervene well in advance of the noxious stimulus occurring. Various strategies have been used in effort to provide preemptive analgesia, including the administration of NSAIDs, opioids, and regional anesthetic techniques, singularly or in combination (20). The purpose of this section is to explore the role of the COX inhibitors as part of a comprehensive treatment strategy for preemptive analgesia. Following tissue injury or the development of an inflammatory state, a "sensitizing soup" of mediators such as hydrogen ions, norepinephrine, bradykinin, histamine, potassium ions, purines, cytokines, 5-hydroxytryptamine, leukotrienes, nerve growth factor, neuropeptides, and prostaglandins is released (20). These mediators act directly on peripheral nociceptors resulting in an increase in spontaneous firing activity, a lower threshold for activation, and a prolonged firing rate (23). Also, there is growing evidence that peripherally released prostaglandins appear to play a role in spinally mediated pain (18). Since prostaglandins are a significant factor involved in the inflammatory process resulting from tissue injury, NSAIDs/COX-2 inhibitors could potentially be part of a preoperative preemption strategy. In addition, NSAIDs have been shown to have an opioid-sparing effect, which is an important consideration since opioids have undesirable adverse side effects (24,25). Ashburn et al. suggested in the 2004 practice guidelines of the American Society of Anesthesiologists that, unless contraindicated, patients should be given NSAIDs, COX-2 inhibitors, or acetaminophen as part of their postoperative pain treatment regimen (26). Beyond their ability to prevent the conversion of arachidonic acid to prostaglandins, NSAIDs may also have some intracellular effects that decrease the release of inflammatory enzymes, thereby further reducing the overall inflammatory response to tissue injury (27). Thus, the NSAIDs may exert their preemptive analgesic effects through multiple cellular mechanisms.

Clinical Evidence for NSAID Preemption

Although many studies have been done using multimodal approaches to preemptive analgesia, for the purposes of this section, only the role of NSAIDs is discussed. Using a review of four studies in which NSAIDs were given both preoperatively and postoperatively in oral surgery patients, McQuay concluded that at normal therapeutic oral doses of NSAIDs, no preemptive effect was demonstrated (28). A review of 66 studies by Ong et al. found preemption when epidural analgesia, local anesthetic infiltration, and NSAIDs were used individually (29). Of the 66 studies, 12 focused on the use of NSAIDs. Six of the studies favored the use of NSAID pretreatment, while the remaining six studies did not show statistical significance. However, NSAID administration improved analgesic consumption and time to first rescue analgesic request, but not postoperative pain scores. Finally, Moïniche et al., using only randomized controlled trials (RCTs), reported on 80 clinical studies of preemptive analgesia (30). Twenty of the 80 RCTs compared preincisional NSAIDs with postincisional NSAIDs or paracetamol using a parallel or crossover design. In only 2 of the 20

trials did pain scores significantly improve immediately after surgery using preemptive treatment compared with postoperative treatment. This begs the question, what could be causing the divergent results noted in the literature? Kissin has suggested that this may be partly due to study design (22). Two different study designs have been used in evaluating preemptive analgesia: (i) preoperative treatment versus nontreatment and (ii) treatment applied before surgery versus the same treatment provided at the end of surgery. He further concluded that future studies need to be directed at not only evaluating the duration of an intervention, but also at the sufficiency of the blockade of nociceptive stimuli. Three studies have compared the preoperative administration of a COX-2 inhibitor with a traditional NSAID for preemptive analgesia (31–33). Only one of the studies noted lower pain scores postoperatively when rofecoxib (50 mg) was used compared to ibuprofen (600 mg) (33). More recently, however, Koplin et al. reported on the use of parecoxib (40 mg) in a randomized double-blinded clinical trial in 32 patients undergoing radical axillary lymph node dissection for melanoma (34). They noted that the parecoxib group had significantly less pain after mobilization, was less fatigued, and required less pain medication. Even though the COX-2 inhibitors may possess a preemptive analgesic effect, they do not appear to have a significant benefit over traditional NSAIDs.

Role of NSAIDs Including COX-2 Inhibitors in Preemptive Treatment

The NSAIDs (including COX-2 inhibitors) appear to have a marginal effect on preemptive analgesic therapy when given as a singular treatment, but they may have a role to play as part of a multimodal pain management regimen, particularly for postoperative pain control. There is clear evidence that the NSAIDs reduce opioid requirements and vomiting postoperatively, improve pain scores, decrease sleep disturbances, and improve patient satisfaction compared with placebo (35). In addition, they have a theoretical role in terms of peripheral and central sensitization (18,36,37). Additional studies will need to be performed to more accurately define the role of NSAIDs/COX-2 inhibitors as part of a multimodal pain management regimen.

CLASSIFICATION OF NSAIDS

NSAIDs are classified according to their chemical structure. Table 4.1 outlines NSAIDs currently in clinical use in the United States, grouped into structurally related compounds and further classified by their COX selectivity. Figure 4.2 further delineates the degree of COX-1/COX-2 inhibition seen with commonly used NSAIDs (12).

The selection of a particular NSAID for use may depend on patient factors, such as previous positive or negative experience with a particular NSAID, underlying comorbidities, the potential for certain drug interactions or organ-specific side effects, and any known allergies to components of a particular NSAID. When a patient experiences inadequate analgesia or an undesired side effect with an NSAID, switching to another agent in a family not structurally related to the initial NSAID trialed may be of potential benefit, provided any side effects experienced would not contraindicate the continued use of an NSAID. Other factors that may influence the choice of an NSAID to be used

TABLE 4.1 NSAID Classification

Nonselective COX inhibitors (NSAIDs)	Salicylates	Aspirin Nonacetylated salicylates Choline magnesium trisalicylate (Trilisate [®]) Diflunisal (Dolobid [®])
	Propionic acid derivatives	Naproxen (Naprosyn [®] , Aleve [®] , Anaprox [®]) Ketorolac (Toradol [®]) Oxaprozin (Daypro [®]) Ketoprofen (Orudis [®] , Oruvail [®]) Ibuprofen (Advil [®] , Motrin [®]) Flurbiprofen (Ansaid [®])
	Indole acetic acids	Etodolac (Lodine [®]) Indomethacin (Indocin [®]) Sulindac (Clinoril [®])
	Phenylacetic acids	Diclofenac (Cataflam [®] , Voltaren [®] , and Arthrotec [®] , which consists of diclofenac in combination with Misoprostol)
	Naphthylalkanones Pyrroleacetic acids	Nabumetone (Relafen [®]) Tolmetin (Tolectin [®])
COX-2 partially selective inhibitors (CPSI)	Oxicams	Piroxicam (Feldene [®]) Meloxicam (Mobic [®]) Celecoxib (Celebrex [®])
COX-2-selective inhibitors (CSI)		Rofecoxib (Vioxx [®]), currently not available in the United States Valdecoxib (Bextra [®]), currently not available in the United States

may include the duration of action of the drug and the perceived efficacy of the NSAID. Although little information is available regarding head-to-head comparisons of NSAIDs for postoperative pain control, the Oxford league table of Analgesics represents a comparison of the analgesic efficacy of a variety of analgesic agents based on at least 3 trials or 200 patients (38). The number needed to treat corresponds to the number of patients that would need to be exposed to the drug for one subject to obtain at least 50% pain relief over four to six hours compared with placebo in a randomized, double-blind, single-dose study in patients with moderate to severe pain (Table 4.2).

PHARMACOLOGY OF NSAIDS

NSAIDs are commonly used to treat many types of acute pain, including headaches, dysmenorrhea, musculoskeletal trauma, and postoperative pain. NSAIDs are generally appropriate for use in the management of acute pain of low to moderate intensity; however, they have not demonstrated benefit in the management of acute pain of visceral origin (5). Currently, there are more than 20 different NSAIDs available for use in the United States. At equipotent doses, the efficacy and tolerability of the various NSAIDs are similar; however, individual response is highly variable (39,40). NSAIDs vary in time of onset and

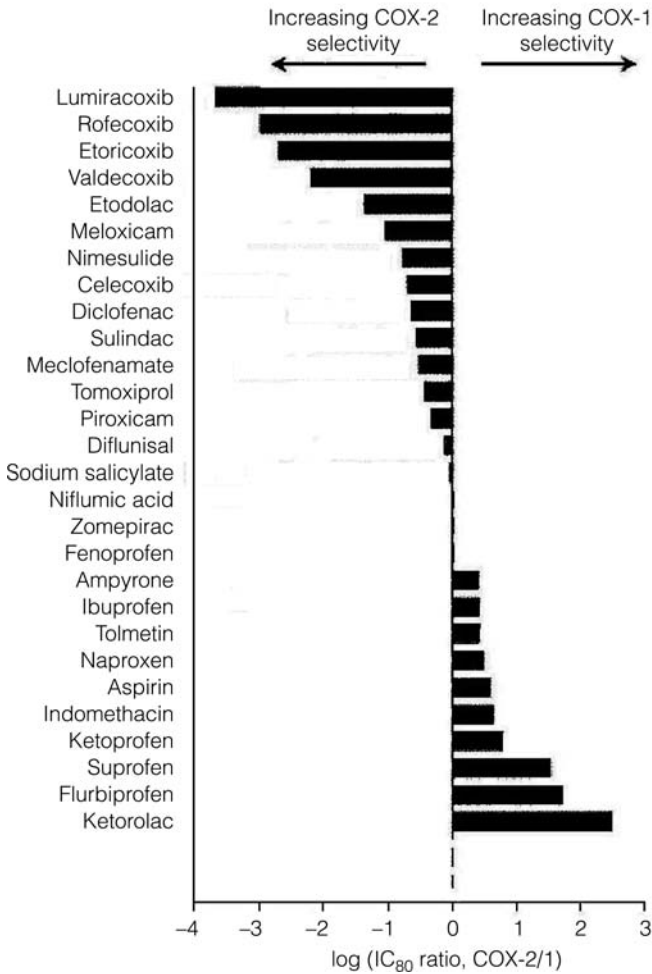


FIGURE 4.2 COX selectivity of commonly used NSAIDs. The log (IC₈₀ ratio, COX-2/COX-1) represents the concentration of an NSAID required to inhibit COX-2 activity by 80% relative to that required to inhibit COX-1 by 80%. The agents with values below 0 have greater COX-2 inhibitory activity, while those with values greater than 0 have greater COX-1 inhibitory activity. Equipotent inhibition of COX-1 and COX-2 occurs at the 0 line. *Source:* Adapted from Ref. 12, with permission of the Federation of American Societies for Experimental Biology.

duration of analgesic action, with NSAIDs having longer half-lives producing slower onset of analgesia. However, wide variations in analgesic activity occur even within the same class of NSAIDs, leading to the suggestion that if a patient fails to respond to an NSAID, it is reasonable to try another agent in a different class, though this has not been validated in controlled studies (40,41). For a comparison of currently utilized NSAIDs, see Table 4.3.

TABLE 4.2 Oxford League Table of Analgesic Efficacy

Analgesic and dose (mg)	Number of patients in comparison	Percent with at least 50% pain relief	NNT	Lower confidence interval	Higher confidence interval
Etoricoxib 180/240	248	77	1.5	1.3	1.7
Etoricoxib 120	500	70	1.6	1.5	1.8
Diclofenac 100	545	69	1.8	1.6	2.1
Celecoxib 400	298	52	2.1	1.8	2.5
Paracetamol 1000 + Codeine 60	197	57	2.2	1.7	2.9
Rofecoxib 50	675	54	2.3	2.0	2.6
Aspirin 1200	279	61	2.4	1.9	3.2
Ibuprofen 400	5456	55	2.5	2.4	2.7
Oxycodone IR 10 + Paracetamol 650	315	66	2.6	2.0	3.5
Diclofenac 25	502	53	2.6	2.2	3.3
Ketorolac 10	790	50	2.6	2.3	3.1
Naproxen 400/440	197	51	2.7	2.1	4.0
Piroxicam 20	280	63	2.7	2.1	3.8
Lumiracoxib 400	370	48	2.7	2.2	3.5
Naproxen 500/550	784	52	2.7	2.3	3.3
Diclofenac 50	1296	57	2.7	2.4	3.1
Ibuprofen 200	3248	48	2.7	2.5	2.9
Pethidine 100 (IM)	364	54	2.9	2.3	3.9
Tramadol 150	561	48	2.9	2.4	3.6
Morphine 10 (IM)	946	50	2.9	2.6	3.6
Naproxen 200/220	202	45	3.4	2.4	5.8
Ketorolac 30 (IM)	359	53	3.4	2.5	4.9
Paracetamol 500	561	61	3.5	2.5	13.3
Celecoxib 200	805	40	3.5	2.9	4.4
Ibuprofen 100	495	36	3.7	2.9	4.9
Paracetamol 1000	2759	46	3.8	3.4	4.4
Paracetamol 600/650 + Codeine 60	1123	42	4.2	3.4	5.3
Paracetamol 650 + Dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate)	963	38	4.4	3.5	5.6

Aspirin 600/650	5061	38	4.4	4.0	4.9
Paracetamol 600/650	1886	38	4.6	3.9	5.5
Ibuprofen 50	316	32	4.7	3.3	8.0
Tramadol 100	882	30	4.8	3.8	6.1
Tramadol 75	563	32	5.3	3.9	8.2
Aspirin 650 + Codeine 60	598	25	5.3	4.1	7.4
Paracetamol 300 + Codeine 30	379	26	5.7	4.0	9.8
Tramadol 50	770	19	8.3	6.0	13.0
Codeine 60	1305	15	16.7	11.0	48.0
Placebo	> 10,000	18	N/A	N/A	N/A

Numbers needed to treat are calculated for the proportion of patients with at least 50% pain relief over four to six hours compared with placebo in randomised, double-blind, single-dose studies in patients with moderate to severe pain. Drugs were oral, unless specified, and doses are milligrams. Shaded rows are intramuscular administration

Source: From Ref. 38.

TABLE 4.3 Analgesic and Anti-inflammatory Action of Currently Utilized NSAIDs

NSAID	Peak effect in hours	Analgesic activity	Anti-inflammatory activity
Aspirin	2	Strong	Strong
Choline magnesium trisalicylate	0.5–1	Strong	Strong
Diflunisal	1–2	Strong	Moderate
Indomethacin	2	Strong	Strong
Sulindac	1–2	Strong	Strong
Etodolac	2	Strong	Strong
Mefanamic acid	2	Moderate	Moderate
Tolmentin	0.5–1	Moderate	Strong
Ketorolac	0.5–1	Strong	Strong
Diclofenac	1	Strong	Strong
Ibuprofen	1–2	Strong	Strong
Naproxen	2	Strong	Strong
Fenoprofen	2	Moderate	Strong
Ketoprofen	1–2	Moderate	Strong
Oxaprozin	3–6	Strong	Strong
Piroxicam	2–4	Strong	Strong
Nabumetone	9–12	Strong	Strong
Celecoxib	3	Strong	Strong

NSAIDs have both analgesic and anti-inflammatory actions, but the analgesic effects are best understood in the context of anti-inflammatory impact. Inflammation is a normal physiologic response to tissue injury and is a very complex process. Many products of COX are involved, but PGE₂ is the primary eicosanoid found in inflammatory conditions and is essential in the production of pain and inflammation. By blocking or inhibiting COX, particularly COX-2 release in inflamed tissues, the synthesis of prostaglandins is reduced, resulting in attenuation of inflammatory hyperalgesia (3,42). Prostaglandins may also reduce excitability in central neurons receiving afferent nociceptor input, indicating NSAIDs may have a central as well as a peripheral effect (42).

NSAIDs are grouped into several chemically diverse classes with broad ranging pharmacokinetic characteristics. Despite these differences, NSAIDs share some common general properties. All are weak acids with the exception of nabumetone, which is a ketone prodrug that is metabolized into an acidic active drug (4). All NSAIDs are effective in reducing acute pain, with numbers needed to treat ranging from 1.6 to 3.0 on the Oxford League Table (Table 4.2) (38,43). NSAIDs are extensively bound to plasma proteins (90–99%), particularly albumin (39,42). Clinically significant decreases in serum albumin levels or administration of other agents that are highly protein bound can, therefore, lead to proportionally higher serum NSAID concentrations (5,39). Most NSAIDs are heavily metabolized in the liver, which results in either activation or inactivation of the NSAID and usually involves hepatic conjugation to either sulfuric or glucuronic compounds that are returned to the plasma (42).

Pharmacokinetics

Bioavailability

NSAIDs are readily absorbed from the upper small intestine, though some absorption may occur in the stomach if the pH is low. Food and altered GI blood

flow or motility can alter the rate but not the extent of absorption (5,39,40,42). NSAIDs are absorbed through any mucus membrane, meaning NSAIDs can be given in rectal suppository form; however, absorption via the rectal route is slower than oral absorption and is incomplete and unreliable; therefore, rectal administration is not recommended when high plasma concentrations of the drug are required (5,42).

Metabolism

Metabolism of NSAIDs occurs via the CYP3A or CYP2C families of the cytochrome P450 enzyme system in the liver, with the exception of nabumetone, which is only 40% metabolized (42). Some of these agents are metabolized by phase I reactions followed by phase II mechanisms, while others are metabolized solely by phase II glucuronidation (4).

Distribution

NSAIDs are rapidly distributed to all body tissues by a passive process. Those that are more lipid soluble have stronger effects on the CNS, which can be positive or negative. Because they are highly bound to plasma proteins, plasma concentrations are much higher than tissue concentrations. Most of these drugs have ionization constants in the range of 3 to 5, making pH important in distribution (42).

Excretion

NSAIDs are primarily renally excreted. Small amounts of these drugs are secreted through the biliary tract and subsequently fecally excreted (4,42).

Chirality

Some NSAIDs, primarily the propionic acid derivatives ketorolac and etodolac, have a chiral center. Though used as racemates, the absorption, distribution, metabolic conjugation, and elimination of these molecules is stereospecific. The S-enantiomer displays much more potent inhibition of COX than does the R-enantiomer. The conversion of the inactive R-enantiomer to the active S-enantiomer is unidirectional in vivo. The extent of the conversion varies widely between the drugs and also among individuals, which may explain why plasma concentrations of propionic acids do not correlate well with their effects, the exception being naproxen, which is a pure active S-enantiomer (42).

Pharmacology of NSAID Subclasses

Salicylic Acid Derivatives

Salicylic acid derivatives (salicylates) include aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazine. Salicylates are constituents of several plants with recorded use dating back to the Egyptians in 3500 B.C. Salicylates are rapidly absorbed when given orally, particularly in the stomach, with most absorption occurring in the upper small intestine. Detection in the plasma occurs in less than 30 minutes, and peak plasma concentrations occur approximately 1 hour after ingestion.

Following absorption, salicylates are widely distributed throughout most body tissues and cellular fluids with 80% to 90% bound to plasma proteins, particularly albumin. Salicylates are metabolized by the liver and excreted renally. Their analgesic action is peripheral, and they are primarily used for low-intensity pain emanating from bones, muscles, joints, tendons, ligaments, and skin (5). For the purposes of effects on acute pain, discussion will be limited to those salicylates with strong analgesic action: aspirin (ASA), choline magnesium trisalicylate (Trilisate[®]), and diflunisal (Dolobid[®]).

Aspirin (ASA). While rarely used as an anti-inflammatory, aspirin has strong anti-inflammatory and analgesic action. Aspirin covalently acetylates the active site of COX nonselectively and irreversibly, resulting in central and peripheral inhibition of prostaglandin production; however, its analgesic effect is peripheral (4,42). It is most effective for mild to moderate pain of somatic origin. It has not been demonstrated to be beneficial for severe visceral pain, though it has been shown to be effective for moderate to severe metastatic bone pain (4,42). ASA is rapidly absorbed from the stomach and small intestine, where approximately 70% is hydrolyzed to salicylate and the remainder to acetic acid by esterases in the blood and tissues, a process that takes approximately 15 to 30 minutes. Salicylate is bound to plasma proteins, particularly albumin, with distribution through most body tissues and fluids occurring by a pH-dependent passive process (4,42). It is metabolized in the liver and excreted in the urine in conjugated forms. Changes in urinary pH have pronounced effects on the rate of excretion, with a high urinary pH resulting in a higher excretion rate. The plasma half-life of ASA is 15 minutes, and for salicylate is 2 to 3 hours with low doses and up to 30 hours with high doses (42). The usual adult dose of ASA is 325 to 1000 mg every four to six hours.

Choline magnesium trisalicylate (Trilisate[®]). Choline magnesium trisalicylate is a mixture of choline salicylate and magnesium salicylate. Like ASA, it possesses strong analgesic and anti-inflammatory action. It is a reversible inhibitor of COX but is less effective as a COX inhibitor than ASA, which may make it preferable in patients with asthma, bleeding tendencies, or renal dysfunction. It does not demonstrate significant inhibition of platelet aggregation. It is water soluble, thereby causing less GI distress compared to ASA (4,42).

Choline magnesium trisalicylate is rapidly absorbed through the GI tract with plasma concentrations detectable 20 minutes after administration and peak plasma concentrations achieved in 1 to 3 hours. It is metabolized in the liver and renally excreted. Its elimination half-life is 9 to 17 hours, which allows for once or twice a day dosing. The usual adult dose of choline magnesium trisalicylate is 1500 mg twice a day or 3000 mg once a day.

Diflunisal (Dolobid[®]). Diflunisal is a difluorophenyl derivative of salicylic acid, but is not metabolized to salicylic acid or salicylate (4). It possesses strong analgesic and moderately strong anti-inflammatory action. It is used primarily as a peripherally acting analgesic and has a long duration of action. When used for musculoskeletal pain, it has been shown to be three to four times more potent than ASA (5). It is particularly effective for metastatic bone pain. Diflunisal is a competitive inhibitor of COX. It is well absorbed orally with

peak plasma levels being reached within two to three hours. Binding to plasma proteins is 98%. Diflunisal is subject to capacity-limited metabolism, meaning the initial plasma half-life is dose dependent, with shorter half-lives after lower doses. Metabolism of diflunisal is through the enterohepatic cycle with reabsorption of its glucuronide metabolites being followed by cleavage of the glucuronide to again release the active moiety (4). Serum drug levels gradually increase over time with continued use; therefore, high loading doses administered for one to two days are necessary to reach initially effective plasma concentrations, with subsequent reduction in dosing for maintenance of plasma concentrations (4,42). Up to 95% of the drug is excreted renally, but clearance is dependent on renal and hepatic function, and doses should be limited in persons with renal insufficiency. Initial adult dosing is 500 to 1000 mg every 12 hours up to 1500 mg daily, followed by 250 mg to 500 mg every 12 hours.

Indole Acetic Acid Derivatives

NSAIDs in this class include indomethacin (Indocin[®]), sulindac (Clinoril[®]), and etodolac (Lodine[®]).

Indomethacin (Indocin[®]) Indomethacin is one of the most potent nonselective inhibitors of COX, making it a very potent analgesic and anti-inflammatory agent. It was introduced to the United States market in 1963 and is widely used and effective. It differs from other NSAIDs in its indications and toxicities, which limits its use (4,41). Indomethacin is rapidly and almost completely absorbed from the GI tract with high bioavailability, though food does delay the rate but not the extent of its absorption. Peak plasma concentrations occur anywhere from 30 minutes to 4 hours after administration (41). Indomethacin is 99% bound to plasma proteins and extensively binds to tissues. It penetrates the blood-brain barrier relatively fast with high concentrations found in the cerebrospinal fluid within two hours of administration. It is demethylated largely by the cytochrome P450 enzyme system and then undergoes extramicrosomal deacylation. The relatively high enterohepatic circulation may contribute to the high incidence of GI mucosal injury seen with indomethacin. Its half-life ranges from 2.2 to 11.2 hours (41). Approximately 35% to 50% of patients taking indomethacin will experience toxicity at therapeutic doses, including GI, CNS, and hematopoietic effects; therefore, once symptoms are controlled, changing to a less toxic NSAID is recommended (4,5,41). The usual adult dose of indomethacin is 25 to 75 mg daily.

Sulindac (Clinoril[®]). Sulindac is an analog of indomethacin developed as a less toxic, equally effective alternative to indomethacin. While it is less toxic than indomethacin, adverse drug effects are more common than with other NSAIDs. Sulindac is a sulfoxide prodrug that is less than half as potent as indomethacin. It is biotransformed into two metabolites in the body, an active sulfide (which exerts its pharmacologic activity), and an inactive sulfone. Conversion of the sulfoxide to the sulfide occurs reversibly, while conversion to the sulfone occurs irreversibly. The sulfide metabolite of sulindac exhibits 500 times more anti-inflammatory activity than its parent drug and is a potent inhibitor of COX (41,42). All forms of the drug are excreted in bile and then reabsorbed from the intestine. This enterohepatic recycling prolongs the drug's duration of action to

12 to 16 hours; however, the complex and enormously variable metabolism and pharmacokinetics of sulindac make its overall activity in the individual hard to predict (4,41). Sulindac may inhibit renal COX to a lesser extent than other NSAIDs because the kidney can reoxidize the sulfide back to the inactive sulfoxide prodrug (41). Oral absorption is 90% with peak plasma levels of sulindac present after one hour and the sulfide metabolite present in two to eight hours (5,41). Sulindac, its sulfone, and its sulfide are all extensively bound to plasma proteins (41,42). The half-life of sulindac is 7 hours, while the half-life of the sulfide metabolite is approximately 16 to 18 hours (5,41). Usual adult dosing of sulindac is 150 to 200 mg twice a day. Doses should be reduced to no more than 200 mg a day in patients with hepatic or renal insufficiency and in the elderly.

Etodolac (Lodine[®]). Etodolac has a pyranocarboxylic acid structure with strong anti-inflammatory and analgesic effects. It is a chiral NSAID marketed as a racemic mixture of S(-) and R(+)-enantiomers (41,42). It does not, however, undergo chiral inversion in the body (4). It is a relatively selective COX-2 inhibitor with a COX-2 to COX-1 ratio of 10:1 and also inhibits bradykinin formation (4,5,42). It appears to selectively spare the cytoprotective prostaglandins in the gastric mucosa and has demonstrated a very low incidence of gastric ulceration in postmarketing surveillance (40,44). Etodolac is rapidly and well absorbed following oral administration. Peak plasma concentrations are evident in one to two hours. Plasma protein binding is extensive at greater than 99%. It is extensively metabolized by the liver to various metabolites that are renally excreted. Maximum analgesia is achieved approximately 1 hour after administration and analgesia may last 6 to 12 hours (39). Etodolac has a plasma half-life of approximately 7 hours. The usual adult dose of etodolac is 200 to 400 mg every 6 to 8 hours.

Pyrazole Derivatives

This class of NSAIDs includes phenylbutazone, oxyphenbutazone, and azapropazone. Phenylbutazone is an extremely potent anti-inflammatory with modest analgesic properties. Because of its unique risk of causing aplastic anemia, its use should be very short term and restricted to situations in which use of less toxic agents is not an option. Today, phenylbutazone is primarily used in veterinary medicine. Oxyphenbutazone was withdrawn from the U.S. and Canadian markets because of its association with toxic epidermal necrolysis, while azapropazone is available outside the United States only.

Anthranilic Acids (Fenamates)

Fenamates are derivatives of *N*-phenylanthranilic acid with modest analgesic and anti-inflammatory actions. Fenamates inhibit COX and may also antagonize certain effects of prostaglandins, distinguishing them from other NSAIDs. Because of the toxicity of this class of NSAIDs, few are available for clinical use.

Mefenamic acid (Ponstel[®]). Mefenamic acid is a COX inhibitor that may also act as a PGE₂ receptor antagonist. It competes for binding sites *in vitro*. It has modest analgesic and anti-inflammatory activity and is used primarily for its analgesic properties in rheumatic diseases, though it has demonstrated benefit in reducing

acute pain associated with musculoskeletal conditions and dysmenorrhea. Mefenamic acid achieves peak serum concentrations two to four hours after ingestion and has a plasma half-life of two to four hours. Twenty-five percent of all patients taking mefenamic acid will develop adverse drug effects on the GI system. The most common complaints are dyspepsia and gastric discomfort. Diarrhea is also common and can be severe. Associated steatorrhea and bowel inflammation are relatively common. Having no clear advantage over the other NSAIDs and with its propensity to cause diarrhea, mefenamic acid is not widely used clinically. The usual adult dose of mefenamic acid is 500 mg every six to eight hours (5).

Pyrroleacetic Acids

Pyrroleacetic acids are a class of NSAIDs with moderate to strong analgesic and anti-inflammatory activity. Pyrroleacetic acids were first developed in the 1970s by researchers looking for analgesic and anti-inflammatory agents with fewer adverse drug effects. Drugs in this category include tolmetin (Tolectin[®]), ketorolac (Toradol[®]), and diclofenac (Voltaren[®], Cataflam[®], Arthrotec[®], Zipsor[®]).

Tolmetin (Tolectin[®]). Tolmetin is a nonselective inhibitor of COX that possesses moderate analgesic and strong anti-inflammatory action with a potency substantially greater than indomethacin or naproxen (4,5). It is rapidly and completely absorbed after oral ingestion. Taking tolmetin with food decreases its plasma concentration and bioavailability. Peak plasma concentrations are achieved 20 to 60 minutes after dosing. Plasma protein binding is extensive at 99%. Tolmetin is extensively metabolized in the liver to inactive oxidative metabolites and conjugates. Its half-life is short, ranging from one to three hours. Ninety-nine percent of tolmetin is excreted in the urine. Although tolmetin is a good analgesic, its primary use is as an anti-inflammatory agent; however, it is ineffective in the treatment of gout. Each 200 mg tablet of tolmetin contains 0.8 mEq of sodium, which should be taken into consideration when patients require severe sodium restriction. The usual adult dose of tolmetin is 200 to 400 mg every six to eight hours (4,5,41,42).

Diclofenac (Voltaren[®], Cataflam[®], Arthrotec[®], Zipsor[®]). Diclofenac is a potent, relatively nonselective inhibitor of COX with equipotent inhibition of COX-1 and COX-2. Research suggests that diclofenac can inhibit the thromboxane-prostanoid receptor, affect arachidonic acid release and uptake, inhibit lipoxigenase enzymes, and activate the nitric oxide-cyclic guanosine monophosphate (cGMP) antinociceptive pathway (45). It possesses strong analgesic and anti-inflammatory activity and a high therapeutic index. The potency of diclofenac is substantially greater than indomethacin or naproxen. Diclofenac is rapidly and completely absorbed following oral ingestion; however, its bioavailability ranges from 30% to 70% because of significant first pass effect (5,41,42). Food slows the rate but not the extent of absorption. Peak plasma concentrations are achieved two to three hours after ingestion. Diclofenac is 99% bound to plasma proteins. Ninety-five percent of diclofenac is metabolized by the liver to inactive metabolites via hydroxylation and conjugation. The half-life of diclofenac is one to two hours. The usual adult dosage of diclofenac is 50 mg orally every eight hours.

Diclofenac is available in combination with misoprostol, a synthetic PGE₁ analog, in the product Arthrotec, which may decrease its GI toxicity. It is also available for topical administration in a patch containing 1.3% diclofenac epolamine (Flector[®] patch) applied over the painful area every 12 hours, and in a 1% gel applied to painful joints four times a day (Voltaren[®] gel). The topical formulations provide the added benefit of markedly decreased systemic exposure.

Ketorolac (Toradol[®]). Ketorolac is available for oral and parenteral (IV or IM) administration and is a racemic mixture with the S(-)-enantiomer being responsible for its pharmacologic action (41). Ketorolac is a potent analgesic with moderate anti-inflammatory activity (42). The analgesic efficacy of ketorolac compares to that of various opioids, including morphine, fentanyl, and meperidine, but without the risk of respiratory depression. There is some evidence that ketorolac indirectly activates opioid receptors, inducing the release of endogenous opioids (46). For treatment of mild to moderate postoperative pain, ketorolac can be used in place of morphine, while concomitant use may reduce opioid requirements by up to 50% (4). It has also been found to be beneficial in the treatment of renal colic, pain related to trauma, pain from sickle cell crises, visceral pain secondary to cancer, and postpartum pain. Ketorolac is rapidly and well absorbed via the oral or IM routes. Its oral bioavailability is approximately 80% (5). Its plasma protein binding ranges from 90% to 99%. Peak plasma levels are achieved 30 to 60 minutes after administration. The half-life of ketorolac is 4 to 6 hours in adults but can increase to 6 to 7 hours in the elderly and 9 to 10 hours in patients with renal insufficiency (42). The usual adult dose of ketorolac is 10 mg orally every 4 to 6 hours, or 15 to 30 mg intravenously every 6 hours to a maximum of 120 mg per day. Although the IM route can be used, it is not the optimal route of administration for the management of acute pain. A nasal formulation of ketorolac for short-term pain management has recently been approved by the U.S. Food and Drug Administration (FDA). Because of the potential for gastric and renal toxicity, use of ketorolac is restricted to a maximum of five days using the lowest effective dose (47).

Propionic Acids

This class of NSAIDs includes ibuprofen (Motrin[®], Advil[®]), naproxen (Naprosyn[®], Aleve[®], Anaprox[®], Naprelan[®]), ketoprofen (Orudis[®], Oruvail[®]), fenoprofen (Nalfon[®]), oxaprozin (Daypro[®]), and flurbiprofen (Ansaid[®]). The pharmacologic properties of the propionic acids do not vary significantly and all are effective inhibitors of COX. These agents do vary considerably in potency, though this has not been shown to be of clinical significance (5,42). All of these agents are chiral in structure (42). They all possess analgesic and anti-inflammatory properties.

Ibuprofen (Motrin[®], Advil[®]). Ibuprofen is a simple derivative of phenylpropionic acid that is administered as a racemic mixture with 56% to 69% of the inactive R-enantiomer converting irreversibly to the active S-enantiomer form in vivo (4,41,42). A nonselective inhibitor of COX, ibuprofen provides strong analgesic activity with somewhat weaker anti-inflammatory activity (42,48). It is rapidly absorbed from the upper GI tract when administered orally. Peak serum concentrations are achieved 15 minutes to 2 hours after ingestion (5,48). Ibuprofen is more than 90% to 99% bound to plasma proteins, but only to a

fraction of total drug binding sites at usual doses (5,42,48). Despite being highly protein bound, displacement interactions are not of clinical significance and do not require alterations in dosing of anticoagulants or oral hypoglycemic agents (OHA) (48). Ibuprofen is extensively metabolized in the liver, where it rapidly undergoes biotransformation with a half-life of 1.8 to 2 hours after multiple doses (5,41,48). Excretion is rapid with more than 90% of the drug excreted renally and complete elimination occurring within 24 hours of the last dose (5,48). Neither age nor renal function impacts its elimination (48). Concomitant administration of ASA antagonizes the irreversible platelet inhibition of ASA and may thereby limit the cardioprotective effects of ASA in persons with coronary artery disease (4). Ibuprofen is analgesic at lower doses and anti-inflammatory at higher doses. Usual adult doses of ibuprofen are 200 to 800 mg every six to eight hours to a maximum dose of 2400 mg/day. An IV formulation of ibuprofen recently received FDA approval for in-hospital use as an alternative to ketorolac in patients who cannot take ibuprofen orally, when bleeding is a concern.

Naproxen (*Naprosyn*[®], *Aleve*[®], *Anaprox*[®], *Naprelan*[®]). Naproxen is a naphthylpropionic acid derivative and is the only NSAID currently marketed as a single enantiomer (4). It is a nonselective inhibitor of COX with strong analgesic and anti-inflammatory activity. Naproxen is essentially completely absorbed when ingested orally. Food slows the rate but not the extent of absorption. Peak plasma concentrations are achieved 2 to 4 hours after administration. Naproxen is highly bound to plasma proteins at 99%. Its half-life ranges from 12 to 15 hours, a value that increases nearly twofold in the elderly (5,41,42). Naproxen is almost entirely excreted in the urine. It is available in a salt form, naproxen sodium, and as a naproxen base, which is clinically important since the salt form is absorbed more rapidly. Naproxen sodium 275 mg is equipotent to naproxen base 250 mg (41). The usual adult dose of naproxen is 250 to 500 mg twice a day, and of naproxen sodium, 275 to 550 mg twice a day.

Ketoprofen (*Orudis*[®], *Oruvail*[®]). Ketoprofen is a nonselective inhibitor of COX. In addition, it stabilizes lysosomal membranes and possibly antagonizes the actions of bradykinin; however, it has not been found superior to other NSAIDs (4,5). Ketoprofen has strong anti-inflammatory and modest analgesic activity and is used primarily as an anti-inflammatory in rheumatologic diseases. It is marketed as a racemic mixture that does not undergo interconversion in vivo. It is rapidly absorbed following oral ingestion with peak serum concentrations achieved in 0.5 to 2 hours (41). Food reduces the rate but not the extent of absorption. Ketoprofen is 99% bound to plasma proteins, primarily albumin, and is metabolized by the liver, where it is extensively glucuronidated and hydroxylated (41). The half-life of ketoprofen varies widely from 1 to 35 hours, with the average being 1 to 8 hours (4,41,42). Advancing age may prolong the half-life slightly. After a single oral dose, approximately 70% to 80% of ketoprofen is excreted in the urine. The clearance of ketoprofen is reduced by approximately 50% in the elderly (41). The usual adult dose of ketoprofen is 50 to 100 mg every six to eight hours.

Oxaprozin (Daypro®). Oxaprozin is unique to the propionic acid group of NSAIDs because of its once a day dosing schedule. Oxaprozin has strong analgesic and anti-inflammatory activity. It is well absorbed orally with a bioavailability of 95% (41). Peak plasma concentrations are achieved three to six hours after administration, which is a disadvantage when treating acute pain (41,42). Oxaprozin is 99% bound to plasma proteins, primarily albumin, which is advantageous in that the drug is less likely to accumulate (42). It is 97% metabolized by the liver but does not undergo enterohepatic circulation (4,41). The remainder of the drug is excreted unchanged in the urine. The elimination half-life of oxaprozin is quite prolonged at 40 to 60 hours after multiple doses (4,41). In addition, its half-life increases with age. The usual adult dose of oxaprozin is 1200 mg once a day.

Flurbiprofen (Ansaid®). Flurbiprofen possibly has a more complex mode of action than other NSAIDs. Its S(-)-enantiomer nonselectively inhibits COX, but has also been shown to affect TNF- α and nitric oxide (NO) synthesis in rats. One of the most potent agents in the propionic acid class, flurbiprofen, is used primarily as an anti-inflammatory agent for the treatment of rheumatologic diseases, such as ankylosing spondylitis (42). It is well absorbed after ingestion, achieving peak plasma levels within one to two hours. Flurbiprofen is extensively metabolized in the liver and undergoes enterohepatic circulation (4). Its plasma half-life is 3.8 to 6 hours. The usual adult dose of flurbiprofen is 300 mg three times a day.

Fenoprofen (Nalfon®). Fenoprofen is used primarily as an anti-inflammatory in the treatment of rheumatologic disorders and is not considered analgesic (42).

Benzothiazine Derivatives (Oxicams)

Piroxicam (Feldene®). Piroxicam is a nonselective inhibitor of COX with strong analgesic and anti-inflammatory activity. At high concentrations, it also inhibits polymorphonuclear leukocyte migration, reduces oxygen-free radical production, and inhibits lymphocyte function (4). Its anti-inflammatory potency equals that of indomethacin as a prostaglandin synthesis inhibitor. It is completely absorbed when taken orally and reaches steady state concentrations in 7 to 12 days, making it a poor choice for the management of acute pain (5,40,42). Piroxicam is 99% bound to plasma proteins and has a half-life of 50 to 57 hours (4,5). Its primary use is for the management of acute musculoskeletal conditions. The usual adult dose of piroxicam is 20 mg every 12 to 24 hours; however, it should be noted that doses above 20 mg a day carry a risk of GI bleeding that is 9.5 times that of other NSAIDs (4).

Meloxicam (Mobic®). Meloxicam is an oxicam derivative with the chemical structure of an enolcarboxamide. It is considered a "preferentially" rather than a "highly" selective inhibitor of COX-2. The COX-2 inhibition of meloxicam is 10 to 25 times that of its COX-1 inhibition and is most pronounced at lower doses (4,5,41,44). A potent anti-inflammatory agent, meloxicam has less inhibitory action on PGE₂ produced in the stomach and kidneys (44). Meloxicam

inhibits synthesis of thromboxane A₂, but even at supratherapeutic doses, it has not been shown to impair platelet function (4). It is well absorbed orally with a bioavailability of 89% (41). It reaches mean maximum concentration in four to five hours with a second peak at 12 to 14 hours (41). Meloxicam is metabolized in the liver to four inactive metabolites, with CYP2C9 playing a major role and CYP3A4 a minor one; however, no significant dose adjustment is required for patients with mild to moderate hepatic insufficiency (41). It demonstrates linear pharmacokinetics and reaches steady state levels after 5 days of daily dosing (41). The half-life of meloxicam is from 15 to 20 hours (4,41). Its higher COX-2 to COX-1 selectivity ratio may make meloxicam a good choice for patients receiving anticoagulation who may benefit from NSAID therapy. The usual adult dose of meloxicam is 7.5 to 15 mg daily.

Alkanones

Nabumetone (Relafen[®]). Nabumetone is the only NSAID in this class and is the only nonacid NSAID in use (4). It has strong analgesic and anti-inflammatory activity. Nabumetone is a nonacidic naphthylalkanone resembling naproxen in structure. It is a prodrug that is converted in the liver to one or more active metabolites, primarily 6-methoxy-2-naphthylacetic acid (6MNA), a very potent inhibitor of COX that is subsequently inactivated by the liver and conjugated before excretion (4,5,41,42). Nabumetone does not undergo enterohepatic circulation. It is rapidly absorbed after oral ingestion. Its half-life is greater than 24 hours (4). At lower doses, nabumetone displays less GI toxicity, but higher doses are frequently required for desired clinical effect. The usual adult dose of nabumetone is 1000 to 2000 mg daily. Doses of 1000 mg a day or less are indicated in the elderly because of kinetic differences in this patient population.

COX-2-Specific Inhibitors

Celecoxib (Celebrex[®]). Celecoxib is the only NSAID in this class currently available in the United States. It is a sulfonamide and a selective inhibitor of COX-2 with 155- to 3200-fold selectivity for COX-2 over COX-1 (4,44). At therapeutic doses, celecoxib is as effective as naproxen, diclofenac, and ibuprofen and has demonstrated efficacy when used for acute postoperative orthopedic pain (44). Celecoxib is moderately to reasonably well absorbed after oral ingestion (5,41). Peak plasma concentrations are achieved two to four hours after administration. It is extensively bound to plasma proteins at 97% (5,41). Celecoxib is metabolized in the liver via CYP2C9 to three active metabolites (41). Its half-life is approximately 11 hours. Its elimination is 27% renal and 57% fecal with 3% of the drug being eliminated unchanged (41). The COX-2 to COX-1 inhibition ratio may make celecoxib a good option for patients who are receiving anticoagulant therapy and need NSAID therapy. The usual adult dose of celecoxib for acute pain is 400 mg on day 1 followed by 200 mg daily or 100 mg twice a day.

ADVERSE EFFECTS OF NSAIDS

In the United States, NSAIDs are responsible for more than 20% of adverse drug events reported to the FDA (49). Because prostaglandins play a role in a wide variety of physiological functions throughout the body, inhibition of their production by NSAIDs may have unintended and deleterious consequences

that prescribers and users should be aware of. Additionally, some NSAIDs may disrupt the balance between the production of PGI₂ (a platelet inhibitor and vasodilator) and thromboxane A₂ (TXA₂, a platelet activator and vasoconstrictor), leading to concerns about the cardiovascular risks of NSAID use. This section explores the impact of NSAIDs on various organ systems and body functions.

GI Adverse Effects of NSAIDs

Prostaglandins play an important role in the maintenance of GI mucosal integrity. They provide a cytoprotective layer on the gastric mucosa and increase the secretion of bicarbonate ions that help to neutralize gastric acid (50). NSAID-related inhibition of COX, particularly COX-1, results in decreased gastric mucus production and bicarbonate excretion (50). In addition to these effects, NSAIDs may cause direct injury to the gastric mucosa due to their acidic properties and may induce vasoconstriction and associated hypoxemia in the gastric mucosa (1,50). NSAIDs permeate the membranes of gastric mucosal cells where they enter a more basic environment than that present in the gastric lumen. They then become ionized, resulting in the trapping of hydrogen ions within the cells, which can create direct cellular damage (1,50). Additionally, NSAIDs may uncouple oxidative phosphorylation in the mitochondria of the GI mucosa (inhibition of the electron transport chain) (51). This causes increased intestinal permeability, which results in exposure of the gastric and intestinal mucosa to luminal aggressive factors such as acid, pepsin and other digestive enzymes, bacteria and their degradation products, and bile (51). Exposure to these luminal contents may cause mucosal neutrophilic infiltration, which ultimately results in nonspecific inflammation of the GI mucosa (51). With the exception of aspirin and nabumetone, most conventional NSAIDs are known to increase intestinal permeability (52–54).

GI complications from the use of NSAIDs may represent the most common drug-induced toxicity that can be fatal (50). It has been estimated that at least 16,500 NSAID-related deaths occur in the United States among patients with rheumatoid arthritis (RA) or osteoarthritis annually, and that if deaths specifically related to NSAID associated GI toxicity were included in the National Vital Statistics reports, this would represent the 15th leading cause of mortality in this country (1,50,55,56). Therefore, more deaths can be attributed to NSAID-associated GI toxicity than to asthma, multiple myeloma, cervical cancer, or Hodgkin's disease on an annual basis in the United States (1). Using sensitive biochemical assays, NSAID or aspirin use has been identified in more than 90% of patients with bleeding peptic ulcers, making the use of these drugs the leading cause of bleeding peptic ulcers (57).

It is estimated that NSAID users have a three to five fold increased risk for serious adverse GI events, including upper GI bleeding, when compared to nonusers (58–60). Among chronic arthritis sufferers treated with NSAIDs, the combined prevalence of gastric and duodenal ulcers is 10% to 25%, which is 5 to 15 times the expected prevalence in an aged-matched healthy population (1). While 5% to 50% of NSAID users may experience upper GI complaints, more than 80% of patients who experience serious adverse GI effects have no premonitory symptoms such as dyspepsia, epigastric pain, nausea, heartburn, reflux, or regurgitation (1,50). Dyspeptic symptoms are an unreliable marker of

gastric ulceration, as some studies have revealed that up to 50% of NSAID users who complain of dyspepsia have normal endoscopic findings, and only 5% have been observed to display frank ulcers (61). The mortality rate among patients hospitalized for upper GI bleeding related to NSAIDs is 5% to 10%; therefore, GI bleeding from NSAID use can be a silent killer, with the first presenting symptom of GI toxicity being fatal hemorrhage (1,55). On the basis of endoscopic studies of NSAID users, ultrastructural damage to the gastroduodenal surface epithelium occurs within minutes of ingestion, and endoscopically detectable erosions and hemorrhages can be observed within several hours (1). Several risk factors for serious GI complications from NSAID use have been identified. These risk factors include advanced age (>65 years), prior peptic ulcer disease history, concomitant use of certain medications [(anticoagulants, aspirin, corticosteroids, selective serotonin reuptake inhibitors (SSRIs)], use of multiple NSAIDs, use of high-dose NSAIDs, significant concomitant illnesses, and certain lifestyle factors (smoking, heavy alcohol or coffee consumption) (1,50,56,58,59,60,62). (Table 4.3) It should be noted, however, that even NSAIDs administered parenterally or rectally, or those given as inactive prodrugs can cause GI ulcers and hemorrhage, indicating that direct contact of these agents with the GI mucosa is not required to cause adverse GI events (61). This seems to indicate that in addition to direct local toxic effects, a systemic effect of NSAIDs may contribute to these complications. It is recommended that patients at high risk for serious adverse GI events (Table 4.4) be given either COX-2 inhibitors or gastroprotective agents

TABLE 4.4 Risk Factors for Serious Adverse GI Effects with NSAID Use

Risk factors for the development of NSAID-associated gastrointestinal ulcers

Demographic factors

Age > 65

Female gender

Medical history/concurrent illnesses

Prior history of peptic ulcer disease

Rheumatoid arthritis with disability

Cardiovascular disease

Hepatorenal dysfunction

H. Pylori infection

Medication-related factors

Use of multiple NSAIDs

Use of high dose NSAIDs

Concomitant use of aspirin (ASA)

Concomitant use of steroids

Concomitant use of warfarin

Concomitant use of clopidogrel

Concomitant use of selective serotonin reuptake inhibitors (SSRI)

Lifestyle factors

Smoking

Alcohol consumption

Heavy coffee consumption

The items in bold represent the more consistently cited factors contributing to NSAID-associated GI ulceration.

Source: From Refs. 1, 48, 58, 59.

such as proton pump inhibitors or misoprostol in conjunction with the lowest effective dose of NSAIDs to reduce their risk of these complications (63). In this regard, a naproxen/esomeprazole magnesium combination product (Vimovo™) has recently been released to the U.S. market.

In addition to serious upper GI bleeding events associated with NSAID use, other GI complications from NSAID use include pill esophagitis, small bowel ulcerations, small bowel strictures, colonic strictures, diverticular disease, appendicitis, colitis, and exacerbations of inflammatory bowel disease (1,51,64). NSAID-related enteropathy may occur in approximately two-thirds of patients taking NSAIDs regularly for at least six months and is characterized by intestinal inflammation, occult blood loss, and protein-losing enteropathy (64). Occult blood loss from the small bowel may account for some cases of iron deficiency anemia as well as hypoalbuminemia seen among patients taking NSAIDs for the management of rheumatologic diseases (64). Some authors suggest that NSAID-associated enteropathy may in fact represent a more clinically important entity than NSAID-related gastropathy (52). NSAID-associated lesions of the small bowel may account for as many serious adverse GI events as gastric lesions (53). Unfortunately, because of limitations in imaging and endoscopic modalities to evaluate the small bowel, diagnosis of NSAID enteropathy has been difficult to establish until recently. The advent of capsule enteroscopy has allowed clinicians to better assess the effects of NSAIDs on the small bowel. A very high rate of small bowel ulceration has been observed when capsule enteroscopy has been used in patients consuming NSAIDs (52,65). Capsule enteroscopy may be the emerging test of choice to diagnose NSAID enteropathy when it is suspected (52). NSAIDs can rarely cause serious hepatocellular injury and may be associated with increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels of three times or more above the upper limit of normal in approximately 1% of users (66). Patients should be monitored for signs of liver disease during NSAID use. Interestingly, although NSAIDs have been implicated in a number of serious adverse GI effects, they are used specifically to prevent the occurrence of colorectal polyps in individuals with familial adenomatous polyposis, which commonly results in colorectal cancer. NSAIDs are also being evaluated for their potential benefits in preventing cancers of other types.

Renal Adverse Effects of NSAIDs

NSAIDs may cause a variety of changes in renal physiology and may be responsible for up to 40% of all cases of drug-induced renal failure (67). Both COX-1 and COX-2 are found in the kidney and play a role in normal renal function. COX-1 has been found in the collecting ducts, renal vasculature, and papillary interstitium (68). COX-2 has been found in the endothelial cells of renal arteries, arterioles, and glomeruli of the cortex; the cortical thick limb of the loop of Henle; the endothelial lining of the vasa recta; and the collecting ducts (68). The renal effects of NSAIDs may occur primarily through the inhibition of COX-2, indicating that the effects of traditional nonselective NSAIDs and COX-2 inhibitors on renal function should be similar (69). In the setting of actual or effective reduced circulating blood volume, the body releases vasoconstrictors into the bloodstream in efforts to maintain blood pressure (69). Under such conditions, the kidney becomes dependent on vasodilatory prostaglandins,

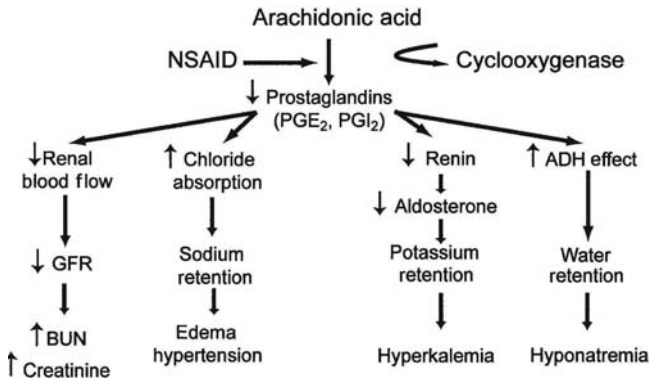


FIGURE 4.3 Renal effects of NSAID-induced prostaglandin inhibition. Prostaglandins are involved in the regulation of renal blood flow and in water and electrolyte excretion. Inhibition of renal prostaglandin production by NSAID administration can therefore result in reduced renal blood flow and glomerular filtration, and retention of water, sodium, and potassium. This can ultimately lead to such effects as edema, hypertension, hyperkalemia, and renal insufficiency, as indicated by elevations in BUN and creatinine. *Abbreviations:* ADH, antidiuretic hormone; BUN, blood urea nitrogen; GFR, glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drugs. *Source:* From Ref. 70, with permission from Elsevier.

particularly prostacyclin, to maintain renal blood flow. Inhibition of the production of these prostaglandins by use of COX-2 inhibitors or nonselective NSAIDs can, therefore, result in precipitous drops in renal perfusion. The consequences of this can include reduced glomerular filtration rates and acute renal failure. In addition, renal prostaglandins constitutively decrease sodium reabsorption and increase potassium excretion (69). Therefore, NSAIDs may cause additional effects of sodium retention with attendant water retention, edema, weight gain, hypertension, and congestive heart failure (69). Potassium retention associated with NSAIDs may result in hyperkalemia in patients with underlying renal insufficiency and in those who take angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), potassium-sparing diuretics, and potassium supplements (69). This may predispose these patients to cardiac arrhythmias (56). See Figure 4.3 for a summary of the renal effects of NSAID-induced prostaglandin inhibition (70).

On the basis of a nested case-control study, the risk of acute renal failure increases threefold among NSAID users relative to the general population (71). Several patient populations may be at particularly high risk of experiencing adverse renal effects of NSAIDs. These include neonates, geriatric patients, patients with renal insufficiency and those who have undergone renal transplantation, patients on salt-restricted diets, hypertensive patients, volume-depleted patients, patients with congestive heart failure, patients with liver dysfunction, and patients receiving ACE inhibitors or ARBs and/or diuretics (56). A nested case-control study indicated that the use of certain cardiovascular medications, such as anti-hypertensives (particularly ACE inhibitors, calcium channel blockers, and diuretics) increased the risk for acute renal failure fivefold among NSAID users (71). Other factors that may increase the risk of adverse renal effects of NSAIDs include exposure to contrast agents, nephrotoxic drugs

(such as aminoglycosides), and use of multiple NSAIDs (72). Serious renal side effects from NSAID use are estimated to occur in 1% to 5% of exposed patients, but this incidence can be as high as 20% in patients at risk for such complications due to comorbidities (68). The most frequent renal side effect of NSAIDs is sodium retention, which may occur in up to 25% of users (68). This can result in edema, weight gain and hypertension, or congestive heart failure in susceptible individuals.

Renal dysfunction during NSAID use has several causes. Prerenal acute renal failure occurs in patients with volume depletion or conditions such as congestive heart failure or cirrhosis. Interstitial nephritis with nephrotic syndrome occurs rarely (0.1% of users) and may be due to inflammation in the kidney caused by NSAID exposure (68). Renal papillary necrosis may occur as a result of reduced blood flow to the inner medulla induced by NSAIDs, causing hypoxemia and necrosis of this part of the kidney (68). It is interesting to note that meloxicam distribution into the kidneys is substantially less than other NSAIDs, suggesting it may have a lower potential for nephrotoxicity (68). While some forms of nephrotoxicity, such as interstitial nephritis, may require weeks to months of NSAID exposure before manifesting, it appears that acute renal failure typically occurs soon after NSAID exposure (69). Even single doses of NSAIDs have been reported to induce acute renal failure in some individuals (73). This may be of particular concern perioperatively, when acute volume depletion may increase the occurrence of such complications. A nested case-control study demonstrated that within one month of a first NSAID prescription, there is a twofold increase in the risk of acute renal failure, and there is a fourfold increase if NSAIDs from more than one category are used (reflecting either a switch in therapy or use of more than one NSAID concurrently) (72). It therefore appears that close monitoring for adverse renal effects early on after initiation of NSAID therapy is indicated.

Hematologic/Platelet Adverse Effects of NSAIDs

Traditional nonselective NSAIDs have an inhibitory effect on platelet aggregation via reductions in COX-1 activity. Platelets contain COX-1, the enzyme responsible for the synthesis of thromboxane A₂, which acts as a platelet activator and vasoconstrictor. Among the NSAIDs, aspirin, in particular, is often used as a prophylactic agent to reduce the risk of cardiovascular events due to this property. Aspirin permanently acetylates COX-1 in the platelets, rendering it inactive. Platelets are not capable of producing new COX-1 enzyme, so the platelet remains dysfunctional for the remainder of its life span (typically 7–14 days). Other nonselective NSAIDs competitively inhibit COX-1, making platelet dysfunction reversible within four to five drug half-lives after drug discontinuation. The antiplatelet activity of NSAIDs can increase the potential for bleeding, with GI and operative site bleeding both being concerns when NSAIDs are used in the postoperative period. One retrospective study of patients undergoing hip arthroplasty who received preoperative NSAIDs revealed an increased incidence of perioperative bleeding and blood transfusion requirements (74). Intraoperative use of NSAIDs has been reported to increase the incidence of significant postoperative hematoma formation among plastic surgery patients (75). Additionally, a meta-analysis of several RCTs to evaluate the impact of postoperative NSAID use on bleeding after tonsillectomy found

that the risk of bleeding among subjects given postoperative NSAIDs increased fourfold (76). It was further suggested that if 29 patients were given NSAIDs for postoperative pain relief after tonsillectomy, at least one patient would experience a hemorrhage severe enough to require reoperation, which carries significant morbidity due to the potential for respiratory complications such as aspiration and difficult intubation (76). The authors indicated that the use of NSAIDs should be abandoned after tonsillectomy (76). Since COX-2 is not significantly involved in the synthesis of thromboxane A₂, COX-2 inhibitors do not have any observable anti-platelet effect at supratherapeutic doses (77). Therefore, COX-2 inhibitors may have a role in perioperative pain management, particularly if bleeding is a concern.

Cardiovascular Adverse Effects of NSAIDs

Significant controversy currently exists regarding the cardiovascular safety of NSAIDs, with COX-2 inhibitors receiving particular scrutiny. Because of concerns that these drugs may increase the potential for adverse cardiovascular events, the FDA has concluded that there is a "class effect" of increased cardiovascular events for all NSAIDs. Package labeling in the United States for all prescription NSAIDs has been modified at the recommendation of the FDA to include a boxed warning of the potential increased risk of cardiovascular events with the use of these drugs. A more comprehensive discussion of these issues is presented in the section on COX-2 inhibitor-specific concerns.

By virtue of their ability to cause sodium (and thereby water) retention, NSAIDs may cause hypertension and congestive heart failure in susceptible individuals (see section on renal adverse effects of NSAIDs for further information on this topic). A variety of NSAIDs have been associated with increases in mean arterial pressure of five to six mmHg in patients with underlying hypertension (70). Although these changes in blood pressure appear modest, a study in patients being treated for hypertension revealed that increases as small as 4 mmHg in systolic blood pressure in patients with hypertension and vascular disease resulted in a relative increase in cardiac events of greater than 40% (70). All NSAIDs may contribute to the development or exacerbation of hypertension, but this effect was particularly notable in patients using rofecoxib, a COX-2 inhibitor that was removed from the market because of concerns about its cardiovascular safety during long-term use. The destabilizing effects of NSAIDs on blood pressure are usually seen early on during therapy (often within the first 2 weeks), so patients with risk factors for hypertension or congestive heart failure should be monitored closely for the development of these conditions soon after anti-inflammatory therapy is initiated (70). It should also be noted that NSAIDs can reduce the effectiveness of certain anti-hypertensive agents, which will be further detailed in section on drug-drug interactions with NSAIDs. In the absence of a history of heart disease, NSAID use increases the risk of first admission for heart failure 1.6-fold, while a history of heart disease confers a 10-fold increase in this risk (67).

CNS Adverse Effects of NSAIDs

CNS side effects of NSAIDs represent one of the most underrecognized adverse events associated with the use of these agents. In the perioperative period, patients are exposed to a number of agents that can potentially impact the CNS.

Often, blame for these effects is attributed to drugs such as opioids, which may not always be the source of the adverse CNS manifestation. Some of the more common adverse CNS effects of NSAIDs include tinnitus, headache, and hearing loss (78). Other adverse CNS effects that have been reported with NSAID use include confusion, depression, hallucinations, lethargy, sleep disturbances, aseptic meningitis, psychosis, cognitive dysfunction, vertigo, giddiness, visual changes, anxiety, amnesia, delirium, paranoia, emotional lability, mood or personality changes, and precipitation or exacerbation of preexisting psychiatric disorders (49,78,79). These adverse CNS events typically occur within 24 hours of NSAID consumption (sometimes even as soon as 1 hour after use), though delayed presentations can occur (49,80). Most cases resolve shortly after discontinuation of the NSAID. Populations that may be at particularly high risk of these side effects include the elderly, parturients, and patients with preexisting psychiatric disorders (49,78,80,81). Aseptic meningitis has been reported most commonly with the use of ibuprofen, particularly in association with patients suffering from lupus, though patients without autoimmune disorders have also been reported to experience NSAID-induced aseptic meningitis (78). These cases can present with fever, headache, stiff neck, and meningismus, and the patient may progress from a mentally alert state to lethargy and then coma (78). This has often occurred when a patient is reexposed to an NSAID previously taken after a period of drug abstinence. This is thought to perhaps represent a hypersensitivity reaction to these drugs (78). There is no apparent cross-reactivity with other NSAIDs, so patients who experience aseptic meningitis with one NSAID do not necessarily develop recurrent aseptic meningitis with exposure to other NSAIDs (78). One proposed mechanism of the adverse psychiatric effects of NSAIDs is alterations in CNS modulatory effects of prostaglandins that may result in stimulation of dopaminergic pathways, predisposing susceptible individuals to adverse psychiatric events (49,80). Another theory regarding the occurrence of psychosis during NSAID (particularly indomethacin) administration implicates the structural similarity between indomethacin and serotonin, an important neurotransmitter in the CNS, as a potential cause (49,80). Given these concerns, it would seem appropriate to exercise caution when NSAID administration is considered in patients with significant underlying psychiatric disorders such as severe depression, paranoid psychiatric tendencies, or prior suicide attempts (81).

Effects of NSAIDs on Bone Healing

Prostaglandins appear to play an important role in bone healing after fractures and following orthopedic procedures such as spinal fusion. After a fracture, an inflammatory response associated with massive production of prostaglandins occurs at the fracture site (82). This prostaglandin response is thought to trigger bone resorption by increasing the number and activity of osteoclasts, and subsequent bone formation by increasing the replication and differentiation of osteoblasts (83). Additionally, prostaglandins cause vasodilation, enhanced blood flow to the fracture site, and angiogenesis (83). COX-1 is found in normal bone as well as at fracture sites, while COX-2 becomes upregulated particularly during the initial stages of bone repair and produces larger amounts of prostaglandins than COX-1 at these locations (83). Some studies suggest that COX-2 function is critical for bone fracture healing, but significant controversy

exists regarding the differential effects of COX-2 inhibitors versus traditional nonselective NSAIDs on this process. Studies in both animals and humans have been performed to evaluate the effects of both COX-2 inhibitors and traditional nonselective NSAIDs on bone healing with conflicting results; some studies indicate a more detrimental impact on bone healing by COX-2 inhibitors, while others implicate the nonselective NSAIDs primarily (82–87). In a retrospective study of patients undergoing spinal fusion, it was found that patients who received ketorolac had a significantly lower rate of successful fusion, exhibiting a fivefold increased probability of nonunion relative to patients who did not receive postoperative ketorolac (83,88,89). This effect appeared to be dose dependent up to 9 to 12 doses, with no further increase in the rate of nonunion beyond 12 doses (doses administered were a 60-mg IM loading dose followed by 30 mg intramuscularly or 10 mg orally as needed every 6–8 hours) (89). Another retrospective review of patients who had undergone spinal fusion found that patients who had used NSAIDs for more than three months postoperatively had significantly lower fusion and clinical success rates than those who did not (37% vs. 93%, respectively) (83,88). It thus appears that exposure to COX inhibitors, both in the immediate postoperative period and in the subsequent months, may result in adverse consequences on bone healing. Given the limited and somewhat conflicting information on the role of COX-2 inhibitors or NSAIDs in delayed bone healing including nonunion, abstinence from these drugs for a period of 6 to 12 weeks after fractures and spinal fusion surgery may be prudent to allow for initial healing to occur (86,87).

DRUG-DRUG INTERACTIONS WITH NSAIDS

Several classes of drugs have the potential to interact adversely with NSAIDs. The clinical effects of these interactions can include reduced effectiveness of certain drugs, resulting in exacerbation of the condition for which they are being used. Interactions can also increase the risk of toxicity from either the drug being administered with the NSAID or the NSAID itself. This section reviews the classes of drugs that have significant potential to negatively interact with NSAIDs.

Anti-hypertensive Agents

Several anti-hypertensive agents may interact with NSAIDs, often resulting in reduced effectiveness of the anti-hypertensive agent. These agents include diuretics, ACE inhibitors, ARBs, calcium channel blockers, and β -blockers (90–92). The presumed mechanism of this interaction is antagonism of the synthesis of vasodilatory prostaglandins by NSAIDs that results in a blunting of the anti-hypertensive action of these drugs. Additionally, NSAIDs reduce the natriuretic effect of diuretics, which results in decreased salt and water excretion and thus less effective diuresis (93).

Selective Serotonin Reuptake Inhibitors

Both NSAIDs and SSRIs are associated with abnormal upper GI bleeding, which may be potentiated when these drugs are combined. The concomitant use of these agents seems to confer a risk beyond that caused by each agent alone. A meta-analysis has shown that SSRIs have more than double the risk of upper GI

hemorrhage, and when combined with NSAIDs, the risk increases by more than 500% (94). The presumed mechanism of this interaction revolves around the effects each of these agents has on platelet aggregation. NSAIDs have anti-platelet effects by suppression of COX-1-mediated thromboxane A₂ production, while SSRIs are presumed to inhibit serotonin uptake by platelets, causing platelet dysfunction and impaired platelet aggregation. SSRI-NSAID combinations are among the most frequently prescribed drug combinations known to induce ulcers (95).

Anticoagulant Agents

NSAID-warfarin combinations are among the most commonly reported adverse drug-drug interactions (96). Use of warfarin in combination with nonselective NSAIDs increase the risk of GI bleed-associated hospitalization more than threefold compared to warfarin use alone (96). Use of COX-2 inhibitors may afford a lower risk of GI hemorrhage when combined with warfarin relative to nonselective NSAIDs (96). NSAIDs can displace warfarin from plasma protein binding sites resulting in overanticoagulation and elevations of INR values above desired therapeutic ranges (5). NSAIDs may also interact with other anti-platelet agents such as clopidogrel to increase the risk of bleeding.

Oral Hypoglycemic Agents

When NSAIDs are combined with OHA, such as glyburide, plasma protein displacement of the OHA can result in increased free fractions of these drugs and thereby cause clinical hypoglycemia (5,97). Close monitoring of patients taking these agents concurrently is advised to reduce the likelihood of hypoglycemic events.

Digoxin

The half-life of digoxin may be increased in the presence of NSAIDs. This could result in the accumulation of digoxin and consequent digoxin toxicity. Caution is warranted when NSAIDs are used in patients receiving digoxin therapy.

Lithium

Patients receiving lithium and NSAIDs in combination may experience lithium toxicity as a result of significantly elevated plasma lithium levels and reduced renal lithium clearance. Impairment of prostaglandin-dependent tubular excretion of lithium is one proposed mechanism of decreased renal lithium clearance in the presence of NSAIDs (90,98). It has been recommended that patients receiving concomitant treatment with lithium and NSAIDs have their serum lithium levels checked every four to five days until the extent of the drug interaction is determined in each individual. Lithium dose reductions may become necessary in some patients to avoid associated toxicity (98).

Immunosuppressant Agents

Methotrexate clearance may be decreased in the presence of NSAIDs, which may increase the potential for methotrexate toxicity (90). Concurrent use of corticosteroids and NSAIDs may increase the risk of GI bleeding (43).

Aspirin

The combined use of aspirin and NSAIDs is known to increase the risk of GI bleeding two- to fourfold compared with aspirin use alone (99). Use of aspirin in conjunction with COX-2 inhibitors also seems to reduce the gastroprotective effect afforded by COX-2 administration relative to the traditional NSAIDs (100). The cardioprotective effects of aspirin may also be reduced when combined with NSAIDs (43). NSAIDs appear to interfere with the irreversible binding of aspirin to platelet COX and thereby inhibition of platelet aggregation, which is the presumed mechanism of aspirin related cardioprotection (43,101–103). This may be related to binding of NSAIDs to one of the COX-1 subunits, preventing the interaction of aspirin with its active site on COX-1 (101). This has also been demonstrated to occur with coxibs even though these agents themselves do not directly inactivate COX-1 (101). It appears that the potency of this inhibition may vary with the COX-2 selectivity of the NSAID given in combination with aspirin, with more COX-2-selective agents causing less antagonism of aspirin (103). Researchers have reported a statistically significant increase in the risk of cardiovascular mortality among patients using ibuprofen in combination with aspirin compared to those using aspirin alone (104). This is not without controversy, however, as another retrospective review of patients using aspirin alone or aspirin plus ibuprofen indicated a 40% lower rate of myocardial infarction among the group taking both aspirin and ibuprofen (105). Therefore, it is difficult to fully predict the cardiovascular consequences of combined therapy with NSAIDs and aspirin.

COX-2-SPECIFIC INHIBITOR CONCERNS

The COX-2 inhibitors were developed in an effort to minimize the side effect profile of the nonspecific nonsteroidal anti-inflammatory drugs. One particular concern when using NSAIDs in the perioperative period is the risk of unintended bleeding. The COX-2 agents inhibit the COX-2 isoform, which is responsible for generating the mediators of pain and inflammation (prostaglandins, bradykinins, substance P, potassium, acetylcholine, and serotonin) while minimizing the impact on COX-1. COX-1 is believed to be involved in protection of the gastric mucosa, the preservation of renal blood flow, and normal platelet function (106). The effectiveness of the COX-2 inhibitors depends on their ability to inhibit prostaglandin production, both peripherally and centrally. Since the prostaglandins are a diverse group of chemical compounds, the response to COX-2 inhibitors will potentially vary. For example, acetaminophen, ketorolac, and rofecoxib are equipotent in inhibiting prostaglandins in the CNS, but differ widely in their ability to inhibit prostaglandins in the periphery (106).

There are several concerns with the use of COX-2 inhibitors in the perioperative period as well as for their use in acute and chronic pain management. These include an increased risk for heart attack and stroke; the risk of systemic and pulmonary hypertension; possible adverse effects on bone healing after joint replacements, spinal fusions, or acute fractures; and the potential for severe allergic reactions and Stevens–Johnson syndrome/toxic epidermal necrolysis. Some of these concerns may also exist with the use of traditional nonselective NSAIDs; however, there are indications that the COX-2 inhibitors may have an improved safety profile compared to traditional NSAIDs with regards to GI bleeding events. The condition of the patient, the duration of drug

administration, and the drug dose may all influence the significance of these issues. Since the introduction of the COX-2 inhibitors in the United States, two of the three-marketed agents, rofecoxib (Vioxx[®]) and valdecoxib (Bextra[®]), have been pulled from the market because of serious cardiovascular side effects. Valdecoxib (Bextra[®]) was also associated with a significant incidence of Stevens-Johnson syndrome (107).

COX-2 Inhibitors and GI Bleeding

NSAID-associated GI bleeding is one of the most significant drug-related adverse events observed around the world. In vitro analysis of COX-1/COX-2 selectivities in human tissues supports the theory that COX-1 inhibition is responsible for the GI toxicity of NSAIDs (108). On the basis of work of Silverstein et al. in 2000, it appears that COX-2 inhibitors produce a lower incidence of GI side effects, including ulceration, compared to nonselective COX inhibitors such as ibuprofen (100). In the CLASS study, patients using celecoxib at doses higher than those used clinically had a lower incidence of symptomatic ulcers and ulcer complications when compared with those using standard doses of the traditional NSAIDs, ibuprofen and diclofenac, when followed for a period of six months (100). However, in subjects taking aspirin, the annualized incidences of symptomatic ulcers and/or upper GI complications did not differ significantly among the subjects taking celecoxib compared with those taking nonselective NSAIDs (100). This data indicates that concomitant aspirin use essentially mitigates the benefit of using COX-2 inhibitors with regards to reductions in serious adverse GI events. Another nested case control study similarly found that COX-2 inhibitors display a better GI safety profile compared with traditional nonselective NSAIDs, reducing the upper GI complication rate by 40%, an effect that was abolished by the concomitant use of aspirin (60). In 2004, a systematic review of the analgesic efficacy and tolerability of COX-2 inhibitors in the postoperative period demonstrated that there was no significant difference between the COX-2 inhibitors and the nonselective NSAIDs in terms of adverse GI effects following administration of single doses (109). Most side effects were mild, with reported GI symptoms consisting of nausea and vomiting. However, Fiechtner et al. in 2001 reported on the extended use of valdecoxib compared to naproxen in patients with osteoarthritis of the knee and demonstrated that upon endoscopy, there was a significantly higher incidence of ulcer formation in the naproxen group (110). Another study comparing valdecoxib (10 or 20 mg daily) for 12 weeks compared with ibuprofen (800 mg three times a day) or diclofenac (75 mg twice a day) demonstrated that valdecoxib was superior to the nonselective NSAIDs in reducing the incidence of GI ulcer formation (111). In this study, 5% of the patients taking 10 mg valdecoxib and 4% of those taking 20 mg of valdecoxib daily developed endoscopically confirmed ulcers, while 16% of the ibuprofen group and 17% of diclofenac group had documented ulcers at week 12 of the study (111). Lastly, the VIGOR study compared use of rofecoxib with naproxen and found a reduced occurrence of complicated confirmed GI adverse events (perforation, obstruction, and severe upper GI bleeding) among the rofecoxib group, with a relative risk of 0.4 versus those taking naproxen (112). However, an increased rate of adverse cardiovascular events was also noted among those

taking rofecoxib, a finding that raised initial concerns about the cardiovascular safety of COX-2 inhibitors (112).

Allergic Reactions to COX-2 Inhibitors/Stevens–Johnson syndrome and Toxic Epidermal Necrolysis

Two of the three COX-2 inhibitors that have been marketed in the United States are sulfonamides (celecoxib and valdecoxib). The primary cause of allergic reactions to the COX-2 inhibitors is thought to be due to their sulfonamide structure. Celecoxib (the only COX-2 inhibitor that remains on the market in the United States) is contraindicated in patients with a known history of sulfonamide allergy (113).

Stevens–Johnson syndrome and toxic epidermal necrolysis are severe, life-threatening skin disorders in which blistering of the skin develops and at least 10% of the body surface area of the epidermis detaches (66). The mortality rate of these conditions ranges from 5% to 30% (66). These conditions almost always represent an adverse drug reaction, with sulfonamides and NSAIDs being among the most common pharmaceuticals to cause such reactions (66). A review of the incidence of episodes of Stevens–Johnson syndrome and toxic epidermal necrolysis during the use of valdecoxib prompted the suspension of marketing of this drug in the United States in April of 2005 (66). It was found that valdecoxib use was associated with an incidence of these severe skin disorders that was 25 to 26 times the baseline incidence seen in the population and 9 times that of celecoxib (66). Valdecoxib associated cases also outnumbered the cases reported for celecoxib and rofecoxib combined (66). Seven deaths due to these severe skin reactions associated with the use of valdecoxib were reported to the FDA prior to its voluntary withdrawal from the U.S. market (114).

Cardiovascular Risks Associated with COX-2 Inhibitors

Concerns about the cardiovascular risks associated with COX-2 inhibitor use initially emerged during the VIGOR trial. During this trial, patients with RA were treated with either rofecoxib 50 mg daily or naproxen 500 mg twice a day. It was noted that the incidence of myocardial infarctions was significantly higher among the rofecoxib-treated group than the naproxen-treated group (0.4% vs. 0.1%, respectively) (112). The authors noted, however, that 4% of the study subjects met criteria for secondary cardiovascular prophylaxis with aspirin but were not taking low-dose aspirin therapy. These subjects accounted for 38% of the myocardial infarctions reported during the study. Excluding the patients who met criteria for (but were not taking) low-dose aspirin as cardiovascular prophylaxis, there was no significant difference in the rate of myocardial infarctions between the treatment groups (112).

Additional data regarding the cardiovascular risks of COX-2 inhibitors emerged during parallel studies assessing use of COX-2 inhibitors in the chemoprevention of colon cancer (115–118). In the APPROVe study, it was found that long-term use of rofecoxib (25 mg daily) was associated with an increased risk of cardiovascular events as well as an increased incidence of hypertension, edema, and congestive heart failure (116). The increased risk of thrombotic and cardiovascular events was first observed after 18 months of treatment (116). These findings resulted in the voluntary withdrawal of rofecoxib from the U.S. market in September 2004 (114). In the APC study, although

the absolute risk of significant adverse cardiovascular events was greatest among subjects with preexisting cardiovascular risk factors, a risk ratio of 3.0 for serious cardiovascular events was noted in all subjects receiving celecoxib compared with those receiving placebo, regardless of the presence of cardiovascular risk factors (115). Because of these findings, the use of celecoxib was terminated in study subjects receiving this drug prior to completion of the study at the recommendation of a data safety monitoring board (115). A similar study (PreSAP) demonstrated the relative risk of serious cardiovascular events in celecoxib-treated subjects compared to placebo-treated subjects to be 1.3, which was much lower than that observed in the APC study (119). However, celecoxib administration was also halted in this trial because of the increased risk of cardiovascular events observed in the APC trial. A combined analysis of the two trials (APC and PreSAP) revealed a nearly twofold increase in the risk of cardiovascular death, myocardial infarction, stroke, or heart failure when celecoxib was used in doses of 400 mg or more per day (118).

Uncertainty about the true extent of the cardiovascular risks of both traditional nonselective NSAIDs and COX-2 inhibitors still exists. Data from trials performed using COX-2 inhibitors inconsistently indicated increased risks of adverse cardiovascular events with these agents. Additionally, comparisons of COX-2 inhibitors and nonselective NSAIDs during these trials did not clearly indicate an increased relative risk of the COX-2 inhibitors, making the conclusion that COX-2 inhibitors as a class carry a greater risk of adverse cardiovascular events than nonselective NSAIDs problematic (114). In view of these concerns, the FDA concluded that an increased risk of adverse cardiovascular events should be considered a "class effect" of all NSAIDs until long-term controlled clinical trials could be completed to further clarify this issue (114). As a result of this controversy, the FDA proposed labeling changes to warn prescribers and patients about the potential cardiovascular adverse effects of these drugs as a class (120). A recent survey of adult Americans who used celecoxib, rofecoxib, or a traditional NSAID found that the adjusted odds ratio for an acute myocardial infarction (AMI) was 3.30 for rofecoxib-exposed subjects, while celecoxib exposed subjects did not exhibit an increased risk for AMI; however, the celecoxib group had an adjusted odds ratio of 2.43 for stroke (121). The subjects reporting use of traditional NSAIDs did not demonstrate an increased incidence of either AMI or stroke (121). In 2010, a nationwide registry-based study in Iceland revealed an increased risk of cardiovascular events (cerebral infarction, myocardial infarction, and unstable angina) among rofecoxib and naproxen users, but not diclofenac or celecoxib users (122). This increased risk was most pronounced among younger adults using rofecoxib (122). Therefore, it appears that the issue of cardiovascular safety of both the COX-2 inhibitors and the traditional nonselective NSAIDs remains an area of ambiguity. Since the data regarding the cardiovascular safety of COX-2 inhibitors is conflicting, a large trial of more than 20,000 patients is under way (which is scheduled to be completed in 2013) to try to definitively answer the question about the association of COX-2 inhibitors and their effect on the incidence of cardiovascular events.

The prevailing theory behind the adverse cardiovascular effects of COX-2 inhibitors involves the selective inhibition of the production of prostacyclin, a vasodilatory prostanoid that is synthesized through the actions of COX-2. COX-1-dependent synthesis of platelet-derived thromboxane A_2 , a vasoconstrictive

prostanoid that promotes platelet aggregation, is unopposed when COX-2 is inhibited (43,117,123). This may result in a prostanoid imbalance that ultimately promotes a prothrombotic state and hence increases the risk of adverse cardiovascular events (43,117,123).

NEW DEVELOPMENTS IN NSAID THERAPY: CINODS, DUAL COX/LOX INHIBITORS, AND HYDROGEN SULFIDE-RELEASING NSAIDS

Three emerging classes of anti-inflammatory agents are the COX-inhibiting nitric oxide donors (CINODs), the dual Cyclooxygenase/5-lipoxygenase (COX/5-LOX) inhibitors, and hydrogen sulfide-releasing NSAIDs. The CINODs and dual COX/LOX inhibitors are undergoing phase III clinical trials, while the hydrogen sulfide-releasing agents are in preclinical development. These agents are under study as alternatives to traditional nonsteroidals with some preliminary evidence of efficacy similar to existing NSAIDs and potentially improved side effect profiles.

CINODs

Nitric oxide (NO) plays an important role in a variety of physiological processes including regulation of blood pressure, inhibition of platelet aggregation and adhesion, and GI mucosal protection (67). In the GI tract, NO modulates blood flow and other components of mucosal defense such as mucus and bicarbonate secretion and epithelial permeability, inhibits leukocyte adherence to the epithelium of the gastric microcirculation, and plays a role in the mucosal healing process (67,124,125). COX-inhibiting NO donators (CINODs) consist of an anti-inflammatory agent linked to an NO-donating chemical group. The addition of the NO-donating chemical group would theoretically enhance the GI tolerability of these agents relative to their parent NSAID and might provide other physiological benefits in regards to cardiovascular effects (see Figure 4.4 for a graphic representation of the mechanism of action of CINODs). Naproxcinod (NO-naproxen) is the first of these agents to be developed and is in phase III clinical trials for the treatment of osteoarthritis (126,127). Animal studies indicated that the incidence of gastric mucosal damage during naproxcinod administration was much lower than that seen with its parent compound, naproxen (63,124). Additional findings of interest in animal studies include reduced myocardial infarct size in ischemia/reperfusion models in rabbits and pigs administered CINODs prior to induction of ischemia (67). In these models, the CINOD dose-dependently reduced left ventricular end-diastolic pressure and improved recovery of myocardial contractility at reperfusion. Reductions in creatine kinase (CK) levels, indicating a reduction in infarct size, were accompanied by a reduction in the mortality rate of the animals from 60% (untreated) to 10% (CINOD treated) (67). These data suggest the potential for CINODs to provide cardioprotective benefits not associated with their parent NSAIDs.

Human trial data on naproxcinod thus far has shown it to be superior to placebo and noninferior to rofecoxib 25 mg daily in doses of 375 and 750 mg twice daily in the management of symptomatic osteoarthritis of the knee (128,129). Naproxcinod had effects similar to placebo on blood pressure, while its parent drug, naproxen, was shown to elevate blood pressure (129). In a study comparing naproxen 500 mg twice a day to naproxcinod 750 mg twice a day or placebo, more patients in the naproxen group were found to have elevations

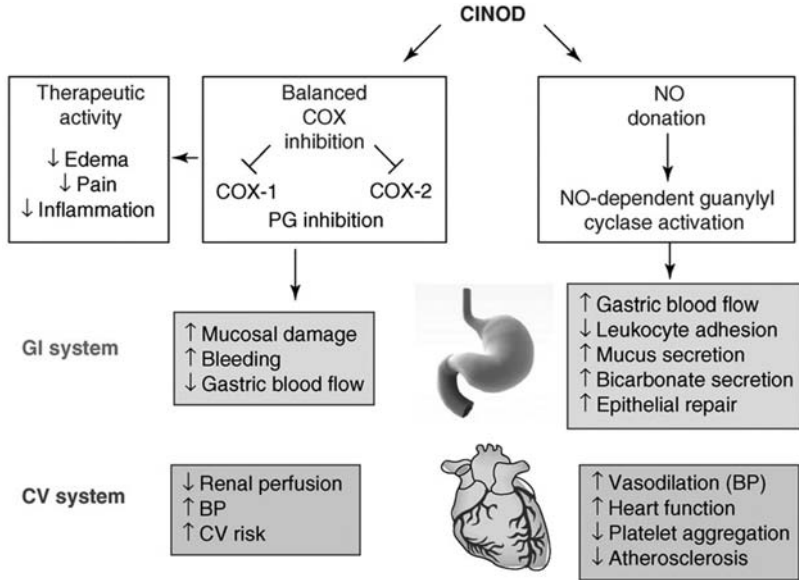


FIGURE 4.4 Mechanism of action of CINODs. Traditional NSAIDs have a broad range of physiological effects, both desirable and undesirable. Their therapeutic action is primarily via reductions in pain and inflammation, but these effects can be accompanied by adverse effects on the gastrointestinal (GI), renal, and cardiovascular (CV) systems. Such effects may include GI mucosal injury and bleeding, reduced GI blood flow, reduced renal perfusion, elevated blood pressure, and increased CV risk. Some of these negative effects of NSAID administration may be mitigated by the use of CINODs, which combine a nitric oxide (NO) donor with an NSAID. NO donors can increase gastric blood flow, gastric mucus and bicarbonate secretion, and epithelial repair, and reduce leukocyte adhesion in the GI microvasculature. They may also cause vasodilation, improved cardiac function, and reduced platelet aggregation and atherosclerosis. *Abbreviation:* CINODs, COX-inhibiting nitric oxide donors; COX, cyclooxygenase. *Source:* From Ref. 124, with permission from Elsevier.

in systolic blood pressure of greater than or equal to 10 mmHg during treatment (22% vs. 14% vs. 15.6%, respectively) (130). In a subgroup of study subjects who were taking diuretics or renin-angiotensin blocking drugs for hypertension, the blood pressure differences were particularly notable, with the mean change in blood pressure being 6.5 mmHg higher among the naproxen-treated individuals than in those on naproxinod (130). In evaluating the GI safety of naproxinod, it was found that the incidence of endoscopically confirmed ulcers after six weeks of treatment was not significantly different between subjects taking naproxinod and those taking naproxen, though other secondary endoscopic GI endpoints favored naproxinod (131). Currently, naproxinod is under evaluation by the European Medicines Agency for marketing in Europe. In the United States, however, an FDA advisory committee indicated that though they were enthusiastic about the potential for naproxinod, additional studies in high-risk populations such as the elderly and patients with cardiovascular or GI risk

factors are needed to further evaluate the safety of naproxinod. They therefore voted against approval of naproxinod on May 12, 2010 (132).

Dual COX/LOX Inhibitors

In addition to the prostaglandins, arachidonic acid is the precursor to the leukotrienes, which are formed via the actions of lipoxygenase (LOX). It has been theorized that inhibition of COX leads to a “shunting” of arachidonic acid into the 5-LOX pathway, leading to increased leukotriene production (133–137). The leukotriene LTB_4 is involved in the pathogenesis of a variety of inflammatory diseases including RA, osteoarthritis (OA), gout, psoriasis, psoriatic arthritis, and inflammatory bowel disease (138). Other leukotriene products of 5-LOX are involved in the pathogenesis of asthma, allergic rhinitis, chronic obstructive pulmonary disease, inflammatory bowel disease, RA (including the juvenile form), and gastric ulceration (138). It has been shown that synthesis of LTB_4 is increased in the gastric mucosa of patients taking NSAIDs compared to non-NSAID users, and these elevated levels of LTB_4 are associated with mucosal injury (133). This finding seems to support the hypothesis of the leukotriene shunting effect of COX inhibition. The leukotrienes are potent mediators of inflammation and are associated with effects such as bronchoconstriction; gastric vessel vasoconstriction; gastric acid secretion; and the release of cytokines, $TNF-\alpha$, and interleukin-1-beta ($IL-1\beta$) (133). These cytokines and inflammatory mediators are thought to generate some of the joint destruction seen in osteoarthritis by reducing the repair of damaged cartilage and stimulating bone resorption (133,136). As with the increase in LTB_4 levels seen in the gastric mucosa of NSAID users, the synthesis of LTB_4 in osteoarthritic synovium may be enhanced during NSAID use (136). See Figure 4.5 for a graphic representation of arachidonic acid metabolism to prostaglandins and leukotrienes and associated effects.

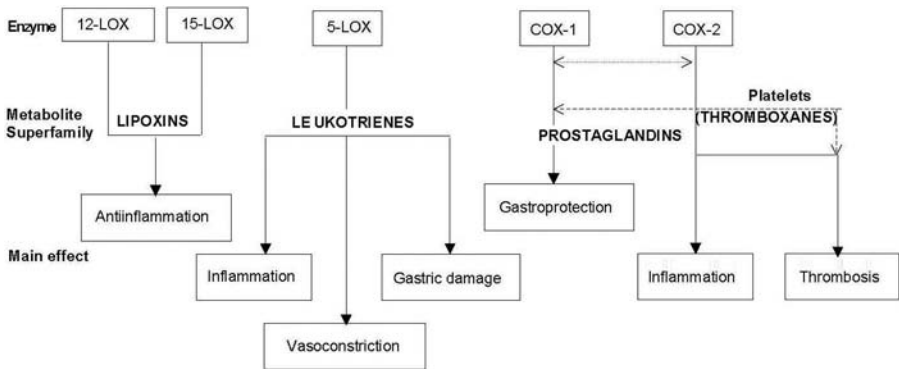


FIGURE 4.5 Actions of eicosanoids. Eicosanoids are derived from arachidonic acid metabolism. Currently available NSAIDs target cyclooxygenase enzymes only, leaving lipoxygenase enzymes unopposed. This may contribute to some of the adverse effects seen during NSAID use. Cyclooxygenase/lipoxygenase (COX/LOX) inhibitors target 5-LOX in addition to COX-1/COX-2, resulting in reduced formation of prostaglandins (PG), thromboxanes (TX), and leukotrienes (LT). By blocking LT production in addition to PG and TX production, COX/LOX inhibitors may provide protection against gastric damage and decrease the risk of hypertension (vasoconstriction) in addition to reducing inflammation. This would seem to confer an advantage over the COX inhibitors with regards to drug side effect profiles. *Source:* Reprinted from Ref. 143, with permission from Elsevier (version modified from original source Ref. 144, with permission Bentham Science Publishers).

As a means of reducing the undesirable effects of COX inhibition related to this shunting effect of arachidonic acid to the 5-LOX pathway, dual COX/ LOX inhibitors have been developed. These drugs simultaneously inhibit the production of prostaglandins, thromboxanes, and leukotrienes, providing anti-inflammatory and anti-thrombotic effects (138). The first of these agents to progress to phase III human studies is licofelone. Licofelone has been demonstrated to have efficacy equal to naproxen and celecoxib in the treatment of osteoarthritis (139). It has also been shown to have excellent GI tolerability, which compares favorably to conventional NSAIDs and is equivalent to the COX-2 inhibitors (140). A 12-week study comparing licofelone 200 mg or naproxen 500 mg dosed twice daily showed the incidence of gastric ulceration to be 1.5% and 15.3%, respectively, between the two groups (139). In a four-week study, endoscopically evaluating the GI tolerability of licofelone versus naproxen or placebo, a 20% incidence of ulcers was noted in the subjects administered naproxen and no ulcers were found in subjects in the licofelone treated or the placebo groups (141). Additionally, the gastric mucosa appeared normal in 93% of patients receiving 200 mg of licofelone twice a day, 89% of those receiving licofelone 400 mg twice a day, 90% of those receiving placebo, and 37% of subjects receiving naproxen 500 mg twice a day (141). It also appears that, in contrast to the COX-2 inhibitors, there is no increase in the risk of gastric mucosal injury when licofelone is combined with aspirin therapy (138,139). In studies utilizing licofelone or naproxen with or without low-dose aspirin therapy for a period of six weeks, the incidence of gastric ulcers in the study subjects not taking aspirin was 2.1% in the licofelone group and 20.8% in the naproxen treated group; with aspirin therapy, the incidence of gastric ulcers was 2.9% and 26.8%, respectively (139). With regards to other adverse effects commonly observed during NSAID therapy, licofelone has demonstrated a lower incidence of peripheral edema compared to both celecoxib and naproxen and a lower incidence of hypertension than naproxen (135,137,139). Beyond the apparent improved side effect profile of the COX/ LOX inhibitors, there seems to be some indication of their potential disease-modifying effects. In a dog model of knee osteoarthritis, administration of licofelone 2.5 or 5 mg/kg versus placebo over a period of eight weeks resulted in reductions in the size and grade of cartilage lesions on the femoral condyles and tibial plateaus (133,138). This effect seemed to be dose-related, with a greater reduction in lesions in the animals treated with higher dose licofelone. These gross findings were accompanied by reductions in synovial synthesis of several inflammatory mediators known to be involved in cartilage degradation such as LTB_4 , PGE_2 , $IL-1\beta$, and collagenase 1 (133,138). A human study of knee OA patients using either naproxen or licofelone for 24 months found that while both agents reduced the symptoms of OA, only licofelone reduced the degree of cartilage volume lost over time as assessed by magnetic resonance imaging (MRI), indicating slowed progression of OA related joint changes with licofelone (142). Thus, from some preliminary studies, it appears that licofelone may provide some improvements over COX inhibitors currently in use in regards to reduced adverse effects such as GI ulceration, bronchoconstriction, peripheral edema, hypertension, and detrimental interaction with aspirin. It may also be the first agent to potentially have disease-modifying effects in inflammatory conditions such as OA (136). It is not clear when licofelone will be submitted for consideration of approval by the FDA.

Hydrogen Sulfide–Releasing NSAIDs

As with NO, hydrogen sulfide (H₂S) appears to play a role in a variety of physiologic processes and disease states. These include neuromodulation, hypertension, inflammation, edema, hemorrhagic shock, pain perception, gastric mucosal integrity, and vascular tone (145). It may also affect non-vascular smooth muscle tone, the induction long-term potentiation in the hippocampus, and the induction of release of corticotropin-releasing hormone from the hypothalamus (146). H₂S is produced endogenously by the metabolism of L-cysteine, cystine, and homocysteine via the enzymes cystathionine-β synthase (CBS) and cystathionine-γ lyase (CSE) (57,145,146). It appears to create some of its effects via activation of ATP-sensitive potassium (K⁺) channels (57). H₂S has potent anti-inflammatory effects and can promote healing (146). It is produced by the gastric mucosa and seems to contribute to gastroprotection. Its production can be suppressed in the setting of NSAID administration, and it has been suggested that this suppression of H₂S production in the gastric mucosa is one of the mechanisms by which COX inhibitors cause gastric injury (57). A new class of H₂S-donating NSAIDs is in development, and several have undergone preclinical testing assessing their impact on GI adverse effects associated with NSAIDs. These drugs have been shown to decrease leukocyte adherence to the vascular endothelium in the mesenteric circulation, which is thought to contribute to NSAID-associated GI damage (146). They also have been found to decrease the expression of several pro-inflammatory cytokines (146). In animal studies, H₂S-releasing versions of diclofenac and naproxen have demonstrated both enhanced efficacy and GI safety in comparison with their parent NSAIDs (57,145,146). In a study on rats, an H₂S-releasing version of diclofenac was found to reduce the degree of intestinal damage seen in diclofenac treated rats by 90% (57). Additionally, in an experimental model of colitis, an H₂S-releasing formulation of mesalamine, a drug commonly used in the management of inflammatory bowel disease, showed markedly enhanced anti-inflammatory activity relative to its parent compound and also appeared to significantly reduce visceral pain associated with the condition (57,145). Thus, as with the CINODs and dual LOX/COX inhibitors, initial preclinical data seems to indicate the potential for the H₂S-releasing NSAIDs to provide efficacy at least equivalent to currently available NSAIDs with the possibility of reduced adverse effects.

CONCLUSION

NSAIDs are commonly used in the management of chronic pain conditions and arthritis but also play an important role in the multimodal treatment of acute pain, including postoperative pain. In appropriately selected patients, NSAIDs can provide relief of pain and inflammation in the absence of some of the adverse effects seen with opioid administration. Despite their wide use, however, NSAIDs are associated with significant morbidity and mortality. Practitioners must carefully evaluate the rationale for use of NSAID analgesics in each patient, with careful attention to comorbid conditions and individual patient related factors that may increase the risks of NSAID therapy. Adverse events that may be observed during NSAID therapy include GI bleeding, acute renal failure, onset or exacerbation of hypertension or congestive heart failure, and cognitive dysfunction. Additionally, perioperative NSAID use may contribute to increased operative site bleeding and delayed bone healing. There is some

evidence that COX-2 inhibitor use may reduce the occurrence of certain adverse effects associated with NSAIDs; however, concerns about the long-term cardiovascular safety of these agents and NSAIDs in general remain. Newer agents in development such as the CINODs, the dual COX and 5-LOX inhibitors, and the hydrogen sulfide-releasing NSAIDs may afford further reductions in some of the more worrisome side effects of NSAID use, but they remain under investigation.

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INTRODUCTION

Opioids are among the most powerful analgesics known to man. These substances have been in use since the beginning of our recorded history. While early preparations containing opioid were typically administered orally, the development of the hollow-bore needle and syringe allowed for much more widespread use of morphine and its derivatives. At present, there are many available options for delivery of opioids, including the oral, intramuscular, subcutaneous, intravenous, transdermal, transmucosal, and neuraxial routes. Such medications are almost universally used in managing acute pain after surgery or injury. Additionally, as chronic pain conditions are becoming more recognized, use of these agents is further expanding. This chapter reviews the evolution of opioid usage and provides information on the pharmacologic properties of individual opioids that may influence use in clinical practice. It also presents details regarding potential side effects of these drugs as well as issues of tolerance, dependence, and addiction.

A BRIEF HISTORY OF OPIOID USE

It is believed that many ancient cultures may have been capable of producing opium; however, it is unclear when the earliest use of opium actually occurred. It is known that the ancient Sumerians cultivated poppies from which they isolated opium at the end of the third millennium B.C. (1,2). In the Renaissance period, Paracelsus reported the use of laudanum, a mixture of alcohol and opium derivatives, which remained a popular remedy for many ailments until early in the 20th century (2). Postoperative use of opium was first described by James Moore in 1784 (3). German pharmacist Freidrich Sertuerner isolated “principium somniferum” (sleep-inducing factor) from the poppy in 1805, later naming this substance morphine after the Greek god of dreams, Morpheus (1–3).

The most critical development that led to widespread use of morphine was the invention of the hollow-bore needle and syringe in the 1850s (1–3). Morphine was widely used during the American Civil War and The French-German War in the late 1800s, with the consequent development of addiction in many soldiers. This led to a search for less addicting opioid compounds and the subsequent production of diacetylmorphine, also known as heroin. In fact, the name “heroin” was chosen to represent the presumably heroic property of diacetylmorphine that allowed it to control pain in the absence of addictive potential (4). Unfortunately, despite initial optimism about the ability of heroin to reduce opioid abuse, it soon became clear that this drug had similar abuse liability to morphine. This led to the withdrawal of heroin from the U.S. market, although it still remains available for use in the management of pain in some European countries, particularly the United Kingdom. Ultimately, as a result of abuse of opioid substances, governmental regulation in the United States, instituted in 1914, restricted such preparations from nonprescribed formulations.

Over the course of the remainder of the 20th century, numerous semi-synthetic and synthetic opioids were developed, including hydromorphone, dihydrocodeine, hydrocodone, oxycodone, meperidine, oxycodone, and methadone (2). Of interest, meperidine was developed in Germany during the Second World War as a substitute for atropine, but instead found widespread use as an analgesic (4). Likewise, methadone was developed during the Second World War in Germany as a substitute for morphine, and is now most widely known for its role in the management of opioid addicts (1,2). The development of fentanyl in 1953 by Paul Jansen has further expanded means of opioid administration, as this drug can be delivered via the transmucosal and transdermal routes.

Sustained release formulations of a number of opioids in recent years have provided benefit to many people suffering from chronic pain conditions including cancer pain. Unfortunately, despite a number of advancements in opioid therapy, abuse of these agents remains a huge societal problem. Currently, several pharmaceutical companies are developing drug delivery systems containing combinations of opioid agonists and antagonists in efforts to deter drug misuse. These formulations are designed such that if the delivery system is tampered with, the opioid antagonist will be released, effectively counteracting the effects of the opioid agonist in the preparation.

OPIOID RECEPTORS AND MECHANISM OF ACTION

Opioid receptors were identified in the 1970s and have been classified into three primary types: mu (μ), kappa (κ), and delta (δ). These receptors have been found in high densities in the substantia gelatinosa of the dorsal horn of the spinal cord and in the limbic system and periaqueductal gray area of the brainstem. Peripheral location of opioid receptors was also discovered in the late 1980s (2). These receptors are G protein-coupled. Activation of opioid receptors results in a variety of actions that diminish transmission of pain impulses. Presynaptically, opioid receptor activation may cause opening of potassium channels or closing of calcium channels. This reduces calcium influx into C-fiber terminals and thereby decreases release of pronociceptive neurotransmitters, such as substance P, from nerve terminals. Likewise, opioid receptor activation can result in postsynaptic hyperpolarization of neurons that transmit pain impulses. Additionally, opioid receptor activation may result in enhanced inhibitory activity in descending inhibitory neurons (5). The μ -receptor is the receptor type most associated with the analgesic actions of opioid agonists. This receptor is also responsible for many of the adverse effects that occur with opioids, such as nausea, vomiting, and the much dreaded respiratory depression. It is also the site where the euphoric effects of these agents originate and may play a role in the development of opioid tolerance.

PHYSIOLOGIC EFFECTS OF OPIOID ADMINISTRATION

The primary goal of opioid administration in medical settings is analgesia. However, many other desirable and undesirable effects may also occur as a result of opioid administration, as outlined in Table 5.1.

Opioid dosing should be titrated to clinical effect. When pure opioid agonists are used, no ceiling exists for opioid analgesic effects, and doses may be incrementally increased until adequate pain relief is achieved. Likewise, there is no specific toxic range for opioid dosing, and as such, all patients receiving opioids will need to be monitored for development of adverse effects. Interindividual

TABLE 5.1 Physiologic Effects of Opioid Administration

Physiologic effects of opioid administration	
CNS effects	<ul style="list-style-type: none"> • Supraspinal/spinal analgesia • Euphoria or dysphoria • Sedation and/or confusion • Seizures (these are usually reversible with naloxone administration except meperidine-induced seizures)
Respiratory effects	<ul style="list-style-type: none"> • Respiratory depression (decreased respiratory rate and tidal volume, decreased responsiveness to CO₂) • Decreased cough reflex (opioids are commonly used as antitussives) • Possible bronchoconstriction (especially with opioids that induce histamine release such as morphine)
Cardiovascular effects	<ul style="list-style-type: none"> • Decreased myocardial oxygen consumption and decreased LVEDP (hence usefulness in cardiac anesthesia) • Hypotension (with opioids that release histamine such as morphine) • Bradycardia or tachycardia (opioids that induce histamine release or have vagolytic activity, e.g., morphine, meperidine, may cause tachycardia; other opioids such as fentanyl may cause bradycardia)
Gastrointestinal effects	<ul style="list-style-type: none"> • Nausea/vomiting (via stimulation of the chemoreceptor trigger zone in the medulla) • Constipation and delayed gastric emptying • Increased biliary tract pressure ("spasm of the Sphincter of Oddi")
Genitourinary effects	<ul style="list-style-type: none"> • Urinary retention (especially with intraspinal opioid administration) • Decreased uterine contractile activity (may prolong labor) • Sexual dysfunction/decreased libido (due to effects on gonadotropins with chronic administration)
Other effects	<ul style="list-style-type: none"> • Pruritus • Miosis • Myoclonus • Chest wall rigidity (usually occurs with rapid administration of high-dose intravenous opioid and can cause difficulty with ventilation) • Development of tolerance and physical dependence (after prolonged administration)

Abbreviation: LVEDP, left ventricular end-diastolic pressure.

variability in opioid dosing can be large and may be influenced by factors such as the patient's pain tolerance, the nature of the pain (e.g., nociceptive vs. neuro-pathic), and the development of drug tolerance.

Another potential cause for variability in opioid dosing is genetic polymorphisms in various enzymes or receptors that mediate opioid-associated analgesia. Single-nucleotide polymorphisms in the μ -opioid receptor gene may result in wide-ranging opioid requirements among individuals expressing different genotypes (6). One such example is a variant of the μ -opioid receptor gene OPRM1 that results in decreased effective opioid potency such that homozygotes for this gene variant often require twice the standard opioid dose for noncarriers. Genetic variations in the μ -receptor may also play a role in the incomplete cross-tolerance seen when opioid rotation is undertaken (7). Variations in CYP2D6, a cytochrome P450 enzyme responsible for the metabolism of a number of opioids, may cause either increased or decreased opioid metabolism and thereby potential for either opioid toxicity or inadequate analgesia. Other genetic variations in the catechol-O-methyltransferase gene or the melanocortin-1 receptor gene may result in increased sensitivity to opioids and may clinically manifest in higher rates of opioid toxicity

and a need for opioid dose reduction in carriers of these genetic variants (8). Additionally, genetic factors may influence how an individual responds to various opioids. It has been observed that patients may experience inadequate relief of pain despite escalations in dosing of an opioid, or in the presence of intolerable side effects from that drug. In such circumstances, rotation to an alternate opioid may result in improved pain control in the absence of significant side effects. Individual differences in opioid metabolism or variations in receptor sensitivity to a particular drug may be genetically determined and might explain these observed phenomena (9).

CLASSIFICATION OF OPIOIDS IN CLINICAL USE

Opioids may be classified in several ways. They may be classified by their activity at opioid receptors (agonists, partial agonists, agonist-antagonists, or pure antagonists), by their derivation (natural opioids, semisynthetic opioids, or synthetic opioids), and by their potency (weak or strong). Further, opioids may be classified by their chemical structure into families of related compounds. Table 5.2 provides a classification scheme for opioids based on their activity at opioid receptors with further breakdown by derivation of these compounds with arrangement into structurally related groups.

PHARMACOLOGY OF CURRENTLY AVAILABLE OPIOIDS

There are a variety of opioids available for clinical use. The selection of opioids employed in the treatment of particular patients may be influenced by underlying disease states, the occurrence of adverse effects with prior use of specific opioids, and the pharmacologic properties of or delivery methods existing for an opioid. This section will review the pharmacologic properties of currently available opioid analgesics. Of note, this discussion will focus on pure opioid agonists, as these are the drugs of choice in the management of both acute and chronic pain. The reader may wish to review another source for more information about opioid agonist-antagonists, partial agonists, and pure antagonists.

Alfentanil

Alfentanil is a synthetic opioid agonist in the phenylpiperidine family. It is approximately 12.5 times as potent as intravenous morphine and is used primarily as an analgesic adjunct to general anesthesia. It is delivered most commonly via the intravenous route, although it is also administered neuraxially. It is lipophilic, less potent than fentanyl, and has an onset of action of less than one minute after intravenous injection. Peak analgesic activity occurs approximately 1.5 minutes after intravenous bolus administration. Its elimination half-life is approximately 90 minutes (10). Alfentanil is marketed in the United States as Alfenta[®].

Codeine

Codeine is a naturally occurring opioid that is derived from the opium poppy. It is significantly less potent than morphine, and much of the analgesia provided by codeine is in fact related to its conversion to morphine via CYP2D6. Approximately 10% of each administered dose of codeine undergoes conversion to morphine (11). Patients deficient in CYP2D6 will be unable to convert codeine to morphine, rendering codeine ineffective in such individuals. Codeine is typically

TABLE 5.2 Classification of Opioids

Opioid agonists

Natural opioids

- Codeine (Tylenol 2,3,4[®])
- Morphine (Avinza[®]/Kadian[®]/MS Contin[®]/MS IR[®]/Oramorph[®]/Roxanol[®]/Embeda[®])

Semisynthetic morphine derivatives

- Diacetylmorphine (Heroin[®])
- Dihydrocodeine (Synalgos DC[®])
- Hydrocodone (Lortab[®]/Lorcet[®]/Norco[®]/Vicodin[®]/Vicoprofen[®])
- Hydromorphone a.k.a. dihydromorphinone (Dilaudid[®]/Exalgo[®])
- Oxycodone a.k.a. dihydroxycodeinone (Oxycontin[®]/Percocet[®]/Percodan[®]/Roxicet[®]/Roxicodone[®])
- Oxymorphone a.k.a. dihydroxymorphinone (Numorphan[®]/Opana[®]/Opana ER[®])

Synthetic opioids

Morphinans

- Levorphanol (Levo-Dromoran[®])

Phenylheptylamines

- Methadone (Dolophine[®]/Methadose[®])
- Propoxyphene (Darvocet[®]/Darvon[®])

Phenylpiperidines

- Alfentanil (Alfenta[®])
- Fentanyl (Actiq[®]/Duragesic[®]/Fentora[®]/Onsolis[®]/Sublimaze[®])
- Meperidine (Demerol[®]/Pethidine[®])
- Remifentanyl (Ultiva[®])
- Sufentanil (Sufenta[®])

Opioid-like agents

- Tapentadol (Nucynta[®])
- Tramadol (Ultram[®]/Ultracet[®]/Ultram ER[®]/Ryzolt[™])

Opioid agonist-antagonists and partial agonists

- Buprenorphine (Buprenex[®]/Suboxone[®])
- Butorphanol (Stadol[®])
- Nalbuphine (Nubain[®])
- Pentazocine (Talwin[®])

Opioid antagonists

- Alvimopan (Entereg[®])^a
- Methylnaltrexone (Relistor[®])^a
- Nalmefene (Revox[®])
- Naloxone (Narcan[®])
- Naltrexone (ReVia[®])

^aPeripherally restricted opioid antagonists.

administered orally, but can also be delivered parenterally. Analgesia from codeine usually onsets within 30 to 60 minutes after oral administration with peak analgesia occurring in 60 to 90 minutes and a duration of effect of 4 to 6 hours. Its elimination half-life is 2.5 to 3.5 hours (12). Codeine is considered to be a relatively weak opioid, and alternative opioids should be considered for use if pain is severe or relief of pain is inadequate after codeine is given. Codeine products available in the United States include Tylenol with codeine (Tylenol 2[®], 3[®], 4[®]).

Dihydrocodeine

Dihydrocodeine is a semisynthetic derivative of codeine. It has been in use since the early 1900s, often as an antitussive agent in cough syrups. Dihydrocodeine is orally administered and has an onset of action of 10 to 30 minutes with a duration of action of 4 to 6 hours and an elimination half-life of 3.4 to 4.5 hours (13,14). It is

metabolized primarily via CYP2D6. Currently, it is available in the United States in combination with aspirin and caffeine in a product known as Synalgos DC[®], a schedule III controlled substance. Each tablet of this preparation contains 16 mg of dihydrocodeine bitartrate, 356.4 mg of aspirin, and 30 mg of caffeine. The maximum recommended daily dose of dihydrocodeine is 192 mg when supplied in this preparation (14).

Fentanyl

Fentanyl, like alfentanil, is a synthetic phenylpiperidine opioid agonist that is frequently used as an analgesic during surgical procedures. It also is used as a major component of anesthesia in cardiac surgery. Fentanyl is a derivative of meperidine that has been designed to be more lipid soluble and more potent than its parent compound (15). It is considered to be approximately 100 times as potent as morphine. Fentanyl is usually administered intravenously, and is commonly used in patient-controlled analgesia. Transdermal and transmucosal fentanyl are other available preparations but are not typically used in acute pain management, although some authors have advocated for the use of transdermal fentanyl in the management of acute postoperative pain (16–18). It should be kept in mind that it takes several hours to achieve steady state plasma levels of fentanyl after patch application, and many studies conducted with the use of this agent for acute postoperative pain involved placing the patch two hours *preoperatively*. Because of the slow onset of analgesic activity and lack of ability to quickly titrate transdermal fentanyl, there is potential for delayed respiratory depression (and possibly death) when this agent is used in conjunction with bolus parenteral opioids for acute pain, particularly in the opioid naive patient. For this reason, the manufacturer has recommended against its use in acute postoperative pain, and the product has a black box warning contraindicating its use for this purpose (19).

Transdermal fentanyl is recommended primarily for use in breakthrough pain, as is transmucosal fentanyl, which is typically used in breakthrough pain of malignant origin. Fentanyl is lipophilic and has a rapid onset of action of approximately 1.5 minutes after intravenous delivery. The analgesic effect of fentanyl peaks about 4.5 minutes after intravenous administration, and it has an elimination half-life of 219 minutes (10). Fentanyl is available in transdermal form in the United States under the trade name Duragesic[®] and in transmucosal forms under the trade names Actiq[®], Fentora[®], and Onsolis[®]. Intravenous fentanyl is marketed under the trade name Sublimaze[®].

Hydrocodone

Hydrocodone is a semisynthetic morphine derivative that is commonly used in both acute and chronic pain management. Its potency is similar to morphine. It is currently a schedule III opioid, allowing it to be obtained via phone order by a physician. It is perhaps this ease of accessibility that has made this drug so popular among the opioid analgesics. Of the opioids, only Tylenol with codeine, dihydrocodeine, and propoxyphene products are subject to this degree of regulation or less. The utility of this agent is limited by the fact that it is available only in combination with coanalgesics acetaminophen or ibuprofen. In patients with high opioid requirements, hydrocodone is not considered an analgesic of choice. When prescribing hydrocodone-containing products, care should be taken to not exceed maximum recommended doses of the coanalgesic. Acetaminophen should not be

administered in doses exceeding 4 g in 24 hours, and ibuprofen doses should total no more than 3200 mg daily. In practical terms, this would allow for use of no more than 8 tablets of hydrocodone/acetaminophen 5/500 preparations and no more than 16 tablets of hydrocodone/ibuprofen combination tablets (each tablet contains 200 mg of ibuprofen). In some combination hydrocodone/acetaminophen tablets, the acetaminophen content may be as much as 750 mg per tablet, further restricting the daily maximum recommended quantity. Hydrocodone is metabolized via CYP2D6 to hydromorphone, which has 30-fold greater affinity for the μ -opioid receptor than hydrocodone (20). This product of hydrocodone metabolism contributes to analgesia associated with its use. Hydrocodone is available only for enteral use. It has an onset of action of approximately 10 to 20 minutes after administration with a duration of action of 4 to 8 hours. Its elimination half-life is 3.3 to 4.4 hours (12). Common hydrocodone preparations available in the United States are marketed under the trade names Lortab[®], Lorcet[®], Norco[®], Vicodin[®], and Vicoprofen[®].

Hydromorphone

Hydromorphone is a semisynthetic morphine derivative that is used frequently in the management of acute postoperative pain. It may be given enterally or parenterally and is commonly employed in patient-controlled analgesia. Hydromorphone is approximately four to seven times as potent as morphine depending on the route of administration. Oral bioavailability of hydromorphone is low due to extensive first-pass hepatic metabolism, and therefore doses must be adjusted accordingly when converting from parenteral hydromorphone. A parenteral to oral conversion ratio of 1:5 is typically used. Hydromorphone is metabolized to hydromorphone-3-glucuronide (H3G), which has neuroexcitatory properties. Steady state plasma levels of H3G may exceed that of hydromorphone by 20- to 50-fold (20). The onset of action of orally administered hydromorphone is 15 to 30 minutes with a peak effect in 30 to 60 minutes. The duration of action is four to five hours with an elimination half-life of one to three hours (12). Hydromorphone is also available in suppository form, which may be helpful in patients with pain who are experiencing nausea or are taking nothing by mouth. The typical dosing regimen for rectal hydromorphone is 3 mg every four to eight hours as needed. Immediate-release hydromorphone is available in the United States under the trade name Dilaudid[®]. Extended-release hydromorphone is marketed under the trade name Exalgo[®].

Levorphanol

Levorphanol is a synthetic opioid classified as a morphinan. It is an enantiomer of dextromethorphan, a commonly used antitussive agent that has *N*-methyl-D-aspartate (NMDA) antagonist properties but lacks μ -agonist activity. It may be given enterally or parenterally. After oral administration, it has an onset of action of 10 to 60 minutes and a duration of 4 to 8 hours. It has an elimination half-life of 11 to 16 hours (12). In the United States, levorphanol has been marketed under the brand name Levo-Dromoran[®].

Meperidine

Meperidine is a synthetic opioid in the phenylpiperidine family. It is frequently used for acute pain but is not recommended for the management of chronic pain. It is 7.5 to 10 times less potent than morphine depending on the route of

administration. Meperidine can be administered orally or parenterally. It has been employed in patient-controlled analgesia, but this use is generally not recommended for periods of greater than 48 hours, with dosing limits of 600 mg in 24 hours. This is due to potential accumulation of one of its metabolites, normeperidine, with prolonged exposure that can result in neuroexcitation and seizures. Seizures related to normeperidine toxicity are not reversible with naloxone, and in fact may be exacerbated by naloxone administration (21). Normeperidine toxicity is especially of concern when meperidine is given to individuals with renal impairment. Elimination of normeperidine may also be impaired in cirrhotics, and as such, if meperidine is to be given to these patients, its dose should be reduced by one-half if administered parenterally and by two-thirds if administered orally (22).

Additionally, meperidine may interact with monoamine oxidase inhibitors causing potential for the development of serotonin excess syndrome. This may be manifested by malignant hypertension, delirium, seizures, hyperpyrexia, and even death. For this reason, use of meperidine is absolutely contraindicated in individuals on concomitant monoamine oxidase inhibitor therapy. The onset of action of meperidine is approximately 10 to 15 minutes after oral administration and 5 minutes after intravenous administration. The peak effect of the drug occurs about two hours after oral administration. The elimination half-life of meperidine is 2.5 to 4 hours, while that of normeperidine may be as long as 15 to 30 hours (12). Meperidine is available in the United States under the trade name Demerol[®], while it is also known as Pethidine[®] in other parts of the world.

Methadone

Methadone is a synthetic opioid in the phenylheptylamine family. It is commonly used in the management of chronic pain as well as in the treatment of opioid dependence and addiction. It is considered by some to be equipotent to morphine, while other practitioners consider it to be significantly more potent than morphine, especially when converting patients to methadone from another opioid. Many practitioners use conversion ratios of morphine: methadone ranging from 4:1 up to 14:1, and will typically select the more conservative conversion ratios when large doses of morphine (greater than about 100 mg) are to be converted to methadone (23). It is typically given orally, but may also be administered parenterally. Methadone may provide some advantages over other opioids in the management of neuropathic pain due to effects on other receptor systems in addition to its μ -receptor activity. This includes NMDA antagonist activity and inhibition of monoamine reuptake in the periaqueductal gray (24). This property of methadone is also thought to possibly attenuate the development of opioid tolerance. The onset of action of methadone is approximately 30 to 60 minutes after oral administration and 10 to 20 minutes after parenteral administration. Analgesia peaks 1 to 2 hours after parenteral administration. The duration of action is 4 to 8 hours with oral administration, which may increase to 22 to 48 hours with prolonged use. Its elimination half-life is variable with a range of 7 to 59 hours (12). Careful titration of methadone is necessary due to its prolonged half-life, with potential for accumulation over time. There is some indication that methadone may cause prolongation of the QT interval, which can predispose patients to cardiac arrhythmia (25). For this reason, some experts recommend use of screening ECGs in patients taking methadone, particularly at high doses. A baseline ECG at the time of methadone initiation and periodic ECGs thereafter in patients taking more than 240 mg

of methadone has been suggested (26). The use of surveillance ECGs is also recommended by the College of Physicians and Surgeons of Ontario in patients taking more than 200 mg of methadone daily. Other factors that may indicate a need to monitor ECGs in patients on high-dose methadone include a prior history of prolonged QT interval or torsades de pointes, or a family history of such; structural heart disease; the presence of an underlying arrhythmia or second- or third-degree atrioventricular block; anorexia nervosa; frequent electrolyte depletion, especially of potassium, calcium, or magnesium; in human immunodeficiency virus (HIV) patients on multiple antiretrovirals; in the presence of active cocaine use; when initiating a cytochrome P450 inhibitor or drugs that are known to cause QT prolongation; in the presence of a history of syncope or presyncopal episodes; or if unexplained tonic-clonic seizures have occurred in association with an abnormal EEG (27). Caution should be observed when methadone is combined with drugs that are known to prolong the QT interval or in patients with known cardiac conduction defects, as QT prolongation or torsades de pointes may occur under these circumstances. This most commonly occurs with high doses of methadone (>200 mg daily), but may also occur with lower doses (12). This has been reported to occur in HIV patients receiving antiretroviral therapy in conjunction with high-dose methadone. In such patients, the risk of cardiac conduction anomalies may be of particular concern when antiretroviral therapy is withheld or abandoned by the patient without concurrent dose reduction in methadone. This may relate to lack of induction of CYP3A4 metabolism of methadone in the absence of antiretroviral therapy (28). Methadone is available in the United States under the trade names Dolophine[®] and Methadose[®].

Morphine

Morphine is a naturally occurring opioid derived from the opium poppy. It is the prototypical opioid to which most other opioids are compared when evaluating such characteristics as potency. Morphine may be given enterally or parenterally. Its onset of action is within 30 minutes when given orally and 5 to 10 minutes when administered intravenously. The duration of action of morphine is approximately four hours. It has an elimination half-life of two to four hours (12). Morphine has two major metabolites that may accumulate and become a concern with repeated dosing and in patients with renal dysfunction. Morphine-3-glucuronide (M3G) has no analgesic properties and in fact is thought to have some antianalgesic properties. Some believe M3G may contribute to hyperalgesia seen in some patients after chronic morphine exposure. However, studies have not shown conclusive evidence that this phenomenon is in fact related to this metabolite (29). Morphine-6-glucuronide (M6G) is felt to be more potent than morphine itself with regards to analgesia and may be responsible for some of the analgesia afforded during chronic morphine administration (30). Morphine is commercially available in the United States under the brand names MSIR[®] and Roxanol[®]. Sustained-release morphine brands include Avinza[®], Kadian[®], MS Contin[®], and Oramorph SR[®]. An extended-release morphine/naltrexone (an opioid antagonist) preparation is available and is marketed under the trade name Embeda[®].

Oxycodone

Oxycodone is a semisynthetic opioid that is commonly used for both acute and chronic pain. It was derived from the natural opioid thebaine in 1916, and has been

in clinical use since 1917 (31). Some practitioners consider the potency of oxycodone to be similar to morphine; however, others consider it to be the third more potent than morphine. Metabolism of oxycodone occurs via CYP2D6, resulting in the production of noroxycodone and oxymorphone. Oxymorphone has higher μ -receptor affinity than oxycodone and may contribute to the analgesic effects of oxycodone (31). Oxycodone is administered orally. Its oral bioavailability is approximately 60% as compared with 20% for orally administered morphine. Use of oxycodone may be associated with a lower incidence of nausea, pruritus, and hallucinations when compared with morphine (31). Onset of analgesia is approximately 10 to 15 minutes after its administration, and peak effects occur in 30 to 60 minutes. Its elimination half-life is two to three hours (12). Immediate release oxycodone is available as a single agent or in combination with acetaminophen or ibuprofen. Brands of immediate-release oxycodone available in the United States include OxyFast[®], OxyIR[®], and Roxicodone[®]. Combination oxycodone products containing acetaminophen include Endocet[®], Percocet[®], Roxicet[®], and Tylox[®]. Oxycodone in combination with aspirin is available under brand names Endodan[®] and Percodan[®], while oxycodone in combination with ibuprofen is available in a product called Combunox[®]. A sustained-release preparation of oxycodone, Oxycontin[®], is also available on the U.S. market.

Oxymorphone

Oxymorphone is a semisynthetic morphine derivative. It is approximately 10 times more potent than morphine when administered parenterally, whereas it is approximately 3 times more potent than morphine when administered orally. This is because its absolute oral bioavailability is approximately 10%. Onset of analgesic action occurs 5 to 10 minutes after parenteral administration and 15 to 30 minutes after oral or rectal administration. Its duration of action is 3 to 4 hours, although this may be increased to 12 hours with the use of the extended-release formulation. Typical starting doses may be 0.5 mg parenterally, 5 mg rectally, and 10 to 20 mg orally. Currently, oxymorphone is available for rectal and parenteral use under the trade name Numorphan[®] in the United States. Oral immediate-release and extended-release preparations are available on the U.S. market under the trade names Opana[®] and Opana ER[®], respectively (12,32).

Propoxyphene

Propoxyphene is a synthetic opioid in the phenylheptylamine family. It is a weak opioid that is administered orally. It has an onset of action of 30 minutes to an hour after administration, and a duration of action of 4 to 6 hours. It has an active metabolite, norpropoxyphene, which may accumulate with repeated administration, especially in patients with renal impairment. Propoxyphene has an elimination half-life of 6 to 12 hours, while that of norpropoxyphene is 30 to 36 hours (12). In patients receiving high doses of propoxyphene, cardiac conduction defects can occur due to lidocaine-like effects of propoxyphene. ECG manifestations of propoxyphene toxicity may include widening of the QRS complex, first-degree atrioventricular block, ventricular arrhythmias, bundle branch block, QT prolongation, and nonspecific ST-T changes (33). It is important to keep in mind that 65 mg of propoxyphene is equipotent to 650 mg of aspirin, while 30 mg is no more effective than placebo. Some experts feel that the administration of propoxyphene should be avoided in the elderly, although its use in this population is common

(34–39). Others believe that propoxyphene is appropriate for use in elderly patients, particularly those who experience inadequate pain control with nonopioids and cannot tolerate stronger opioid preparations or alternate analgesics (40,41). In the United States, propoxyphene is commercially available as Darvon[®] and Darvon-N[®]. Propoxyphene is available in combination with acetaminophen in Darvocet[®] and Darvocet-N[®], and in combination with aspirin and caffeine in Darvon Compound[®].

Remifentanyl

Remifentanyl is a synthetic opioid in the phenylpiperidine family. It is a unique opioid that is broken down by plasma and tissue esterases. Its metabolism is not significantly impacted by the presence of hepatic or renal impairment. It has a very predictable half-life regardless of the duration of its infusion. It is administered primarily as an analgesic adjunct to general anesthetics for short highly stimulating procedures such as rigid laryngoscopy and adenotonsillectomy. The onset of action of remifentanyl is within one to three minutes of initiation of infusion. Its terminal half-life is 10 to 20 minutes after conclusion of infusion, while its effective half-life is 3 to 10 minutes after termination of infusion (12). It is important to remember that because of its short half-life, remifentanyl cannot be relied upon to provide postoperative pain relief. It is *always* necessary to administer another opioid if significant postoperative pain is anticipated from the procedure performed. This should ideally be administered prior to termination of remifentanyl infusion so as to allow for minimal pain upon emergence from anesthesia. This drug is marketed in the United States under the trade name Ultiva[®].

Sufentanyl

Sufentanyl is a synthetic opioid in the phenylpiperidine family. Its potency is approximately five times that of fentanyl. Like alfentanyl and remifentanyl, its primary use is as an analgesic adjunct to general anesthesia. It is administered primarily via the intravenous route but is also used for neuraxial analgesia. It has an onset of action of less than 1 minute after intravenous administration with peak effects occurring in 2.5 minutes. Its elimination half-life is 164 minutes. Sufentanyl is marketed in the United States under the brand name Sufenta[®] (10,12).

Tapentadol

Tapentadol is a synthetic opioid-like agent that became available on the U.S. market in 2009 for the treatment of acute pain of moderate to severe intensity. It is the newest opioid-like analgesic to be developed and is thought to act via μ -opioid receptor agonism and norepinephrine reuptake inhibition. It is classified as a CII controlled substance. Its absorption after oral administration is rapid and complete. It is extensively metabolized, undergoing glucuronidation, with some additional metabolism via several cytochrome P450 isoenzymes. All metabolites are inactive. The bioavailability of tapentadol is 32% and its half-life is four hours. Peak plasma levels occur 1.25 hours after administration. Tapentadol and its metabolites are nearly 100% renally excreted. Use of tapentadol is not advised in patients with severe renal or hepatic impairment or in patients who have used monoamine oxidase inhibitors within 14 days of tapentadol administration. Caution should also be exercised when tapentadol is given in conjunction with selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake

inhibitors, triptans, or tricyclic antidepressants due to the possibility of serotonin syndrome. It is a category C drug for use in pregnancy. Typical dosing regimens for tapentadol are 50 to 100 mg every four to six hours, with a maximum daily dose of 600 mg. Upon initiation of therapy, the first dose of tapentadol can be followed by a repeat dose in one hour, with a first-day dose maximum of 700 mg. Dose reduction is recommended in moderate hepatic impairment (50 mg every 8 hours or less frequently), but no dose adjustment is needed with moderate renal impairment (42,43). In a study in patients with uncontrolled osteoarthritis pain awaiting joint replacement surgery, tapentadol had enhanced gastrointestinal tolerability with regards to the incidence of nausea, vomiting, and constipation as compared to oxycodone (44). It is believed that 50 mg of tapentadol roughly approximates the potency of 10 mg of oxycodone. Tapentadol is marketed under the trade name of Nucynta[®] in the United States, and is available in strengths of 50, 75, and 100 mg.

Tramadol

Tramadol is not technically classified as an opioid, but many clinicians consider it an atypical opioid due to its weak binding of opioid receptors. Tramadol is not currently a controlled substance, and its abuse potential appears low (45). However, some cases of tramadol addiction have been reported, especially in individuals with a prior history of drug or alcohol abuse (46). μ -Receptor binding of tramadol is 10-fold lower than that of codeine, 60-fold lower than that of propoxyphene, 100-fold lower than that of methadone, and 6000-fold lower than that of morphine. Only a small amount of the analgesia afforded by tramadol appears to be related to opioid receptor activation (47,48). In contrast to morphine and codeine, the antinociceptive effects of tramadol are not completely reversed by naloxone, suggesting an additional mechanism aside from μ -receptor agonism for its analgesic activity (48). In fact, the major analgesic activity of tramadol seems to be mediated by its inhibition of norepinephrine and serotonin reuptake, similar to the effects of tricyclic antidepressants (49). The onset of analgesia from tramadol is within an hour of administration with peak effects within two hours. Its duration of action is nine hours. The elimination half-life of tramadol is approximately six hours with that of an active metabolite being about seven hours, which may be prolonged in the setting of renal or hepatic dysfunction. Tramadol dosing should not exceed 400 mg/day in healthy adults younger than 75 years, 300 mg in adults older than 75 years, 200 mg in patients with severe renal dysfunction ($\text{CrCl} < 30 \text{ mL/min}$), and 100 mg in patients with significant hepatic dysfunction (12). Seizures may occur with the use of tramadol, particularly if dose recommendations are exceeded (50–52), or if tramadol is combined with drugs that lower the seizure threshold, such as neuroleptics and tricyclic antidepressants (53). The highest risk of tramadol-associated seizures may occur when tramadol is used in conjunction with bupropion (Wellbutrin[®], Zyban[®]). Tramadol use should probably be avoided in patients with a history of an underlying seizure disorder as well. Caution is warranted when tramadol is combined with antidepressants, including tricyclics, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors. Serotonin syndrome, which can be life threatening, may occur when tramadol is combined with these drugs (54–56). Tramadol is available in the United States under the trade name Ultram[®] and in combination with acetaminophen in Ultracet[®]. Extended-release tramadol is available under the trade names Ultram ER[®] and Ryzolt[™].

COMPARATIVE PROPERTIES OF CURRENTLY AVAILABLE OPIOIDS

Pharmacokinetic properties of opioids used in clinical anesthesia and acute pain management, including equianalgesic doses, are detailed in Table 5.3. Some of the profiled opioids, including alfentanil, sufentanil, and remifentanil, are primarily administered in continuous infusions as adjuncts to general anesthesia or for postoperative pain control.

ADVERSE EFFECTS OF OPIOID ADMINISTRATION

A number of side effects commonly occur with opioid administration. Many of these adverse effects are mediated through activation of the μ -receptor, the same receptor responsible for opioid-associated analgesia. The most common adverse effects from opioid administration are constipation, sedation, nausea, and cognitive disturbance (58). Less frequent in occurrence, but much more serious and feared is the potential for development of respiratory depression with opioid administration. Other adverse effects may include pruritus, myoclonus, and urinary retention. Opioids may also affect immune function in a variety of ways.

One general approach to the management of opioid-induced side effects is dose reduction of the culprit opioid. However, dose reduction alone may be problematic as patients may subsequently experience increased pain. Other measures that can be taken to reduce opioid exposure include the addition of analgesic adjuvants that may have synergistic interaction with opioids (59). Such agents include nonsteroidal anti-inflammatory agents (NSAIDs), acetaminophen, local anesthetics, α_2 -agonists, NMDA receptor antagonists, antidepressants, and anti-convulsants. The use of physical modalities such as transcutaneous electrical nerve stimulation (TENS) may also be considered. If opioid toxicity is related to high-peak serum opioid concentrations that may occur after intermittent parenteral bolus opioid administration, use of patient-controlled analgesia should be considered. This modality often allows for decreased overall opioid consumption and reduction in peaks and troughs of opioid levels. In this way, patients are able to maintain relatively steady serum opioid levels and experience fewer episodes of opioid toxicity such as nausea or sedation as well as less frequent inadequacy of analgesia. Opioid rotation might also be a consideration when adverse effects from opioids occur, as the experience of analgesia and opioid-associated side effects may be highly variable among different individuals using the same drug. There may also be a role for the use of opioid antagonists in the management of certain opioid-associated adverse effects, which will be further explored in this section.

Pruritus

Itching commonly occurs with opioid administration, especially that via the neuraxial route (60,61). It does not appear that this is strictly related to the release of histamine induced by opioids, as itching often accompanies use of opioids that do not cause histamine release as well as those that do. Despite this fact, antihistamines are often used for this complaint with good result. Itching may be a central phenomenon related to opioid receptor binding in the spinal cord and medulla, which may also account for the increased incidence of itching with neuraxial opioid administration as compared with systemic administration (62). Low doses of naloxone, an opioid antagonist, have successfully alleviated intractable opioid-associated pruritus. Doses of 2 to 4 $\mu\text{g}/\text{kg}$ of naloxone have been employed in the

TABLE 5.3 Comparative Properties of Opioids

Drug	Peak (hr)	Duration (hr)	Half-life (hr)	Equianalgesic doses	
				Parenteral (mg)	Oral (mg)
Alfentanil (Alfenta [®])	<0.5	Dependent on dose, duration of infusion	1.5	0.8	NA
Codeine (Tylenol 2,3,4 [®])	1-1.5	4-6	2.5-3.5	130	200
Dihydrocodeine (Synalgos DC [®])	1.3	4-6	3.8	NA	150
Fentanyl (Actiq [®] , Fentora [®] , Onsolis [®] , Duragesic [®] , Sublimaze [®])	<0.5 ^b	1-2	1.5-6	0.1	NA
Hydrocodone (Lortab [®] , Lorcet [®] , Norco [®] , Vicodin [®] , Vicoprofen [®])	1	4-8	3.3-4.4	NA	30
Hydromorphone (Dilaudid [®] , Exalgo [®] ^a)	0.5-1	4-5	1-3	1.5	7.5
Levorphanol (Levo-Dromoran [®])	0.5-1	4-8	11-16	2	4
Mepidine (Demerol [®] , Pethidine [®])	0.5-2	2-4	2.5-4	75	300
Methadone (Dolophine [®] , Methadose [®])	0.5-2	4-6	7-59	10	20
Morphine (Avinza [®] , Kadian [®] , MS Contin [®] , MSIR [®] , Oramorph SR [®] , Roxanol [®] , Embeda [®] ^{a,c})	0.5-1	3-7	2-4	10	30
Oxycodone (Combunox [®] , Endocet [®] , Endodan [®] , Oxycontin [®] ^a , Percocet [®] , Percodan [®] , Roxicet [®] , Tylox [®])	0.5-1	4-6	2-3	NA	20
Oxymorphone (Numorphan [®] , Opana [®] , Opana ER [®] ^a)	<0.5	3-4	7.5-9.5	1	10
Propoxyphene (Darvocet [®] , Darvon [®])	2-2.5	4-6	6-12	NA	130
Remifentanyl (Ultiva [®])	<0.5	Dependent on duration of infusion	0.17-0.33	UNK ^d	NA
Sufentanil (Sufenta [®])	<0.5	Dependent on dose, duration of infusion	2.5	0.02	NA
Tapentadol ^e (Nuovynta [®])	1.25	4-6	4	NA	100
Tramadol ^e (Ultram [®] , Ultracet [®] , Ultram ER [®] ^a , Ryzolt [™])	2	9	6	NA ^f	150

^aThese are long-acting formulations and have longer durations of action than indicated in this table.

^bWith parenteral administration.

^cEmbeda is a combination product containing extended-release morphine with nalbexone, an opioid antagonist (one of the first "abuse deterrent" sustained-release opioid preparations).

^dUNK, unknown; Remifentanyl is usually infused in a dose range of 0.5 to 1 µg/kg/min for anesthetic induction in adults and in a range of 0.025 to 0.2 µg/kg/min in adults for postoperative pain control. Its potency appears to be similar to that of fentanyl (57).

^eTapentadol and tramadol are not technically classified as opioids; both have µ-opioid receptor agonist activity as a component of their mechanism of action, and tapentadol is classified as a schedule II controlled substance.

^fTramadol is not available for parenteral use in the United States but has been administered parenterally in Europe.

management of itching caused by neuraxial opioid administration. Subhypnotic doses of the anesthetic induction agent propofol have also been used for this indication with success (63). When compared with naloxone in a study of 40 patients with pruritus related to neuraxial opioid administration, 10 mg doses of propofol were administered with the same degree of relief as that seen after 2 µg/kg of naloxone was given. There was some suggestion that propofol administration might be better tolerated for this complaint than naloxone, as a number of patients who received naloxone in this study also experienced decreased levels of analgesia. However, many other studies utilizing similar doses of naloxone for this complaint did not display a tendency toward diminished analgesia (64). Other authors have reported improved complaints of nausea and vomiting in addition to relief of itching with the use of subhypnotic doses of propofol (65).

Nausea and Vomiting

Nausea and vomiting commonly accompany opioid administration. These effects may be mediated by stimulation of the chemoreceptor trigger zone in the medulla. Tolerance to this effect of opioid administration often occurs after several days of exposure. A number of antiemetic agents are available for the management of this side effect of opioid administration including 5-HT₃ (serotonin) receptor antagonists, dopamine receptor agonists, muscarinic receptor antagonists, cannabinoid receptor agonists, and H₁ (histamine) receptor antagonists. These agents are further outlined in Table 5.4. Some of these agents act at multiple receptor types to exert their antiemetic effects and may therefore be listed under more than one antiemetic class (66,67).

Sedation

Sedation in the postoperative patient may be related to the administration of a variety of drugs including opioids. Residual effects from general anesthesia and preoperative anxiolytic agents may also contribute. Sedation usually precedes the onset of respiratory depressant effects from opioid administration, and patients experiencing sedation should be monitored accordingly for the development of respiratory depression. In patients who cannot tolerate opioid dose reduction due to poor pain control or who have not had improvement in sedation with opioid

TABLE 5.4 Antiemetics

Antiemetic class	Example agents
5-HT ₃ receptor antagonists	Dolasetron (Anzemet [®]), granisetron (Kytril [®]), ondansetron (Zofran [®]), palonosetron (Aloxi [®])
Dopamine receptor antagonists	Chlorpromazine (Thorazine [®]), droperidol (Inapsine [®]), fluphenazine (Prolixin [®] , Permitil [®]), haloperidol (Haldol [®]), metoclopramide (Reglan [®]), prochlorperazine (Compazine [®])
Muscarinic receptor antagonists	Scopolamine (Transderm-Scop [®])
Cannabinoid receptor agonists	Dronabinol (Marinol [®])
H ₁ receptor antagonists	Chlorpromazine (Thorazine [®]), diphenhydramine (Benadryl [®]), hydroxyzine (Atarax [®] , Vistaril [®]), meclizine (Antivert [®] , Bonine [®]), promethazine (Phenergan [®])

rotation or addition of nonopioid analgesics, the use of a stimulant may be considered. Stimulants available for the management of opioid-associated sedation include amphetamines (e.g., methylphenidate, dextroamphetamine), and nonamphetamine agents (e.g., modafinil). In addition to decreasing sedation, use of amphetamines in conjunction with opioid therapy may enhance analgesia. This has been demonstrated in a study involving approximately 450 postoperative patients. When 10 mg of dextroamphetamine was added to morphine therapy, the combination was found to be twice as potent as the morphine dose alone. With a dose of 5 mg of dextroamphetamine, morphine analgesia was enhanced by a factor of 1.5 (68). This effect on analgesia has also been seen in patients with cancer-related pain who received methylphenidate in conjunction with their opioid therapy (69). At this point, no information is available regarding whether analgesia may be enhanced with the use of nonamphetamine stimulants such as modafinil.

Respiratory Depression

Respiratory depression is the most serious possible adverse effect of opioid administration. This side effect is typically preceded in onset by the occurrence of sedation, which should be recognized as an early warning sign for the potential development of respiratory depression. Unfortunately, fear of this complication of opioid administration may lead to inadequate dosing of opioids. This is especially true in the opioid tolerant patient, who may be accustomed to doses much larger than the average health care practitioner typically prescribes. The mechanism by which respiratory depression occurs appears to relate to reduction in the sensitivity of brainstem respiratory centers to CO₂ with attendant decreases in respiratory drive. This is typically manifest by the development of slow, shallow respirations that may progress to frank apnea. The development of significant respiratory depression necessitates immediate treatment with an opioid antagonist. Administration of naloxone 0.4 to 2 mg every 2 minutes, up to a total dose of 10 mg in 10 minutes, may be used to reverse respiratory depression associated with opioid administration (70). Use of opioid antagonist therapy should be reserved for significant episodes of respiratory depression, as several complications may arise from indiscriminate administration of these reversal agents. This may include increased pain or, in opioid tolerant individuals, withdrawal syndromes, both of which may be accompanied by deleterious hemodynamic changes. Patients with underlying cardiac disease may develop ischemia under such circumstances. Acute pulmonary edema has also been reported after naloxone administration (71). There is a risk of recurrent respiratory depression following naloxone administration, as many opioids have a duration of action that exceeds that of naloxone. Any patient who receives naloxone for reversal of respiratory depression associated with the use of opioids is best managed in a monitored setting in case of recurrent respiratory depression. It may even be necessary to initiate a continuous infusion of naloxone. If significant sedation or mild respiratory depressant effects are observed after opioid administration, small aliquots of naloxone (e.g., 10–40 µg doses) may be administered with careful observation such that adverse effects of naloxone are avoided.

Certain patient populations may be more susceptible to the respiratory depressant effects of opioids. Patients with obstructive sleep apnea may be particularly sensitive to opioids and other sedatives. It has also been noted that patients who have undergone bilateral carotid endarterectomy may experience increased

sensitivity to the respiratory depressant effects of opioids for up to 10 months after their endarterectomy procedures. This may be related to alterations in the carotid bodies caused by damage to their nerve or vascular supply (72). It should be kept in mind that the presence of uncontrolled pain typically counterbalances the respiratory depressant effects of opioids. In patients who have received significant quantities of opioid, sudden removal of a painful stimulus, such as decompression of a distended bladder, may result in the subsequent development of respiratory depression. This mandates careful observation and assessment of postoperative patients for easily remediable sources of pain and judicious use of opioid analgesia.

Constipation

Constipation is a common complaint among patients on opioid therapy, occurring in more than 50% of patients using these agents (73). It is a side effect to which little tolerance develops over time. Constipation may be related to a number of changes in the gastrointestinal system with opioid administration. These include decreased peristalsis, decreases in intestinal fluid volume due to increased fluid absorption, increased sphincter tone, and increased nonpropulsive segmental contractions in the gut (58). In addition to typical symptoms of constipation such as hard, dry stools, straining, abdominal bloating, and incomplete bowel evacuation, patients may also experience anorexia, nausea, and delayed gastric emptying as manifestations of opioid bowel syndrome (74). In some patients, symptoms of opioid bowel dysfunction may become so severe that they elect to discontinue opioid therapy in preference to enduring the constipation. Constipating effects of opioids may be compounded when they are coadministered with such drugs as tricyclic antidepressants, selective serotonin reuptake inhibitors, and calcium channel blockers (73). A number of remedies have been used in the management of opioid-induced constipation (Table 5.5). Stool softeners such as docusate and stimulant laxatives such as senna and bisacodyl are often used as first-line therapy for this complaint. Osmotic laxatives such as lactulose, polyethylene glycol, and magnesium hydroxide are also commonly used. Other agents that have been tried or remain to be studied include erythromycin, misoprostol, colchicine, and lubiprostone (75). Intractable

TABLE 5.5 Management of Opioid-Induced Constipation

Laxative class	Agents available
Stool softener	Docusate (Colace [®] , Surfak [®])
Bulk laxative	Methylcellulose (Citrucel [®]), psyllium (Metamucil [®] , Fiberall [®] , Konsyl [®] , Hydrocil [®]), polycarbophil (FiberCon [®] , Fiberall [®] , Konsyl Fiber [®] , Equalactin [®])
Lubricant laxative	Mineral oil (Agoral [®] , Kondremul [®] , Fleet Mineral Oil Enema [®])
Saline laxative	Magnesium citrate (Citro-Mag [®]), magnesium hydroxide (Phillip's Milk of Magnesia [®]), sodium phosphates (Fleet Enema [®] , Fleet Phospho-Soda [®])
Stimulant laxative	Senna (Senokot [®] , Ex-lax [®]), bisacodyl (Dulcolax [®] , Correctol [®] , Feen-a-Mint [®]), castor oil, cascara
Osmotic laxative	Glycerin suppository, lactulose (Chronulac [®] , Cephulac [®] , Kristalose [®]), polyethylene glycol (MiraLax [®] , Glycolax [®]), sorbitol
Chloride channel activator	Lubiprostone (Amitiza [®])
Opioid antagonist	Naloxone (Narcan [®]), alvimopan (Entereg [®]), methylnaltrexone (Relistor [®])
Other	Misoprostol (Cytotec [®]), erythromycin, colchicine

cases of opioid-induced constipation have been managed with the administration of oral naloxone, typically in doses ranging from 2 to 12 mg, three times daily (76,77). One drawback of this approach is the potential induction of opioid withdrawal despite the relatively low (~3%) bioavailability of oral naloxone. Some patients who have experienced decreased analgesia with oral naloxone administration may realize restoration of analgesia without exacerbation of constipation when their opioid dose is increased (typically by 10–15%) (78).

Currently, two peripherally restricted opioid antagonists are available for the management of opioid-associated bowel dysfunction, methylnaltrexone (Relistor[®]) and alvimopan (Entereg[®]) (79). Methylnaltrexone is derived from naltrexone. Unlike naltrexone, it is a charged molecule that cannot penetrate the blood-brain barrier (80). It can be administered orally or parenterally (81). In a study utilizing intravenous methylnaltrexone, laxation occurred within one minute of administration in patients on chronic methadone maintenance therapy. Several study subjects complained of mild to moderate abdominal cramping after administration of methylnaltrexone, but none of the subjects experienced symptoms of opioid withdrawal (82). It has also been observed that opioid tolerant patients require lower doses of methylnaltrexone as compared with opioid naive patients to obtain a laxation response. Use of oral methylnaltrexone has allowed for laxation within five hours of administration (83). Methylnaltrexone is currently labeled for use in the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care and who have had inadequate response to conventional laxatives. The method of administration for commercially available methylnaltrexone is subcutaneous injection. It may be given every other day as needed, but the dosing frequency can be increased to every 24 hours if results are inadequate with initial administration. Dosing is weight based and is as follows: patients weighing less than 38 kg are given 0.15 mg/kg; patients weighing between 38 and less than 62 kg are given 8 mg; patients weighing 62 to 114 kg are given 12 mg; and patients weighing greater than 114 kg are given a dose of 0.15 mg/kg (84). Dosing should be reduced by 50% in patients with a creatinine clearance less than 30 mL/min. Methylnaltrexone use has not been studied in patients who are dialysis dependent or in those with severe liver disease (84).

Like methylnaltrexone, alvimopan is a polar molecule. Its molecular structure and size prevent penetration of the blood-brain barrier and limit its oral absorption. Human studies of alvimopan have focused primarily on oral administration as compared with methylnaltrexone. When given at least 90 minutes preoperatively and repeated twice daily until first bowel movement postoperatively in a group of patients undergoing partial colectomy or total abdominal hysterectomy, the incidence of postoperative ileus was reduced (85). In addition to reduction in the occurrence of postoperative ileus, use of alvimopan resulted in an overall faster return of gastrointestinal function, shortened duration of hospitalization, and no reduction in opioid-associated analgesia (86,87). It appears that exposure to alvimopan prior to administration of opioid is necessary to achieve a reduction in the incidence of postoperative ileus. This may be because it is a competitive inhibitor of opioid agonists and must occupy the μ -receptor before opioid agonists are present, to have maximal effect (88). In patients on chronic opioid therapy, use of doses of alvimopan from 0.5 to 3 mg resulted in laxation within four to seven hours of administration without evident opioid withdrawal. Currently, alvimopan is labeled to accelerate the time to upper and lower GI recovery following partial large- or small-bowel resection with primary anastomosis. It should be

administered in a dose of 12 mg orally, 30 minutes to 5 hours *preoperatively*, and then maintained at a dose of 12 mg orally twice daily beginning the day after surgery and continuing until hospital discharge or for seven days (15 total doses), whichever occurs first. No dose adjustment is needed in patients with mild-to-moderate hepatic or renal impairment, but use of alvimopan is not recommended in patients with Child Pugh class C liver disease or those with end-stage renal disease (89).

Immune Effects

Immune function may be influenced by both pain and opioid analgesic administration. T lymphocytes have been found to release β -endorphin when responding to sites of inflammation, perhaps as a means to limit the experience of pain associated with local inflammation (90). β -Endorphin has been shown to have an immunosuppressive effect (91). However, some researchers have observed increased macrophage activation by β -endorphin (92). There is evidence that both acute and chronic opioid exposure may induce immunosuppression. This effect of opioid administration may be related to multiple alterations in immune function including depressed natural killer cell activity, decreased T lymphocyte proliferation, inhibition of antibody production, reduced cytokine liberation, and diminished phagocytic action of macrophages (93). It appears that these effects on immune function may depend on μ -receptor stimulation, as mice lacking functional μ -receptors do not demonstrate these effects in contrast to those with normal μ -receptors (94). The suppression of natural killer cell activity associated with opioid administration may be mediated by central opioid receptors. These effects may be dose related, with higher opioid doses causing more pronounced immune suppression (95). Acute opioid exposure may cause immune suppression via hypothalamic-pituitary axis activation, whereas chronic opioid exposure may exert immune suppressant effects via activation of the sympathetic nervous system (96). It has also been noted that intravenous opioid abusers experience increased rates of infection as compared with members of the general population. It was surmised that this was due to poor hygiene and use of contaminated needles; however, it has subsequently been found that opioids seem to enhance HIV infection of human macrophages (97). This effect of opioid therapy may be prevented by the use of opioid antagonists. Peripherally restricted opioid antagonists such as methylnaltrexone and alvimopan may be especially useful in this regard, as their administration will not result in reversal of central opioid effects, making them acceptable for use in opioid-dependent patients. It remains unclear whether chronic opioid exposure predisposes to the development of certain infections or malignancies. However, there is some evidence suggesting that the use of opioids in the setting of malignancy may decrease the occurrence of metastases (95).

While it appears that opioids exert some immune suppressant action, it is also apparent that inadequately treated pain may lead to depressed immune function. In cancer patients undergoing surgery for primary tumor resection, concern about promotion of metastases is considerable. Immune suppression, particularly depression of natural killer cell activity, occurs as a result of surgery. This decreased natural killer cell activity perioperatively has been associated with increased recurrence rates and metastases in patients with several types of cancer. Animal studies suggest that a significant contributor to this effect is poor control of postoperative pain. Use of morphine to control postoperative pain in animals has

been shown to attenuate suppression of natural killer cell activity. There is some suggestion that elevations in adrenal corticosteroid levels related to the stress of surgery and attendant postoperative pain may contribute to this modulation in immune function postoperatively. Preemptive analgesia with sustained postoperative analgesia may provide the greatest benefit in prevention of perioperative tumor spread (98,99). Researchers have also found that opioids induce apoptosis of human lung cancer cells, which may contribute to tumor necrosis (100).

Other Adverse Effects of Opioids

The majority of common adverse effects of opioid administration have been outlined. A few additional, although less frequently occurring or less well recognized, side effects deserve mention. Urinary retention is often associated with neuraxial opioid administration but may also occur with oral or parenteral opioid use. This effect may be more significant in male patients. This side effect may be reversed by opioid antagonist agents. Alvimopan, which has previously been described in the section on opioid-associated constipation, also appears effective in the management of opioid-induced urinary retention. This is of considerable importance, again, as the systemic analgesic effect of opioids is maintained with the use of this peripherally restricted opioid antagonist. Hypogonadism has also been reported, particularly among male patients, but may occur in patients of either gender with chronic opioid use (101,102). This side effect may be caused by alterations in pituitary gland secretory function with decreased release of follicle-stimulating hormone and luteinizing hormone. These alterations in pituitary function may be related to opioid effects in the hypothalamus that in turn influence pituitary function (103). Adrenal hormone production including cortisol and adrenal androgens can also be influenced by opioid administration. Decreased dehydroepiandrosterone (DHEAS) levels seen in chronic opioid consumers appear to be opioid related and may be associated with suppression of hypothalamic corticotropin-releasing hormone secretion (104). Symptoms associated with hormonal deficiencies that should prompt evaluation in patients on opioid therapy include fatigue, depression, weakness, hot flashes, sexual dysfunction, and osteoporosis (104). Peripheral edema may be observed in some patients using opioid analgesics. The underlying mechanism of this effect is not clear but may involve increased release of antidiuretic hormone from the pituitary gland (105,106). Effects of opioids on the kidney may include proliferation of interstitial cells, mesangial cells, and epithelial cells. Morphine also increases superoxide production in kidney cells, which could possibly contribute to progression of chronic kidney disease (107). Heroin-induced nephropathy has also been described, but it is unclear whether this is caused by injected contaminants or heroin itself. Hearing loss and frank deafness have been reported with the use of both heroin and hydrocodone (108,109). The cases linked to hydrocodone were noted to occur after extremely high doses of the drug were used. These doses were far in excess of recommended maximum doses based on the amount of coanalgesic consumed. Vicodin-induced fulminant hepatic failure has also been reported with consumption of large quantities of this drug. This is likely attributable to acetaminophen overdose causing hepatocellular necrosis (110). One area of evolving concern is the occurrence of hyperalgesia after opioid exposure. This effect of opioid administration may occur even after short-term opioid exposure as with perioperative use of opioids (111). The long-term implications of this effect of opioid administration remain under investigation.

DRUG DISEASE INTERACTIONS WITH OPIOIDS

The presence of certain underlying medical conditions can complicate opioid therapy. This may be due to altered drug metabolism or elimination or due to increased sensitivity to opioid effects that could exacerbate such conditions. There is currently ongoing debate regarding postoperative monitoring of patients receiving opioids. Some experts advise that patients with risk factors for opioid-associated adverse events, such as those with obstructive sleep apnea, have apnea monitors and pulse oximetry applied if opioids are to be administered perioperatively. Others suggest that these monitoring modalities be utilized in all patients who are to receive perioperative opioids (112). Caution may be warranted particularly when opioids are administered in conjunction with the medical conditions to follow.

Hepatic Dysfunction

Most opioids are biotransformed in the liver, typically via oxidation by enzymes in the cytochrome P450 system. Glucuronidation plays an important role in the biotransformation of several opioids, while remifentanyl is unique among opioids in that it undergoes hydrolysis by plasma esterases (113). In patients with significant liver disease, decreased biotransformation of opioids may result in prolongation of opioid effects, and thus potential for opioid-associated toxicity. Oral bioavailability of many opioids is increased in the presence of hepatic impairment due to decreased first pass effect.

There is no clear "opioid of choice" for use in the hepatically impaired patient, although it is recommended that most opioids be dose reduced in patients with liver disease. One example of the need for dose reduction occurs with morphine. Decreased rates of morphine biotransformation in the presence of significant liver disease may result in morphine accumulation and prolongation of its half-life. Oral morphine bioavailability may approach 100% in patients with advanced cirrhosis, which needs to be considered when converting a morphine regimen from the parenteral to the enteral route of administration (113). The dose of oral morphine may therefore need to be proportionately reduced during such a conversion and titrated to effect. The dosing of tramadol, a drug considered to have opioid-like effects, should be reduced to no more than 100 mg daily in patients with severe hepatic disease.

It should be kept in mind that many opioids are metabolized by the hepatic cytochrome P450 enzymes CYP2D6 and CYP3A4. Their metabolism may be impacted significantly in the presence of other drugs that induce or inhibit cytochrome P450 enzymatic pathways and in patients who have a congenital deficiency of CYP2D6. This can result in decreased analgesic efficacy of opioids that rely on active metabolites for their analgesic action, or can result in opioid toxicity related to delayed metabolism of drugs that are transformed to inactive metabolites prior to elimination from the body. This is detailed further in the section on drug interactions of concern with opioids.

Renal Dysfunction

Renal impairment may affect elimination of opioids and their metabolites and can thereby result in prolongation of opioid effects or opioid-associated toxicity. Much

of this toxicity may result from accumulation of metabolites from opioids. Of particular concern may be the use of meperidine in patients with renal dysfunction. Normeperidine, a major metabolite of meperidine, may accumulate when this drug is used in patients with renal dysfunction. The manifestations of normeperidine toxicity may include central nervous system excitation and seizures. Propoxyphene also produces an active metabolite, norpropoxyphene, which may accumulate in renal failure.

Morphine metabolite accumulation may cause toxicity in patients with renal impairment. M6G, a major metabolite of morphine, may accumulate in the setting of renal dysfunction. This metabolite is more potent than morphine itself, and its accumulation may result in delayed onset of opioid toxicity, such as oversedation occurring several days after initiation of morphine administration. This may, in part, be related to elevations of cerebrospinal fluid concentrations of M6G, with cerebrospinal fluid concentrations that have been found to peak later and reach levels 15 times higher than in patients with normal renal function (114,115). It is important to recognize that this phenomenon is more likely to be of significance with oral morphine administration as compared with parenteral administration, as the larger enteral doses needed to create equianalgesia with parenteral morphine will increase the amount of this metabolite that is produced.

Because of the accumulation of active metabolites and potential attendant toxicity, codeine, meperidine, morphine, and propoxyphene are best avoided when managing pain in patients with significant renal dysfunction or who are on dialysis. Fatal cardiotoxicity from propoxyphene accumulation may occur in patients with end-stage renal disease (116). Hydromorphone and oxycodone may be used with caution in this patient population. Both of these agents have active metabolites that may accumulate in renal failure posing potential for toxicity in these patients. In the setting of renal failure, H3G may accumulate, and the serum ratio of H3G to hydromorphone may increase to 100:1 (117). Neuroexcitation related to H3G is 10 times greater than that seen with hydromorphone and 2.5 times greater than with M3G (20). Use of high-dose hydromorphone in patients with severe renal impairment may result in nausea, delirium, and myoclonus due to metabolite buildup (118). Opioid rotation should be undertaken if these symptoms manifest during hydromorphone administration in this patient population. Accumulation of oxycodone and its metabolite oxymorphone may result in central nervous system depression (119,120). Fentanyl and methadone are perhaps the drugs of choice in management of pain in the renally impaired patient, especially if the need for repeated or prolonged administration of an analgesic is anticipated. Methadone is converted to primarily inactive metabolites, and in anuric patients, undergoes elimination primarily through fecal excretion (121). When initiating methadone in patients with renal failure, it is generally recommended that lower initial doses be used with gradual titration to effect (114,122).

Dialysis may remove some opioids and their metabolites from the body. Morphine and its metabolites can be removed with dialysis, but sedation or other adverse central nervous system effects may persist for long periods after dialysis due to slow re-equilibration between the plasma and the central nervous system (123). Propoxyphene and its metabolite norpropoxyphene are not removed by dialysis (124). Methadone and fentanyl, which do not produce active metabolites, are also not dialyzable (120).

Chronic Obstructive Pulmonary Disease and Obstructive Sleep Apnea

Pulmonary reserve may be compromised when opioids are used in patients with significant pulmonary disease due to effects on respiratory centers, especially alterations in responsiveness to CO₂. Additionally, patients with obstructive sleep apnea have an increased sensitivity to the sedative effects of opioids. Recognition of the hazards associated with sleep apnea has prompted the development of practice guidelines regarding the perioperative management of these patients by the American Society of Anesthesiologists. The guidelines recommend use of regional anesthetic techniques when feasible, use of adjuvant analgesics such as NSAIDs or physical modalities such as TENS to reduce opioid requirements, and avoidance of concurrent sedative administration with opioids. These guidelines further encourage consideration for the use of neuraxial techniques for postoperative analgesia that omit opioid as possible, and avoidance of basal opioid administration if a patient-controlled analgesia technique is employed for postoperative analgesia (125). Careful monitoring with continuous pulse oximetry and capnography may also be prudent in these patients when administering postoperative opioids.

Asthma

There may be potential for the induction of bronchospasm in susceptible individuals with the administration of opioids, particularly those that cause histamine release such as morphine. Selection of an opioid that does not cause considerable histamine release, such as fentanyl, may be sensible for pain management in the asthmatic patient.

Hypotension and Shock

Hypotension and shock may be exacerbated by opioid administration. This can relate to histamine release that causes vasodilation, or to increases in vagal tone caused by opioid administration. Underlying volume depletion is usually present in these cases and may be unmasked in some individuals after opioid administration. Decreased sympathetic drive related to pain control may contribute to this phenomenon.

Cor Pulmonale

Sudden death has been reported with the use of morphine in patients with cor pulmonale (126). Patients with cor pulmonale are often living at the limits of physiologic compensation. These individuals depend on increased respiratory drive to maintain oxygenation. Decreased respiratory rate and effort related to morphine administration can cause acute decompensation that may be fatal. Although sudden death has specifically been reported in cor pulmonale patients given morphine, caution must be exercised when any opioid is used in this patient population.

Increased Intracranial Pressure

In patients suffering from increased intracranial pressure, such as those with head injuries, opioid administration can be problematic for several reasons. These

patients may have increased sensitivity to the sedating and respiratory depressant effects of opioids. Sedation may interfere with neurological assessments in these patients. Also, respiratory depression with resultant increases in PCO_2 will exacerbate intracranial hypertension, possibly causing clinical deterioration in these patients. Pupillary constricting effects of opioids may also confound the neurologic examination in these individuals.

Pregnancy

Pregnancy is a condition in which concern exists about administration of a variety of drugs, including opioids. Opioids are generally categorized as being safe for use in pregnancy with regards to potential teratogenicity. They have been used throughout gestation without significant adverse effects on the fetus. The most substantial risk with these agents occurs when they are used in high doses for a significant duration close to term. Under these circumstances, it is likely that the infant will experience withdrawal, necessitating close monitoring in the perinatal period. Opioids are often administered in small doses intravenously or via the epidural route to manage the pain of labor. The risk of perinatal respiratory depression in the newborn remains rare unless large quantities of opioid are administered during parturition.

DRUG INTERACTIONS OF CONCERN WITH OPIOIDS

Opioids are metabolized primarily in the liver by enzymes in the cytochrome P450 system. The metabolism of opioids can be affected by drugs that induce or inhibit the cytochrome P450 enzyme system. The two enzymes primarily responsible for opioid metabolism are CYP2D6 and CYP3A4 (127). Certain opioids must be converted by CYP2D6 to active metabolites in order to produce analgesia. Codeine in particular is dependent on this enzyme for metabolism to morphine, which appears to be the primary source of codeine-related analgesia (128). Presence of inhibitors of this enzyme or congenital deficiency of CYP2D6 may therefore reduce analgesia afforded by these opioids. Quinidine and ritonavir are examples of drugs that may significantly inhibit CYP2D6 such that analgesia may be impacted if administered concomitantly with opioid substrates of CYP2D6. It is estimated that 10% of the Caucasian population is deficient in CYP2D6, rendering some opioids metabolized by this enzyme ineffective in these individuals. Conversely, another population known as ultrarapid metabolizers carries a gene duplication that results in unusually quick conversion of CYP2D6 substrates (129). These individuals may manifest opioid toxicity from administration of prodrugs such as codeine. It is important to recognize that while inhibition of opioid metabolism may manifest as inadequate analgesia when opioids that must be converted to active analgesic metabolites are given, coadministration of cytochrome P450 inhibitors may also result in delayed metabolism of other opioids and thereby enhanced potential for opioid toxicity. Also, when inducers of cytochrome P450 are administered at the same time as opioids that rely on this enzyme system for metabolism, opioid metabolism may be accelerated, possibly resulting in decreased analgesia or frank opioid withdrawal. Table 5.6 details common inducers and inhibitors of CYP2D6 and CYP3A4 along with opioids metabolized via these enzymes.

There are a few drugs that have been specifically cited as having potential to create clinically significant interactions with opioids on the basis of alterations in drug metabolism that deserve additional mention. Several anticonvulsant agents

TABLE 5.6 Cytochrome P450 Inducers, Inhibitors, and Substrates

 Cytochrome P450—potential inducers, inhibitors, and opioid substrates

Inducers of cytochrome P450 enzymes: May result in diminished apparent analgesic efficacy, duration of analgesia, or frank opioid withdrawal when administered with opioids metabolized via these enzymes.

CYP2D6

- St. John's wort

CYP3A4

- Antiepileptic drugs (barbiturates, benzodiazepines, carbamazepine, ethosuximide, oxcarbazepine, phenytoin, primidone)
- Antimicrobials (efavirenz, griseofulvin, nafcillin, nevirapine, rifabutin, rifampin)
- Other (dexamethasone, modafinil, St. John's wort)

Inhibitors of cytochrome P450 enzymes: May result in decreased analgesic efficacy of opioids requiring conversion to active metabolites; may increase potential for opioid toxicity due to delayed metabolism of relevant opioids.

CYP2D6

- Antiarrhythmics (amiodarone, propafenone, quinidine)
- Antidepressants (citalopram, clomipramine, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine)
- Antimicrobials (chloroquine, delavirdine, ritonavir, terbinafine)
- Antipsychotics (fluphenazine, haloperidol, perphenazine, thioridazine)
- β -Blockers (pindolol, propranolol)
- Histamine antagonists (cimetidine, diphenhydramine)
- Other (propoxyphene, tolterodine)

CYP3A4

- Antiarrhythmics (amiodarone)
- Antidepressants (fluoxetine, fluvoxamine, nefazodone, sertraline)
- Antimicrobials (amprenavir, clarithromycin, delavirdine, efavirenz, erythromycin, fluconazole, indinavir, itraconazole, ketoconazole, miconazole, nelfinavir, ritonavir, saquinavir, voriconazole)
- Calcium channel blockers (diltiazem, verapamil)
- Other (cyclosporine, danazol, ethinyl estradiol, grapefruit juice, quinine, zafirlukast)

Opioid substrates of cytochrome P450 enzymes

CYP2D6

- Codeine^a, hydrocodone^a, methadone, morphine, oxycodone, propoxyphene, tramadol^a

CYP3A4

- Alfentanil, fentanyl, hydrocodone, methadone, tramadol
-

^aCYP2D6 enzyme is required for conversion of these agents to active analgesic metabolites.

have been found to accelerate methadone metabolism resulting in symptoms of withdrawal in patients on methadone maintenance therapy. These agents include carbamazepine, phenytoin, and phenobarbital (130). Rifampicin has also precipitated opioid withdrawal when administered to patients being treated for tuberculosis while on methadone maintenance. Likewise, methadone withdrawal has been observed in patients on methadone maintenance therapy who elected to self-administer St. John's wort, a popular over-the-counter remedy for depression (131).

Opioid toxicity has been observed when an alfentanil anesthetic was administered to patients who had received a week of erythromycin therapy prior to surgery. Cimetidine given in combination with intramuscular morphine in a patient with renal failure also caused opioid toxicity manifested by apnea (132). Additionally, toxicity related to increased serum levels of other drugs may occur

when opioids are coadministered. Examples of this include potential for increased serum desipramine levels when given with methadone, and carbamazepine or benzodiazepine toxicity when administered along with propoxyphene (132,133). Serum methadone levels may increase when selective serotonin reuptake inhibitors are used in conjunction with methadone (132,134). Patients taking methadone should be advised to refrain from consumption of grapefruit juice due to potential for elevated methadone serum levels and associated opioid toxicity (135). It should be remembered that when a patient discontinues a medication that can increase or decrease methadone metabolism, symptoms of methadone withdrawal or toxicity may occur if methadone dosing is not adjusted accordingly. Close clinical monitoring is warranted under these circumstances.

Another area of particular concern is the interaction between methadone and antiretroviral agents used in the management of HIV. Antiretroviral agents may interact with methadone to cause either increased or decreased serum antiretroviral levels, or methadone toxicity or withdrawal syndrome due to effects of CYP3A4 inhibition or induction. This may have important clinical implications, as methadone withdrawal associated with antiretroviral therapy may result in decreased adherence with antiretroviral use and consequent progression of HIV disease or the development of viral resistance. Likewise, HIV disease may progress if methadone given in conjunction with antiretroviral therapy causes inadequate serum antiretroviral levels, allowing for enhanced viral replication. The potential effects of combining various antiretroviral agents with methadone are further outlined in Table 5.7.

Beyond drug interactions involving alterations in opioid metabolism, a number of other drug interactions may be of clinical concern. Many drugs may enhance the sedative effects of opioids, including benzodiazepines, antihistamines, metoclopramide, phenothiazines, and barbiturates. This may be of particular concern in individuals who may have increased sensitivity to sedatives, such as patients with obstructive sleep apnea. The combination of tramadol with antidepressants such as tricyclic antidepressants and selective serotonin reuptake inhibitors may result in serotonin excess syndrome. Likewise, meperidine or tapentadol when given concomitantly with monoamine oxidase inhibitors can result in serotonin excess syndrome. This may manifest with malignant hypertension, delirium, seizures, hyperpyrexia, and even death. The use of tramadol with many antidepressant agents is generally not recommended, while the combination of meperidine or tapentadol and monoamine oxidase inhibitors is contraindicated.

TABLE 5.7 Antiretrovirals and Methadone

Antiretroviral level may be decreased in the presence of methadone	Antiretroviral level may be increased in the presence of methadone	Methadone withdrawal may occur in the presence of antiretroviral agent	Plasma methadone levels may increase in the presence of antiretroviral agent
Amprenavir	Zidovudine	Abacavir	Delaverdine
Didanosine		Efavirenz	Indinavir
Fosamprenavir		Lopinavir	Zidovudine
Nelfinavir		Nelfinavir	
Stavudine		Nevirapine	
		Ritonavir	
		Tipranavir	

Source: From Refs. 136–151.

OPIOID TOLERANCE, DEPENDENCE, AND ADDICTION

The concepts of tolerance, dependence, and addiction are a source of confusion for many patients and clinicians, and may lead to inappropriate judgments about opioid therapy and the persons prescribed such treatment. Tolerance and dependence describe normal physiologic adaptations that occur with repetitive administration of opioids over time. Addiction refers to an abnormal psychologic condition that causes harm to the individual, and is reported to be rare among patients receiving opioids for the management of pain. Pseudoaddiction is a more recently described phenomenon that mimics addiction but is in fact caused by inadequate treatment of pain. These entities will be further detailed below.

Tolerance

Tolerance is defined as the reduction in response to a drug after repeated administration, resulting in the need to increase the dose of the drug over time to achieve effects previously attained at lower doses (152). Tolerance occurs with the use of many common drugs, including opioids. Tolerance may be innate or acquired. Acquired tolerance may be further classified as pharmacokinetic, pharmacodynamic, or learned in nature (153). Tolerance to various effects of a drug may occur at different times along the continuum of drug exposure. With respect to opioids, tolerance to euphoric effects occurs early in the course of treatment, whereas tolerance to constipating effects may not occur at all, even after long-term exposure. Tolerance to other opioid effects such as sedation, nausea/vomiting, analgesia, and respiratory depression occurs at some interval between that of euphoria and constipation. Tolerance may result in the need for dose escalation over time, although many patients on chronic opioid therapy will remain stable on a dose for extended periods of time. Tolerance plays a role in the compulsive drug seeking behavior of heroin addicts, as continually increasing doses are required to achieve the euphoria sought by such individuals. One situation in which dose escalation should not be attributed to tolerance is disease progression, which may be seen, for example, in patients with rapidly growing cancer. In patients with an underlying source of pain such as cancer, this possibility should always be considered and investigated when opioid dose escalation is needed. Psychological factors such as stress, anxiety, or depression may also be contributory in both acute and chronic pain, and should be assessed and managed in conjunction with physical complaints (154).

The development of tolerance may be related to alterations in drug metabolism, or changes in receptor density or the receptor-linked second messenger systems involved in signal transduction. Such changes may result in decreased apparent effectiveness of a drug (155). Changes in receptor density or signaling are presumed mechanisms by which opioid tolerance occurs (156). Activation of NMDA receptors may also play a role in the development of opioid tolerance, and use of NMDA receptor antagonists in conjunction with opioids may attenuate the development of tolerance and the onset of opioid-associated hyperalgesia (111). Likewise, use of calcium channel antagonists may potentially prevent the development of opioid tolerance and reduce dose requirements (157).

It appears that opioids exert their effects via two types of G protein-linked receptors. One of these receptor subtypes is inhibitory in action. Activation of this receptor results in decreased levels of intracellular cAMP with attendant increased potassium conductance and decreased calcium conductance. This results in diminished neurotransmitter release and thereby the clinical effect of analgesia

associated with opioid administration. The other receptor subtype is excitatory in nature, and its activation is thought to be associated with such phenomena as opioid tolerance, dependence, and hyperalgesia. It is believed that the excitatory effects of opioid administration occur with exposure to subclinical doses of opioids and are usually masked by inhibitory effects with the use of typical opioid doses needed for analgesia (158). Some researchers have found that use of ultralow doses of opioid antagonists (1000-fold lower than that required for clinical opioid antagonism) in conjunction with opioid agonist analgesia may have opioid sparing effects and may limit the development of opioid tolerance and dependence. Use of opioid antagonists such as naloxone and nalmefene in low doses in conjunction with intravenous patient-controlled analgesia has been studied to evaluate whether there is an impact on opioid consumption and opioid-induced side effects. Some studies suggest opioid sparing effects of such treatment (159). However, others show no reduction in opioid consumption, and in fact, indicate higher opioid requirements in individuals given low doses of opioid antagonists with patient-controlled analgesia (160). Other studies indicate no reduction in opioid requirements but reduction in nausea and pruritus when low-dose opioid antagonists are combined with patient-controlled analgesia postoperatively (161,162). At this point it remains unclear whether the addition of low-dose opioid antagonist therapy to postoperative analgesic regimens provides substantial clinical benefit in reducing opioid requirements or side effects from opioid administration.

Cross-Tolerance

Cross-tolerance is a term used to describe the observation that individuals repeatedly exposed to one opioid will often manifest tolerance to the effects of other opioids if these drugs are substituted for the original opioid. This typically results in the need for higher doses of the alternate opioid as compared with individuals who are opioid naive. However, cross-tolerance may be incomplete, and therefore conversion of one opioid to the exact equianalgesic dose of another opioid may not be necessary. It is difficult to predict the degree of cross-tolerance that exists when an individual is exposed to various opioids, and therefore, most clinicians will factor in a dose reduction of 20% to 50% when switching from one opioid to another. In individuals using very high doses of opioid or in those being switched to methadone from another opioid, the dose reduction undertaken may be even greater.

Physical Dependence

Physical dependence is a phenomenon closely associated with tolerance. It is characterized by the onset of an abstinence or withdrawal syndrome upon abrupt drug discontinuation, drastic dose reduction of the object drug, or with administration of an antagonist of that drug. As with tolerance, physical dependence is considered a normal physiologic consequence of opioid administration. It should generally be assumed that a patient who has received repeated doses of an opioid for more than a few days may be physically dependent on that drug (163). It is important to recognize that physical dependence does not indicate *addiction*. Unfortunately, this relationship is often inferred by both patients and health care professionals and may lead to inadequate treatment of pain because of inflated fears about the development of addiction. Withdrawal may be manifest by the occurrence of a number of signs and symptoms as outlined in Table 5.8.

TABLE 5.8 Signs and Symptoms of Opioid Abstinence Syndrome

Yawning	Piloerection	Nausea
Lacrimation	Fever	Vomiting
Rhinorrhea	Chills	Abdominal cramping
Sneezing	Diaphoresis	Diarrhea
Mydriasis	Myalgias	Tachypnea
Agitation	Tremor	Tachycardia
Dysphoria	Insomnia	Hypertension

While opioid withdrawal certainly is unpleasant to the individual experiencing it, it is generally not life threatening, in contrast to withdrawal associated with such drugs as alcohol, barbiturates, or benzodiazepines. However, some vulnerable patient populations, such as those with coronary artery disease, may be at risk of complications from their underlying disease processes as a result of the stresses induced during withdrawal. If a patient experiences symptoms of withdrawal and has an appropriate history for such an occurrence, a number of steps may be taken to alleviate the symptoms of, or terminate the withdrawal syndrome altogether. Reinstating the opioid at the dose taken prior to its discontinuation may eliminate withdrawal, while resuming a dose of at least 25% of that prior to discontinuation or adding an α_2 -adrenergic agonist such as clonidine may ameliorate the severity of withdrawal symptoms. In general, opioid withdrawal may be avoided by gradual tapering of opioids, with dose reductions of no greater than 20% every 24 to 48 hours.

Addiction

Addiction refers to an aberrant pattern of behavior that is characterized by compulsive drug use, use despite harm, and drug craving. The American Society of Addiction Medicine, The American Pain Society, and The American Academy of Pain Medicine defines addiction when using opioids for the management of pain to include adverse consequences of the use of opioids, loss of control over the use of opioids, and preoccupation with obtaining opioids despite the presence of adequate analgesia (164). This is a psychological condition that must be distinguished from physical dependence, which is a natural consequence of repeated opioid use. A number of aberrant behaviors associated with addiction have been described to include forging of prescriptions, stealing drugs, injecting oral formulations, repeated prescription loss, obtaining drugs from nonmedical sources, and deterioration of function in work and social situations (165). Evidence of addiction requires medical and psychiatric intervention. However, this problem is rare when managing acute pain, especially in patients without a prior history of substance abuse (166). At the same time, fear of addiction should not be an impediment to adequate pain control. Both health care providers and patients may express concern about the potential for the development of addiction during opioid treatment (167). Education and counseling regarding concerns about iatrogenic addiction should be offered to both patients and providers to help minimize the risk of undertreated pain.

Pseudoaddiction

Pseudoaddiction is characterized by behaviors that resemble those seen in addiction, but are caused by inadequate management of pain. Providers may perceive

that the patient is preoccupied with obtaining opioids, but in fact, the patient is seeking treatment of uncontrolled pain. This may occur relatively commonly when opioid tolerant patients seek acute medical care and are administered opioid doses typically used in the opioid naive. It may also be observed when inappropriately long intervals between available opioid doses are selected. Patients with rapidly progressive cancer who experience escalating pain may also request expedient titration of analgesia, and may unfortunately be inappropriately suspected of addiction to opioids. Behaviors associated with pseudoaddiction promptly resolve once adequate analgesia is achieved. Hopefully, this objective can be accomplished before mistrust between the patient and providers occurs, which is often a regrettable consequence of attributing these behaviors to addiction as opposed to poorly controlled pain (168).

CONCLUSION

Opioids have been used for much of human history. These agents remain a mainstay of therapy in the management of acute pain, and are increasingly being used for chronic pain. Many options are available with regards to drugs and routes of administration. Opioids have a variety of physiologic effects, some desired and others undesired. When selecting an opioid, clinicians must keep in mind how these drugs are metabolized and should recognize any medical conditions that may make use of specific opioids problematic in an individual patient. Common side effects of opioids as well as potential adverse drug interactions should be anticipated and appropriately managed. Likewise, potential for the development of opioid tolerance and dependence must be expected and appropriate precautions should be taken to avoid opioid withdrawal. Finally, the entities of addiction and pseudoaddiction should be properly distinguished and appropriately managed to avoid harm as well as undue suffering.

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6

Patient-controlled analgesia in the management of acute pain

Jennifer A. Elliott

INTRODUCTION

Patient-controlled analgesia (PCA) was introduced into medical practice in the late 1960s (1). It has become a widely used means of controlling pain over the past few decades. PCA has been commonly applied in the management of acute postoperative pain and has also found use in the management of other acute pain problems such as acute pancreatitis and sickle cell crisis. Additionally, it has been used in the management of pain crises in patients with cancer pain and with acute or chronic nonmalignant pain. Patients typically demonstrate high levels of satisfaction with this analgesic technique and many studies indicate they prefer it to the traditional practice of intermittent intramuscular opioid administration.

Most commonly, PCA involves the administration of intravenous opioids via the use of a patient-activated delivery system. Alternate options for analgesic delivery include patient-controlled oral, intranasal, and subcutaneous analgesia. Additionally, newer options for PCA such as patient-controlled epidural analgesia and patient-controlled regional analgesia are increasingly being used.

PCA may offer advantages over other traditional means of providing analgesia. These advantages include potential for fewer fluctuations in plasma analgesic concentrations and thereby minimization of the occurrence of adverse effects or inadequate analgesia. Additionally, many patients find that the ability to control their analgesic delivery provides a level of satisfaction greater than when they must rely on others to administer pain medication.

There are generally few contraindications to the use of PCA. Patient refusal, inadequate monitoring capability, and inadequate ability to comprehend use of PCA due to extremes of age or lack of mental capacity are among the reasons PCA may be contraindicated. Caution must also be used when PCA is instituted in the setting of severe organ dysfunction, such as chronic obstructive pulmonary disease, significant renal or hepatic dysfunction, or in the presence of obstructive sleep apnea.

To properly prescribe PCA, the practitioner must select appropriate dosing parameters for each patient and must have an adequate understanding of the pharmacokinetics of the drug employed. The patient should be monitored for evidence of adverse effects such as nausea, sedation, and respiratory depression. Care must be taken to avoid PCA-related complications due to device misprogramming, inappropriate analgesic use or prescribing, and technical errors. This chapter will describe the potential benefits and drawbacks of PCA, as well as the dosing parameters that should be established when ordering PCA. It will also provide information about alternative options to conventional intravenous PCA.

PATIENT SELECTION AND POTENTIAL ADVANTAGES OF PCA THERAPY

PCA has been used successfully in a wide variety of patient populations including those at extremes of age. It has also been applied in a wide range of clinical scenarios. When deciding to initiate PCA, proper patient selection is important to the achievement of the objective of pain control. Patient factors that may increase the risks of adverse events associated with PCA such as the presence of hepatic, renal, or pulmonary dysfunction must also be considered. Prescribers of PCA must have appropriate knowledge of the pharmacology of the drugs used and must select dosing parameters suitable for each individual patient. Patients must be capable of understanding how to use the device to obtain adequate analgesia and must be physically able to activate the device. Patient education is an important component to successful use of PCA (2).

Potential advantages of PCA over conventional intramuscular opioid administration include improved pain relief, lower total opioid consumption, and reduction in opioid associated side effects such as nausea and sedation (3). Some investigators have also found that the use of PCA can reduce postoperative pulmonary complications, allow for earlier postoperative mobilization, and may be associated with shorter lengths of hospitalization (4-9). Rapid ability of the patient to obtain analgesia as well as reduced demand on nursing staff has also been cited as a potential advantage of this therapy. Nurse managed intravenous analgesia may provide comparable pain control to PCA when patients are in closely monitored settings such as the postanesthesia care unit or intensive care unit. However, in settings where the nurse to patient ratio is lower such as a general surgical ward, PCA seems to provide more optimal analgesia (10).

Patient psychologic factors must be considered when deciding whether to use PCA. While many patients find the control and autonomy provided by PCA to be comforting, some do not. Patients with an internal locus of control tend to prefer PCA, while those with an external locus of control may desire to have their analgesia managed by nursing staff (11). Additionally, factors such as trait anxiety (baseline underlying level of anxiety), state anxiety (anxiety related to the situation), depression, coping style, social support, and patient expectations may play a role in satisfaction with PCA and total opioid consumption perioperatively (12-15). Patients may also have concerns about the possibility of accidentally overdosing or becoming addicted to the pain medication, which may result in underutilization of PCA with consequent inadequate pain control and dissatisfaction with this technique (16,17).

When patients use PCA, they typically dose themselves to the minimum effective serum analgesic concentration. This usually results in adequate pain control without the occurrence of undesired adverse effects such as nausea and sedation. In contrast, traditional intermittent p.r.n. parenteral analgesic administration may involve use of larger drug doses so as to allow for sustained serum analgesic levels above the minimum effective concentration until the next dosing interval. Unfortunately, the result of this technique may be wide fluctuations in serum analgesic concentrations such that patients may experience adverse effects as the analgesic level peaks and then inadequate analgesia as the serum opioid concentration drops off prior to the next available dose. As the patient is able to self-administer small opioid doses frequently with PCA, serum fluctuations in analgesic levels are minimized with resultant improvement in pain control and reduction in adverse effects.

PATIENT-CONTROLLED ANALGESIA DEVICES AND THEIR SETUP

PCA devices consist of a programmable pump with an integrated timer. The patient is able to activate the pump through the use of a handheld button that connects to the pump via a cord. The medication is typically contained in a syringe or cartridge loaded in secure pump housing that can only be accessed by a key. Upon activation, a motor drives the desired medication volume out of the syringe or cartridge and into intravenous (or other applicable) tubing that is connected to the patient. PCA pumps are equipped with alarms that can alert to the presence of an empty syringe, low battery, tubing occlusion, or air entrainment into the system. PCA devices can be programmed only through the use of a key or an integrated keypad that requires entry of a code to change programming parameters. The use of keys or codes helps to prevent device tampering or attempts to alter prescribed PCA settings by patients and their visitors (18).

When PCA devices are connected to a patient, a number of things can be done to reduce the risk of adverse equipment and user related events. PCA devices and any syringes or cartridges used in these devices should be inspected for evidence of damage prior to use (19). Addition of antireflux (unidirectional) valves and antisiphon (positive pressure) valves to pump tubing reduces the likelihood of a large medication bolus being delivered to the patient if an occlusion in the tubing that leads to the patient's intravenous line develops or in the presence of a syringe or cartridge defect. Use of relatively dilute drug solutions may reduce the risk of overdose that could occur if an obstruction in the intravenous tubing were to develop and then was suddenly relieved after several patient activations of the device (20). Larger fluid volumes relative to drug dose would decrease the total amount of drug that could accumulate in intravenous tubing dead space under such circumstances. Placement of the drug containing syringe or cartridge at an appropriate height so that there is no elevation above the level of the patient may eliminate the risk of uncontrolled gravity free-flow of medication if there is a defect in the medication containing syringe or cartridge (21–24). Confirmation of correct drug, concentration, and device programming are essential prior to initiation of PCA and after changes to the PCA prescription, as clinician and programming errors are a substantial cause of PCA-related mishaps (25–27). Patient and family education about appropriate use of the PCA device may help reduce problems such as confusion of the PCA activation button for the nurse call button and misunderstandings that could lead to excessive device activation in the attempt to maintain analgesia (28). It may also decrease the occurrence of PCA by proxy, in which a well intentioned visitor activates the button whether the patient requires analgesia at the time or not (29,30).

PRESCRIBING PATIENT-CONTROLLED ANALGESIA

Once the decision is made to employ PCA, the prescribing practitioner will need to select a medication to deliver and program the PCA delivery system. Parameters that must be programmed include the loading dose, demand dose, bolus dose (for unrelieved pain), basal dose (if desired), lockout interval, and one- or four-hour maximum dose. Each of these options will be further detailed below.

Selection of Medication to Be Employed and Its Concentration

The first choice to be made when instituting PCA is the opioid to be used. Factors that may influence drug selection include concurrent medical illnesses, which may

impact drug metabolism or increase risk of drug toxicity, and a prior history of adverse effect from exposure to particular opioids. Drugs that are typically employed in PCA include morphine, fentanyl, hydromorphone, and meperidine. Methadone, alfentanil, and oxymorphone have also been used in PCA. Most pain practitioners refrain from use of meperidine because of the potential for normeperidine accumulation with administration of high doses or prolonged exposures (greater than 24 hours) to meperidine. Neuroexcitatory and seizure activity may occur in this setting (31–33). Meperidine use is contraindicated in the presence of renal impairment because of the risk of normeperidine accumulation in this patient population. In my institution, doses of meperidine are restricted to 600 mg or less daily. In general, no more than 1000 to 1200 mg of meperidine should be administered during the first 24 hours of use, and doses should be further restricted after 24 hours (34). Use of standardized concentrations for each agent to be employed in a particular institution may reduce the potential for errors related to incorrect drug concentration programming.

Loading Dose

A loading dose is a dose of medication given prior to the initiation of PCA to quickly achieve a serum level of opioid concentration at which the patient experiences effective analgesia. Additional doses of opioid given via the demand mode can then be self-administered by the patient to maintain satisfactory analgesia. A loading dose should be employed whenever pain is of significant severity, as demand doses alone may not be enough to establish adequate analgesic serum opioid concentrations. It should be remembered that PCA is intended to *maintain* adequate analgesia, and if the patient is not reasonably comfortable at the time the PCA is started, satisfaction with this technique may be poor (35). Loading doses should be titrated to effect in each patient. Typical loading doses in the opioid naïve patient might be 5 to 10 mg of morphine, 50 to 100 µg of fentanyl, 0.5 to 1 mg of hydromorphone, or 50 to 100 mg of meperidine.

Demand Dose

The demand dose is the dose of drug that will be delivered to the patient each time he or she presses the PCA system button, except during the lockout interval. The size of the demand dose is usually selected on the basis of such factors as patient age and prior opioid exposure history. Elderly patients may require smaller doses than younger adult patients, while pediatric dosing is usually weight based. In opioid tolerant patients, doses will typically be larger than in the opioid naïve patient. Typical demand doses in the opioid naïve patient might be 1 to 1.5 mg of morphine, 10 to 15 µg of fentanyl, 0.1 to 0.2 mg of hydromorphone, and 10 to 15 mg of meperidine.

Lockout Interval

The lockout interval is the period of time between demand doses when the PCA device cannot deliver additional medication. The typical lockout interval can range from 5 to 10 minutes. This is the time it usually takes for the patient to realize the effects of a delivered opioid dose. The lockout period serves a protective function to limit the total amount of opioid delivered over a specific time frame. In this way, it lessens the potential for inadvertent overdosage of medication. Allowing for relatively short lockout intervals may decrease the impact of different opioid

requirements among patients, which may vary by up to 10 fold (36). When a patient attempts to activate the PCA button during a lockout period, the PCA machine will not deliver medication, but will record these additional demand attempts. When examining the history on the PCA pump, failed demand attempts will appear as "PCA demands," while actual doses delivered are recorded as "PCA injected." If there appears to be a high ratio of PCA demands/PCA injected, it may indicate that the patient is attempting demands frequently during the lockout interval, and the patient may require reinstruction on proper use of the PCA device. If the patient has a high total number of injected doses over a particular time frame, it may indicate a need to adjust the demand dose so that better analgesia is afforded (36). Adjustment of the demand dose under these circumstances appears to be more beneficial than reduction in the lockout interval, patients do not seem to increase the rate of demands beyond a self-imposed maximum (on average approximately four doses/hr) even when they are very uncomfortable (37). The optimal demand/delivery ratio appears to be less than 1.35, and adjustment of the PCA prescription may be indicated if this ratio is exceeded (38).

Bolus Dose

A bolus dose is an additional dose of medication that can be delivered at a set interval to help boost the level of analgesia. This may be necessary when patients are engaged in activity that increases pain, such as physical therapy, or if long periods elapse between delivered demand doses such that serum analgesic concentrations have begun to drop off. An especially common cause of this is periods of sleep during which the patient is not using the PCA device. Typical bolus doses are two to three times the demand dose, which are usually delivered every few hours as needed.

Basal (Continuous) Infusion

A basal infusion is a continuous dose of medication that is delivered whether or not the patient presses the PCA button. Basal infusions are generally not routinely instituted with PCA. There may be an increased risk of opioid toxicity in the presence of a basal infusion, while analgesia is not generally enhanced (39–46). Studies also suggest that demand frequencies are not decreased in the presence of a basal infusion, and in fact, opioid consumption may increase when a basal infusion is introduced. Patients may therefore receive more analgesic than they actually require for control of their pain when a basal infusion is added to PCA (47). The occurrence of respiratory depression when basal infusions are added to PCA may be increased in the immediate postoperative period, perhaps as a result of residual anesthetic effects. Some authors therefore recommend deferring initiation of basal infusions in the postoperative setting until postoperative day one (48). The primary indication for the use of a basal infusion is replacement of baseline opioid requirements in opioid tolerant patients who are unable to continue their chronic opioids while on PCA.

One- or Four-Hour Maximum Dose

A one- or four-hour maximum dose limit enables the prescriber to set a limit on the total amount of medication delivered in that time frame. This option is of particular importance when drugs such as meperidine are employed for PCA. Since

TABLE 6.1 Patient-Controlled Analgesia Setup

Parameter	Setting range
Loading dose ^a	Morphine 5–10 mg Meperidine 50–100 mg Fentanyl 50–100 µg Hydromorphone 0.5–1 mg
Demand dose ^a	Morphine 1–1.5 mg Meperidine 10–15 mg Fentanyl 10–15 µg Hydromorphone 0.1–0.2 mg
Lockout interval	5–10 min
Bolus dose	2–3 times the selected demand dose
Continuous dose	This setting is not routinely used by many pain practitioners, but if a continuous infusion is desired, typical initial doses are as follows: Morphine 1 mg/hr Meperidine 10 mg/hr Fentanyl 10 µg/hr Hydromorphone 0.1 mg/hr
1- or 4-hr maximum dose limit	Setting a time-contingent dosing limit is optional with most agents, but a limit of 100 mg every 4 hr is advisable for meperidine (total daily doses should not exceed 600 mg).

^aThese parameters reflect average ranges for opioid naive patients. All doses must be titrated to appropriate effect in each patient. Opioid-tolerant patients may require larger doses, while frail or elderly patients may require smaller doses. *Source:* Reproduced from Ref. 50.

meperidine metabolites may accumulate if large doses of the drug are given for prolonged periods (greater than 24 hours), restriction in the total dose may be necessary. Setting dose limits in patients at risk of respiratory depression during PCA, such as those with obstructive sleep apnea, may be advisable (49). Selecting a time contingent maximum dose limit may also provide additional safety in case certain PCA programming errors are made when setting demand doses or lockout intervals. It should be remembered that some misprogramming errors will not be overcome by using dose limits (e.g., entering a drug concentration that is incorrect) (Table 6.1).

USE OF PATIENT-CONTROLLED ANALGESIA IN PEDIATRIC AND GERIATRIC PATIENTS

When determining whether a patient is an appropriate candidate for PCA, age alone should not be a basis for denying this form of therapy. Patients as young as five years of age have successfully used PCA (51). Likewise, very elderly individuals have benefited from this analgesic technique. Children who are able to appropriately understand use of the PCA device generally prefer this technique to traditional intramuscular analgesic administration. In fact, children often suffer unnecessary pain rather than requesting intramuscular analgesic administration due the pain associated with intramuscular injections (52). In children who are not able to properly utilize the PCA device, a nurse or a family member may be designated to administer analgesia in lieu of the patient activating the device (53). This obviously requires education of the family designee regarding appropriate use of the device, including the instruction to avoid activating the device when the patient is asleep (54).

In elderly patients, PCA is appropriate if there is no cognitive or physical impairment that may interfere with use of the delivery device. Physiologic changes that occur with age, such as declines in hepatic and renal function as well as decreased serum albumin levels, decreased total body water, and increased body fat, may influence drug distribution and duration of action (55,56). Because of these changes in drug distribution and elimination, lower opioid doses are typically required in the elderly as compared with younger individuals. Average daily morphine requirements are estimated to decline by approximately 1 mg for each year above the age of 20 years. Thus, the average morphine requirement in adults over 20 years old can be estimated using the equation $100 - \text{age} = \text{average morphine requirement for the first 24 hours postoperatively}$ (55,57). While some practitioners might avoid use of PCA in the elderly because of concerns that it may increase the risk of postoperative delirium or confusion, there is evidence that mental status changes may actually occur less frequently with PCA than with the use of intermittent intramuscular injections (58). Inadequately controlled pain may in fact be a more significant cause for the development of confusion or delirium in this patient population.

MONITORING OF THE PATIENT RECEIVING PATIENT-CONTROLLED ANALGESIA

All patients receiving PCA should be appropriately monitored for treatment efficacy and the development of associated adverse effects. Pain assessments can be made using verbal pain ratings, visual analog pain scores, or the faces pain scale (in pediatric patients). Total opioid consumption should be quantified on a regular basis, and significant changes in need for analgesia should be evaluated. In some cases, increased use of analgesia may reflect complications from surgery, such as wound infection or disruption, or may indicate the presence of a problem not related to the surgical procedure. Easily remediable sources of pain, such as bladder distension should be properly managed, and the patient should be observed for evidence of the onset of opioid toxicity if they have been using frequent doses of opioid prior to resolution of such a problem (59). Some authors have raised concerns that postoperative complications such as myocardial ischemia, pulmonary embolism, or the onset of acute compartment syndromes may be masked by PCA (60–62). Patients therefore should be educated not to medicate themselves for new or worsening pain without alerting their caregivers in the effort to help minimize the risk of unrecognized complications. Regular assessment by physicians and nursing staff with attention to changes in analgesic requirements remains a critical component to the detection of potential medical complications.

Patients should be monitored for evidence of the development of adverse effects when receiving PCA. Assessments of vital signs with particular attention to respiratory rate should be performed regularly. Use of pulse oximetry may provide an additional means to monitor for adverse respiratory effects of PCA. It should be remembered, however, that desaturation is a late indicator of respiratory depression and therefore oxygen saturation monitoring should not substitute for close clinical observation. It appears that the most reliable indicator of impending respiratory depression is the onset of sedation (34). Therefore, assessment of level of consciousness is an important component of documentation in patients receiving PCA. Sedation scales are commonly used to indicate whether a patient is wide awake, drowsy, sleeping but easily arousable, or difficult to arouse. It may be

necessary to decrease opioid dosing or terminate opioid administration via PCA altogether if a patient's level of consciousness declines during PCA therapy. Continuous infusions employed during PCA may be associated with increased potential for the development of respiratory depression, and discontinuation of such infusions is advised if sedation is evident during their delivery.

Other risk factors for the development of respiratory depression during PCA therapy include the presence of underlying obstructive sleep apnea, obesity, smoking, age greater than 65, preoperative ASA physical status of 3 or higher, intra-abdominal procedures, impaired renal, hepatic, or cardiac function, and the presence of abnormal preoperative pulmonary function or arterial blood gas values (63,64). Concomitant use of sedatives may further increase the risk of respiratory depression, and it is recommended that prescribing of sedatives such as benzodiazepines in conjunction with PCA be undertaken with caution (65). It is generally advisable that the service or provider prescribing PCA also be in control of any orders for additional sedative or hypnotic administration to reduce inadvertent oversedation (45,46).

End tidal carbon dioxide (ETCO₂) monitoring is an emerging means of surveillance for signs of developing respiratory depression. This technology offers the promise of detecting adverse respiratory events much earlier than pulse oximetry, which hopefully will reduce the incidence of fatal respiratory depression in at risk patient populations. Side effects such as nausea, pruritis, and constipation often accompany PCA therapy and remedies for such complaints should be made available for all patients receiving PCA (Table 6.2).

Extra vigilance in certain patient populations may be required to reduce the potential for adverse respiratory events during PCA, as mentioned above. In particular, patients with underlying renal or hepatic dysfunction may be predisposed to drug or metabolite accumulation during PCA with the risk of attendant drug toxicity. Patients with decreased pulmonary reserve such as those with chronic obstructive pulmonary disease and patients with obstructive sleep apnea may be more sensitive to the respiratory depressant effects of opioids (66). Sensitivity to opioid effects may also be enhanced in the presence of significant hypotension. This increased opioid sensitivity may be related to reduced cerebral perfusion resulting in increased clinical drug effects. Also, reduced renal and hepatic blood flow may cause prolongation of drug effects due to delayed drug metabolism and elimination (67). Hypotension caused by hypovolemia may be exacerbated by opioid administration because of opioid-related vasodilation or reduced sympathetic outflow resulting from the relief of pain. Opioid dose reduction and omission of basal opioid infusion may decrease the occurrence of respiratory depression in these susceptible patient populations. Risk factors for the development of respiratory depression in the setting of PCA are summarized in Table 6.3.

POTENTIAL SOURCES OF PCA-RELATED MISHAPS

PCA-related adverse events have numerous potential causes (68–70). Some adverse events are related to the physiologic effects of opioids. Nausea related to stimulation of the chemoreceptor trigger zone of the medulla by opioids, and constipation related to stimulation of gut opioid receptors are examples of such adverse effects. As previously mentioned, use of PCA in patients with a variety of comorbidities may increase the potential for undesired respiratory depression.

TABLE 6.2 Monitoring PCA Therapy

Patient monitoring during PCA therapy

The following parameters should be assessed regularly in patients receiving PCA:

- Vital signs with particular attention to respirations (breathing rate/depth)
Normal respiratory rates are in the range of 10–20 breaths/min.
- Visual analog, verbal or faces pain scores
Typically numeric pain scores are scaled 0–10 or 0–100. Higher scores indicate increased severity of pain.
- Sedation scores
Sedation usually precedes onset of significant respiratory depression. Assessment of sedation usually involves documenting the patient's level of consciousness via a numeric rating system such as the following:
 - 1 = wide awake
 - 2 = drowsy
 - 3 = sleeping but arousable
 - 4 = difficult to arouse
 - 5 = unable to arouse
- Opioid consumption
Evaluation of medication use by the patient helps to guide adjustments in therapy. Assessment of opioid consumption allows for more accurate conversion between opioids and routes of administration. This is of particular importance in determining the needs of the opioid-tolerant patient when switching to oral medication.
- Oxygen saturation
Monitoring of oxygen saturation is not mandatory, but may be useful particularly in individuals at risk of respiratory depression with opioid therapy. Desaturation is a late indicator of respiratory depression, and thus, oxygen saturation monitoring should not be the only means used to assess for this adverse effect of opioid therapy.
- ETCO₂
Adequacy of ventilation can be assessed through use of ETCO₂ monitoring. This allows for earlier detection of respiratory depression related to opioid therapy. This type of monitoring may not yet be widely available in most institutions.
- Side effects
Common side effects of opioid therapy include nausea, sedation, pruritus, and constipation. Monitoring for these and any other adverse effects of therapy should be included in patient assessments. Treatment for any untoward effects should be provided as indicated.

Abbreviations: PCA, patient-controlled analgesia; ETCO₂, end tidal carbon dioxide.

Source: Reproduced from Ref. 50.

Use of concomitant sedatives including benzodiazepines, antidepressants, antipsychotic agents, and antihistamines may increase the potential for significant episodes of sedation. Human errors such as improper PCA prescribing or pump programming and mechanical malfunctions are other sources of PCA-related complications. Additionally, PCA by proxy and intentional device tampering can result in adverse events.

Operator Errors

While the incidence of serious PCA-related complications is low, many of these complications result from prescribing and programming errors (71). Use of basal infusions often increases the potential for adverse events. Likewise, use of generous dosing parameters can contribute to nausea, oversedation, and respiratory depression, especially in the opioid naive. Conversely, overly restrictive dosing parameters may result in inadequate analgesia in the opioid tolerant patient. The person

TABLE 6.3 Factors That Increase the Risk of Respiratory Depression During PCA

Patient related	<ul style="list-style-type: none"> ● Patient age >65 ● Obesity (BMI > 30 kg/m²) ● Chronic obstructive pulmonary disease ● Abnormal preoperative ABGs and PFTs ● ASA physical status of 3 or higher ● Obstructive sleep apnea ● Renal dysfunction ● Hepatic dysfunction ● Cardiac dysfunction ● Hypotension ● Upper abdominal surgery
Prescription related	<ul style="list-style-type: none"> ● Use of basal infusion ● Use of concurrent sedatives ● Large demand doses in the opioid naïve

Abbreviations: ASA, American Society of Anesthesiologists; ABG, arterial blood gas; BMI, body mass index; PCA, patient-controlled analgesia; PFT, pulmonary function tests.

programming the PCA device should ensure that all dosing parameters are properly entered whenever PCA is initiated or if the prescription is changed. Care should also be taken to verify that the drug being used and its concentration are correct. These settings should be reconfirmed with any prescription changes, syringe replacements, and whenever new personnel take over care of the patient, such as with nursing shift changes. Other operator errors that can contribute to problems during PCA include improper loading of the medication syringe or cartridge into the PCA pump, failure to use antireflux tubing or incorrect attachment of the antireflux tubing to the patient’s intravenous line, failure to clamp or unclamp PCA tubing, failure to turn the PCA pump on after syringe or cartridge change, and misplacement of the PCA key causing inability to alter the program or access the medication containing reservoir (72). Overdosage of medication can occur if antireflux tubing is absent and PCA tubing becomes obstructed, allowing the medication to accumulate in bags connected to the patient’s intravenous tubing. After recognition of an obstruction under such circumstances, failure to replace the tubing connecting the patient to such reservoirs as IV bags may allow sudden delivery of large opioid boluses to the patient (72,73). PCA pump power failure may occur if the device is not plugged in to a power source, allowing the battery to be drained. This may occur when the patient returns to the care ward after being transported for medial procedures or physical therapy. Other sources of operator errors may include failure to appropriately monitor the patient for evidence of adverse effects of PCA therapy and failure to respond to PCA or monitor alarms.

Mechanical Problems

PCA device malfunction can be related to hardware or software failure. It can also be caused by electrical problems. Short circuiting of PCA devices resulting in massive opioid dose delivery in the absence of patient device activation as well as corruption of PCA pumps by power surges or other electrical interference have been described (74,75). Other PCA device faults may occur without clear evidence of a specific cause (76,77). Siphoning of medication may occur in the presence of a cracked cartridge or syringe, with improper seating of the medication reservoir in the pump, or if an antisiphon valve is placed improperly during tubing setup (78).

Placement of the medication reservoir above the level of the patient is typically a contributing factor in these situations. Malfunctions in alarms or defects in tubing components such as antireflux valves are other potential sources of mechanical problems that may result in adverse events during PCA therapy.

Patient Errors

Patient related errors seen during PCA therapy include failure to understand use of the PCA device or confusion of the PCA device with the nurse call button. Some patients may not be physically capable of properly activating the PCA button because of such conditions as arthritis. PCA by proxy, in which a person other than the patient activates the device, has been associated with a number of PCA-related deaths. Unfortunately, some deaths have occurred even when the proxy has been a nurse (79). If PCA by proxy is elected, proper instruction of the proxy must be given prior to initiation of PCA by proxy. This includes the instruction that the proxy is to deliver medication only when specifically requested by the patient for unrelieved pain. The proxy should be directed to avoid activating the PCA device when the patient is sleeping, and should not wake the patient to assess for pain. Unless a proxy has been designated, no one other than the patient should be authorized to activate the PCA device. Intentional device tampering by patients in the attempt to obtain large amounts of drug has also been reported with PCA (Table 6.4).

TABLE 6.4 Potential Sources of PCA-Related Mishaps

Operator errors

- Inappropriate patient selection
- Selection of inappropriate medication
- Inappropriate prescribed dosing parameters
- Insertion of wrong syringe into PCA device
- PCA pump misprogramming
- Improper loading of syringe into PCA device
- Failure to clamp or unclamp PCA tubing
- Failure to turn on PCA machine after syringe change
- PCA key misplacement
- Inadequate training of staff regarding PCA and setup
- Failure to respond to device or monitor alarms

Patient errors

- Failure to understand PCA therapy or use of device
- Confusion between PCA button and nurse call button
- Physical inability to activate demand button
- PCA by proxy
- Intentional device tampering

Mechanical problems

- Electrical failure/battery failure
 - Short circuiting of PCA device
 - Siphoning of medication
 - Alarm malfunctions
 - Tubing defects/lack of antireflux valves
 - Accumulation of drug in tubing dead space
 - Hardware or software failure in PCA machine
-

Abbreviation: PCA, patient-controlled analgesia.

Source: From Refs. 1, 50, 67, 68, 70, and 71.

ALTERNATE OPTIONS FOR PATIENT-CONTROLLED ANALGESIA

The most commonly used form of PCA is that delivered via the intravenous route. As PCA has become a widely used means of pain control, newer options for its delivery have evolved. Patient-controlled epidural analgesia and patient-controlled regional analgesia incorporate use of local anesthetics and may allow superior pain control and substantially reduce postoperative opioid requirements. Adaptations of standard PCA delivery devices have allowed for noninvasive modes of drug delivery, such as patient-controlled oral analgesia and patient-controlled intranasal analgesia. PCA can also be delivered via subcutaneous administration, which may be particularly useful in patients without ready intravenous access.

Patient-Controlled Epidural Analgesia

Patient-controlled epidural analgesia has been most extensively used in the obstetric population, in which epidural analgesia is frequently elected for pain control. When used for labor analgesia, PCEA appears to provide superior pain relief with a lower incidence of maternal and neonatal sedation when compared with standard intravenous PCA (80). One meta-analysis of studies comparing PCEA with continuous epidural infusion in obstetric patients also indicated that patients receiving PCEA required fewer anesthetic interventions, consumed lower total doses of local anesthetic and had less motor block than those receiving continuous epidural infusion (81). PCEA has also been successfully employed in the management of postoperative pain, including that related to extensive abdominal and spinal surgery (82,83).

Patient-Controlled Regional Analgesia

Patient-controlled regional analgesia has been used to provide plexus analgesia and direct wound infiltration analgesia. Catheters for delivery of patient-controlled regional analgesia may be placed for plexus analgesia using ultrasound or nerve stimulator guidance. They may be placed by the surgeon under direct visualization or with the guidance of instruments such as an arthroscope at the time of the operation for wound infiltration analgesia (84). Some centers allow for continuation of PCRA after patient discharge to home (85). This is accomplished through the use of disposable elastomeric infusion pumps. Use of PCRA at home requires that the patient and any caregivers receive proper instruction regarding dose administration, catheter care, and catheter removal. The patient should be made aware of any signs or symptoms of local anesthetic toxicity or catheter site infection and should be instructed to report them if present. A physician must remain readily available to address concerns about potential problems or complications of this treatment, and the patient should be given information on how to contact the on-call anesthesiologist if necessary.

Patient-Controlled Oral and Intranasal Analgesia

Modifications of standard intravenous PCA devices have allowed for alternate noninvasive modes of patient-controlled analgesic delivery such as the oral and intranasal routes (86–90). These techniques appear to provide analgesia comparable to intravenous PCA as long as adjustments to dosing are made to account for differences in bioavailability as compared with intravenous administration. These techniques may provide a reasonable alternative to intravenous PCA, particularly when intravenous access is absent or difficult to obtain.

Patient-Controlled Transdermal Fentanyl

A device has been developed to deliver transdermal fentanyl on demand (Ionsys[®]). This device delivers 40 µg of fentanyl upon patient activation. The drug is propelled through the skin by iontophoresis, which is accomplished by application of a low intensity electrical current. Fentanyl demand doses can be delivered in intervals no shorter than 10 minutes. There is no basal delivery of fentanyl between activations, making this device a purely on demand system that would be appropriate for use in the postoperative setting. Studies evaluating this delivery system have indicated it is effective for postoperative pain management in that it provides analgesia comparable to intravenous PCA (91–96). This mode of PCA may provide an appealing alternative to intravenous PCA as it requires less nursing time to implement, the potential for programming errors is nonexistent, and no expensive equipment is needed for its use. Unfortunately, after its release to the market in Europe, it was found that a component in the Ionsys delivery system was susceptible to corrosion, which might result in device failure. After review of these concerns, marketing approval for Ionsys was suspended and it was withdrawn from the European market. At this time, it is unclear whether the device might be further modified in efforts to bring it back to market.

SMART INFUSION AND MONITORING SYSTEMS FOR PATIENT-CONTROLLED ANALGESIA

The development of smart infusion systems and enhancements in monitoring techniques represent some of the most recent advancements in PCA therapy. Smart infusion systems consist of computer integrated systems that incorporate monitoring into the PCA platform. These systems allow for monitoring of patient ventilation and oxygenation, and will terminate infusion of opioids if respiratory parameters fall outside prescribed limits (97). ETCO₂ monitoring or capnography, which reflects the effectiveness of ventilation, is increasingly being used as a means of detecting early signs of respiratory depression in patients receiving PCA. It has been demonstrated to detect episodes of clinically significant respiratory depression with much greater frequency than pulse oximetry or clinician observation in patients receiving procedural sedation in an emergency department setting (98). Addition of this modality to monitoring systems appears to increase patient safety, as oxygenation may be maintained even during significant episodes of respiratory depression, especially when supplemental oxygen is being administered (99). The availability of capnography is especially useful in patients at risk for respiratory depression, such as those with obstructive sleep apnea, and in patients who require large amounts of opioid but manifest sedation despite complaints of inadequate analgesia. Identification of other postoperative adverse respiratory events such as pneumonia, pulmonary embolism, and congestive heart failure may also be facilitated by monitoring of ETCO₂ (100).

The sophistication of PCA systems continues to evolve. PCA systems that vary analgesic delivery on the basis of patient needs have been developed. One such device uses an algorithmic approach to opioid bolus dose delivery that is based on patient pain intensity ratings. This device uses a computer integrated handset that allows patients to enter a pain intensity rating from 1 to 10 prior to delivering an opioid bolus (101). The bolus dose delivered is based on the pain intensity rating selected by the patient. A basal infusion that is adjusted on the basis of frequency of patient demands is also delivered. If the patient stops making

demands, the infusion is decreased and then discontinued if no further demands are made with a specified amount of time. Use of this device resulted in increased opioid consumption as compared with conventional PCA. However, the incidence of opioid associated adverse effects did not increase and patient bolus requests decreased as the device adjusted the infusion rate on the basis of patient usage patterns. Pharmacokinetically based PCA, in which opioids are delivered to achieve target plasma opioid concentrations in each individual as determined by blood sampling, has also been described (102,103). With this technique, patients are also able to individually tailor their level of analgesia by adjustment of the predetermined opioid infusion rate through the use of a handheld control.

A similar innovation in this technology involves a computer integrated patient-controlled epidural analgesia device that initiates a basal infusion of a local anesthetic/opioid mixture on the basis of patient demands. With this device, if the patient demands a PCEA bolus, the device initiates a basal infusion of 5 mL/hr. This infusion is increased in 5-mL increments to a maximum of 15 mL/hr on the basis of continued patient demands. If the patient fails to make any demands over the specified time interval, the device will subsequently decrease the rate of the basal infusion in 5-mL increments. In a study of obstetric patients using this device, the total volume of analgesic mixture used did not significantly differ when compared with conventional PCEA, but there was increased maternal satisfaction with this mode of analgesia (104). It appears that in the future, the optimal balance between patient satisfaction and safety will be afforded by PCA systems that combine options for variable infusion on the basis of individual patient needs with the ability to monitor for evidence of adverse effects on respiration.

CONCLUSION

PCA represents an important advancement in postoperative pain management that continues to evolve. Patient-controlled intravenous analgesia is widely used for a variety of acute pain problems, and is especially useful in the management of postoperative pain. Other options for PCA include patient-controlled epidural analgesia, patient-controlled regional analgesia, and noninvasive forms of PCA such as patient-controlled oral and intranasal analgesia. When PCA is elected, the prescriber must have appropriate knowledge of the pharmacokinetics of the drug to be employed, the dosing parameters to be used, and patient factors that may increase the potential for adverse events during PCA. Patients must be properly selected for PCA, and both patients and practitioners must be adequately educated for it to be properly utilized. Optimization of this therapy in the future is likely to involve use of computer integrated technology that allows for individual tailoring of PCA and enhanced patient monitoring.

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Laura Textor

INTRODUCTION

Patient-controlled analgesia (PCA) devices have been used in the management of pain since the 1970s. Since that time, great improvements have been made in pain control and patient satisfaction related to pain control. Today, PCA is considered the standard of care for managing acute postoperative pain. Patients who desire to control their own pain and have the cognitive and physical capabilities of doing so are generally considered good candidates for PCA; however, some patients may not have the cognitive and/or physical capabilities to utilize PCA in an effective way. This may include patients at either end of the life span, those with severe dementia or impaired cognitive development, those with physically impairing neuromuscular or musculoskeletal diseases, intubated patients, comatose patients, and dying patients. The argument can be made that these patients, because of their inability to self-report pain or utilize a PCA device, are at greatest risk for unrecognized and undertreated pain, and often receive lesser-quality pain management. This has led to the practice of authorized agent controlled analgesia (AACA).

AUTHORIZED AGENT CONTROLLED ANALGESIA

AACA is not a new concept. Providing medications to patients who cannot medicate themselves for a variety of symptoms such as nausea, vomiting, diarrhea, insomnia, and pain has long been traditional nursing practice. AACA merges long-standing practices and new technology to provide appropriate patient care. Moreover, the ability to achieve safe AACA utilizing a nonprofessional caregiver as the authorized agent (AA) is supported by the fact that families have successfully been educated to perform highly technical care and provide complicated medical therapies for both adults and children in the home setting (1,2). Recent studies and expert practice confirm that, under specific circumstances in which the patient and the AA are carefully selected and properly educated, AACA is a safe and effective approach to provide analgesia to patients who cannot do so for themselves (3–8).

According to the American Society for Pain Management Nursing, AACA offers multiple advantages over the traditional practice of nurse administered “as needed” doses of analgesia (9). First, it reduces the potential for a variety of medication administration errors. Second, it reduces the amount of time between when a patient requires and receives medication. Third, it utilizes a closed system for the infusion of medication, thus reducing the risk of infection that accompanies more traditional methods. Fourth, it reduces nursing time and eliminates waste created by partially administered doses of opioids, as well as the cost of syringes (10). Likely, the greatest advantage of AACA is the proximity of the medication to the patient when needed for the timely management of incident pain.

PCA BY PROXY SAFETY CONCERNS

AACA is often referred to as *PCA by proxy*; however, this description may be somewhat misleading. PCA by proxy is a term that describes activation of the analgesic infusion pump by *anyone other than the patient* and includes a variety of practices, including *authorized* and *unauthorized* activation of the pump (9). Unauthorized PCA by proxy has been associated with multiple adverse events, up to and including patient death. Clearly, for good reason, this practice has many opponents. The primary concern is that PCA by proxy bypasses one powerful PCA safeguard, that being a sedated patient is unlikely to self-administer pain medication. In 1994, Ashburn and colleagues reported on critical respiratory events with PCA (11). They found that out of 3785 patients using PCA, 14 had critical respiratory events, 3 of which were related to unauthorized dosing by an individual other than the patient. In 2002, the Institute for Safe Medication Practices (ISMP) published the first of several warnings regarding PCA by proxy following the death of a 72-year-old woman whose nurses had administered multiple PCA opioid doses over 48 hours despite the patient being obtunded following surgery (12).

In 2004, the Joint Commission for the Accreditation of Healthcare Organizations (JCAHO) published a sentinel event alert following a report on PCA errors from the U.S. Pharmacopeia (USP) (13). The USP medication error database contained 6069 PCA errors over a period of five years. Out of those, 460 resulted in harm to patients. Five events were fatal, while 455 involved physical, psychological, or emotional harm or pain. Further review found 15 of these events resulted from PCA by proxy. The proxy was found to be a patient's family member in 12 cases, a nurse in 2 cases, and a pharmacist in one case.

Several institutions have, however, used AACA for many years safely and effectively. Pediatric hospitals frequently employ AACA for children with cancer or postoperative pain following spinal instrumentation for correction of scoliosis. One study from a pediatric hospital found that despite frequent use of AACA, whether nurse or family administered, there was a lower incidence of serious adverse events with AACA than with standard PCA use (3). However, the patient population was pediatric oncology patients who were opioid tolerant and whose families were very involved in their care, often managing complicated infusion pumps in the home setting.

Monitto and colleagues found AACA to be safe and effective in a study of 212 children less than six years (4). Opioids were administered at low continuous doses with low-dose AACA. Pain was well controlled, with numeric pain scores of 3 out of 10 in 81% to 95% of the children. Twenty-five percent of unintubated children in the study required oxygen; however, comorbid medical conditions were often present. While 4 (1.7%) required naloxone for oxygen desaturation or apnea, no specific risk factor could be correlated with the need for naloxone administration, leading the researchers to conclude the events were unrelated to AACA and that AACA is safe even in high-risk pediatric patients.

In 1991, Gureno and Reisinger studied eight children aged three to five years who received AACA, either nurse or family administered, following surgery. They found good pain control in the acute postoperative period, with pain scores on a scale of 0 to 5 of 1 in 72% of patients or 2 in 18% of patients. No episodes of respiratory depression or other adverse events were noted (14).

Weldon and colleagues studied the efficacy and safety of intensive care nurses as the AA for children and adolescents following major surgery. It was

found that ICU nurses could safely and effectively control the PCA device for pediatric patients who were unable to operate the device for themselves. There were no major complications or adverse events noted despite nearly 1000 patient hours of AACA by nurses. In addition, more than 90% of the nurses were highly satisfied with this method of pain control (15).

Current recommended practices for safe use of PCA include the following: (i) developing criteria for appropriate patient selection, (ii) careful monitoring of level of sedation, respiratory rate and depth, heart rate, and blood pressure, (iii) teaching the patient and family proper use of the PCA and the dangers of anyone other than the patient pushing the PCA dosing button, (iv) alerting the nursing staff to the dangers of nurse-administered doses outside of a nurse-controlled analgesia protocol, and (v) consideration for placing warning tags on all PCA delivery devices that state only the patient should press the dosing button (16). Modifications of these recommendations for the provision of AACA are detailed as follows.

AUTHORIZED AGENT CONTROLLED ANALGESIA RECOMMENDATIONS

Undertaking the development of an AACA process requires a multidisciplinary approach with input from physicians, nursing, pharmacy, ethics committees, administration, education committees, and risk management. The American Society for Pain Management Nursing has published a position statement that can guide in the development of the process (9). Guidelines should be developed that promote the safe and effective management of pain. These guidelines should address the following:

- Use of AACA must be patient specific to ensure that patients who are critically ill, terminal, unresponsive, or at the end of life are not excluded.
- There must be a stipulation that AACA will be administered only in patient care areas where the staff is already familiar with the use of PCA.
- The use of AACA must be limited to only those patients who cannot safely self-administer analgesia doses via PCA due to physical or cognitive limitations.
- There must be a mechanism to readily communicate to all members of the health care team that the patient is receiving AACA.
- There must be a stipulation that the nonprofessional AA must be an adult who is consistently with the patient, is willing and able to learn to provide AACA, and demonstrates the ability to safely execute this responsibility.
- Only one person can be designated an AA at any given time.
- There must be a mechanism to designate second- and third-line AAs during times of primary AA absence.
- There must be a specific AACA prescribing mechanism such as an AACA order set.

The multidisciplinary team must develop criteria for patient selection by identifying patient populations who may benefit from AACA and establishing risk factors such as age, weight, comorbidities, and medications that may elevate the risk of this therapy. Monitoring parameters should be developed that include frequency of monitoring of respiratory rate, heart rate, blood pressure, and level of consciousness. Capnography is the recommended standard of care in patients receiving AACA (10) with the possible exclusion of terminal or end-of-life cases; however, pulse oximetry may also be an option. The team must also decide which,

if any, population of patients would be exempted from usual monitoring parameters and how that information is to be relayed to the nursing staff. For example, it may not be appropriate to discontinue AACA on a terminal patient whose respiratory rate is low. In addition, a system must be developed that allows for easy identification, by all health care providers, of patients who are receiving AACA and their AAs. Last, a mechanism to monitor outcomes on all patients receiving AACA should be developed.

Educational materials for patients and families must be developed that address the principles of PCA and AACA as well as the risks and dangers of *unauthorized* activation of the dosing mechanism of the analgesia infusion pump. Both written and verbal instructions should be conveyed to all parties. Educational materials should be provided to each AA, specifically addressing the requirements of being an AA and the policies and practices that must be followed by the AA when AACA is used. These educational materials should include, but not be limited to, the following:

- The AA should be instructed on how to recognize specific patient behaviors or circumstances that may indicate the need for analgesia. Behavioral indicators of pain are patient specific, but certain behaviors are frequently associated with pain and vary with age group. Behavioral signs of pain in infants may include facial expression, gross motor movement, the flexor reflex threshold, and changes in usual behavior and function such as sleeping or eating patterns. The cry of an infant in pain is typically high pitched, tense, harsh, non-melodious, short, sharp, and loud (17). Behavioral signs of pain in the cognitively impaired adult may include noisy breathing, sad or frightened appearance, frowning, stiff body posture, fidgeting, mental status changes, agitation, repeated verbalization/shouting, aggressiveness, and resisting care (18–20).
- Instruction on how to activate the analgesia infusion pump dosing mechanism should be provided to the AA.
- The AA should be instructed to recognize patient-specific indicators that would indicate activation of the dosing mechanism is inappropriate. Such indicators include sedation, shallow or irregular breathing (unless directed otherwise by the prescriber), use during periods of patient sleep, or use if the patient cannot be awakened to baseline level of consciousness. The AA should also be instructed to refrain from activating the device to provide relief of anxiety or any other complaints aside from pain.
- The AA must be made aware of actions to take in the event of pump malfunction or alarm, unrelieved pain, side effects of medication, or medical emergencies such as shortness of breath or chest pain.
- The AA must be informed that the dosing mechanism is only to be activated if the patient's behavior or words indicate that the patient is in pain, or prior to activities known to cause pain.

A comprehensive educational program designed for the patient care staff must also be developed and implemented prior to beginning the process of AACA to ensure that staff members understand the process and are aware of the risks and benefits of AACA.

The nursing staff has multiple responsibilities when a patient is receiving AACA. One is to be involved in the selection of patients and family members who

may be appropriate candidates for AACA. This selection should be based on individual patient needs and the availability and willingness of an appropriate AA. Another is to provide and document the necessary education to the patient, family, AA, and visitors regarding the appropriate use of the analgesic pump. A third is to continually assess the competence of the AA to provide AACA. If there are concerns regarding the competency of the AA, the nurse should intervene, stop AACA, and notify the prescriber. Next is the careful documentation of the patient's response to AACA as well as the AA's performance. Further, the nurse must continue to vigilantly assess and monitor the patient for signs of pain or complications of therapy rather than relying solely on the AA. There are times when the nurse is the appropriate AA. This may be best suited for the intensive care setting for several reasons. One, the nurse to patient ratio is generally low, allowing the nurse to have more time to spend at the bedside. Two, patients' family members are rarely at the bedside continuously in critical care areas, which diminishes their ability to serve as AAs. Third, critical care patients frequently find common care procedures, such as turning and suctioning, painful. Having easy access to analgesics would likely encourage nurses to provide opioid analgesia prior to such procedures.

The role of the prescriber is foremost in promoting appropriate and safe AACA. This is accomplished in many ways. First, an order set developed specifically for use with AACA should be employed, which clearly delineates whether a patient's family member or nurse is the AA. For example, modifying a PCA order set to allow for AACA is not appropriate. Second, monitoring parameters, including frequency of vital signs, assessment of level of consciousness, and use of capnography or oximetry, must be included in the orders. Third, the dose of analgesia ordered must be appropriate for the individual patient based on physiologic parameters such as age, weight, comorbidities, concurrent medications, diagnosis, or desired outcomes. Particular attention should be paid to concurrent medications that may increase the risk of adverse events, and steps should be taken to reduce or eliminate those risks.

CONCLUSION

This chapter has provided an overview of AACA including indications, risks, benefits, and recommendations for the development of processes to promote safe and effective use of AACA. While AACA remains controversial, the practice has been endorsed by the American Society for Pain Management Nursing, the Oncology Nursing Society, and the Hospice and Palliative Nurses Association (21). By employing a multidisciplinary approach that incorporates careful patient selection; appropriate AA selection; monitoring of patient outcomes; and nursing, patient, and family education, those patients at greatest risk for undertreated pain can be safely and effectively managed with AACA.

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INTRODUCTION

α_2 Agonists are widely known for their use in the management of hypertensive disorders. These agents have also been found useful in anesthetic and pain management applications. Three α_2 agonists are clinically available in the United States: clonidine, tizanidine, and dexmedetomidine. These are imidazolines with varying affinities for α_2 receptors, dexmedetomidine being much more selective in binding the α_2 receptor as compared with clonidine. These agents act via binding to G protein-linked receptors of three types: α_{2A} , α_{2B} , and α_{2C} . These receptors have been found in both presynaptic and postsynaptic locations, and are distributed centrally and peripherally. Presynaptic activation of α_2 receptors may inhibit release of pronociceptive substances such as substance P and calcitonin gene-related peptide from afferent nerves. Many of the clinical analgesic effects of α_2 agonists are mediated by activation of receptors in the dorsal horn of the spinal cord resulting in decreased transmission of nerve impulses via wide dynamic range neurons. Activation of receptors in supraspinal sites may also result in analgesia via activation of descending inhibitory pathways.

The range of pain management and anesthetic applications of α_2 agonists continues to expand. Clonidine has been used in the management of a variety of pain syndromes including cancer pain, acute postoperative pain, and neuropathic pain. It is available for delivery via oral, transdermal and neuraxial routes. It has also been added to regional anesthetics as an adjuvant for enhanced analgesia. Tizanidine has been used in the management of painful conditions such as chronic headaches, myofascial pain, fibromyalgia, and has been particularly useful in painful conditions in which spasticity is present. It is administered orally. Dexmedetomidine is currently indicated for use as a short-term (<24 hours) sedative agent in mechanically ventilated postoperative patients in the intensive care unit. It has also been studied for use as an adjunct to general anesthesia and has promise in providing postoperative analgesia as well. This agent is administered intravenously. All of these agents may provide analgesic synergy with opioids, local anesthetics, *N*-methyl-D-aspartic acid (NMDA) receptor antagonists, gabapentin, glutamate receptor antagonists, and other drugs used to treat pain (1–3).

This chapter will explore the mechanism of action of α_2 agonists, their pharmacology, and current and future uses of these agents in anesthesia and pain management.

MECHANISM OF ACTION OF α_2 AGONISTS

α_2 Agonists exert their effects via binding G protein-coupled receptors. Activation of these receptors results in neural membrane hyperpolarization. This occurs by a variety of mechanisms including decreased 3'-5'-cyclic adenosine monophosphate (cAMP) formation, opening of potassium (K^+) channels causing efflux of the ion from nerve cells, and decreased opening of voltage-gated N-type calcium (Ca^{2+}) channels (4). These changes diminish the release of neurotransmitters, including

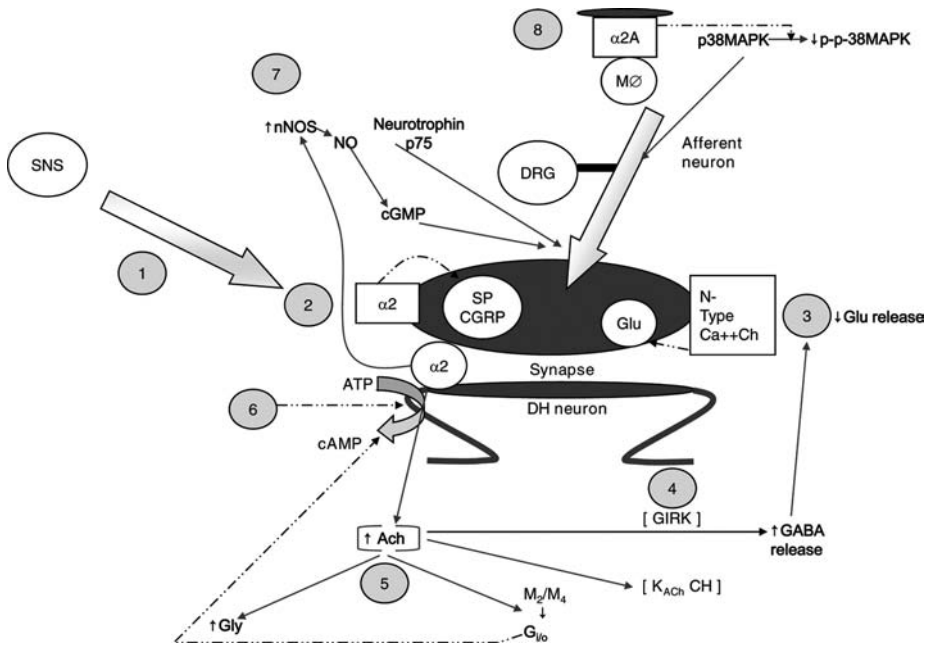


FIGURE 8.1 Potential mechanisms of α_2 -adrenergic-mediated analgesia.

substance P, from the affected neuron causing decreased impulse transmission (5). Other pathways through which α_2 agonists may act to decrease nociception include the activation of phospholipase C second messenger systems, and accelerated sodium-hydrogen exchange across neuronal membranes, resulting in cell alkalization (Fig. 8.1) (4–6).

Three subtypes of the α_2 receptor have been identified: α_{2A} , α_{2B} , and α_{2C} (7). It appears that the antinociceptive actions of α_2 agonists as well as α_2 agonist-opioid synergy may be mediated primarily via the α_{2A} and α_{2C} receptor subtypes (8,9). Ironically, the α_{2A} receptor subtype may also play a role in the development of thermal hyperalgesia after peripheral nerve injury (10). Binding affinities of α_2 agonists at spinal α_2 receptors correlates with their antinociceptive potency, regardless of their route of administration. On the basis of such binding affinities, dexmedetomidine is the most potent of the available α_2 agonists, while tizanidine is the least potent. While most of the analgesia afforded by α_2 agonists relates to their binding at α_2 receptors in the dorsal horn of the spinal cord, decreased sympathetic outflow both centrally and peripherally may also contribute.

Yaksh and colleagues demonstrated reversal of nerve ligation-induced allodynia by administration of a spinal α_2 adrenoceptor agonist (e.g., clonidine) (11). Clonidine was also shown to provide analgesia in neuropathic pain patients after spinal injection (12).

Experimental preclinical evidence has revealed that α_2 -adrenergic agonists (e.g., clonidine) produce analgesic effects in acute pain models (9,13–15) and chronic pain models (11,16–18). Furthermore, there is data to support analgesic efficacy in human patients suffering from acute pain (19,20) and chronic pain (21,22).

Activation of spinal α_2 -adrenergic receptors is followed by the release of spinal acetylcholine and nitric oxide, which may contribute to the analgesic action of clonidine in the spinal cord (17,23,24). It is conceivable that spinal noradrenergic signaling may play a role in the analgesia, which various "adjuvant" agents [e.g., gabapentinoids, 5-HT (2C) receptor agonists] may produce.

It is currently appreciated that gabapentin possesses analgesic qualities. The precise analgesic mechanisms for gabapentin remain uncertain. Gabapentin reduces the release of substance P and calcitonin gene-related peptide from spinal tissues after inflammation-induced sensitization (25), likely via binding to and activating the $\alpha_2\text{-}\delta\text{-1}$ subunit of the (N-type) voltage-dependent calcium channel (the only known specific binding site of gabapentin) (26). However, it is also conceivable that gabapentin's analgesic qualities may be mediated by the descending noradrenergic system via activation of spinal α_2 -adrenergic receptors. Although gabapentin is not considered a "functional" α_2 -adrenergic agonist (like clonidine), some of its analgesic properties may be at least partly due to indirect activation of spinal α_2 -adrenergic receptors from gabapentin activating the descending noradrenergic inhibitory systems (27).

Tanabe et al. studied mice in which central noradrenaline levels were depleted by 6-hydroxydopamine (6-OHDA), and found that the antihyperalgesic activity of intraperitoneal and intracerebroventricular gabapentin was strongly suppressed (27). Tanabe and colleagues found that the antihyperalgesic and antiallodynic effects of systemic gabapentin were reduced by both systemic and intrathecal administration of yohimbine (an α_2 -adrenergic receptor antagonist) (27).

Obata et al. suggested that spinal noradrenergic mechanisms are involved in the antiallodynic effects of intrathecally administered 5-HT (2C) receptor agonists (28). Yohimbine reversed the antiallodynic effects of intrathecal 5-HT (2C) receptor agonists (28).

Lavand'homme et al. showed that perineural injection of the α_2 -adrenergic agonist clonidine at the site of peripheral nerve injury inhibits spinal cord neuroplasticity and tactile allodynia (29), and reduces pain behavior and local tissue proinflammatory cytokine content in rats (30).

Romero-Sandoval et al., utilizing a model of acute inflammatory neuritis (from zymogen on the sciatic nerve), demonstrated that perineural injection of clonidine prevented both the increase in leukocyte number and the expression of proinflammatory cytokines (e.g., tumor necrosis factor α) (31). All the effects of clonidine were prevented by coadministration of an α_{2A} adrenoceptor preferring antagonist (31). Therefore, one potential mechanism by which clonidine may relieve neuritis-induced pain is by transforming cytokine gene expression in macrophages and lymphocytes from a proinflammatory to an anti-inflammatory profile (31).

Liu and Eisenach published preclinical data suggesting that activation of α_2 adrenoceptors at the site of nerve injury, probably by immune modulation, reduces intracellular nociceptive signaling in primary afferents, thereby diminishing hypersensitivity (32).

The role of G inhibitory proteins in antinociception produced by α_2 agonists and opioids has been explored. Utilizing antisense oligodeoxynucleotides directed against the inhibitory G protein α subunit $G_{\alpha i}$ in a mouse model, investigators evaluated whether it is involved in mediating the antinociceptive synergism of morphine and clonidine (33). The antinociceptive effects of clonidine were attenuated after the administration of oligodeoxynucleotides to $G_{\alpha i}$, whereas the

antinociceptive effects of morphine were not changed. Synergism between clonidine and morphine remained despite the administration of these oligodeoxynucleotides. When additional testing was performed to determine whether the efficacy of selective opioid receptor agonists was affected by the presence of oligodeoxynucleotides against G_{α_z} , only a delta receptor agonist was found to have diminished activity. A further experiment was conducted to explore the effect of the administration of antisense oligodeoxynucleotides against another G protein α subunit, G_{α_o} . Morphine and clonidine induced antinociception were both reduced after the administration of this antisense oligodeoxynucleotide (against G_{α_o}); however, the synergistic relationship between morphine and clonidine was unaffected. Different $G\alpha$ subunits may play various roles in morphine and clonidine related antinociception, and synergism between these agents is not dependent on the stimulation of a single $G\alpha$ subunit.

The following are potential mechanisms of α_2 -adrenergic-mediated analgesia:

There are eight major potential mechanisms to explain the analgesia produced via α_2 -adrenergic receptors.

1. α_2 -Adrenergic agonists can reduce sympathetic outflow by a direct effect on preganglionic outflow at the spinal level as well as by diminished free norepinephrine levels via effects on adrenal secretion. These effects would seem to be intuitively beneficial in pain states in which the sympathetic nervous system is playing a significant proalgesic role.
2. α_2 -Adrenergic receptors appear to play a role in the inhibition of neurotransmitter release from primary afferent neurons, probably via effects on a pertussis toxin-sensitive G protein, likely G_o . Activation of this subunit could potentially lead to the opening of neighboring voltage-gated potassium channels or G protein-coupled inwardly rectifying (GIRK) channels.
3. In addition, the activation of the G_o subunit via the α_2 -adrenergic receptor could potentially diminish the opening of voltage-gated N-type calcium channels. This would also lead to a dampening effect on neurotransmitter release. The G protein interaction with N-type voltage-gated calcium channels may result in a significant slowing of calcium conductance and a shift in the voltage dependence of these channels to more positive potentials (i.e., more polarization is needed to open channels). This appears to be caused by a shift in the channel gating mode from high probability of opening to low and medium probability (i.e., "willing" mode to "reluctant" mode). Therefore α_2 adrenergic receptor agonists may be synergistic with ziconotide and baclofen.
4. α_2 -Adrenergic receptors may inhibit dorsal horn neurons by hyperpolarization secondary to potassium flux stimulation of G protein ($G_{i/o}$)-coupled inwardly rectifying channels. It is conceivable that α_2 -adrenergic receptors may be coupled to ion channels or adenylate cyclase also producing antinociceptive effects.
5. Stimulation of α_2 -adrenergic spinal receptors increases acetylcholine concentrations in the dorsal horn and cerebrospinal fluid. Increases in acetylcholine results in cholinergic activation of the M_2 and M_4 spinal muscarinic acetylcholine receptors. Duttaroy et al. revealed evidence of oxotremorine (a nonselective muscarinic agonist)-mediated antinociception but its complete lack of efficacy in the M_2/M_4 double knockout animal. This provides evidence that the M_2 and M_4 receptors are important subtypes in muscarinic receptor mediated analgesia (34). The mechanisms for muscarinic-mediated analgesia may be in part related to M_2/M_4 coupling through the inhibitory G protein, $G_{i/o}$, with

subsequent inhibition of cAMP formation. This occurs via inhibition of adenylate cyclase. There are also increased antinociceptive inhibitory currents, partly from promotion of GABA release, thereby stimulating GABA_B with resultant enhanced inhibitory effects on glutamate release, as well as from increased spinal release of the inhibitory transmitter glycine (34).

6. The activation of G_{i/o} by α_2 agonist binding to α_2 -adrenergic receptors inhibits adenylate cyclase and thereby inhibits cAMP formation.
7. It also appears that α_2 -adrenergic receptor activation indirectly stimulates nitric oxide synthase (NOS) in a subset of primary afferent fibers affecting signaling pathways, which may play an important role in transducing the antihyperalgesic effects of α_2 agonists. It has been shown that the destruction of neurons expressing these elements does not affect the development of mechanical hyperalgesia, but inhibits the antihyperalgesic effects of clonidine (35,36).
8. Activation of α_2 adrenoceptors at the perineural site of nerve injury (perhaps in association with macrophages) significantly increased withdrawal thresholds, and concomitantly reduced phosphorylation of p38 mitogen-activated protein kinase in sensory neurons ipsilateral to the injury (32).

PHARMACOLOGY AND METABOLISM OF α_2 Agonists

Clonidine, tizanidine, and dexmedetomidine, the α_2 agonists currently used for anesthetic and pain management applications, are imidazoline compounds. These drugs are known to produce sympatholysis, anxiolysis, analgesia, and sedation. This class of agents has long been used as a component of veterinary anesthesia, in part because of the lack of respiratory depressant effects, which allows for surgery to be performed in spontaneously breathing animals. These drugs have anesthetic and analgesic sparing effects as demonstrated in a number of clinical studies. α_2 Agonists are predominantly hepatically metabolized with subsequent renal and fecal excretion of metabolites (Table 8.1).

TABLE 8.1 Pharmacologic Properties of α_2 Agonists

Drug	Clonidine	Tizanidine	Dexmedetomidine
Formulations available	Oral: (Catapres [®]), Transdermal (Catapres-TTS [®]), Epidural (Duraclon [®])	Oral: tablet, capsule (Zanaflex [®])	Intravenous (Precedex [®])
Time to peak effect	Oral: 3–5 hr Transdermal: 48 hr Epidural: 19 min	1 hr (fasted state) 1.5–3 hr (fed state)	60 min
T _{1/2}	Elimination: 12–16 hr	2–2.5 hr	Distribution: 6 min Elimination: 2 hr
Route of metabolism/ elimination	Hepatic: 50% Renal: 40–60%	Hepatic: 95% with renal (60%) and fecal (20%) excretion of metabolites	Hepatic (nearly 100%)
Dosage	Oral: 0.2–2.4 mg/day Transdermal: 0.1–0.6 mg/day Epidural: 30–40 μ g/hr; maximum single dose 700 μ g	4–36 mg total per day (limited information exists for long-term use of single doses greater than 8–12 mg or total daily doses greater than 24–36 mg)	Loading: 1 μ g/kg Maintenance: 0.2–0.7 μ g/kg/hr

Source: Reproduced from Ref. 37.

Clonidine

Clonidine (Catapres[®], Catapres-TTS[®], Duraclon[®]) is an α_2 agonist with an $\alpha_2:\alpha_1$ affinity ratio of 200:1 (38). It has been available for use since the 1970s and is most widely recognized for its use in the management of hypertensive disorders. With the development of newer pharmacologic agents for treatment of hypertension, use of clonidine for this indication has declined. Interestingly, as use of clonidine for hypertension has declined, research has demonstrated utility of this agent in the management of a variety of pain conditions. While many of the pain disorders for which clonidine is used are chronic in nature, a number of studies have indicated a role for clonidine in the management of acute pain as well.

Clonidine preparations are available for oral, transdermal and neuraxial administration in the United States. It has also been administered intravenously, but is not available for use in this form in the United States. Clonidine levels peak within 3 to 5 hours, and it has an elimination half life of 12 to 16 hours after oral administration. With transdermal administration, it may take two days to achieve peak plasma levels of clonidine. Peak concentrations are achieved in the plasma and cerebrospinal fluid 19 and 26 minutes, respectively, after epidural administration of clonidine. Approximately 50% of an administered clonidine dose undergoes hepatic metabolism while the remainder is eliminated unchanged in the urine within 24 hours. Dosing adjustments may be advisable in the setting of hepatic or renal insufficiency. Typical dosing of oral clonidine is 0.1 mg twice daily, which may be titrated up to a total daily dose of 2.4 mg. The transdermal patch may be started at a dose of 0.1 mg (total daily delivered dose) and titrated to 0.6 mg. This transdermal formulation is changed on a weekly basis. When administered via the epidural route, clonidine infusions are typically initiated at a rate of 30 $\mu\text{g/hr}$ and can be increased to 40 $\mu\text{g/hr}$. Little information is currently available regarding use of infusions exceeding 40 $\mu\text{g/hr}$. Single bolus doses of up to 700 μg have been administered via the epidural route (39–41).

Tizanidine

Tizanidine (Zanaflex[®]) is available for use in the form of tablets and capsules for oral administration in the United States. After oral administration, tizanidine is nearly completely absorbed, but because of extensive first pass hepatic metabolism, its bioavailability is only 40%. In the fasted state, peak plasma tizanidine concentrations are achieved approximately one hour after dosing, and it has a half life of 2 to 2.5 hours (42). Tizanidine metabolism occurs primarily via the cytochrome P (CYP)450 enzyme CYP1A2, with nearly 95% of each dose undergoing hepatic metabolism. The inactive metabolites of tizanidine have half lives of 20 to 40 hours. Elimination of tizanidine metabolites occurs via the renal (60%) and fecal (20%) routes. The pharmacokinetics of tizanidine may be altered in the presence of food. When using tizanidine *tablets* in the fed state, peak plasma tizanidine concentrations increase by 30% and time to peak plasma concentration is delayed by approximately 30 minutes as compared with use in the fasted state. With tizanidine *capsules*, mean plasma concentrations decrease by 20% and peak plasma concentrations are achieved two hours later in the fed state as compared with the fasted state (43). These two formulations are considered bioequivalent when ingested in a fasted state. It is therefore recommended that patients using tizanidine be advised to take it when fasted and substitution between capsules and tablets generally be avoided.

The clearance of tizanidine may be considerably delayed in the presence of significant renal or hepatic impairment. Dose reduction is recommended in patients with a creatinine clearance of less than 25 mL/min, and use in patients with severe liver disease is not advised. The clearance of tizanidine may be decreased in the presence of drugs that are inhibitors of CYP1A2. Such drugs include oral contraceptives, fluvoxamine, ciprofloxacin and other fluoroquinolones, cimetidine, famotidine, acyclovir, ticlopidine, and several antiarrhythmics (amiodarone, mexiletine, propafenone, and verapamil) (44–47). Increased plasma tizanidine levels in the presence of these other drugs may enhance bradycardia, hypotension, dizziness, and sedation that may occur with tizanidine administration. In view of this interaction, caution is advised whenever tizanidine is used in combination with any of these agents, and dose reduction of tizanidine may be necessary. Hypotension has also been reported because of an interaction between angiotensin converting enzyme inhibitors and tizanidine (48).

When initiating tizanidine therapy, a typical starting dose of 4 mg is used, which may be titrated in 2- to 4-mg increments until adequate control of pain or spasticity is achieved. Tizanidine is dosed in two to three divided doses with a maximum daily recommended dose of 36 mg. Experience with individual tizanidine doses of more than 8 to 16 mg and daily doses of 24 to 36 mg is limited (49).

Dexmedetomidine

Dexmedetomidine (Precedex[®]) has an $\alpha_2:\alpha_1$ affinity ratio of 1600:1 (7). It is available for parenteral administration in the United States. It is primarily known for its α_2 agonist action, but when infused rapidly or in high doses, α_1 agonist activity also occurs, which may account for some episodes of hypertension seen during loading dose administration. Dexmedetomidine has a distribution half life of six minutes and an elimination half life of two hours. Like tizanidine, its metabolism occurs via the hepatic CYP450 enzyme system and glucuronidation, with very little unchanged dexmedetomidine being excreted in the urine and feces. It is advisable to reduce dexmedetomidine doses in patients with substantial liver impairment because of its extensive hepatic metabolism. It may also be necessary to adjust doses in patients with significant renal disease, as prolonged sedation has been observed in patients with severe renal impairment even though the terminal elimination half life of the drug is unchanged. It is surmised that this effect may relate to decreased protein binding of the drug in patients with significant renal impairment (50). When dexmedetomidine is used in older individuals, dose reduction may also be necessary, as there is an increased incidence of bradycardia and hypotension with the use of this drug in the elderly as compared with younger patients (51–53).

Human studies on healthy volunteers have been performed to evaluate the sedative, amnestic, analgesic, hemodynamic, and respiratory effects of dexmedetomidine infusions. These studies showed that escalating dexmedetomidine doses resulted in progressive increases in sedation and analgesia and decreases in heart rate, cardiac output, and memory while respiratory function was preserved (54,55).

Dexmedetomidine is typically initiated by administration of a loading dose of 1 $\mu\text{g}/\text{kg}$ over a period of 10 minutes followed by a maintenance infusion of 0.2 to 0.7 $\mu\text{g}/\text{kg}/\text{hr}$. Use of dexmedetomidine for periods exceeding 24 hours is currently not recommended, though several studies appear to indicate safe use of this agent for longer periods without evidence of adverse sequelae (56,57). Dexmedetomidine is predominantly used in the perioperative period, particularly for sedation in the

intensive care unit, though use for other indications is currently under investigation (58).

CLINICAL APPLICATION OF α_2 AGONISTS IN ANESTHESIA AND PAIN MANAGEMENT

α_2 Agonists have seen expanded use in the fields of anesthesia and pain management in the past few decades. Some of the beneficial effects of α_2 agonists when used during the perioperative period include reductions in anesthetic and analgesic requirements, as well as stress responses associated with surgical stimulation. The fact that these agents lack respiratory depressant effects also makes them particularly attractive for use perioperatively. α_2 Agonists also exhibit hemodynamic effects that may be desirable, especially in patients at risk for coronary ischemia. Wide swings in heart rate and blood pressure associated with stressful stimuli such as airway manipulation and surgical incision may be attenuated with the use of α_2 agonists (59). Hemodynamic stability and decreased oxygen consumption afforded by the use of α_2 agonists appear to decrease the likelihood of perioperative myocardial ischemic events and associated mortality (59,60). α_2 Agonists also enhance analgesia and provide synergy with opioids. Significant reductions in opioid and α_2 agonist dose requirements can be achieved when they are administered in combination, particularly via the intrathecal route (61).

Clonidine

Substantial scientific literature supports the use of clonidine in the treatment of a wide variety of painful conditions. It has also been used as an adjuvant to general and regional anesthetics in a variety of surgical patients. When added to an anesthetic regimen, clonidine may decrease stress responses including the release of cortisol and norepinephrine, and may reduce the occurrence of perioperative hypertension (62). Clonidine has been found useful as adjuvant therapy in the management of postoperative pain. Preoperative administration of oral clonidine has been demonstrated to enhance postoperative analgesia of neuraxially delivered opioids (63–65). It has also allowed for enhanced pain control, reductions in opioid requirements, decreased nausea and vomiting, and improved patient satisfaction in patients on patient-controlled analgesia (66,67).

Epidural clonidine used as the sole analgesic agent during and after abdominal surgery has been shown to dose dependently control the hemodynamic changes associated with surgical stimulation and produce dose dependent postoperative analgesia (68). High dose epidural clonidine has also been shown to potentiate general anesthetics and provide improved analgesia when compared with two doses of epidural bupivacaine as the sole analgesic during and after abdominal surgery (69).

Clonidine has been administered by both the intrathecal and epidural routes in obstetric patients. Prolonged motor and sensory block as well as increased duration of analgesia has been demonstrated with use in this patient population. Reductions in total morphine usage by patient-controlled analgesia may also be afforded when epidural clonidine is infused after cesarean section (70). One concern when using clonidine in this patient population is the potential for hypotension, so close monitoring for this effect is essential.

The effects of intrathecal clonidine as an analgesic may extend beyond the perioperative period when it is used as part of the perioperative analgesic regimen.

In patients undergoing colonic surgery, intrathecal clonidine not only reduced postoperative opioid consumption as compared with intrathecal bupivacaine, it also was more effective in reducing secondary hyperalgesia around the surgical wound (71). This effect was demonstrated to be significant when the patients were followed for a period of six months after surgery, with less residual pain reported by those individuals who had received intrathecal clonidine preoperatively. It has been demonstrated that the potency of epidural to intrathecal clonidine varies with the type of painful stimulus applied. Intrathecal clonidine is approximately ten times as potent as epidural clonidine when used to treat acute thermal pain, whereas it is about twice as potent as epidural clonidine when used in the management of mechanical hyperalgesia and allodynia (72).

Aside from being delivered by the oral and neuraxial routes, clonidine has also been administered intraarticularly for the treatment of postoperative pain with apparent efficacy (73–75). It has also been used as an additive to local anesthetics used for peripheral nerve block resulting in prolonged duration of motor and sensory block and analgesia (70,76,77). Clonidine has been added to local anesthetics for peribulbar block prior to eye surgery with enhancement of anesthesia and analgesia (78,79). When added to intravenous regional anesthesia, clonidine may help to prolong tourniquet time by delaying the onset of tourniquet related pain (80).

In addition to perioperative use for acute pain, clonidine has been used to treat a number of conditions causing chronic pain. Epidural clonidine has been demonstrated to provide benefit in patients with intractable cancer pain, especially that of a neuropathic nature (12). Intrathecal clonidine is commonly used as an analgesic adjuvant in patients receiving chronic intrathecal opioid therapy via implanted drug delivery systems (81).

Tizanidine

Tizanidine is most commonly used in the management of chronic pain, principally for conditions related to spasticity, myofascial pain, and headache and facial pain. However, tizanidine has also been used in the management of acute back pain and as an adjuvant to general anesthesia. With regard to use in the treatment of spasticity, tizanidine appears to be as efficacious as the traditional muscle relaxants diazepam and baclofen, but may be better tolerated because of less sedation and muscle weakness than these agents, respectively (82–86). Tizanidine appears to affect only muscles with spasm, which may account for the reduced incidence of weakness when compared with other muscle relaxant agents (87). Some authors suggest that tizanidine should be considered a first line agent in the management of stroke associated spasticity (88).

In the management of acute back pain, tizanidine compared favorably to diazepam for the treatment of paravertebral muscle spasm, with some measures of mobility being significantly better in the patients receiving tizanidine (89). Additionally, when tizanidine has been used in conjunction with ibuprofen for the treatment of acute low back pain, significantly fewer patients experienced gastrointestinal side effects as compared with patients receiving ibuprofen with placebo (90). It appears that tizanidine not only improves the gastrointestinal tolerability of NSAIDs via gastroprotective effects, it also potentiates the antinociceptive and anti-inflammatory effects of these agents (91).

Tizanidine has been found beneficial in the management of a variety of headache and facial pain disorders. In the treatment of chronic daily headache,

tizanidine has been shown to decrease the frequency, intensity, and duration of headaches whether they are migrainous or tension type in nature (92–95). Some clinicians have used tizanidine in the management of chronic cluster headaches and for detoxification from analgesic rebound headache in conjunction with NSAIDs with evident success (96,97). Thus far, use of tizanidine for trigeminal neuralgia has not proven as beneficial. In some patients with refractory tic douloureux, tizanidine seems to reduce painful paroxysms, but this effect does not appear to be sustained for more than a few months (98).

In the treatment of neuropathic pain, tizanidine at mean doses of 23 mg daily appeared to be efficacious in patients who had failed to respond to multiple other medications including amitriptyline and gabapentin (99). Studies in laboratory animals also suggest that tizanidine might be helpful in the management of thermal hyperalgesia after nerve injury, and indicate a potential role for tizanidine in the treatment of neuropathic pain including that related to complex regional pain syndrome (100). Additionally, study in rats indicates a potential role for tizanidine in the reduction of postoperative pain (101). In humans, preoperative administration of tizanidine has been shown to reduce the minimum alveolar concentration of sevoflurane by nearly 20%, indicating a potential role for tizanidine as an anesthetic adjuvant (102).

Dexmedetomidine

Presently, dexmedetomidine is FDA approved for short-term (24 hours or less) use in critically ill mechanically ventilated patients as a sedative. It has also been used intraoperatively and for the treatment of pain, with studies underway to further evaluate such applications. Thus far, dexmedetomidine has been used as an adjunct to general anesthesia in a variety of surgical procedures with evident reductions in hemodynamic variability associated with stimuli such as tracheal intubation and surgical incision (103–105). This effect is of particular importance in patients susceptible to myocardial ischemia, such as those with coronary artery disease, as tachycardia and hypertension may result in myocardial ischemic events. Because of its ability to blunt hemodynamic responses to intubation and surgery, dexmedetomidine has been used in the management of patients undergoing coronary artery bypass grafting (106). Because dexmedetomidine minimally impacts respiration, it has also been useful in the perioperative management of patients at risk for opioid induced respiratory depression, such as the morbidly obese, and in patients with potential airway management problems (107–110). Since dexmedetomidine can allow for patient cooperation while still providing procedural sedation and analgesia, it has been used to facilitate awake intubation, awake craniotomy, and carotid endarterectomy under regional anesthesia (111–116).

Dexmedetomidine has been shown to decrease anesthetic and perioperative analgesic requirements (117–124). It has also been successfully used in the palliative care population to facilitate withdrawal of ventilator support and reduce distress in the dying (125–127). Addition of dexmedetomidine to lidocaine for intravenous regional anesthesia also appears to enhance the quality of anesthesia and reduce analgesic requirements (128,129). It has also been used in conjunction with patient-controlled analgesia to facilitate shockwave lithotripsy (130). Dexmedetomidine may have neuroprotective effects, possibly by reducing release of excitatory neurotransmitters such as glutamate (112,131,132). Dexmedetomidine does not appear to inhibit steroidogenesis, unlike etomidate, another imidazole agent, and may reduce the inflammatory response to surgery and trauma (133).

When used for sedation in the intensive care unit, dexmedetomidine appears to produce sedation resembling that of normal physiologic sleep, which likely relates to its actions on the locus ceruleus. This may indicate a role for dexmedetomidine in reducing the occurrence of delirium in the critically ill patient that often accompanies sleep deprivation (134,135). One study in the intensive care unit demonstrated that patients receiving dexmedetomidine required 80% less midazolam and 50% less morphine than those receiving placebo (136). This reduction in requirement for opioid analgesia has also been seen in other studies of dexmedetomidine for intensive care unit sedation as well as in a study of dexmedetomidine compared with propofol for intraoperative sedation (135,137). At this point in time, dexmedetomidine has not been labeled for use exceeding 24 hours. In the few studies that have evaluated use of dexmedetomidine for longer periods (up to seven days), no evidence of withdrawal phenomena has been observed (56,57). However, it would appear prudent to consider the possible occurrence of withdrawal if dexmedetomidine is used for extended periods.

PRECAUTIONS AND ADVERSE EFFECTS ASSOCIATED WITH α_2 AGONIST THERAPY

α_2 Agonists appear to provide beneficial hemodynamic effects in patients susceptible to myocardial ischemia, particularly those undergoing stresses related to anesthesia and surgery. At the same time, significant hypotension induced by α_2 agonists may pose a risk for adverse outcomes, especially in patients with cerebrovascular disease, chronic renal insufficiency, and in those who have recently suffered a myocardial infarction. Elderly patients receiving α_2 agonists should be closely observed for evidence of orthostatic hypotension associated with these agents. This effect may result in syncope with the attendant risk of fall associated injuries such as fractures in this population.

Caution should be taken when α_2 agonists are used in combination with cardiovascular agents such as β blockers, calcium channel blockers, and digitalis, as there may be an increased potential for significant bradycardia or atrioventricular block. Rapid infusion of dexmedetomidine has been associated with some cases of sinus arrest, and it appears that use of α_2 agonists might best be avoided in patients with preexisting cardiac conduction abnormalities (51).

All of the α_2 agonists currently in clinical use are considered category C drugs when used during pregnancy. Common adverse effects associated with α_2 agonist administration include dry mouth, sedation, and dizziness (138). Fever and nausea may also accompany their use. New onset or exacerbation of preexisting depression has been documented with the use of clonidine and tizanidine. Asthenia has been fairly frequently reported with tizanidine administration, while hallucinations occur infrequently. One case of an eosinophilic exudative pleural effusion thought to represent a drug reaction to tizanidine has been reported (139).

The most significant source for concern with the use of tizanidine is the potential for hepatotoxicity (140). Approximately 5% of patients exposed to tizanidine will manifest elevations in liver enzymes (AST/ALT) of greater than three times the upper limit of normal. In most cases, patients have been asymptomatic and their liver function test values have returned to normal shortly after discontinuation of tizanidine. However, several patients on tizanidine have died from fulminant hepatic failure that could not be attributed to any other cause aside from a reaction to tizanidine. For this reason, the manufacturer recommends

regular monitoring of liver enzymes in patients receiving tizanidine. Liver function tests should be obtained prior to initiation of tizanidine and then one, three, and six months after it is started (49). Additional periodic monitoring of liver enzymes may be indicated if the patient manifests any symptoms suggestive of liver problems.

Overdosage of α_2 agonists may result in a number of untoward effects including bradycardia, hypotension, sedation, and alterations in mental status (141). It has been noted that one potential source for error that may lead to dexmedetomidine overdosage is misprogramming of its infusion in $\mu\text{g}/\text{kg}/\text{min}$ rather than $\mu\text{g}/\text{kg}/\text{hr}$ (142). A withdrawal syndrome has been reported with abrupt discontinuation of clonidine, even after epidural administration (143). This may manifest with severe hypertension that could potentially result in myocardial or cerebral infarction. Thus it is recommended that clonidine doses be gradually tapered prior to its discontinuation. At this point, no similar episodes of withdrawal have been reported with tizanidine or dexmedetomidine (Table 8.2).

TABLE 8.2 α_2 Agonists: Drug Interactions, Precautions, and Adverse Effects

Drug interactions	<p>General: sedatives (enhanced sedation); β blockers, calcium channel blockers, digitalis (increased risk of heart block)</p> <p>Clonidine: local anesthetics (prolonged sensory and motor block); cyclosporine (increased serum levels of cyclosporine/cyclosporine toxicity); tricyclic antidepressants (decreased antihypertensive action of clonidine)</p> <p>Tizanidine: oral contraceptives, fluvoxamine, ciprofloxacin, zileuton, amiodarone, mexiletine, propafenone, verapamil, cimetidine, famotidine, acyclovir, ticlopidine (increased serum tizanidine levels, decreased tizanidine clearance—due to CYP1A2 inhibition)</p> <p>Dexmedetomidine: no specific interactions (except as above in general drug interactions with α_2 agonists)</p>
Precautions	<p>General: pregnancy (category C), use in patients with known cardiac conduction defects</p> <p>Clonidine: potential for rebound hypertension with abrupt discontinuation regardless of route of administration; cautious use in obstetrical patients due to potential for hypotension; cautious use in patients with cerebrovascular disease, chronic renal failure, coronary artery disease or recent myocardial infarction (due to potential for hypotension)^a</p> <p>Tizanidine: Dose reduction is advised in patients using oral contraceptives, renal insufficiency (due to decreased clearance of tizanidine); avoid use in the presence of liver disease (due to risk of hepatotoxicity).</p> <p>Dexmedetomidine: Use for periods exceeding 24 hours is not recommended (though several reports of use for longer periods have been described); due to its ability to blunt sympathetically mediated blood pressure and heart rate responses, there may be increased risk of failure to detect signs of awareness under anesthesia if this drug is incorporated into an anesthetic regimen.</p>
Adverse effects	<p>General: hypotension, bradycardia, heart block, sedation, dizziness, dry mouth, asthenia, orthostasis, rash, nausea</p> <p>Clonidine: depression, constipation, nervousness/agitation</p> <p>Tizanidine: elevation of LFTs (5%) with rare incidence of fulminant hepatic failure, hallucinations, muscle spasm, fever, abdominal pain, diarrhea, dyspepsia, depression</p> <p>Dexmedetomidine: sinus arrest, hypertension (with rapid infusion or loading dose administration); fever, tachycardia, anemia, hypoxia, atrial fibrillation</p>

^amay apply to α_2 agonists in general, but is especially relevant to the use of clonidine.

Source: Reproduced from Ref. 37.

FUTURE DEVELOPMENTS IN α_2 AGONIST THERAPY

α_2 Agonist therapy may see expanded use in pain management in the future, particularly when agents in this therapeutic class that produce fewer adverse effects such as sedation become available for use in humans. Two such agents are moxonidine and radolmidine, which have undergone study in animal models. Like clonidine, moxonidine has been found to provide analgesic synergy with morphine when administered intrathecally in mice, but appears to be less sedating (144,145). It also appears that moxonidine exerts its analgesic effects at a different α_2 agonist subtype than clonidine, which may indicate a role for combined α_2 agonist therapy in the future to enhance analgesic synergism (146). This could potentially allow for reductions in total analgesic consumption and associated side effects. Currently, moxonidine is available for human use outside the United States in the management of hypertension. The antinociceptive effects of radolmidine were compared with those of dexmedetomidine when these agents were administered intrathecally in a rat model. These agents were found to be equipotent in their antinociceptive effects, but rat locomotor activity decreased less with radolmidine, suggesting less sedation with its use (147). This effect of radolmidine may relate to its inability to cross the blood-brain barrier with consequent reduction in central effects. Therefore, it appears that if radolmidine becomes available for use in humans in the future, it may allow for substantial analgesia without significant effects on level of consciousness. Likewise, tizanidine and dexmedetomidine may find broader use in pain management if formulations for neuraxial administration become available.

CONCLUSION

α_2 Agonists have seen expanded use in the fields of anesthesia and pain management in the past few decades. These agents are available for administration by a variety of routes and can be used to enhance analgesia, provide procedural and intensive care unit sedation, and reduce hemodynamic variability during surgery. In pain management, these agents may provide benefit for the treatment of acute pain, cancer related pain, headaches, neuropathies, complex regional pain syndrome, myofascial pain, and spasticity. Reduction in anesthetic and analgesic requirements may be afforded by α_2 agonists, and synergistic activity of α_2 agonists with a number of analgesic agents has been demonstrated. While clonidine is the most broadly used of the α_2 agonists, tizanidine has found a role in the management of spasticity and other painful disorders, and dexmedetomidine is valuable in perioperative and critical care applications. Development of new α_2 agonists with fewer dose limiting side effects may further increase the utilization of these agents in anesthesia and pain management.

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Nonpharmacological modalities for the treatment of acute pain

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INTRODUCTION

Trauma and pain associated with surgery cause an endocrine response that increases the secretion of cortisol, catecholamines, and other stress hormones. This results in tachycardia, hypertension, regional reductions in blood flow, altered immune responses, hyperglycemia, lipolysis, and negative nitrogen balance, all of which may play a role in postoperative morbidity and mortality (1,2). Opioids are the mainstay of managing most acute pain. There are times, however, when reducing the amount of opioid may be desirable for a number of reasons, including patient age, comorbidities, and intolerance of adverse effects from the medication. In these situations, the addition of nondrug methods to manage acute pain can be very useful in promoting comfort and improving outcomes. Many pain experts have discovered that combining nonpharmacological with pharmacological modalities is most effective in controlling pain.

Nondrug methods are divided into two general categories, physical modalities and psychological modalities, with a variety of options within each category. Which option may be best for an individual patient is based on trial and error, but once that option is found, the results can be well worth the effort. Nondrug approaches for the management of acute pain are most appropriate for patients who (i) find such therapy appealing, (ii) express fear and anxiety, but are not overwhelmed by it, (iii) may benefit from a decrease in drug use, (iv) are likely to have long-standing postoperative pain, and (v) obtain incomplete relief of pain from drug therapy (3).

PHYSICAL MODALITIES

The role of physical modalities in the control of acute pain are comfort, correcting physical dysfunction, altering physical responses to pain and inflammation, and decreasing fear associated with immobility and restriction of activity (3). Treatment options include thermal, electrical, mechanical, and tactile modalities.

Thermal Modalities

Thermal modalities include heat and cold. Heat can decrease pain, muscle stiffness, and guarding; increase flexibility; and reduce muscle spasm resulting from skeletal or neurological pathology (4–6). Although the physiological basis by which thermal therapy works for pain is not fully understood, the gate control theory of pain inhibition is one hypothetical basis for the mechanism of action of heat. The application of heat externally increases the temperature of the skin and deep tissue, stimulating thermoreceptors, which inhibits the transmission of nociceptive signals to the spinal cord and the brain (7). Heat, at higher levels, has a relaxing effect on skeletal muscle tone by decreasing the stimulus threshold of muscle spindles and efferent firing rate. Heat also has an effect on multiple pain generators, including

TABLE 9.1 Superficial Heat Modalities: Types and Applications

Type	Applications
• Hot pack	<ul style="list-style-type: none"> • Increase circulation • Increase muscle and tissue temperature • Relax muscle spasm
• Paraffin bath	<ul style="list-style-type: none"> • Provide localized heat at fairly high temperature
• Fluidotherapy	<ul style="list-style-type: none"> • Provide heat, massage, sensory stimulation, levitation, and pressure oscillations without skin irritation
• Hydrotherapy	<ul style="list-style-type: none"> • Increase systemic blood flow • Mobilization of affected extremity or body part

inflammation, ischemia, and triggers involved in the development of peripheral neuropathy (7). The effect of heat is primarily local, where it increases the metabolic rate of local tissue. This, in turn, increases the production of metabolites and additional heat, and changes neuromuscular activity, blood flow, capillary permeability, enzyme activity, and pain threshold to varying degrees. These changes may be influenced by the amount of heat applied. This supports the usefulness of heat therapy when pain results from ischemia, spasm, or accumulation of inflammatory agents such as prostaglandins. The result of such treatment is increased edema and swelling; improved tissue oxygenation, delivery of essential nutrients, and clearance of metabolites; and enhanced production of antibodies and leukocytes (4,8).

Superficial Heat Modalities

Superficial heat methods include hot packs, paraffin baths, fluidotherapy, hydrotherapy, and radiant heat (8,9) (Table 9.1). These primarily provide a superficial direct effect on cutaneous blood vessels and nerves. Contraindications to consider when making the decision to use heat modalities include the following (8–10):

- Acute inflammatory conditions, such as sprains or strains, as such conditions may also be aggravated by heat.
- Fevers may be further elevated by systemic warming induced with heat therapies.
- Increased blood flow may hypothetically cause malignancies to metastasize if heat is applied directly over a cancerous lesion.
- Active bleeding secondary to acute trauma may be prolonged when heat is used over the injured tissue due to vasodilatory effects.
- Generalized heating may be poorly tolerated by those with cardiac insufficiency.
- Elders and children under four years of age may not be able to regulate body temperature changes resulting from systemic warming.
- Tissues treated with radiation therapy should not be heated.
- Persons with peripheral vascular disease may not be able to tolerate the increased production of metabolic byproducts induced by heat therapy. Heat-related thermal injuries may also occur when heat is applied over areas with inadequate perfusion.
- Application of heat should generally be avoided in areas where the skin is anesthetized.
- Acute musculoskeletal or inflammatory conditions may be exacerbated by tissue edema and swelling produced from heating.

Hot-pack therapy includes the use of hydrocollator or warm moist heat pads, and is a conductive means of delivering moist heat. Commercial hydrocollator packs are canvas pouches of petroleum distillate and come in multiple sizes. Warm moist heat is used to increase circulation and muscle and tissue temperature, and to relax muscle spasm. Treatment time is from 15 to 30 minutes once a day (9).

Paraffin bath is a simple and efficient technique for the application of localized, fairly high temperature heat. Paraffin wax has a very high heat capacity. The usual temperature range for paraffin therapy is 118 to 126°F. Unlike water, paraffin absorbs and retains a great amount of heat due to the mineral oil in the paraffin that lowers the melting point of the paraffin. The combination of paraffin and mineral oil has a low specific heat. The end result is the ability to comfortably provide six times the amount of heat as water (8). Six layers of paraffin are applied to the treatment area, wrapped in plastic, and left in place for 20 to 30 minutes. As the paraffin solidifies, the heat is transferred by convection to the treated area. Paraffin baths are particularly effective for small, irregular shaped areas of the body such as the fingers, elbows, and feet, which are not easily treated with liquid heat modalities. Treatment during acute pain is daily.

Fluidotherapy is a dry heat modality that uses a suspended air stream that has the properties of a liquid and the ability to provide heat, massage, sensory stimulation, levitation, and pressure oscillations simultaneously, without the skin irritation of water (8,9). Fine cellulose particles from ground corn husks are suspended in a warm stream of air, at temperatures of 110 to 123°F, to heat the extremity. Because there is no skin irritation or thermal shock, higher treatment temperature transfer occurs than with water or paraffin. The pressure oscillations may reduce edema, while the sensory stimulation may aid in desensitizing nerves and thereby reducing sensitivity. Fluidotherapy treatment results in a sixfold increase in blood flow and a fourfold increase in tissue metabolism, including a twofold rate of release of oxygen from the hemoglobin molecule and increased excretion of cellular waste products, thus promoting healing (8). Daily treatment time lasts from 15 to 20 minutes.

Warm hydrotherapy involves use of a warm whirlpool and is an excellent way to provide moist heat to increase systemic blood flow and allow for mobilization of the affected extremity or body part. In addition to providing superficial heat, water produces an inward hydrostatic pressure that may minimize edema. Hydrotherapy delivers heat by conduction (direct contact with heat) and by convection (heat gained through the movement of water molecules across the skin). Hydrotherapy of a body part or the entire body can be used in the treatment of wounds and burns, subacute traumatic or inflammatory conditions, early peripheral vascular disease, peripheral nerve injuries, or conditions producing muscle weakness (9). Recommended treatment time is 15 to 20 minutes. Hydrotherapy should be avoided when venous ulcers are present due to the risk of venous congestion.

Superficial heat penetrates only a few millimeters and is absorbed only by the epidermis and dermis. The effects depend on the target tissue. Tissue temperatures reach approximately 41 to 45°C (105.8–113°F) in 8 to 10 minutes. After 30 minutes, thermal equilibrium is reached and further heating is not beneficial (9).

Superficial heat is indicated for subacute inflammatory conditions, subacute pain, subacute edema, myofascial trigger points, muscle guarding, muscle spasm, subacute sprain or strain, and subacute contusion (Table 9.2). Heat has been found

TABLE 9.2 Superficial Heat Modalities: Indications and Contraindications

Indications	Contraindications
<ul style="list-style-type: none"> ● Pain from ischemia, spasm, or accumulation of inflammatory agents ● Inflammation, acute or subacute ● Resolution of edema and swelling ● Decreased range of motion ● Myofascial trigger points ● Muscle guarding and spasm ● Muscle strain ● Muscle sprain ● Subacute contusion ● Infection 	<ul style="list-style-type: none"> ● Febrile illness ● Malignancies ● Active bleeding secondary to trauma ● Cardiac insufficiency ● Elders and children under 4 years of age ● Radiated tissue ● Peripheral vascular disease ● Anesthetized skin ● Acute musculoskeletal conditions

TABLE 9.3 Deep Heat Modalities

Uses	Precautions	Contraindications
<ul style="list-style-type: none"> ● Sprains ● Strains ● Contusions ● Inflammation ● Muscle spasm ● Tendinitis ● Tenosynovitis ● Bursitis ● Myofascial trigger points ● Contractures ● Soft tissue healing and repair ● Tissue regeneration ● Hematoma resolution 	<ul style="list-style-type: none"> ● Pregnancy ● Acute bleeding ● Acute inflammation ● Ischemic areas ● Pelvic area during menses ● Obese persons ● Over testes ● Cancer ● Infection ● Certain types of pacemakers ● Areas with decreased sensitivity to pain and temperature 	<ul style="list-style-type: none"> ● Debilitated persons ● Over epiphyses of growing bones ● Metal implants (relative) ● Over eyes ● Over radiated skin

useful in the treatment of acute low back pain, neck pain and muscle tension, and wrist pain (4,11,12).

Deep Heat Modalities

Vigorous deep heat methods include shortwave diathermy, microwaves, and ultrasound (Table 9.3). Shortwave diathermy and microwaves heat subcutaneous tissue and superficial muscle, while ultrasound heats deep muscles, joints, tendons, tendon sheaths, and nerve trunks.

Diathermy converts high-frequency electromagnetic energy into heat energy within tissues. Heat is produced primarily by resistance of the tissue to the passage of energy and by the vibration and distortion of molecules within the tissue (13,14). The primary benefits of diathermy are the same as those for heat in general, that is, increased blood flow, dilatation of blood vessels, more rapid resolution of inflammatory process, increased metabolic rate, increased removal of cellular metabolic and waste products, changes in some enzyme reactions, decreased joint stiffness, some muscle relaxation, an increase in the pain threshold, healing, and altered

physical properties of fibrous tissue (14). Diathermy is the treatment of choice when the tissue is too tender for moist heat packs or ultrasound, when the aim is for a higher temperature at a greater depth, and when subcutaneous fat is thick and deep heat is desired.

Pulsed shortwave diathermy is the therapeutic application of high-radio-frequency electrical currents used primarily for its nonthermal effect. Damage to cells that frequently occurs with soft tissue injuries often causes cellular dysfunction. The result can include loss of cell division and regenerative capabilities (14). In this situation, pulsed shortwave diathermy is hypothesized to remedy cell dysfunction. Pulsed shortwave diathermy has been shown to increase the rates of fibroblast and chondrocyte proliferation *in vitro* (15).

Diathermy is used in the treatment of sprains, strains, contusions, inflammation, muscle spasm, tendonitis, tenosynovitis, bursitis, myofascial trigger points, and contractures (14). Treatment is 20 to 30 minutes once or twice a day. Diathermy should be used with caution during pregnancy as it may create a modest increase in the risk of miscarriage. Other conditions requiring precaution include musculoskeletal trauma with acute bleeding; acute inflammation; pelvic application during menses; use in obese persons; and use over testes, cancer, infection, ischemic areas, and areas with decreased sensitivity to temperature and pain. Contraindications to the use of diathermy include use in debilitated persons and over the epiphyses of growing bones, metal implants, and eyes or skin treated with radiation. Persons with pacemakers must not receive diathermy without consulting the pacemaker manufacturer, as the electromagnetic energy may interfere with pacemaker function (13,14).

Ultrasound is classically a deep heat modality used to reach deep tissues. The therapeutic effects of ultrasound have been known for more than half a century (16,17). Since 1955, the American Medical Association Council on Physical Medicine and Rehabilitation has recommended therapeutic ultrasound as an adjunct to the treatment of pain, soft tissue injury, joint dysfunction, and a variety of musculoskeletal syndromes (18-20). Ultrasound is a type of energy produced from sound waves, which produces deep heat when absorbed by tissues. The absorption is greatest in tissues that are dense or high in protein. Ultrasound penetrates tissue to a depth of approximately 5 cm or 2 in. (21).

The physiological effects of ultrasound are the result of four actions: attenuation, cavitation, acoustic streaming, and micromassage. As the beam travels through tissue, it loses energy through a combination of scattering and absorption in a process known as attenuation. Attenuation is responsible for generating the thermal effects of ultrasound. The energy from the beam is then transferred into the tissues. In the line of the ultrasound beam, gas bubbles form secondary to the vibrational effect. This is known as cavitation. As a result of cavitation, gas-filled bubbles expand and compress in response to pressure changes in tissue and fluid caused by ultrasound. This results in increased flow in fluid around the vibrating bubbles and can be therapeutic in accelerating the healing process by altering cell membrane permeability to sodium and calcium ions (5). Additional significant nonthermal effects of cavitation include soft tissue repair via stimulation of fibroblast activity, tissue regeneration, increased blood flow, and bone healing (5). Acoustic streaming is the mechanical pressure of the sound wave moving fluids along the boundaries of the cell membranes. It has been shown to cause increased cell membrane permeability, ion flux, capillary density, protein synthesis of cells, and mast cell production. It is this effect that is thought to produce healing.

Micromassage refers to the oscillatory movement of tissues and cells, which stimulates mechanoreceptors and the autonomic nervous system, and is thought to be responsible for reducing edema (22).

The primary advantage of ultrasound is the ability to provide deep heat to tissues high in collagen, such as tendons, muscles, ligaments, joint capsules, joint menisci, intermuscle interfaces, nerve roots, periosteum, and other deep tissue, without significantly increasing temperature in surrounding skin or fat (5). The thermal effects of ultrasound include increased extensibility of collagen fibers in tendons and joint capsules; improved blood flow; and decreased joint stiffness, muscle spasm, and pain. It also has a mild inflammatory effect that is thought to accelerate the healing process (23). The combination of thermal and nonthermal ultrasound effects may result in stimulation of fibroblast activity, increased protein synthesis, and increased blood flow and tissue regeneration (23).

Ultrasound is indicated for the treatment of acute and postacute conditions, muscle spasm, myofascial trigger points, multiple inflammatory conditions, and pain, and to stimulate repair of soft tissue and bone (5). There is one case report of ultrasound reducing pain and hematoma size after five sessions in a patient with a rectus sheath hematoma (24). Ultrasound is contraindicated in the presence of poor arterial circulation; local bleeding; and over eyes, the gravid uterus, the carotid sinus, the cervical ganglia, joints during acute inflammatory joint pathology, cancerous lesions, or the spinal cord after laminectomy (21).

Maximum impact on the healing process is achieved if treatment is implemented within 48 hours after the acute event, and is administered once or twice a day for 6 to 8 days with minimum treatment time of 5 to 10 minutes (5).

Ultrasound can also be used to drive medication into subcutaneous tissue over a local area without invading the skin in a modality known as phonophoresis. Phonophoresis is a safe, painless, and noninvasive way to drive whole medication molecules into tissues to a greater depth than other similar modalities. Phonophoresis has been studied in the treatment of a variety of musculoskeletal conditions including lateral epicondylitis, tendonitis, and plantar fasciitis. Conclusive evidence to support use of phonophoresis was not found; however, none of the studies were randomized controlled trials (25). Agents used with phonophoresis include local anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs) (primarily salicylate), and the steroids hydrocortisone and dexamethasone.

Cryotherapy

Like heat, cold or cryotherapy can be very beneficial in management of acute pain (Table 9.4). Cryotherapy results in local vasoconstriction with a resultant decrease in blood flow to the treatment area. In response, local metabolism is decreased along with oxygen demand. This reduces edema, inflammation, and cellular responses to local acute injury, and it is analgesic. If applied for more than 30 minutes, cold can lower intra-articular temperature, reducing joint metabolism and activity of cartilage degrading enzymes. Cold slows the conduction of nerve impulses leading to their eventual failure. Through a counterirritant effect, cold increases the pain threshold and promotes release of endorphins. It is thought that cold bombards central pain receptors with so much stimulation that pain impulse transmission is prevented. Cold also has a direct effect on firing of peripheral nerves and free nerve endings. A minimum of 15 minutes of cold therapy is necessary to achieve analgesia.

TABLE 9.4 Actions and Effects of Heat and Cold

Heat	Cold
Actions <ul style="list-style-type: none"> • Reduces pain • Decreases muscle stiffness • Decreases muscle guarding • Decreases muscle spasm 	Actions <ul style="list-style-type: none"> • Slows conduction of peripheral nerve impulses leading to eventual failure • Raises pain threshold • Reduces pain • Promotes endorphin release • Decreases muscle spasm • Decreases muscle spasticity
Local effects <ul style="list-style-type: none"> • Increases metabolic rate • Changes neuromuscular activity • Increases blood flow to area • Increases capillary permeability • Increases enzyme activity 	Local effects <ul style="list-style-type: none"> • Promotes vasoconstriction • Decreases blood flow to area • Decreases local metabolism • Reduces oxygen demand
Results <ul style="list-style-type: none"> • Promotes edema and swelling • Promotes tissue oxygenation • Influx of antibodies and leukocytes • Influx of essential nutrients • Clears byproducts of cellular metabolism 	Results <ul style="list-style-type: none"> • Reduces edema and swelling • Decreases inflammation • Minimizes cellular response to local acute injury • Decreases pain

While both heat and cold significantly increase pain thresholds, cold has an even more significant effect than heat. Ice has been found to be more effective than shortwave diathermy in elevating the pain threshold. When comparing the effect of ice and shortwave diathermy on the pain threshold, both had an immediate maximum effect. However, the effect of diathermy lasted 15 minutes, while the effect of ice lasted 30 minutes (10). When used as part of the regimen for treating postoperative pain following reconstruction of the anterior cruciate ligament, patients receiving cryotherapy reported significantly less pain, required less opioid analgesia, converted to oral analgesics sooner, were more compliant with rehabilitation, ambulated sooner, and returned to normal activities quicker than those who were not treated with cryotherapy (26,27).

Cold is very effective in the treatment of muscle spasm and spasticity. Cold reduces muscle spasm by raising the stimulus threshold of muscle spindles, decreasing spindle response as well as substantially decreasing the frequency of muscle action potentials and muscle tone. It decreases or modifies the stretch-reflex mechanism in muscle, making cold effective in reducing spasticity. Cold may actually be better for reducing muscle spasm than heat. The effects of cold begin in 15 to 30 seconds and last 60 to 90 minutes after treatment (8,28).

There are a variety of cryotherapy modalities, including ice packs, ice massage, cold immersion baths, cold hydrocollator packs, and vapocoolant spray (ethyl chloride or fluoromethane), that are appropriate for acute pain. The goal is to reduce tissue temperature and decrease blood flow to the area. When moisture is used in conjunction with cold, the effect of the cold is enhanced.

Ice packs are indicated following acute injury and to prevent swelling associated with exercise. Ice packs are simple to make and easy to use. Some

simple ice packs include melting ice and water slush in a plastic bag, bags of frozen corn or peas, or crushed ice in a plastic bag. It is best if the ice pack can be molded to the affected area. Application for 20 to 30 minutes several times a day is desirable.

Ice massage involves rubbing a large cube of ice over the affected area. This can be done by a therapist or the patient, following proper instruction. Ice massage is most appropriate for small areas of pain or muscle guarding following acute injury to decrease pain and edema, and to control bleeding. Ice massage decreases temperature rapidly, and is effective enough to decrease intramuscular temperature with ample time (8,28).

Cold immersion baths or whirlpool therapy is useful for acute injury in which exercise of the injured part is desired. The affected part is placed in a water bath at a temperature of between 32 and 80°F, with 50 to 60°F as the norm. Temperature selection depends on the reason the treatment is being used. For example, the lowest temperature is used for pain relief. Treatment time is between 7 and 20 minutes daily (8,28).

Commercial cold hydrocollator packs are generally made of plastic and filled with a hydrated gel. These packs can be kept in a refrigeration unit. They maintain their low temperature for a long period of time, but do not lower skin temperature as much as ice does. It is not likely that hydrocollator packs will result in analgesia (28).

Vapocoolant spray does not provide adequate deep penetration but does produce significant cooling through evaporation when sprayed on the skin. It reduces the pain of muscle spasm presumably by stimulation of A-fibers, a mechanism explained by the gate control theory. The physiological response to this treatment includes reduction of muscle spasm, inhibition of muscle spindle responses, and stimulation of other musculoskeletal structures, such as ligaments. Vapocoolant spray breaks the pain cycle, allowing the muscle to be stretched to its normal length, and is very helpful in treating myofascial trigger points (8,28).

Cryotherapy is indicated in the treatment of acute and subacute inflammation, acute pain, acute swelling, control of bleeding, myofascial trigger points, small burns, limited range of motion secondary to pain, muscle guarding and spasm, acute strains and sprains, acute contusion, bursitis, tenosynovitis, tendonitis, and muscle soreness. Contraindications include use in patients with angina pectoris, cardiac dysfunction, open wounds, arterial insufficiency, increased sensitivity to cold (e.g., Raynaud's phenomenon), regenerating peripheral nerves, use over anesthetized skin, and in the elderly.

Electrical Modalities

The electrical stimulating (E stim) current modalities use an electrical current across the skin to modulate pain through the stimulation of cutaneous sensory nerves at high frequencies or through the production of β -endorphins at lower frequencies (29). E stim affects both nerve and muscle tissue. It is capable of modulating pain, producing muscle contraction or relaxation, facilitating soft tissue and bone healing, producing a net movement of ions through the use of continuous direct current, and generating a chemical change in tissues (29). When large diameter sensory fibers are electrically stimulated, the brain is forced to recognize that particular area of tactile input, making it less aware of pain. There are many types of E stim; however, two are important to consider as adjuvants for the control

of acute pain: transcutaneous electrical nerve stimulation (TENS) and interferential stimulation (IFS).

Transcutaneous Electrical Nerve Stimulation

Since the late 1950s, many physiological studies have supported the notion that activity in large diameter afferents may alter the transmission of pain impulses in central pathways. This is theorized to occur in the dorsal horn of the spinal cord and the thalamus; however, there are few randomized controlled trials to support this (30). TENS is a form of electroanalgesia that activates peripheral A β -fibers, which is theorized to activate A δ - and C-fibers at the dorsal horn. The more slowly conducting A δ -fibers show the greatest change, activating the release of endogenous opioids (31,32). These primary afferents are stimulated by low-voltage electrical impulses through electrodes applied to the skin. The analgesic effect is thought to be primarily a peripheral one (33). Although well-designed research evidence remains low, anecdotal evidence supports TENS as a useful noninvasive nondrug modality for acute, chronic, and cancer pain. TENS is designed to control pain; however, its effectiveness is difficult to predict and it should therefore be viewed as one tool in a comprehensive pain management treatment plan.

There are three common pulse patterns used with TENS: high frequency (HF), low frequency (LF), and acupuncture-like (AL). HF-TENS intensity is just below the level that induces pain, while LF- and AL-TENS are used when HF-TENS is not tolerable (30). TENS intensity should be enough to result in paresthesia in the painful region, but not pain.

Conventional-mode TENS is designed to control pain by providing a comfortable tingling sensation at a submotor stimulation level that activates large diameter peripheral nerve fibers. It is usually perceived as comfortable by users, is relatively fast acting, may be used for both acute and chronic pain, and may be worn for 24 hours a day if desired. One drawback is that adaptation to the stimulus is common (34).

LF-TENS is designed to engage a variety of deep afferent nerves to produce central inhibition of pain through production of endogenous opioids (34). This is evidenced by the fact that naloxone has successfully reversed the analgesic action of LF-TENS (35,36). The onset of analgesia takes 20 to 30 minutes. The advantage of LF is that the duration of pain relief lengthens after each session and can last two to six hours or more. Adaptation to LF-TENS is minimal. Some patients find muscle contractions associated with the use of this modality annoying, and it may limit function during treatment times (34).

Burst TENS is similar to LF in clinical response and mechanism of action. Burst TENS uses a combination of HF and LF pulses at amplitudes strong enough to produce local muscle contraction. The advantages of burst TENS are its long duration of effect, increased comfort when compared with a single-frequency stimulus, and low adaptation to the stimulus (34).

Brief intense-mode TENS uses high ranges of frequency, pulse duration, and amplitude to modulate pain. The onset of action is almost immediate. The stimulation is very comfortable. However, once the unit is turned off, return of normal sensation is quite rapid (34).

Modulation-mode TENS uses a cyclical amplitude, pulse duration, and frequency to provide an ever-changing comfortable stimulus that can be customized to individual preference. It is hypothesized that using different stimuli will decrease nerve or perceptual adaptation to stimulation. This TENS is relatively fast

acting and may be used up to 24 hours a day for acute and chronic pain. The duration of pain relief following a session, however, is short. Some find the changing stimulation annoying or uncomfortable (34).

TENS has been found to be a useful adjuvant to the management of pain from many conditions including acute musculoskeletal pain, postoperative pain, pain of peripheral vascular origin, and cardiac ischemia (37). TENS has also been used successfully in the treatment of acute postoperative pain. In one study of patients following abdominal and thoracic surgery, 77% of TENS users reported pain relief (38). Other studies found TENS no more beneficial than sham TENS for control of acute pain following appendectomy and herniorrhaphy, on the basis of pain intensity ratings and opioid use, even though patients reported it to be helpful (39,40). TENS has been shown to be very effective for controlling postoperative pain after muscle-sparing thoracotomy, costotomy, sternotomy, and video-assisted thoracotomy, but not with posterolateral thoracotomy (41). This may be because posterolateral thoracotomy causes severe pain, while the other procedures produce mild-to-moderate pain. TENS has been found useful in controlling acute orofacial pain and dysmenorrhea, and pain associated with rib fractures, major abdominal surgery, orthopedic surgery, musculoskeletal mechanical degeneration, peripheral nerve damage, and angina secondary to ischemic heart disease (30,42,43). TENS has also been found to be an effective adjuvant modality for painful dressing changes in children (44).

In general, TENS reduces pain in 10 to 15 minutes with the duration of pain relief lasting 30 to 45 minutes, although pain relief may persist for hours with some modes. While there are no major side effects or adverse reactions noted with TENS, there are contraindications to its use. It is considered prudent to avoid placing TENS over or near a pregnant uterus, as safety during pregnancy has not been determined (30,34). On demand cardiac pacemakers may malfunction if TENS interferes with their electrical impulses. However, TENS does not appear to affect mixed frequency pacemakers. TENS should not be used over the anterolateral neck as it may induce spasm of the intrinsic muscles of the larynx and activate cells in the carotid sinus, resulting in hypotension (30). TENS has not been found beneficial in those with psychological or social distress, central pain syndromes, and autonomic nervous system dysfunction (43).

Interferential Stimulation

IFS therapy was introduced over 40 years ago. IFS is a modality that uses two medium-frequency currents, one fixed and the other a variable frequency that faces low impedance as it crosses the skin. The two waveforms work together to stimulate large-diameter nerve fibers to inhibit pain. As the two waveforms mix within tissue, they produce a train of pulses whose frequencies and amplitudes are dependent on the treatment parameters. The body then responds to the difference between the two currents. IFS differs from TENS in that it provides deeper stimulation of tissue while the patient perceives very little stimulation over the site (45). IFS is used for the management of pain, to increase blood flow, relax muscles, and reduce edema. IFS may possibly promote tissue and bone healing (45). While TENS and IFS both elevate the pain threshold, the effect of IFS lasts longer (46). IFS has been found to reduce pain, edema, and opioid use and increase range of motion in patients undergoing knee surgery (47). It has also been found beneficial for the treatment of inflammatory pain and ischemic pain (48,49) IFS is applied for 15 minutes three times a day for acute postoperative pain.

Myofascial Therapy

Myofascial therapy involves myofascial release techniques and special massage techniques performed by trained therapists and simple massage techniques that can be performed by caregivers or family members. Massage therapy has been in use for many years. It is likely an offshoot of the natural reaction to rub a painful area to achieve pain relief, which again can be explained by the gate control theory of pain relief. The word massage comes from the Arabic verb *mass* meaning “to touch” and the Greek word *massein* meaning “to knead,” though Egyptians, Persians, Romans, Japanese, and Chinese commonly practiced massage as well.

In the early 19th century, Peter Ling (1779–1839) developed, as a branch of gymnastics, the common massage techniques that continue to be used today. Although massage techniques have changed, they are based on the teachings and research of Albert Hoffa (1859–1907), James B. Mennell (1800–1957), and Gertrude Beard (1887–1971). Today, a scientific basis has been added to the modalities of myofascial release and massage (50). The intent of this section is not to teach professional myofascial release or massage techniques, but to provide the reader with the understanding of these nonpharmacological methods that can easily be incorporated into the plan of care for the acute pain patient.

Myofascial Release

Normal healthy fascia is a relaxed, wavy, web-like structure that surrounds all internal structures and has the ability to stretch and move with ease. As a result of injury, scarring, or inflammation, the fascia can lose its ability to stretch and move without restriction, resulting in pain and reduced range of motion. Myofascial release is a physical therapy technique that uses manipulation of soft tissue to free adhesions and restrictions of the fascial network that have developed as a result of injury or through growth under chronic muscular tension. It is a combination of sustained moderate pressure on myofascial tissues and stretching of the muscles while the fascia is slowly moved, stretched, and lengthened. Myofascial release techniques can be very effective in treating pain from muscle spasm, myofascial trigger points, and fibromyalgia (50). Possible contraindications to myofascial release are malignancy, severe osteoporosis, osteomyelitis, acute rheumatoid arthritis, open wounds, healing fractures, cellulitis, obstructive edema, aneurysm, advanced diabetes mellitus, hematoma, or systemic/localized infection.

Massage

Massage is an effective nonpharmacological pain management tool that can reduce the emotional component of pain, strengthen coping ability, promote a sense of control, reduce pain and fatigue, and promote sleep. Massage has been shown to significantly reduce blood pressure, anxiety, distress, and nausea. It also increases superficial blood flow, improves venous and lymphatic return, enhances muscle relaxation, and minimizes formation of adhesions following acute soft tissue injury (50–52). An added bonus may be that the recipients feel someone is helping to reduce their distress.

Massage is the systematic manipulation of muscles, tendons, and ligaments without change in joint position, by mechanically stimulating tissues through rhythmic pressure and stretching (50,52,53). The physiological effects of massage are divided into two categories: mechanical effects and reflexive effects (50). Mechanical effects involve the stretching of muscle, elongation of fascia, and

mobilization of soft tissue, scar tissue, or restrictions. The effect of massage on muscles includes increased range of motion, improved blood flow to skeletal muscle as well as venous return, and hindered muscle atrophy following injury. The pain and discomfort of trigger points is also decreased. The effect of massage on skin includes increased temperature as well as stretching and breakdown of scar tissue and adhesions between skin and subcutaneous tissue. The reflexive effects of massage include sedation, decreased tension, and increased blood flow. Stimulation of large cutaneous nerve fibers blocks transmission of pain signals resulting in decreased pain. Lymphatics and small capillaries dilate, increasing blood volume, blood flow, and temperature in the area being massaged. This has the added effect of increasing the removal of waste products as well as increasing oxygen supply to the area (50).

A variety of massage techniques can be used including effleurage, friction, petrissage, tapotement, and vibrations. Effleurage is from the French word *effleurer*, which means to “touch lightly” or “skim over.” It is a wide-area stroke that can be done using the palms of two hands, the palm of one hand, the knuckles, the ball of the thumb, and the fingertips. The aim is to massage in a rhythmic, smooth, flowing, gliding manner in an upward direction using constant pressure. Effleurage begins in the periphery and moves toward the heart. Light effleurage promotes relaxation, alleviates pain, and encourages sleep. Deep effleurage improves circulation, stretches and relaxes tense muscles, aids lymphatic drainage and elimination of waste products, and improves elasticity of skin. The use of oil or lotion may enhance the effect of effleurage. This technique can be easily done by anyone.

Friction massage uses the thumb and tips of the fingers or the palm of the hand to move over a small area around the joints using a circular motion. A parallel or perpendicular application to muscles, tendons, or ligaments may be used (52). Friction massage makes the joints, tendons, and muscles more limber by breaking up and facilitating the removal of deposits that may impede joint mobility. It aids in decreasing swelling after nerve injury, absorption of local edema or effusions, and reducing local muscle spasm (50).

Petrissage is a way to treat muscles by repeatedly grasping and releasing tissue using kneading, lifting, pressing, and rolling out motion. It is performed with one or both hands, with two thumbs, or with the thumbs and fingers. Heavy pressure is used for deep kneading and light pressure for superficial kneading. Petrissage increases tissue nutrition, strengthens muscles, relieves intestinal congestion, and facilitates elimination of waste products. It also boosts lung activity and cellular respiration, and tones nerve endings (50).

Tapotement involves hacking, tapping, clapping, and beating using a series of brisk blows in rapid succession. This method uses percussion to increase blood supply, soothe nerves, and strengthen muscles.

Vibration is achieved using shaking or fine tremulous movement of the hand or fingers firmly against the body. This causes the part to vibrate, which has a soothing effect. In addition, vibration stimulates circulation, glandular activity, and nerve plexuses.

Studies have shown that simple hand and foot massage done for 5 minutes on each extremity, for a total of 20 minutes, accelerates the rate at which pain unpleasantness, intensity, and distress decline postoperatively (54,55). Massage has been found effective for control of postoperative pain following total joint replacement, coronary artery bypass grafting, and abdominal laparotomy, as well as in the management of acute sickle cell pain (56–59).

Clinically, massage can be useful in the treatment of adhesions, muscle spasm, myositis, bursitis, tendonitis, muscle strain, back pain, myofascial pain, and arthritis (50,52). Massage is contraindicated in areas where arteriosclerosis, thrombosis or embolism, severe varicose veins, acute phlebitis, cellulitis, synovitis, abscess, skin infection, open wounds, cancer, and acute inflammation of the skin or joint are present (50).

PSYCHOLOGICAL TECHNIQUES

There are a variety of psychological techniques that are useful for the management of pain. Many are learned over time with repeated practice, making them beneficial for chronic rather than acute pain. However, there are some psychological techniques that can successfully be used for acute pain. Pain is a very complex interaction between physical, psychological, emotional, and spiritual factors that affect the way one responds to pain. These techniques change the perception of pain, alter pain behavior, and provide a sense of self-control. Psychological techniques most applicable to acute pain management are distraction, music, relaxation, and imagery. Although these methods will be presented as separate entities, combining psychological techniques is often more beneficial than using any one technique.

Distraction

Distraction uses everyday activities to divert attention away from the pain sensation to a pleasant or neutral stimulus. Distraction is a common technique used in the management of acute pain in children. It is based on the premise that the mind's capacity for processing information is limited. Allocation of attention to one task limits attention that may be given to another. In order for distraction to be effective, pain should be brief and at a mild-to-moderate level, such as procedural pain. It also requires the involvement of the one experiencing pain. The more senses that are involved, the more likely it is that distraction will be helpful. Common distraction techniques include reading, conversation, watching television, humor, and music.

Music

Music is a form of distraction that uses pleasing sounds to focus attention on something other than pain. Music is comforting and has been shown to make pain more bearable and to improve mood, as well as provide a sense of control over the pain sensation. Music has been found to reduce pain during debridement of burns, and decrease blood pressure, heart rate, and opioid consumption after surgery (60–64). It has also been shown to decrease the distress of active labor and reduce pain associated with cancer (65,66). The type of music selected should be the music the patient most enjoys. Music works best as a form of distraction if the patient interacts with the music in the form of singing along, snapping fingers, or tapping or moving the feet to the beat. Music therapy should be done several times a day for best results. If at all possible, the patient should not be disturbed during times of music therapy in order to give full attention to the music.

Relaxation

There are many relaxation techniques that are employed in the management of pain. Relaxation is known to decrease heart rate, blood pressure, muscle tension,

and pain, and to improve sleep. In addition, it enhances coping by reducing anxiety and increasing self-control (67). Relaxation techniques are easily taught and quickly learned, but require reinforcement.

Relaxation therapy has been used for many years. Johannes Schultz was a Western scientist who conducted early research on relaxation and introduced autogenic training in the 1920s. At about the same time, Edmund Jacobson began to study progressive muscle relaxation. Herbert Benson, in 1975, was the first to describe the physiological effects of relaxation that came to be known as "the relaxation response," which included a decrease in the heart rate, blood pressure, respiratory rate, and brain wave activity (68). Relaxation has been found to reduce cancer pain and pain following gynecological and abdominal surgery (69–72). Relaxation has even been shown to be as effective as opioids in increasing incentive spirometry volumes following thoracotomy (73). Relaxation techniques should be done with the patient in a comfortable position and in a comfortable environment that includes privacy, freedom from noise and distractions, as well as dim lighting (68).

Diaphragmatic breathing is a simple, yet effective, way to induce relaxation. It promotes internal quiet and relaxing warming of the extremities. This type of breathing uses the abdominal wall, rather than the chest wall. In teaching the patient this technique, the patient should be told to place a hand on his or her chest, take a deep breath, and feel the chest wall rise. The patient should then be instructed to place a hand on his or her abdomen and make it rise with each breath instead of the chest. Instruct the patient to breathe in through the nose to the count of four, or whatever is comfortable for the individual, hold the breath to the count of four, then exhale through the mouth to the count of four. The patient's respiratory rate should be approximately five to seven breaths a minute, as tolerated. This exercise should continue for 20 minutes. The patient should be encouraged not to worry if deep relaxation does not occur immediately, but rather to allow it to occur naturally (68). Combining diaphragmatic breathing with visualization is a particularly effective way to control acute pain. Ask the patient to imagine that each breath inhaled reaches the pain and each breath exhaled takes the pain with it. Diaphragmatic breathing for relaxation should be avoided in those with breathing difficulties.

Autogenics involves generating a feeling of warmth or heaviness by using statements such as "my legs are heavy" or "my arms are warm" to induce relaxation (68,74). The phrase is repeated over and over with the eyes closed for 20 minutes.

Progressive muscle relaxation is an active exercise that involves the systematic tensing and relaxing of all the major muscle groups in the body one group at a time. The patient is instructed to tighten the large muscle groups, hold for five seconds, and then gradually release. A typical pattern might start with the jaw, then the neck, shoulders, upper arms, lower arms, hands, abdomen, buttocks, thighs, lower legs, and feet. This exercise should be finished by tensing the entire body and relaxing the entire body four to five times. This process should be repeated at least once. To benefit from this relaxation technique, it is recommended to be practiced for 10 minutes twice a day (75).

Imagery

It has long been thought that imagery can be used to decrease pain by enhancing endorphin secretion. Imagery is a form of relaxation that assists the patient in

imagining a place he or she would like to be and incorporates most senses—sight, sound, touch, and smell. Using visual images of sights, sounds, music, and words, the patient creates a state of focused concentration that induces a feeling of empowerment and relaxation. The patient uses his or her imagination to influence psychological and physiological states. The goal is to divert one's attention and focus away from an unpleasant experience to a pleasant and relaxing one (75).

Imagery has been found effective in reducing pain, including pain during childbirth; that from cancer; postoperative pain following anterior cruciate ligament replacement, cardiac surgery, total joint replacement; and procedural and acute trauma pain (75–80). Imagery has been demonstrated to allow for reductions in opioid requirements, sometimes by 50% or more (78–82). Following anterior cruciate ligament (ACL) replacement, patients who utilized imagery had statistically significant improvement in physical and psychological outcomes including strength and extension of the affected knee for up to 24 weeks after surgery (78). In addition, patients using imagery techniques reported ability to manage stress, empowerment, control of recovery and overall wellness, high levels of satisfaction with care and treatment, improved ability to cope, less anxiety, and had reduced lengths of stay (75,78–80,83).

As with any therapeutic intervention, imagery is not appropriate for all patients and should be reserved for those who show an interest in or are open to alternative therapy, as they are more likely to have a positive response. Patients must be able to concentrate for at least 20 minutes. Imagery is not indicated for those who experience excessive sedation, exhaustion, have a full bladder, or for those with severe acute pain. Patients must be able to control their own breathing; however, being on a respirator does not necessarily exclude one from being a candidate for this therapy (83). Imagery can, rarely, result in disturbing thoughts, fear of losing control, and uncomfortable sensory experiences. Therefore, imagery should be avoided in individuals with posttraumatic stress disorder or thought disorders, such as dementia or schizophrenia, or those taking medication for thought disorders (84).

To practice the use of imagery, a setting with minimal distracting noise or interruption should be chosen. The room should be at a comfortable temperature with the patient in a comfortable position. Imagery can be guided or autogenic. Guided imagery involves another person who verbally guides the patient into a relaxed, focused state through slow and quiet instruction. For example, a session might begin by the guide telling the patient to close his or her eyes and begin breathing deeply in through the nose and out through the mouth. The patient should be encouraged to feel calmer and more peaceful with each breath. Suggestions may be added, such as “imagine your pain as bright red color and change it to a calming blue,” or “imagine your pain as a sharp knife and change it to a feather.” Autogenic imagery is a technique whereby the patient uses his or her own mind as a nonverbal guide to a relaxed focused state. Different images can be used for different distresses. To reduce anxiety, the patient should be guided to revisit a safe and happy place. To reduce fear, the patient should be guided to a place where he or she feels completely safe from harm. To reduce exhaustion and fatigue, the patient should be guided to a place of great energy and vitality, or a place of rest, renewal, and revitalization. To reduce pain, the patient should create a mental image of the pain and then change it. Imagery should be used at least 20 minutes a day. It is most effective if used before acute pain becomes severe in intensity.

CONCLUSION

Nonpharmacological pain management methods should never be used as a substitute for opioid analgesics or to extend the time between doses of analgesics for acute pain. Although these modalities may not be effective for everyone, they are safe for most patients, and therefore deserve a trial to determine its effectiveness. Nonpharmacological modalities are simple, inexpensive, and can be utilized by almost any caregiver. The potential benefits are many and the drawbacks few.

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Perioperative epidural analgesia and patient-controlled epidural analgesia

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INTRODUCTION

Epidural Analgesia is one of the most effective methods of providing perioperative pain control. It is ideal for patients undergoing thoracic, abdominal, and certain lower extremity orthopedic surgeries. Epidural catheters are best placed preoperatively in an awake and cooperative patient to minimize the risks. The most common medications infused through the catheter are opioids and/or local anesthetics, which can be utilized both for postoperative analgesia and intraoperative analgesia/anesthesia with or without a general anesthetic.

Postoperatively, the epidural catheter can be connected to a pump infusing the medication either on a continuous hourly basis, or with a demand capability for the patient to administer self-bolus doses at preset intervals.

Epidurals can decrease postoperative splinting, resulting in improved pulmonary mechanics. They can also lead to earlier ambulation and a decreased incidence of postoperative ileus. Choosing the appropriate patient who might benefit from epidural analgesia involves correlating the type and extent of surgery with a thorough evaluation of patient history, physical exam, and any necessary laboratory studies. It is important to review the risks and benefits with the patient and obtain informed consent prior to proceeding with epidural catheter placement (Table 10.1).

HOW EPIDURAL ANALGESIA AND PCEA WORK

The extent of epidural analgesia provided is determined by the type of medication injected and the level at which the catheter is placed. Most commonly, infusions of opioids alone, local anesthetics alone, or a combination of the two are utilized.

Opioids principally act at spinal and supraspinal levels through specific receptors that decrease the release of neurotransmitters and stop the propagation of pain signals. Intravenous (IV) opioids have to be absorbed systemically before exerting their effect on the spinal cord and brainstem. This can lead to a higher potential for side effects. Epidural opioids are delivered directly to the site of action, thereby minimizing the side effect profile.

Local anesthetics in the epidural space provide analgesia by blocking the conduction of nerve impulses to the brain without directly modulating the neurotransmitter levels. Some centers are starting to place clonidine and other vasoactive agents into the epidural space for analgesia because of their ability to affect synaptic transmission by modulating descending pathways.

POTENTIAL ADVANTAGES OF EPIDURAL/PCEA THERAPY

- Epidural analgesia may provide better pain control with fewer side effects than oral or IV medications.
- The medications are delivered directly to their primary site of action, allowing for dose reductions to one-tenth of that required when medications are delivered intravenously, intramuscularly, or subcutaneously.

TABLE 10.1 Common Terms to Be Familiar with in This Chapter

PCA	Patient-controlled analgesia intravenously
ACA	Anesthesia-controlled analgesia intravenously
PCEA	Patient-controlled epidural analgesia
Demand rate	Dose of medication in mg/ μ g administered every <i>X</i> min (i.e., 2 mg/10 min)
Basal rate	Dose of medication in mg/ μ g administered every hour on continuous basis (i.e., 1.5 mg/hr)
Bolus dosing	Extra doses that can be administered by nursing staff for breakthrough pain not relieved with both demand and/or continuous dosing

TABLE 10.2 Contraindications to Epidural/PCEA

Absolute	Relative
1. Localized skin infection	1. Spine deformity
2. Septicemia or bacteremia	2. Previous spine surgery
3. Abnormal coagulation profile	3. Increased ICP
4. Patient refusal	4. Fever
	5. Patient unable to remain still during procedure

- Combining agents such as local anesthetics and opioids improves pain via synergistic action and lowers the potential for side effects related to each drug. Reducing opioid exposure may also reduce the occurrence of postoperative ileus.
- Epidural analgesia may reduce the occurrence of postoperative respiratory complications such as atelectasis.
- Earlier postoperative ambulation with epidural analgesia may reduce the incidence of deep venous thrombosis (DVT).

INITIATING EPIDURAL ANALGESIA AND PCEA

Indications

Epidural analgesia and PCEA should be used to provide intraoperative and postoperative analgesia for abdominal, thoracic, and lower extremity surgeries.

Timing of Placement

Preoperative placement in an awake patient is safest and allows for intraoperative use.

Risks

Risks that should be discussed with the patient prior to catheter placement include pain, infection, bleeding, spinal headache, and rarely neurological injury or paralysis.

Contraindications

See Table 10.2.

PATIENT SELECTION

As with any medical procedure, proper patient selection is key to the success of this technique. Failure to recognize contraindications or possible technical difficulties that may occur with these techniques can result in patient injury.

History

It is important to obtain a full medical history prior to initiating neuraxial anesthesia. Factors that may influence selection of these techniques in an individual patient may include the following:

- The type of procedure the patient is undergoing.
- The presence of a prior history of back pain or radiculopathy.
- A previous history of surgical or interventional treatment for back pain.
- Previous epidural catheter experience, including obstetric epidurals.
- Prior complications with an epidural placement, including postdural puncture headache.
- A history of allergies or adverse reactions to medications. Nausea and gastric upset related to opioids are not true allergies and should be discussed with the patient. One should be most concerned about any history of anaphylactic reactions to opioids.
- The presence of certain medical conditions such as cardiovascular or pulmonary disease may make the use of neuraxial analgesic techniques desirable. These techniques may help to reduce hemodynamic stress responses to surgery and pain. They may also allow for reductions in opioid dosing as compared with systemic administration, which may decrease the likelihood of adverse respiratory events in patients with chronic obstructive pulmonary disease (COPD) or obstructive sleep apnea (OSA).

Physical Examination

In evaluating a potential candidate for epidural analgesia or PCEA, the clinician should pay particular attention to the following during physical examination.

- The spine should be visually inspected for any deformity.
- Localized infection at the site of catheter placement should be ruled out. Infection away from the epidural site is not a contraindication to epidural catheter placement, however, bacteremia or septicemia are.
- Review any imaging studies if available. It may help to know the height of intervertebral disks and degree of spinal stenosis or other spinal pathology present.

Laboratory Analysis

The most likely tests that may be needed prior to neuraxial needle placement involve assessment of hemostatic variables. Normal healthy individuals do not need coagulation profiles to be checked unless the following:

- The patient is taking Coumadin[®] or heparin
- There is a history of alcoholism or liver disease
- There is a history of bleeding diathesis

Platelet Count

Typically, platelet counts greater than 100,000 are adequate for epidural placement. The absolute lowest acceptable platelet count may vary from practitioner to practitioner, but generally is no lower than 70 to 75,000. If a low platelet count is identified on laboratory testing, an effort should be made to identify whether this is significantly different from previous tests. Trending is perhaps more important under this circumstance than the absolute count. A rapid drop in platelet count

over a few days indicates that platelet consumption is faster than production. The physician should look for an explanation for this trend, such as recent administration of chemotherapy. In this case, the patient may require platelet transfusion prior to epidural catheter placement.

Prothrombin Time/Partial Thromboplastin Time/International Normalized Ratio

Obtaining a prothrombin time and international normalized ratio (PT/INR) is important in patients taking Coumadin. Most institutions rely on the INR as the primary measure of the extrinsic clotting pathway. The half-life of Coumadin is 36 hours. Therefore, Coumadin should be stopped for a minimum of five days before planned epidural catheter placement, and the coagulation profile has to be normalized before the procedure. Nutritional factors and significant hepatic disease may contribute to elevations in the PT/INR as well. The widely accepted normalized value for an INR is in the range of 0.8 to 1.2. Fresh frozen plasma (FFP) should be given to patients with high INR requiring emergency surgery and when an epidural catheter is a must. An elevated INR due to nutritional reasons, however, does not respond to FFP. Vitamin K should be given to patients with a high INR because of nutritional reasons. Partial thromboplastin time is a measure of intrinsic clotting pathways and normally ranges from 22 to 35 seconds. Elevated Partial Thromboplastin Time (PTT) values are expected in patients on IV heparin. Heparin has an elimination half-life of approximately 1.5 hours, and should be discontinued at least 6 hours prior to planned neuraxial techniques. An elevated PTT may respond to protamine but its administration is not practical.

ANTICOAGULANTS AND NEURAXIAL ANESTHESIA

Warfarin Therapy

- Warfarin (Coumadin) must be stopped four to five days before the planned procedure
- A PT/INR should be measured before the procedure
- Concurrent medications [nonsteroidal anti-inflammatory drugs (NSAIDs), heparin, etc.] can increase the risk of bleeding and this may not be reflected on PT/INR

Antiplatelet Therapy

Antiplatelet agents include the thienopyridines, comprised of ticlopidine (Ticlid[®]) and clopidogrel (Plavix[®]), and the glycoprotein IIb/IIIa receptor antagonists, consisting of abciximab (ReoPro[®]), eptifibatid (Integrilin[®]), and tirofiban (Aggrastat[®]).

- Ticlopidine and clopidogrel inhibit ADP induced platelet aggregation. Currently, the American Society of Regional Anesthesia (ASRA) guidelines recommend discontinuation of ticlopidine 14 days and clopidogrel 7 days prior to neuraxial anesthesia.
- Use of the glycoprotein IIb/IIIa receptor antagonists is contraindicated within four weeks of surgery. These agents profoundly affect platelet aggregation and neuraxial techniques should be avoided until recovery of platelet function has occurred. Eptifibatid interferes with normal platelet aggregation for 24 to 48 hours. Tirofiban and abciximab interfere with platelet aggregation for four to eight hours.

- There is no specific laboratory test, including bleeding time, which can guide antiplatelet therapy. The above guidelines are based on product labeling and surgical reviews, but the actual risks are unknown with regards to use of these agents around the time of neuraxial anesthesia.

NSAIDs

NSAIDs inhibit platelet aggregation through inhibition of cyclooxygenase. This prevents the formation of thromboxane, a potent stimulator of platelet aggregation. Aspirin irreversibly inhibits cyclooxygenase, but the other NSAIDs exhibit competitive, reversible binding of cyclooxygenase.

- NSAIDs do not need to be discontinued prior to neuraxial anesthesia. There is no evidence that they increase the risk of spinal or epidural hematoma.
- When aspirin and clopidogrel are used together, it is recommended that they be stopped 8 to 10 days prior to epidural catheter placement.

Unfractionated Heparin

- Subcutaneous (SQ) heparin administration is not a contraindication for neuraxial blocks.
- Intraoperative IV heparin may be administered one hour after epidural needle or catheter placement.
- An indwelling epidural catheter may be removed two to four hours after the last dose of IV heparin is given.
- In patients receiving prolonged heparin therapy, a platelet count should be checked prior to neuraxial blockade to exclude heparin-induced thrombocytopenia (HIT).
- There is insufficient data to determine the risk of neuraxial hematoma after the administration of full anticoagulation required for cardiac surgery. Close neurological monitoring is advised in patients receiving neuraxial anesthesia in conjunction with such procedures.
- Heparin used in combination with fibrinolytics carries a higher risk of epidural hematoma. Extreme caution is warranted when considering neuraxial anesthesia under such circumstances.

Low-Molecular Weight Heparin

- Neuraxial blocks should be postponed for 12 hours after a thromboprophylactic dose of LMWH. Typical thromboprophylactic doses of enoxaparin are 0.5 mg/kg every 12 hours or 1 mg/kg daily.
- When therapeutic doses of LMWH are used, neuraxial blocks should be postponed for 24 hours. Therapeutic use of enoxaparin involves administration of doses of 1 mg/kg every 12 hours or 1.5 mg/kg daily.
- Neuraxial block should be avoided if LMWH is given within two hours prior to surgery.
- The first postoperative single daily dose of LMWH may be given six to eight hours after surgery, and subsequent doses may be given 24 hours after the previous dose.
- The first postoperative dose of LMWH to be given on a twice daily dosing schedule may be administered 24 hours after surgery.

Herbal Therapy

- Herbal medications alone do not appear to increase the risk of epidural or spinal hematoma. Some herbal compounds that are thought to have potential adverse effects on coagulation include coenzyme Q10, ginseng, green tea, papain, and vitamin E.
- There is no data regarding use of herbal medications in combination with anticoagulant therapy.

Thrombolytic Therapy

- Thrombolytic therapy should be avoided for 10 days after neuraxial blockade.
- There is no data regarding the time interval required between administration of thrombolytic therapy and the performance of neuraxial blockade. Caution and close monitoring for neurological changes is warranted in patients considered for neuraxial blockade after receiving thrombolytics.

Catheter Removal

- Catheter removal during single drug therapy with aspirin, NSAIDs, and SQ heparin appears safe. When SQ heparin is being used, catheter removal should occur eight hours after the last administered dose.
- When warfarin therapy is initiated, safe catheter removal can be performed when the INR is <1.5 (with clotting factor levels $>40\%$).
- When IV heparin is being administered, it should be stopped four hours prior to planned catheter removal and a PTT should be obtained before the catheter is removed.
- When LMWH is being administered, catheter removal should be postponed 12 hours after administration of thromboprophylactic doses and 24 hours after full treatment doses used for management of thromboembolic disorders. Additional LMWH dosing should be delayed at least two hours after catheter removal.

TECHNICAL ASPECTS

When initiating neuraxial anesthesia, strict sterile conditions should be maintained throughout the procedure.

Selection of Location for Catheter Placement

When deciding where to place an epidural catheter, consideration of the location of the surgical site is critical to the success of this analgesic technique. Appropriate spinal levels for catheter insertion and associated landmarks based on surgical site are outlined in the following table (Table 10.3).

Positioning

Placing the patient in a seated position with the neck flexed minimizes lumbar lordosis and opens the space between the spinous processes to facilitate the midline approach for needle placement. Flexing the spine does not increase the trans-laminar space when the paramedian approach is selected. Alternatively, the patient

TABLE 10.3 Location of Epidural Catheter Placement

Type of surgery	Level of catheter placement	Landmarks
Thoracic	T4-T6	Level of nipple
Upper abdominal	T6-T8	Inferior border of scapula
Midlower abdominal	T9-T10	Tip of xiphoid process
Lower extremities	L2-L3	Above iliac crest (L4-L5)

can be placed in the lateral decubitus position with the head and knees flexed to maximally open the intervertebral space.

Landmarks

Lumbar Epidural

Palpate the spinous processes and define the midline or any curvature of the spine. Draw an imaginary line that connects the iliac crests. That line will pass through the body of L4. The space above this line is L3-L4, and that below it is L4-L5.

Thoracic Epidural

An imaginary line drawn to connect the inferior tips of the scapulae passes through the T7 vertebra. The space above this line is T6-T7, and the space below it is T7-T8. Winging of the scapula will move this line cephalad. Fluoroscopy may be used to confirm the exact interspace if needed.

Technique

The most common method to identify the epidural space is the “loss of resistance” technique. This can be performed using either air or fluid.

Procedure

The patient should be placed in the appropriate position and monitors such as a blood pressure cuff and pulse oximeter should be applied. After sterile preparation and draping, local anesthesia should be administered to the appropriate needle insertion site. A 17-gauge stylet Tuohy is used for catheter placement. The needle is slowly and gently advanced in increments of 0.5 to 1 mm while performing the loss of resistance technique. This may be achieved using a plastic or glass syringe designed especially for this technique. After filling the syringe with 3 mL of air or fluid (saline), the syringe is attached to the needle and the needle is advanced until a loss of resistance is perceived. After negative aspiration for blood or cerebrospinal fluid (CSF), a catheter is slowly threaded into the epidural space. During this process, patients may feel transient paresthesias, but if these paresthesias are sustained or intense, the needle and catheter should be removed and repositioned. The epidural catheter is typically threaded 3 to 5 cm into the epidural space. Longer lengths of insertion may be associated with intrathecal or intravascular migration, or may allow for exit of the catheter from the spinal canal through an intervertebral foramen. Shorter insertion lengths may increase the risk of catheter dislodgement. The needle should then be removed and the catheter secured with a dressing and tape to prevent inadvertent migration. It is best to clearly label the catheter “for epidural use only” to minimize the potential for accidental medication or fluid administration through the epidural catheter.

Test Dose

Administration of a test dose of 3 mL of 1.5% lidocaine with 1:200,000 epinephrine is used to detect accidental intravascular or intrathecal catheter placement. Increases in heart rate by 15 beats/min within 60 seconds of administration of the test dose are indicative of intravascular catheter location, whereas significant sensory motor block indicates intrathecal catheter placement. It should be kept in mind that negative aspiration for blood or CSF does not definitively rule out intravascular or intrathecal catheter placement.

MAINTENANCE OF EPIDURAL/PCEA THERAPY

Medications Used for Epidural Analgesia

Medications used for epidural analgesia include local anesthetics (e.g., bupivacaine, lidocaine, and ropivacaine), opioids (e.g., morphine, fentanyl, and hydromorphone), or combinations thereof. The use of combined local anesthetic and opioid is often superior to one drug alone in terms of pain control and reduction in side effects of therapy. Adequate pain control often involves finding a balance between effective analgesia and side effects.

Common Medications Used for Epidural Analgesia

Local anesthetics

- Bupivacaine 0.125% (1.2 mg/mL)
- Bupivacaine 0.1% (1 mg/mL)
- Bupivacaine 0.05% (0.5 mg/mL)
- Ropivacaine 0.2% (2 mg/mL)

Opioids

- Morphine 50 µg/mL
- Fentanyl 2 to 5 µg/mL
- Hydromorphone 10 µg/mL
- Meperidine 2 mg/mL

Modes of Epidural Drug Delivery

Continuous Infusion Only

- This mode provides baseline, steady-state analgesia.
- This mode is often used alone, especially when patients are sedated or unable to use the demand delivery function.

Demand Only

- This mode provides relief of breakthrough pain, but should not be used as a means to achieve steady-state analgesia.

Continuous Infusion Plus Demand

- This is the most commonly used mode to provide both steady-state analgesia and relief of breakthrough pain.

Epidural PCEA Orders

Upon initiation of PCEA, medication(s) should be selected, and a continuous, demand, or continuous plus demand mode should be ordered.

Most commonly, combinations of local anesthetic and opioid are selected for PCEA administration (e.g., bupivacaine 0.125% and fentanyl 2 µg/mL). Bolus doses are usually set at 1 to 2 mL with demand doses of 2 mL every 15 minutes. When continuous infusions are included, typical rates of infusion are 5 to 14 mL/hr. It is recommended that low doses be selected upon initiation of therapy with upward titration to effect.

If pain control is inadequate after initiation of PCEA, the rate of infusion should be increased and/ or if a demand dose is available, the dose should be increased or the lockout time should be decreased. If necessary, extra boluses may be administered by nursing personnel to control acute pain (e.g., 1 mg morphine every two hours p.r.n.).

If a patient is experiencing side effects during PCEA therapy, the continuous infusion can be discontinued (if applicable), the demand dose may be decreased, or the lockout interval increased. Additional treatments, such as antiemetic therapy may be used if indicated as well. Standing orders should include contingencies for the management of side effects such as nausea, sedation, and respiratory depression.

Monitoring of the Catheter

Close monitoring of patients with an indwelling epidural catheter is critical. During daily follow up visits, the following items should be assessed.

- Check the catheter insertion site for evidence of infection (redness, tenderness, or exudate).
- Check white blood cell counts (WBC) for evidence of occult infection (look for a trend rather than an absolute number).
- Check the patient's temperature curve (increased temperatures on postoperative day 1 may be due to postanesthesia/surgery atelectasis).

If a patient has a persistent temperature with an upward WBC trend, and if there is no clear source of infection, the epidural catheter should probably be removed, because a negative local examination for infection at the catheter site does not rule out an epidural infection.

PCEA Troubleshooting

During PCEA therapy, common problems that may require assessment include loss of analgesia, numbness or motor weakness, and unilateral block. The following discussion will address potential causes for these complaints and provide means to remedy them.

Loss of Analgesia

If lack of analgesia is present immediately after catheter placement, the catheter should be checked to assess whether it is in the epidural space. The catheter and connections should be examined for evidence of leakage. If leakage at a connector is evident, this may indicate that the patient is not receiving the anticipated amount of drug. Any loose connections should be tightened and the patient should be

reassessed after delivery of an additional drug bolus. If there is no evidence of a significant leak from the delivery tubing, the catheter should be disconnected from the tubing and aspirated for evidence of CSF or blood. If either fluid is freely aspirated from the catheter, the catheter should be removed and replaced. An additional test dose may be administered in the absence of CSF or blood return to further assess for catheter misplacement. If lack of analgesia persists after these manipulations, and after administration of additional analgesic mixture, it should be assumed that the catheter is not in the epidural space. It should be removed and replaced in an effort to reestablish analgesia.

When analgesia is lost after establishment of initial analgesia, the situation should be assessed as described above for lack of analgesia immediately after catheter placement. Additionally, the catheter insertion site should be checked for evidence of catheter kinking, movement, or dislodgement. The pump should also be checked for appropriate settings and battery life to rule out pump malfunction as a source of loss of analgesia. After these assessments, the epidural dose should be increased in attempt to restore analgesia. If these interventions do not result in return of analgesia, consider replacing the epidural.

Numbness or Motor Weakness

If a patient develops complaints of significant numbness or motor weakness, the infusion of local anesthetic should be discontinued. The catheter should be assessed for intrathecal migration by aspirating for CSF. The patient should have regular neurological assessments to identify recession of numbness and weakness. If symptoms persist significantly after cessation of infusion, the catheter should be removed, and it may be necessary to obtain MRI imaging to rule out epidural hematoma or abscess. If suspicious for these complications, prompt neurosurgical consultation is essential.

Unilateral Blockade

If a patient develops unilateral block with epidural infusion, the catheter should be withdrawn 1 to 2 cm. The patient should be placed in the lateral decubitus position with the unblocked side down, and the catheter should be rebolused with epidural solution. If this does not resolve the unilateral block, consideration should be made for replacement of the epidural catheter.

COMPLICATIONS

Complications related to epidural catheter placement and infusion may include the following:

- Systemic toxicity may occur with inadvertent intravascular injection of local anesthetic. This may manifest with seizures.
- Hypotension may occur because of sympathectomy associated with local anesthetic administration. Adequate hydration to maintain appropriate intravascular volume may help to reduce this effect.
- Accidental intrathecal injection of local anesthetic may cause high/total spinal. Apnea may be a possible consequence of high spinal, and thus this complication may be life threatening.
- Postdural puncture headache may occur with inadvertent dural puncture during epidural needle placement.

- Shearing of the epidural catheter may occur, especially if the catheter is withdrawn through the epidural needle.
- Respiratory depression may result from administration of high doses of epidural opioid, or if opioid is inadvertently administered intrathecally.
- Epidural hematoma may occur, especially in the presence of coagulopathy or anticoagulant therapy. It should be noted that 50% of reported epidural hematomas have occurred at the time of catheter removal (this complication is not strictly related to needle placement).
- Epidural abscess.
- Low back pain has been reported after epidural placement. However, the literature does not support an increased incidence of back pain after epidural placement. Any contributing local tissue reaction to medication or the catheter should resolve fairly quickly after cessation of epidural analgesia.

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Upper-extremity regional anesthetic techniques in the management of postoperative pain

James Rasinsky

INTRODUCTION

There are many advantages to the application of regional anesthesia. It can be used as the sole anesthetic for surgical procedures or for the management of postoperative pain. Regional anesthesia can also be used in conjunction with a general anesthetic, providing a smooth transition to the recovery room and into the postoperative period. Perception of pain leads to an increased stress response, causing the release of endogenous catecholamines. Hypertension, tachycardia, and tachypnea are the result of catecholamine discharge, which should be minimized, particularly in postoperative patients who are predisposed to myocardial ischemia.

When used with general anesthesia, upper-extremity blocks provide a balanced approach, which decreases the requirements of volatile inhalational agents as well as those of intravenous anesthetic infusions. When used as the sole anesthetic, the effects of general anesthesia such as delayed emergence, postoperative sedation, and nausea/vomiting are greatly minimized or eliminated. Under urgent conditions, an awake patient with an upper-extremity sensory motor block poses less risk of aspiration due to increased ability to protect his or her own airway.

It is not uncommon for patients who received upper-extremity regional anesthetics to meet discharge criteria from the postoperation anesthesia care unit more readily (1). They are more alert and are more able to effectively manage their pain from surgical procedures. These anesthetics are well suited for outpatient surgery and provide continued pain relief with the duration of the block dependent on practitioner expertise, the specific local anesthetic used, and the concentration and volume of the selected local anesthetic (2).

The brachial plexus is composed of cervical nerve roots C5 through T1. They in turn give rise to the musculocutaneous, median, ulnar, and radial nerves. These peripheral nerves provide motor and sensory innervation to the upper extremity and are the ultimate targets of upper-extremity regional anesthetics. There are multiple sites to approach these nerves as they exit from the spinal cord in the neck and course distally toward the hand (3). The nerves can be blocked proximally as a unit (brachial plexus), or distally individually, depending on the surgical procedure and need for pain management.

It is important to have intimate knowledge of the anatomy involved when blocking the brachial plexus, as it is possible to miss specific nerves that might diverge from the plexus proximal to the site of injection. Awareness of the relationship of nerves to adjacent vascular structures is also important. These relationships may serve as both landmarks for injection of local anesthetic or as areas of caution to avoid complications associated with intravascular injection. Various approaches have their advantages and disadvantages, which will be discussed as this chapter evolves (Fig. 11.1).

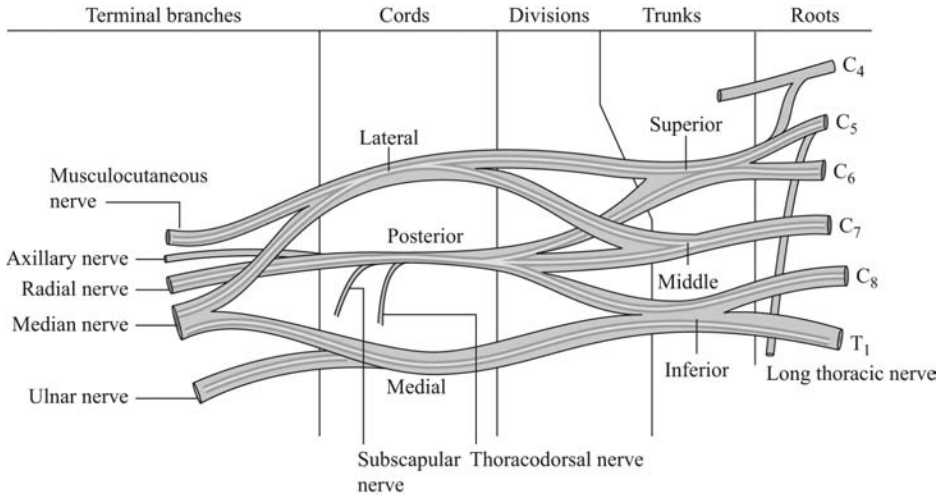


FIGURE 11.1 Anatomy of the brachial plexus.

BRACHIAL PLEXUS BLOCKS

Interscalene Block

The interscalene block may be used for surgery of the shoulder and of the upper arm (4). It may also be used effectively for postoperative pain management and is well tolerated by most patients. One must cautiously approach patients with a significant history of pulmonary dysfunction because of the probability of blocking the phrenic nerve on the side being injected and further exacerbating their condition.

While performing an interscalene block, the patient is placed in the supine position with the head turned away from the side being blocked. The patient should be asked to lift his or her head against gravity to help identify the posterior border of the clavicular head of the sternocleidomastoid (SCM) muscle. Asking the patient to inhale against a closed glottis will also help to locate your landmarks. One must next identify the cricoid cartilage (level of C₆) because it is at this level that you must extend a lateral line to intersect with the posterior border of the clavicular head of the SCM muscle (Fig. 11.2).

The interscalene groove is formed where the Scalenus Anterior and Scalenus Medius meet slightly posterior to the clavicular head of the SCM. It can be palpated with your fingers as they roll off the posterior border of the SCM at the level of C₆. After prepping the neck with an alcohol or betadine solution, raise a skin wheal with local anesthetic and insert a 3-cm, 22-gauge short beveled insulated electrical stimulator needle perpendicular to the skin. The needle should be aimed slightly caudad and slightly posterior. The depth of the brachial plexus is rather superficial at 1 to 2 cm, and care should be used to avoid inadvertent epidural, subarachnoid, or intravascular injection (Fig. 11.3).

The local anesthetics of choice may include bupivacaine 0.375% to 0.5% or ropivacaine 0.35% to 0.5% with or without epinephrine in a 1:200,000 solution. These are longer acting local anesthetics that are well suited for postoperative pain



FIGURE 11.2 Lines are drawn intersecting the posterior border of the clavicular head of the sternocleidomastoid at the level of C6.



FIGURE 11.3 The point of injection for the interscalene block is in the interscalene groove.

management. The total volume of local anesthetic injected may vary from 20 to 40 mL, and should not exceed 2 mg/kg on the basis of the weight of the patient. The addition of epinephrine should provide significant longevity to the block due to vasoconstriction, which inhibits vascular washout of local anesthetic and subsequent metabolism and elimination by the liver and kidneys.

When using a nerve stimulator to locate the brachial plexus, the stimulating current should be set between 1 and 3 mA and adjusted to determine the lowest voltage necessary to stimulate the brachial plexus. The closer the needle is to the

brachial plexus, the lower the current necessary for stimulation. Should you notice stimulation of the diaphragm rather than the brachial plexus during needle insertion, the needle should be withdrawn and redirected posteriorly. The needle should be constantly aspirated until the brachial plexus is located. A test dose of 1 mL of local anesthetic is then injected to determine that the tip of the needle is not intravascular (5). It is recommended that no more than 5 mL of local anesthetic be injected at any time, and aspirations be performed between subsequent injections until the entire dose of local anesthetic has been delivered.

Depending on the concentration and volume of local anesthetic delivered, your patient can comfortably obtain 8 to 10 hours of pain relief or more from this block. Longevity of any block is also dependent on the patient, as all patients are different and metabolize local anesthetics at different rates. It should be noted that in the performance of these blocks, some practitioners prefer eliciting paresthesias, which indicates contact of the sensory nerves by the tip of the needle. Stimulation of the motor component of the brachial plexus using electrical stimulation may occur without direct contact of the motor nerves, even when low current settings are used (6). This does not preclude successful brachial plexus block, and in fact may help prevent direct intraneural injection.

Upon successful completion of this block, it is not uncommon for the patient to experience a Horner's syndrome or anesthesia of the ipsilateral phrenic nerve due to cephalad migration of local anesthetic in the fascial sheath (7). It is also common for patients to experience hoarseness, as the recurrent laryngeal nerve is affected by the local anesthetic as well. Reassurance should comfort your patients if they experience these symptoms.

Supraclavicular Block

The supraclavicular block is effectively used for surgery and postoperative pain management of the arm or hand (8). This block may be easily placed by an experienced practitioner, and confers the advantage of blocking all the nerves at their trunks where the brachial plexus is most tightly arranged. Unlike with the interscalene approach, there is no sparing of the ulnar nerve, which comes off of C8 distal to the point of injection.

Caution should be used in patients with a history of severe pulmonary disease because of the probability of blocking the ipsilateral phrenic nerve and impairing pulmonary function. Whether one uses the classic approach or the plumb-bob technique, care must be taken to minimize or avoid directing the needle medially from the point of entry. A pneumothorax can be caused by inadvertent puncture of the cupula of the lung if this occurs.

As with the interscalene block, one may choose to use either electrical stimulation or paresthesias to locate the brachial plexus. Using the plumb-bob technique, the patient should be placed in the supine position with the head turned away from the side being blocked. The arm may be placed in any position relatively comfortable to the patient. The site of needle insertion should be aseptically prepped with an appropriate solution. The patient should be asked to lift his or her head against gravity to better delineate the clavicular head of the SCM muscle. A skin wheal is then placed.

The insertion site of the needle should be at a 90° angle to the table, lateral to the SCM (approximately the midpoint of the clavicle), and just above the clavicle. The subclavian artery may be palpated in the supraclavicular fossa, as it is anterior



FIGURE 11.4 The supraclavicular plumb-bob technique is done at the approximate midpoint of the clavicle at a 90° angle to the table.

and inferior to the brachial plexus and may be used as a landmark. The block needle of choice should be a 2- to 3-cm 22-gauge short beveled insulated electrical stimulator needle. Stimulation current can be set between 1 and 3 mA. Constant aspiration should be performed to avoid direct intravascular injection as the needle is advanced in a parasagittal direction. If no electrical stimulation is evident, then the needle may subsequently be redirected cephalad, to avoid the pleura and vascular structures, and then caudad (Fig. 11.4) (9).

If the first rib is contacted without noticeable stimulation of the arm or hand, then the needle should be walked off the first rib in a cephalad direction. The brachial plexus passes superior to the first rib. Once the brachial plexus has been located, the current should be adjusted to determine at which position a minimum of current (approximately 0.9 mA) is necessary to stimulate finger movement (10). The local anesthetic of choice for long acting postoperative pain relief would be the same as for the interscalene block. Bupivacaine 0.375% to 0.5% with a 1:200,000 concentration of epinephrine can be used as well as ropivacaine 0.35% to 0.5% with

epinephrine 1:200,000. A total of 20 to 30 mL should be injected, not to exceed 2 mg/kg of the patient's body weight.

The classical approach to the supraclavicular block is more technically challenging to learn than the plumb-bob technique. Patient positioning is the same. After aseptic preparation, a skin wheal is placed and a 5-cm short beveled insulated electrical stimulation needle is inserted at the clavicular midline approximately 1 cm above the clavicle. The choice of the longer block needle is necessary, as the distance to the brachial plexus is longer from this point of insertion.

The needle is advanced in a caudad and slightly posterior direction. Caution should be taken not to aim medially, as the cupula of the lung may be inadvertently contacted. The direction of needle advancement should be in close alignment with the head and neck. If, during aspiration, the subclavian artery is encountered, then this medial landmark will direct you to withdraw the needle and redirect it laterally toward the brachial plexus. If the first rib is contacted, then the needle can be walked off the rib. First attempts should be in an anterior and posterior direction followed by lateral, and most cautiously, medial direction.

When the brachial plexus is located, the electrical current should be adjusted to determine the lowest current necessary to provide stimulation. Local anesthetic should then be injected after negative aspiration of the syringe. As with all blocks of the upper extremity, adequate time should be allotted to determine effectiveness. Fifteen to twenty minutes should be adequate to assess flexion and extension of the arm, and the ability to adduct the thumb and index finger as well as the thumb and little finger. This selectively tests the musculocutaneous, radial, median, and ulnar nerves in that order.

Infraclavicular Block

The infraclavicular block may be used as a surgical anesthetic or for postoperative pain management for procedures involving the shoulder or the hand. The object of this block is to locate the brachial plexus (preferably the posterior cord or multiple cords) and to deposit local anesthetic into the brachial plexus sheath (11). The posterior cord innervates the triceps and extensor carpi ulnaris. The success of this block is dependent on bidirectional spread of local anesthetic within the sheath, which blocks the brachial plexus at the level of the branches and the cords. A complete block may be obtained with this technique, as the individual nerves will all be anesthetized at this level.

The patient should be placed in the supine position. The midpoint of the clavicle lateral to the clavicular head of the SCM and subclavian artery should be identified. This may be facilitated by having your patient turn his or her head away from the side being blocked and lifting it against gravity. Once the midpoint is located and marked you may prep the area with an aseptic solution. Raise a skin wheal using local anesthetic at the clavicular midpoint approximately 2 cm below the clavicle.

A 5-cm 22-gauge insulated short beveled electrical stimulator needle is inserted at that point and directed posterolaterally. Electrical stimulation may be set at 2 to 4 mA at 1 pulse/sec. As the needle advances, you may first notice direct stimulation of the pectoral muscles. Continue to advance slowly while aspirating, as the brachial plexus is deep to the pectoral muscles. Once you see direct stimulation of the hand with negative aspiration, you should reduce the current and direct the needle to determine the lowest amount of current necessary to



FIGURE 11.5 The infraclavicular block is placed 2 cm below the clavicle and aimed posterolaterally to avoid the subclavian artery and lung.

stimulate the nerves. You may then inject 20 to 30 mL of local anesthetic. It is recommended that you inject 5 mL at a time, aspirating between each dose to decrease the likelihood of inadvertent intravascular needle placement with the attendant risk of local anesthetic toxicity (Fig. 11.5).

Negative aspiration and a negative subjective response to questions regarding local anesthetic toxicity should rule out intravascular injection. Because of the location and direction of needle placement lateral to the ribs, it is uncommon to cause a pneumothorax. Any medial redirection of the needle increases this possibility, however.

Axillary Block

The Axillary approach to the brachial plexus is easily accomplished and provides excellent anesthesia and postoperative pain relief for surgeries of the hand and forearm. There are several different techniques used to perform the Axillary block, with this author's preference being the perivascular infiltration of local anesthetic so well described by David L. Brown, MD (12). This technique requires less local anesthetic than the transarterial infiltration of the perivascular sheath that contains

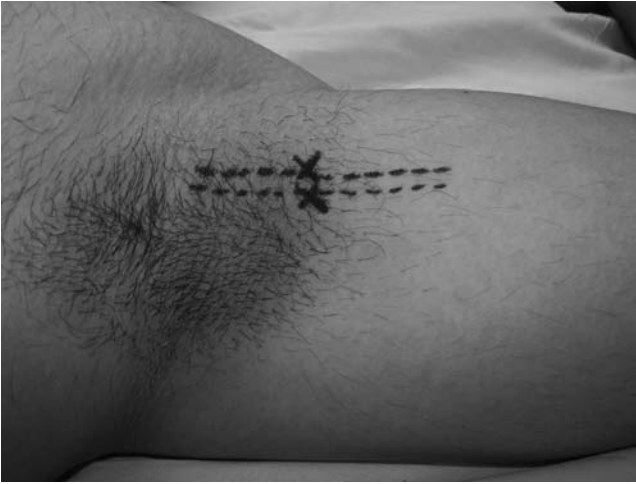


FIGURE 11.6 The axillary artery is identified for injection above and below it.

the brachial plexus. There is therefore less chance of local anesthetic toxicity and bleeding, as the block needle does not penetrate the Axillary artery.

The long acting local anesthetics of choice would be either bupivacaine or ropivacaine as previously described. Longevity of the block is significantly enhanced by the addition of epinephrine in a 1:200,000 solution (5 $\mu\text{g}/\text{mL}$). The only equipment necessary to perform the perivascular Axillary block is a 10-mL three-ring control syringe and a 25- or 27-gauge 1.25-in needle. A small sterile cup may be used to pour the local anesthetic into, making it easier to aspirate local anesthetic into the syringe.

The patient should be placed in the supine position with the arm to be blocked abducted to approximately 90° . The forearm should also be bent at the elbow as close to 90° as tolerated by the patient. The Axillary artery should then be palpated high in the axilla with your nondominant hand while your dominant hand is used to inject the local anesthetic (Fig. 11.6).

Comprehension of the anatomical arrangement of nerves surrounding the axillary artery will improve the outcome of your block. In this position, the median and ulnar nerves are the most superficial. The median nerve is located above the artery while the ulnar nerve is located below the artery. Deep to these nerves and the axillary artery are the musculocutaneous and radial nerves. The musculocutaneous nerve lays posterosuperior to the median nerve at an angle approximating 30° , whereas the radial nerve is aligned more directly posterior or deep to the ulnar nerve. A cross-sectional view of the nerves reveals their location in quadrants. The median nerve is located in the 12 to 3 o'clock quadrant, the ulnar nerve in the 3 to 6 o'clock quadrant, the radial nerve in the 6 to 9 o'clock quadrant, and the musculocutaneous nerve in the 9 to 12 o'clock quadrant.

After prepping the axilla with an appropriate aseptic solution, insert the needle attached to the three ring control syringe perpendicular to the skin and above the artery. Continually aspirate until the needle is completely advanced. If you are above the artery, you will likely contact the humerus. Inject several mL of



FIGURE 11.7 A three ring control syringe is used to deposit perivascular local anesthetic for axillary nerve block.

local anesthetic as you withdraw the needle to skin without removing it. Reinsert the needle and aspirate while fanning slightly upward away from the artery. Reinject and repeat this step until all 10 mL of local anesthetic is used (Fig. 11.7).

Next insert another 10-mL syringe of local below the artery perpendicular to the skin. Aspirate the syringe continually as the needle is advanced, trying to avoid the axillary artery. If the artery is contacted, always withdraw the needle and fan away from it. Once the needle is completely inserted, inject several mL as the needle is withdrawn toward but not removed from the skin. Repeat this step until the syringe is empty. Should any of the nerves be missed, they may be selectively blocked by injecting a few more mL in the quadrant where the target nerve is located.

The block may be tested by strength, or lack thereof, in the patient's ability to flex the arm (musculocutaneous), extend the arm (radial), adduct the index finger and thumb (median), and adduct the thumb and pinky (ulnar nerve). While performing this block, your patient may experience paresthesias, which although not necessary for successful block, will confirm needle placement. It is even

possible to get an adequate block without being able to palpate the artery if the injections are infiltrated in the area where the artery is normally located. Occasionally, the axillary arterial pulsation is too weak to palpate.

DISTAL NERVE BLOCKS OF THE UPPER EXTREMITY

Nerve blocks that are performed distal to the axillary block include those of the ulnar, median, and radial nerves. As stated previously, knowledge of the anatomy and course of these nerves is necessary to provide the best possible outcomes when performing these procedures. These nerves are blocked in and around the elbow and antecubital fossa and may be used as supplementation for the nerves that have been spared from a more proximal block.

Ulnar Nerve

When blocking the ulnar nerve, care must be taken not to inject the local anesthetic directly into the nerve or the ulnar groove. The ulnar nerve is contained in a canal of fibrous tissue and fascia, which sits in the ulnar groove between the medial surface of the olecranon and the medial epicondyle. Injection of large volumes of local into the ulnar groove significantly increases the pressure within it, leading to possible compressive damage to the nerve. Blocking the ulnar nerve provides analgesia to the proximal ring finger, pinky, and ulnar portion of the hand.

The patient should be supine while the forearm is in the flexed position. The ulnar groove can be palpated between the medial surface of the olecranon and the medial epicondyle. A sterile prep should always be performed prior to the block. Using a 25- or 27-gauge 1-in needle, a paresthesia should be sought 1 cm proximal to the midpoint of the ulnar groove. The needle should be withdrawn slightly (2 mm) to avoid direct intraneural injection, and 3 to 5 mL local anesthetic should then be injected (Fig. 11.8).



FIGURE 11.8 The ulnar nerve is blocked 1 cm proximal to the ulnar groove.



FIGURE 11.9 The median nerve is blocked medial to the brachial artery.

Median Nerve

The median nerve block is also performed with the patient in the supine position with the arm extended and supinated. A line should be drawn across the antecubital fossa from the lateral epicondyle to the medial epicondyle. Once the brachial artery is palpated, a 25-gauge 1-in needle is inserted medial to the artery and perpendicular to the skin using continuous aspiration. When paresthesias have been obtained, inject 3 to 5 mL of local anesthetic. If no paresthesias have been obtained, withdraw the needle and redirect it as you advance medially and away from the artery (Fig. 11.9).

Radial Nerve

The radial nerve can be located lateral to the insertion of the biceps tendon and medial to the lateral epicondyle approximately 1 to 2 cm proximal from the antecubital fossa. With your patient positioned the same as when performing the median nerve block, insert and advance a 25-gauge 1-in needle at the midpoint between the biceps tendon and the lateral epicondyle. Once paresthesias have been



FIGURE 11.10 Radial nerve block.

obtained, inject 3 to 5 mL of local anesthetic. If you have not obtained paresthesias, withdraw the needle to skin and redirect as you advance the needle, fanning in a medial and lateral direction until paresthesias are obtained. Your local anesthetic may then be injected (Fig. 11.10).

Wrist Blocks

The median and ulnar nerves can also be blocked distally at the wrist. These blocks can be used to provide postoperative analgesia on the medial and lateral sides of the hand after a general anesthetic, or to supplement a more proximal block of the brachial plexus. The anatomy is readily accessible and the nerves easy to anesthetize.

The median nerve block is performed with the patient supine. The arm is extended laterally and supinated to expose the tendons of the palmaris longus and flexor carpi radialis. The median nerve is located deep between these two tendons and may be best accessed with the wrist slightly extended over a wrist board or rolled up towel. After sterile preparation and placement of a skin wheal using local anesthetic on the volar surface of the wrist 1 to 2 cm proximal from the wrist creases, insert a short beveled 22-gauge needle perpendicular to the skin. Advance the needle until you have obtained paresthesias and then inject 3 to 5 mL of local anesthetic. If paresthesias are not obtained, you may inject the local anesthetic, fanning both laterally and medially. This field block should readily provide adequate analgesia to the distribution of the median nerve distal to the injection (Fig. 11.11).

The ulnar nerve can be located medial to the ulnar artery and lateral to the flexor carpi ulnaris. Patient positioning is the same as when blocking the median nerve. A short beveled 22-gauge block needle should be inserted perpendicular to the skin on the volar surface of the wrist 1 to 2 cm proximal from the wrist creases and advanced while aspirating until paresthesias have been elicited. At that point 3 to 5 mL of local anesthetic should be injected. If paresthesias are unobtainable, then inject the local anesthetic fanning both medially and laterally to provide a field



FIGURE 11.11 The median nerve block at the wrist is placed between the tendons of the palmaris longus and the flexor carpi radialis.



FIGURE 11.12 The ulnar nerve block at the wrist is placed medial to the ulnar artery and lateral to the flexor carpi ulnaris.

block to the area. When fanning laterally, you are more prone to encounter the ulnar artery, which supports the importance of aspirating prior to injection when using this method (Fig. 11.12).

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Lower-extremity regional anesthetic techniques in the management of postoperative pain

J. Mark Matthews

INTRODUCTION

For more than a century, local anesthetic peripheral nerve block (PNB) has been used to provide anesthesia and analgesia for surgery of the extremities. Historically, lower-extremity PNB has been underutilized when compared with nerve blocks of the upper extremity. The reasons for this are several. Unlike the upper extremity, no single injection of local anesthetic can produce anesthesia of the entire lower limb unless neuraxial (spinal/epidural) anesthesia is used. The operating room (OR) team may have the perception that PNB adversely affects OR efficiency by delaying cases or patient discharge, a perception not borne out by data (1,2). Additionally, competency with these techniques may be limited by inadequate training. Of responders to a recent survey of American anesthesiology training programs, slightly more than half had a specific PNB rotation (3). Predictably, the residents in the programs with a formal rotation performed more PNB compared with those without. A 1995 survey of practicing anesthesiologists confirmed the infrequent use of lower-extremity PNB, but also expressed the perception that subsequent use would increase in the future (4). Numerous studies have shown PNB to provide excellent analgesia with associated opioid-sparing effects, low complication rates, competitive discharge times, and high patient satisfaction ratings (2,5,6).

PNB is an attractive alternative to neuraxial anesthesia in the patient with congenital or acquired coagulopathy. More and more frequently, patients are presenting for surgery while receiving anticoagulants or antiplatelet drugs. Many hospitals have implemented protocols for prevention of perioperative deep venous thrombosis utilizing low-molecular weight heparins. Lower-extremity PNB is thought to have lower risk of neurologic injury due to hematoma formation, as compared with neuraxial blockade, in those with impaired coagulation, although some bleeding complications have been reported after lumbar plexus block (LPB) (7). Case reports of neurologic injury due to hematoma are noticeably lacking with use of PNB of the lower extremity. Despite the potential barriers, lower-extremity PNB will likely continue to grow in popularity as the benefits of low cost, safe, and effective postoperative analgesia become more evident.

LOWER-EXTREMITY INNERVATION

The nerves responsible for motor and sensory innervation of the lower extremity are contained within two major bundles, the lumbar plexus and the sacral plexus. These bundles should be considered distinct and separate entities. In general, the lumbar plexus innervates the anterior leg, and the sacral plexus the posterior leg.

Lumbar Plexus

The lumbar plexus is formed from branches of L1-4 and courses inferiorly through the psoas muscle. The cephalad portion separates into superior and inferior branches that form the iliohypogastric, ilioinguinal and genitofemoral nerves. These nerves provide sensation to the suprapubic and genital regions as well as the uppermost thigh. The caudad portion of the lumbar plexus exits the pelvis anteriorly, giving rise to the lateral femoral cutaneous, obturator, and femoral nerves. Together these nerves provide sensation to the remainder of the thigh and the medial aspect of the lower leg to the foot. The femoral nerve also supplies sensory nerves to the hip and knee joints and motor nerves to the muscles of the anterior thigh. The lateral femoral cutaneous nerve (LFCN) is completely sensory, supplying the lateral thigh down to the knee. The obturator nerve exits the pelvis via the obturator foramen and promptly divides into anterior and posterior branches. The obturator nerve supplies sensory nerves to the hip and knee joint in addition to motor nerves of adductor muscles of the medial thigh with a small and variable sensory branch to the medial thigh. The saphenous nerve, the most distal branch of the lumbar plexus, provides sensation to the medial lower leg and foot.

Sacral Plexus

The sacral plexus consists of the anterior and posterior branches of the ventral rami from L4-5 and S1-3. The lumbosacral plexus courses deep to the gluteal and piriformis muscles and exits the pelvis posteriorly as the sciatic nerve. Although somewhat variable, the sciatic nerve usually branches into the tibial and common peroneal nerves at the level of the superior popliteal fossa. The distal branches of the lumbosacral plexus are the lateral sural cutaneous, superficial peroneal and the deep peroneal. The lateral sural cutaneous nerve is a distal branch of the common peroneal nerve and provides cutaneous innervation to the anterolateral surface of the proximal lower leg. The superficial peroneal nerve supplies motor fibers to muscles of the lower leg and sensory branches to the lateral lower leg and dorsum of the foot. The deep peroneal nerve provides motor fibers to muscles of the lower leg and foot and sensory fibers to the foot joints and the skin between the first and second toes. The cutaneous innervation of the lower extremity is shown in Figure 12.1.

INDICATIONS FOR LOWER-EXTREMITY PNB

Lower-extremity PNB can be used as primary anesthesia for operations on the lower extremity, as an adjunct to general anesthesia or for postoperative analgesia. Procedures amenable to postoperative analgesia with lower-extremity PNB include major surgery of the hip and knee (including joint replacement), repair of femur fractures and other fractures of the distal leg, and major surgery of the ankle and foot, as well as other skin and soft-tissue surgeries. Long acting local anesthetics can provide postoperative analgesia for up to 24 hours when epinephrine is added to the solution. Extended analgesia can be achieved by the use of indwelling catheters.

TECHNIQUES OF LOWER-EXTREMITY PNB

The lumbar and lumbosacral plexuses, and associated branches, can be blocked at various points along their paths. The choice of local anesthetic, location of injection,

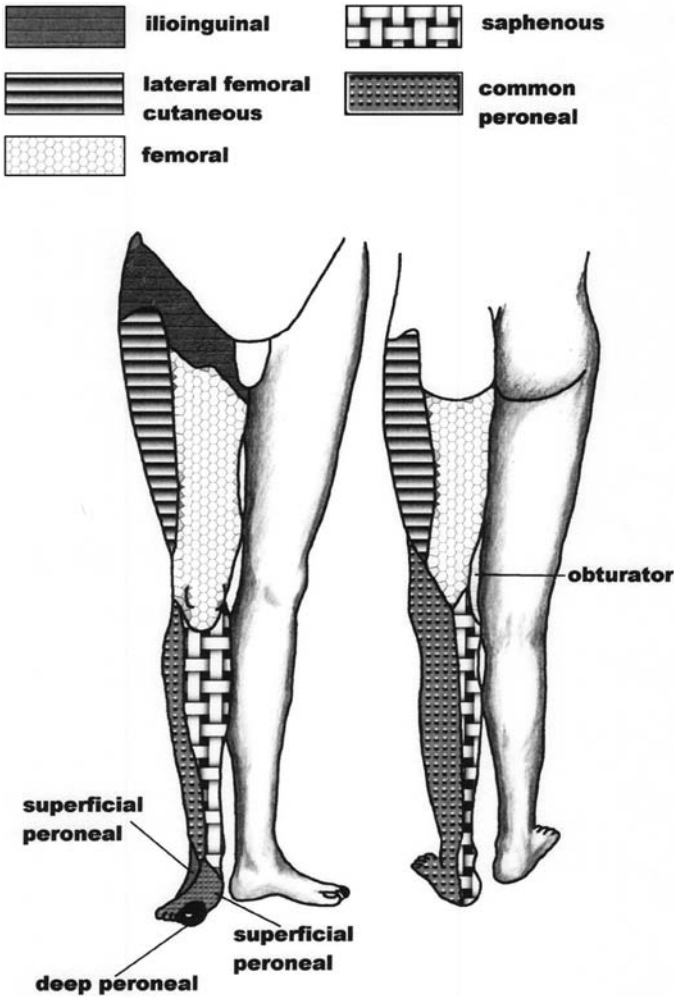


FIGURE 12.1 Cutaneous innervation of the lower extremity.

anatomic approach, and technique of nerve identification will vary according to the anticipated procedure, factors intrinsic to the patient, and operator experience and skill. The following descriptions of PNB cover the most commonly used techniques, including anatomic landmarks, approaches, and assessment of successful blockade. All PNBs carry the risk of local anesthetic toxicity. Peak local anesthetic concentrations from absorption into the blood occur approximately one hour after PNB of the lower extremity (8). The risk of toxicity can be reduced by staying within accepted dosing guidelines, adding epinephrine to the solution, and using slow incremental injection with frequent aspiration. Additionally, all PNBs carry a small risk of transient or permanent nerve injury. The true incidence of this complication is unknown, but is probably higher than the figures generally reported (9). Recommended strategies to reduce the risk of unintentional nerve

injury include avoiding deep sedation during the injection, ceasing injection if it results in severe patient discomfort, or when unexpected resistance to injection of local anesthetic is encountered.

TECHNIQUES OF NERVE LOCALIZATION

The success rate of PNB is highly dependent on correct positioning of the needle as close to the nerve as possible. Techniques for nerve identification include “fanning” an injection through the typical pathway of a nerve, the “feel” of the needle as it contacts bony landmarks or pierces fascial layers, eliciting paresthesias, electrical nerve stimulation (PNS), and ultrasound guidance.

Although studies are limited, success rates for nerve localization using paresthesias versus PNS are similar (9). Multistimulation has been shown superior to single-stimulation PNS with popliteal and sciatic nerve blocks (10). Contrary to popular belief, nerve localization with PNS is not affected by the proximity of the cutaneous electrode to the site of injection (11). Ultrasound guidance has been shown superior to PNS for success with femoral nerve blockade (12,13). Regardless of the method, any of the previous techniques can result in a high success rate for PNB when practice and experience is gained.

CHOICE OF AGENTS FOR PNB

In general, longer acting local anesthetics are preferred for lower-extremity PNB. The difference between ropivacaine, bupivacaine, and levobupivacaine when used in equipotent concentrations and doses is probably not clinically significant in relation to success rate, latency, and duration (9). Adjuvants such as epinephrine, opioids, clonidine, bicarbonate and ketorolac have been used commonly in lower-extremity PNB. Epinephrine prolongs the duration and quality of most local anesthetics when used in this setting. Epinephrine’s effect is due to vasoconstriction of perineural vessels resulting in decreased vascular uptake of local anesthetic, and thereby increased exposure of neural tissue to the local anesthetic solution. This effect is less pronounced with ropivacaine because of its intrinsic vasoconstrictive properties. A 1:400,000 dilution is as effective as higher concentrations of epinephrine and is probably preferable to higher concentrations that are likely to result in side effects (9). Opioids and bicarbonate do not appear to offer any benefit for PNB. Clonidine and ketorolac have shown some beneficial effects when added to local anesthetic solution for PNB. Clonidine’s side effects of hypotension, bradycardia, and sedation do not occur with doses less than 1.5 µg/kg (9). Additional studies are needed to determine the benefits and risks of using adjuvants other than epinephrine before definitive recommendations can be made.

EVALUATION OF LOWER-EXTREMITY PNB

Neal has proposed a simple evaluation to assess whether successful blockade of lower-extremity nerves has occurred (14). This evaluation is based on inability to perform the four Ps: push, pull, pinch, and punt. Having the patient *push* the examiner’s hand with his or her foot, as in stepping on the gas pedal of an automobile, evaluates successful sciatic nerve block. To evaluate obturator nerve block, the examiner abducts the patient’s thigh and asks the patient to *pull* his or her leg back to the midline. A *pinch* of the lateral proximal thigh will determine successful blockade of the LFCN. Finally, adequacy of femoral nerve motor

blockade is assessed by lifting the patient's leg off the table, with the knee flexed, and having the patient attempt to *punt* a football. Extension of the lower leg requires quadriceps contraction, the motor supply of which is supplied by the femoral nerve.

LUMBAR PLEXUS BLOCK

Indications

LPB can be used to provide anesthesia/analgesia in the distal distribution of the terminal branches of the lumbar plexus: the femoral, obturator, and LFCN. LPB can provide good pain control for hip and femur fractures, major surgery of the hip and knee joints, and other soft-tissue or cutaneous procedures above the knee. Continuous LPB after major orthopedic surgery has been shown to provide excellent analgesia with few side effects and complications (5-7,15). Utilization of combined lumbar plexus and sciatic nerve blocks in a series of patients having outpatient knee arthroscopy showed excellent operating conditions and analgesia with a high percentage of patients able to bypass the PACU (2,8).

Technique of Lumbar Plexus/Psoas Compartment Block

Blockade of the lumbar plexus can be achieved by injection of local anesthetic into the psoas compartment, where the nerves pass immediately anterior to the lumbar transverse processes and posterior to the psoas muscle. Needle placement for this block is based on the anatomic relationship of the lumbar plexus to the transverse process of L5. Typically, a PNS can be used to elicit quadriceps contraction.

The psoas compartment is approached posteriorly, with the patient in the lateral position and the side to be blocked up. A line connecting the superior iliac crests usually crosses the midline at the level of L4. The site for needle insertion is located by drawing a 5-cm line perpendicular to this line, extending toward the side to be blocked and then going 3 cm caudad. This will put the injection site close to the medial border of the iliac crest (Fig. 12.2). A 20-g, 15-cm needle is inserted, perpendicular to the skin, and advanced slowly until the tip contacts the L5 transverse process. The needle is walked off the superior aspect of the transverse process. The average skin to lumbar plexus distance is approximately 70 mm in females and 85 mm in males (10,16). While increased BMI increases the skin to lumbar plexus distance, the transverse process to lumbar plexus distance remains

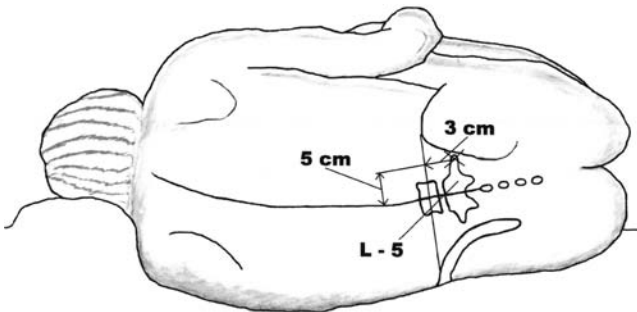


FIGURE 12.2 Lumbar plexus block.

unchanged (10,16). Hence, although the needle may need to be inserted deeper to contact the transverse process, the distance from there to the nerve should be consistent. Quadriceps stimulation with PNS indicates correct needle placement. A minimum of 30 mL of local anesthetic is deposited incrementally with frequent aspiration. Anatomic landmarks for LPB are illustrated in Figure 12.2.

Complications

LPB occasionally results in epidural blockade due to lateral spread of local anesthetic (9). Patients should be observed carefully for signs of epidural block that may result in anesthesia/analgesia of the contralateral side, as well as hypotension from the resulting sympathetic blockade. Typically, epidural block recedes in the usual time interval, leaving the ipsilateral lumbar plexus blocked. Retroperitoneal bleeding has been reported with use of LPB in patients with abnormal coagulation.

FEMORAL NERVE BLOCK

Much has been written about the traditional “three-in-one” femoral nerve block originally described by Winnie (9). In this technique, firm digital pressure is exerted distal to the femoral sheath as a large volume, (40 mL) of local anesthetic is injected in close proximity to the femoral nerve. In theory, this results in cephalad spread of the local anesthetic into the lumbar plexus with blockade of the femoral, obturator, and LFCN. Recent data contradicts the premise of cephalad spread of anesthetic when injected in this manner. MRI inspection of local anesthetic spread after femoral block demonstrates lateral, but not superior spread of the injected agent (10). Studies have shown a high rate of failure of obturator nerve block when the three-in-one technique is employed (11). Additionally, continuous three-in-one block with catheter position assessed by radiography shows a high rate of obturator block when the catheter can be advanced 16 to 20 cm in a cephalad direction and into the lumbar plexus (11). However, the majority of catheter tips could not be advanced significantly from the point of insertion, resulting in an overall low success rate of obturator nerve block. From the preceding data, it seems reasonable to view the three-in-one technique as a “femoral” block rather than an alternative route to the lumbar plexus. Regardless, femoral nerve block has been shown to be a very effective adjuvant analgesic for major surgery of the knee (12).

Technique of Femoral Nerve Block

The patient is placed in the supine position with the leg to be blocked slightly externally rotated. A line is drawn between the anterior superior iliac spine and the symphysis pubis, representing the inguinal ligament. The femoral artery is palpated 1 to 2 cm below this line. A 3- to 4-cm needle is placed immediately lateral to the artery. Nerve localization can be achieved by seeking paresthesias, achieving quadriceps contraction with a PNS, using a short beveled needle and feeling for the “double pop” as the needle pierces the fascia lata, and fascia iliaca, or fanning an injection lateral to the artery. As mentioned previously, ultrasonic visualization of needle proximity to the nerve appears to result in faster onset, decreased local anesthetic requirement, and greater success rate as compared with the previous techniques (13). Twenty to 30 mL of local anesthetic is then injected incrementally and with frequent aspiration, considering the close proximity of the femoral artery and vein.

LATERAL FEMORAL CUTANEOUS NERVE BLOCK

The LFCN leaves the lumbar plexus and passes deep to the inguinal ligament approximately 1 to 2 cm medial to the anterior superior iliac spine. It then passes deep to the fascia lata before piercing it approximately 10 cm inferior to the anterior superior iliac spine. The LFCN provides sensation to the lateral aspect of the thigh with terminal branches forming part of the patellar plexus. Indications for LFCN block include skin graft harvesting from the lateral thigh, control of upper leg tourniquet pain during distal procedures, and major knee surgery regardless of tourniquet use.

Technique of Lateral Femoral Cutaneous Nerve Block

The patient is placed in the supine position. The anterior superior iliac spine is palpated and marked. The location for needle insertion is approximately 2.5 cm inferior and 2.5 cm medial to the mark. A distinct “pop” should be felt as the needle pierces the fascia lata. Then 10 mL of local anesthetic is deposited in a medial to lateral fan-shaped distribution.

OBTURATOR NERVE BLOCK

The obturator nerve (L2-4) leaves the lumbar plexus and passes through the pelvis posterior to the iliac vessels before exiting the obturator foramen. At this level, the nerve separates into anterior and posterior branches. The cutaneous innervation from the obturator nerve is small and variable. Accordingly, cutaneous sensory loss is not a good measure of obturator nerve blockade. The terminal branches of the obturator nerve provide sensory input to both the hip and knee joints and motor input to the adductor muscles of the upper leg. Because of its articular branches, obturator nerve block is required for PNB anesthesia for major hip and knee joint surgery.

Technique of Obturator Nerve Block

The patient is placed in the supine position with the leg slightly abducted. The pubic tubercle is palpated and a skin wheal is made 1.5 cm below and 1.5 cm lateral to it. A 7- to 8-cm needle is directed in a slightly medial direction to contact the horizontal pubic ramus. It is then directed about 45° superiorly and advanced until the superior bony portion of the obturator canal is contacted. The needle is then withdrawn slightly and redirected in a slightly lateral and inferior direction to enter the obturator foramen (Fig. 12.3). Ten to 15 mL of local anesthetic is injected with careful aspiration, considering the proximity of the obturator vessels.

SCIATIC NERVE BLOCK

Considering the complex distal distribution of the lower extremity, isolated sciatic nerve block is rarely used for anesthesia or postoperative analgesia of the lower extremity, with the exception of surgical procedures on the foot or toes. Sciatic nerve block is most frequently combined with other nerve blocks, such as femoral block or LPB, to provide postoperative analgesia after various surgical procedures on the lower extremity. Good postoperative analgesia for surgery of the hip can be obtained when sciatic nerve block is combined with LPB.

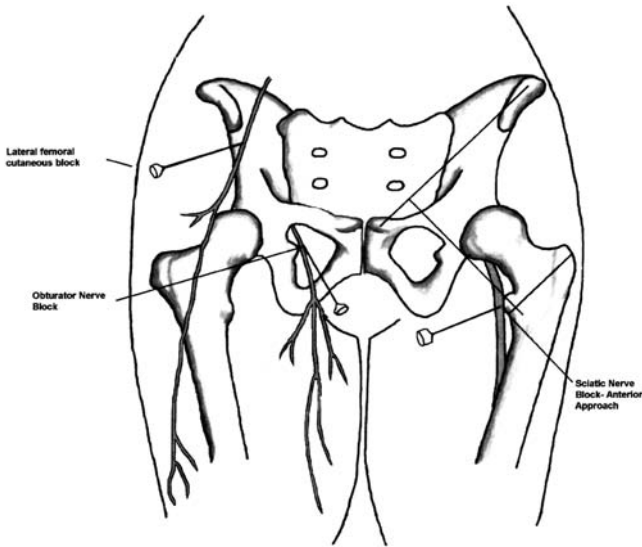


FIGURE 12.3 Anatomic landmarks for lateral femoral cutaneous nerve, obturator, and sciatic nerve block: anterior approach.

Technique of Sciatic Nerve Block

Sciatic Nerve Block: Classic Posterior Approach

The patient is placed in the lateral position with the side to be blocked up. The knee of the leg to be blocked is flexed with the foot resting atop the dependent leg. A line is drawn from the posterior superior iliac spine to the midpoint of the greater trochanter. Perpendicular to the midpoint of this line, a second line is extended caudad 5 cm. A 22-gauge, 10- to 12-cm needle is inserted at this point and directed toward an imaginary point on the opposite side of the leg, corresponding to the center point of the inguinal ligament. Alternatively, a line can be drawn connecting the sacral hiatus to the middle of the greater trochanter and the needle inserted at the center point of this line. Eliciting a muscle contraction in the leg with a nerve stimulator or eliciting paresthesias in the sacral nerve distribution signifies correct needle placement. If bone is contacted without nerve stimulation, the needle is withdrawn and “walked” laterally along the line connecting the sacral hiatus to the middle of the greater trochanter. Then 20 to 25 mL of local anesthetic is injected once the nerve is identified (Fig. 12.4).

Anterior Approach

The patient is placed supine with the leg to be blocked in a neutral position. A line is drawn connecting the anterior superior iliac spine to the pubic tubercle. Caudal to this line, another line is drawn parallel to the above line extending from the middle of the greater trochanter and directed medially. The upper line is divided into equal thirds. At a point marking the medial one-third of this line, a perpendicular line is drawn and extended down until it intersects the lower line. This point should be directly anterior to the lesser trochanter of the femur. A 22-gauge, 10- to 12-cm needle is inserted at this point and advanced until it contacts the

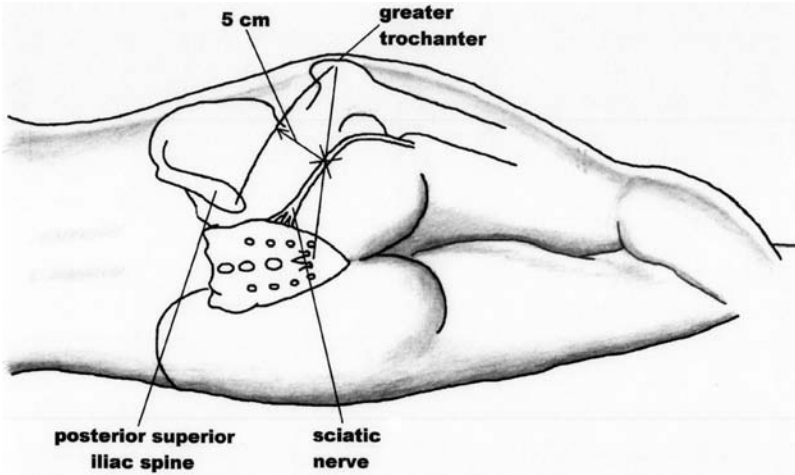


FIGURE 12.4 Sciatic nerve block: posterior approach.

medial border of the femur. The needle is then directed slightly medial and walked over the medial femur. The sciatic nerve should be contacted approximately 5 cm past the depth at which the femur was contacted (Fig. 12.3). Then 20 to 25 mL of local anesthetic is injected once the nerve has been identified. The anterior approach may have a slightly lower success rate compared with the posterior approach, but it is useful when the posterior approach is not feasible.

POPLITEAL NERVE BLOCK

Popliteal nerve block can be effectively used for postoperative analgesia after ankle and foot surgery. The popliteal nerve is typically approached proximal to the knee joint where the nerve divides into its terminal branches, the peroneal nerve and the tibial nerve. The popliteal nerve can be accessed from either a posterior or lateral approach. Both techniques have demonstrated high rates of success and satisfactory analgesia (17,18).

Anatomic Considerations

The popliteal fossa is bordered by muscles of the thigh and lower leg. Behind the knee, a lateral line is drawn over the skin crease. Cephalad to this line, a triangle is formed by the biceps femoris muscle laterally and the semitendinosus muscle medially. Although variable, the tibial and common peroneal nerves separate near the apex of this triangle, with the common peroneal nerve passing more laterally. The nerves are typically approached near the apex of this triangle. Both posterior and lateral approaches will be described. A PNS is typically used for nerve localization. A motor response of foot inversion is associated with a higher rate of block success (19). Ultrasound guidance has also been successfully used to verify needle placement (20).

Technique of Popliteal Nerve Block

Posterior Approach

The patient is positioned prone or laterally with the side to be blocked up. In the classic technique, a vertical line is extended approximately 5 to 6 cm up from the skin crease in the popliteal fossa. The needle is inserted 1 cm lateral to this point. However, recent cadaver studies show a more cephalad division of the tibial and common peroneal nerves, suggesting needle insertion 10 cm above the popliteal crease may result in greater success (21). Alternatively, palpation of the apex of the triangle and injection 0.5 cm below that point provides a high rate of successful block (19). A PNS can be used to elicit lower leg movement or, alternatively, paresthesias can be sought. After localization of the nerve, 30 to 40 mL of local anesthetic is injected in 5-mL increments.

Lateral Approach

The lateral approach, being performed in the supine position, can be used when the prone or lateral position is impractical. With the patient supine, the skin is marked immediately lateral to the popliteal crease. Laterally, a groove is felt between the vastus lateralis muscle anteriorly and the biceps femoris posteriorly. Needle insertion is 8 cm proximal to the popliteal crease and into the crease between the two muscles. A 10-cm insulated needle is inserted and motor stimulation of the foot is elicited with a PNS.

ANKLE BLOCK

The ankle block can be used to provide anesthesia or postoperative analgesia for operations of the forefoot and toes. Ankle block essentially blocks four distal branches of the sciatic nerve (the deep and superficial peroneal nerves, tibial nerve, and sural nerve), and one distal branch of the femoral nerve (the saphenous nerve). Two of these nerves lie deep to the superficial fascia, whereas three of the nerves are superficial and can be blocked by subcutaneous injection. Epinephrine containing solutions should be avoided because of the circumferential distribution of the injections (Fig. 12.5).

Anatomic Considerations and Technique

Common Peroneal Nerve

The common peroneal nerve separates from the tibial nerve and descends along the tendon of the biceps femoris muscle and around the neck of the fibula. Just below this point the nerve divides into its terminal branches, the deep and superficial peroneal nerves.

Deep Peroneal Nerve

The deep peroneal nerve courses to the front of the leg where, at the level of the ankle, it lies anterior to the tibia and immediately lateral to the anterior tibial artery. Its path typically lies directly between the tendons of the anterior tibial and extensor digitorum longus muscles. The nerve then divides into medial and lateral branches. The medial branch passes over the dorsum of the foot, medial to the dorsalis pedis artery, where it eventually innervates the area between the great and second toes. The lateral branch terminates as the second, third, and fourth interosseous nerves. The deep peroneal nerve is blocked between the tendons of

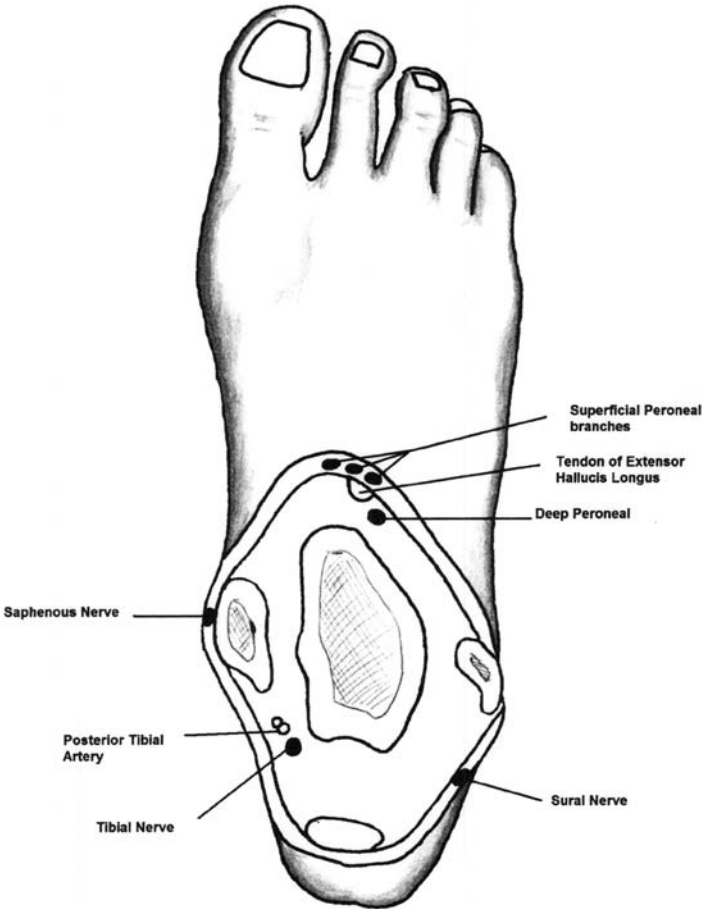


FIGURE 12.5 Ankle block.

the anterior tibial muscle medially and the extensor hallucis longus laterally. The needle is directed between these tendons with a slight lateral tilt. The tibia is contacted, the needle is withdrawn slightly, and 3 to 5 mL of local anesthetic is deposited.

Superficial Peroneal Nerve

The superficial peroneal nerve provides muscle innervation to the lower leg before emerging through the deep fascia at a point 5 to 10 cm above the lateral malleolus. The terminal branches mainly supply sensory innervation to the dorsum of the foot. The superficial peroneal nerve is blocked with a subcutaneous injection of 5 mL of local anesthetic starting at the anterior aspect of the ankle and extending to the lateral malleolus. Raising a good subcutaneous “wheal” will insure proper depth of injection.

Tibial Nerve

After separating from the common peroneal nerve in the popliteal fossa, the tibial nerve courses with the popliteal vessels deep in the lower leg. At the ankle, the tibial nerve lies beneath the deep fascia between the medial malleolus and the Achilles tendon, just posterior to the tibial artery. Distal branches supply cutaneous and articular innervation to the medial ankle and Achilles tendon. It ends in cutaneous branches to the sole of the foot.

Sural Nerve

The sural nerve becomes superficial below the middle of the lower leg and follows the short saphenous vein behind the lateral malleolus to innervate the lateral side of the foot and the lateral portion of the fifth toe. The needle is inserted at the posterior border of the lateral malleolus and a subcutaneous wheal is raised extending to the Achilles tendon. Injection of 5 mL of local anesthetic is adequate for sural nerve blockade.

Saphenous Nerve

The lone distal remnant of the lumbar plexus, the saphenous nerve courses subcutaneously at the posterior border of the medial malleolus. It provides cutaneous innervation to the skin of the medial lower leg, across the medial malleolus to the sole of the foot. The needle is inserted at the posterior margin of the medial malleolus and subcutaneous injection of 5 mL is extended to the Achilles tendon.

BLOCK OF THE FOREFOOT AND TOES

Distal branches of the deep peroneal nerve course deep between the metatarsal bones. Block of the forefoot and toes can be accomplished by injection of 4 to 5 mL of local anesthetic between the metatarsal bones. Injection in these areas is often painful and appropriate patient sedation should be considered when performing these blocks. A subcutaneous wheal is raised from the medial to lateral aspect of the middle dorsum of the foot, with 8 to 10 mL of local anesthetic solution. Individual toes can be blocked by injection of 2 mL of local anesthetic on either side of the digit, close to the lateral aspect of the proximal phalanx.

SUMMARY

PNB of the lower extremity can provide excellent postoperative analgesia for many operations of the hip, thigh, knee, and lower leg. PNB frequently results in high patient satisfaction rates and lower narcotic requirements, along with opioid associated side effects. When performed efficiently, PNB should not be viewed as an impediment to OR efficiency. Lastly, PNB, when compared with neuraxial block, may be preferred in patients with abnormal blood coagulation. The current trend of increased use of lower-extremity PNB suggests the benefits of this mode of postoperative analgesia are beginning to be appreciated. The full spectrum of pain management requires knowledge and skill in the performance of these valuable blocks.

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INTRODUCTION

Regional anesthesia has been shown to be an effective therapy for postoperative analgesia in numerous clinical scenarios. Continuous infusions of local anesthetic via perineural catheters not only capitalize on this technique, but extend the therapeutic window for several days. Patients have better outcomes, require less opioid, and therapy can be continued at home in most situations. In this chapter we will describe various upper and lower-extremity blocks and placement of catheters for continuous infusions.

TECHNIQUE AND NEEDLE TYPE

While historically various approaches have been described for performing single injection nerve blocks, when considering a catheter placement, we feel that the most reliable technique incorporates localization of the nerve via a nerve stimulator and advancement of the catheter through the needle. Various products exist; we are comfortable with the practicality, ease of use and success rate that we obtain using the Contiplex Touhy Continuous Nerve Block catheter products by B. Braun (Bethlehem, Pennsylvania, U.S.).

STANDARD PREPARATION

Following consent, patients are monitored, provided supplemental oxygen and lightly sedated for the block procedure. Sedation generally is achieved with midazolam 1 to 2 mg and fentanyl 50 to 100 µg. The blocks are performed in a well-light area with the techniques performed in a draped and sterile fashion. Local anesthesia at the skin site is achieved with subdermal 1% lidocaine. A small skin nick can be used to facilitate needle insertion. The stimulating needle is advanced while attempting to elicit the desired motor response. Once achieved, the milli-ampereage from the nerve stimulator is reduced with the aim to maintain a motor response at 0.5 mAmp. Following negative aspiration, the local anesthetic is delivered in 5 mL sequential aliquots with intermittent aspiration, thus establishing an initial "block." The agents commonly used are ropivacaine (0.5%) or bupivacaine (0.5%). A 20-gauge catheter is then inserted and advanced 5 to 7 cm beyond the needle tip. The catheter is then secured, bandaged and labeled. We follow the American Society of Regional Anesthesia (ASRA) guidelines for catheter placement and removal in patients taking anticoagulant medications.

POSTOPERATIVE CONTINUOUS INFUSION SETUPS AND ALGORITHM

Continuous analgesia is obtained by a continuous infusion of local anesthetic in addition to a multimodal analgesic regimen. The desired effect is achieved by administering a long-acting local anesthetic such as ropivacaine (0.2%), bupivacaine (0.1%) or levobupivacaine (0.1%). Compared with bupivacaine, ropivacaine

has been shown to produce less motor block, which may be a desirable feature in ambulatory patients.

Generally, upper-extremity infusions may start at 5 to 8 mL/hr, and lower-extremity infusions at 8 to 10 mL/hr. A patient-controlled analgesia (PCA) supplemental bolus of 4 mL every 30 minutes is included in the continuous infusion therapy, along with opioid supplementation if needed.

A multimodal approach to postoperative analgesia emphasizes the role of continuous peripheral nerve blocks with local anesthetic infusions. The protocol we follow is outlined in Figure 13.1. It consists of acetaminophen and a daily oral

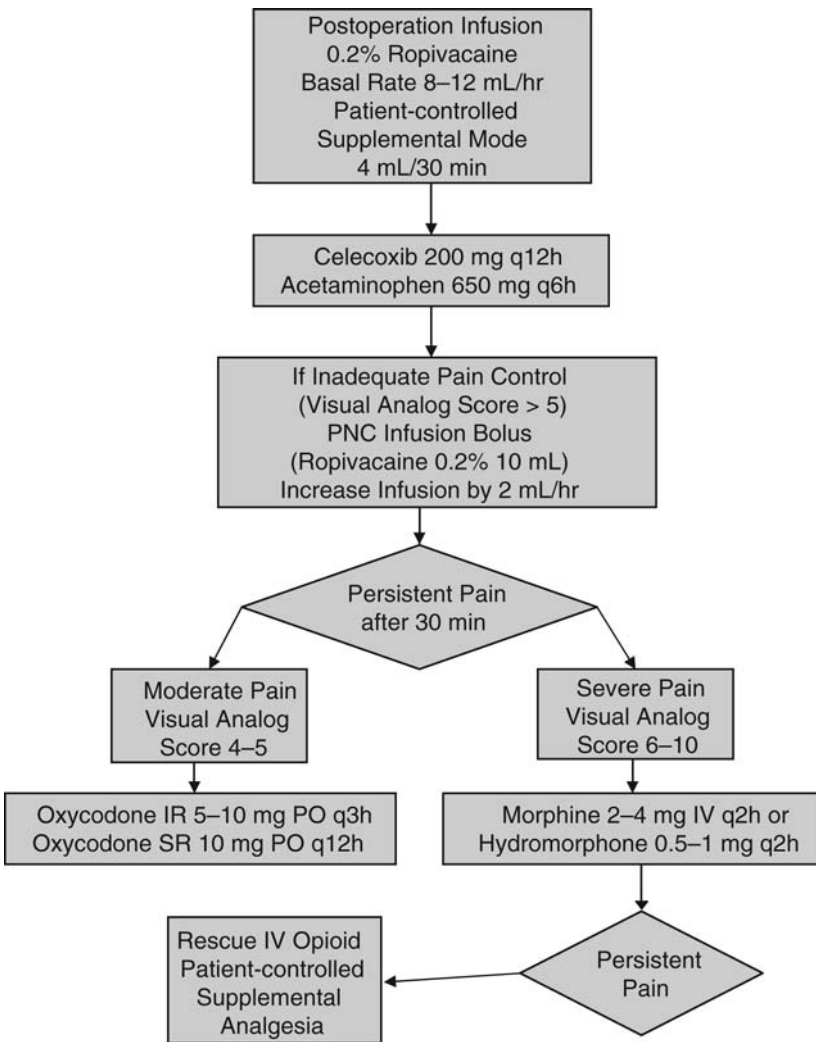


FIGURE 13.1 Multimodal analgesic algorithm. Postoperative analgesia algorithm in patients with peripheral perineural continuous infusion. *Abbreviations:* IV, intravenous; IR, immediate release; PNC, peripheral nerve catheter; SR, sustained release.

nonsteroidal anti-inflammatory drug such as the cyclooxygenase 2 (COX-2) inhibitor Celebrex. Further pain control modalities include adjustment of local anesthetic infusion rates, addition of both immediate-release (IR) and sustained-release (SR) oral narcotics, and addition of an intravenous (IV) PCA.

UPPER-EXTREMITY TECHNIQUES

Blockade of the upper extremity is performed by blocking the brachial plexus. Blocks can be performed at numerous locations along the brachial plexus, with some sites being more amenable to continuous catheter placement than others. Secondly, each site possesses certain merits, advantages, and disadvantages to continuous infusions, and this will be pointed out with each procedure.

Interscalene Approach

Blocks

Brachial plexus (C5-T1)

Indications The interscalene approach to brachial plexus block is commonly used for open shoulder surgery, rotator cuff repair, acromioplasty, shoulder arthroplasty, proximal upper limb surgery (1,2).

Technique Landmarks and patient positioning for continuous interscalene brachial plexus block are the same as for the single-shot technique. The anesthesiologist should stand at the head of the patient, facing caudad (or toward the feet). This positioning facilitates stabilization of the needle and advancement of the catheter in a caudal direction. A 3- to 5-cm stimulating needle is inserted at a slightly caudad angle and advanced until a brachial plexus twitch is elicited. After stabilizing the needle, 20 to 40 mL of local anesthetic is delivered and then the catheter is inserted.

The interscalene site is shallow and catheters not uncommonly leak and may easily become dislodged. In effort to minimize this observation, some providers prefer to "tunnel" the catheter. Utilizing a 3.5-in Touhy needle, the catheter can be tracked subdermally to a distant exit site.

Postoperatively, a continuous infusion of local anesthetic is started in the recovery room and maintained on the hospital ward.

Evidence for continuous nerve block Prospective, randomized, controlled trials have demonstrated that continuous interscalene analgesia reduced opioid requirements compared with placebo (1). For open shoulder surgery, prospective, randomized, controlled trials showed that continuous interscalene analgesia reduced the requirement for postoperative opioids when compared with IV PCA. Continuous analgesia also provided better patient satisfaction and reduced opioid-related side effects (1). A retrospective, case-controlled study demonstrated increased shoulder range of motion the day after total shoulder arthroplasty in patients with continuous interscalene nerve block when compared with patients treated with IV opioids (3,4).

Caveats The interscalene block is unreliable in providing satisfactory anesthetic blockade to the inferior trunk of the brachial plexus. As a result, analgesia of the ulnar nerve is unreliable. In practice, a continuous catheter is not placed in this location for postoperative analgesia associated with hand surgery (2,5). Secondly, the initial loading bolus will often produce phrenic nerve blockade (85–100%), therefore proper patient selection must be considered. Less frequently and less troublesome are associated hoarseness secondary to blockade of the recurrent laryngeal nerve and a Horner's syndrome secondary to sympathetic blockade (Fig. 13.2) (1).



FIGURE 13.2 Interscalene block. *Abbreviations:* IS, interscalene; SCM, sternocleidomastoid.

Infraclavicular Block

Blocks

Brachial plexus (C5-T1)

Indications The infraclavicular approach to brachial plexus block easily facilitates catheter placement for continuous postoperative analgesia following surgery involving the humerus, elbow, forearm, wrist, and hand. It also can provide sympathetic (and motor) block in patients suffering with vascular insufficiency or sympathetically mediated pain (2).

Technique The landmarks are the same as for the single-shot technique, including the medial clavicular head, coracoid process and the midpoint of the clavicle. The coracoid process can be located by palpating just medial to the anterior shoulder while the patient elevates the arm. Two common approaches have been described that facilitate catheter placement. The classic approach described by Raj, and the vertical coracoid approach described by Wilson.

For the Raj approach, the patient lies supine with his or her head slightly turned away from the side of the procedure. The anesthesiologist should stand at the patient's head on either the side to be blocked or on the opposite side. Correct positioning by the anesthesiologist and convenient placement of equipment make catheter advancement proceed smoothly. The operative limb is abducted to 90° at the shoulder and flexed at the elbow. The axillary pulse is identified. If this is not possible, the arm can remain neutral at the shoulder, in which case the groove between the deltoid and pectoralis muscle is used as a landmark.

The midpoint of a line connecting the medial clavicular head and the coracoid process is identified. The axillary artery can be marked on the skin. A 4-in nerve stimulator needle is inserted 2 to 3 cm caudal to the midclavicular point at a 45° angle to the horizontal plane. The needle is advanced parallel to the medial clavicular head coracoid process line toward the axillary artery pulse. Stimulation of the brachial plexus occurs soon after pectoralis muscle twitches cease (5). Motor activity in the hand is identified. After reducing the stimulation current to



FIGURE 13.3 Infraclavicular block.

<0.5 mA, witnessing fade of motor activity along with negative aspiration for blood, between 30 and 40 mL of local anesthetic is delivered and the catheter is inserted toward the apex of the axilla.

For the coracoid approach, the patient's arm may remain adducted. The coracoid process is identified and marked. The stimulating needle is inserted perpendicular to the floor at a point 2 cm caudal and 2 cm medial from the coracoid process. The bevel is directed toward the apex of the axilla (Fig. 13.3). The end point again is achievement of a satisfactory motor response with a 4-in nerve-stimulating needle. Then, after reducing the stimulation current to <0.5 mA, witnessing fade of motor activity along with negative aspiration for blood, between 30 and 40 mL of local anesthetic is delivered.

It should be noted that accepting activity of the musculocutaneous nerve (i.e., biceps or brachialis twitch) may result in unsatisfactory blocks. In a significant percentage of patients, the musculocutaneous nerve splits early from the brachial plexus, and delivery of the local anesthetic at that site will fail to adequately block the plexus. This approach avoids phrenic nerve blockade, thus can be used in patients with lung disease (2).

Evidence for continuous nerve block A prospective, randomized, double-blinded, controlled trial showed that infraclavicular brachial plexus block decreased pain, opioid use, sleep disturbances, and opioid-related side effects after orthopedic procedures of the forearm and hand (4).

A randomized, double-blinded, prospective study compared the following regimens for continuous catheters placed for orthopedic surgery at or distal to the elbow: basal rate, versus basal with bolus, versus bolus only. Patients in the continuous infusion with patient-controlled bolus group had lower levels of oral analgesic use, longer durations of infusion (for the same volume of anesthetic), and higher satisfaction ratings than those patients with a basal infusion alone. These patients also had more potent analgesia, fewer sleep disturbances, and higher satisfaction when compared with the bolus group (6).

Axillary Brachial Plexus Block

Blocks

Brachial plexus (C5-T1)

Indications The axillary block is the most commonly used brachial plexus block for procedures on the forearm, wrist, and hand, as well as for chronic pain syndromes and vascular diseases (2).

Technique Landmarks in the axilla are the same as for the single-shot technique and include the axillary artery, the inferior border of the pectoralis muscle medially, and the long head of the biceps muscle laterally. The median, ulnar, and radial nerves are most compactly arranged at the proximal aspect of the axilla (lateral edge of the pectoralis minor) and diverge as they travel distally (1). The patient lies supine, with the arm to be blocked abducted at 90° and the forearm flexed at 90°. The anesthesiologist is positioned on the side of the patient that is to be blocked. It is important to firmly fix the axillary artery with the palpating hand to facilitate accurate location of the catheter during placement. A 2-in nerve stimulator needle is inserted at a 45° angle to the skin and directed proximally. The needle is carefully advanced toward the axillary artery pulse until the required motor response is elicited at the wrist or fingers. To achieve the highest level of success, a motor response should be elicited from the nerve most involved by the surgery. After reducing the stimulation current to <0.5 mA, witnessing fade of motor activity along with negative aspiration for blood, between 30 and 40 mL of local anesthetic is delivered. A catheter is advanced toward the apex of the axilla.

Since the brachial plexus can be superficial at the level of the axilla, the catheter is sometimes tunneled for 2 to 3 cm using an 18-gauge angiocatheter. As with a single-shot axillary nerve block, the musculocutaneous nerve may need supplementation for blockade using 5 mL of additional local anesthetic deposited in the coracobrachial muscle (2).

Evidence for continuous nerve block Case series show satisfactory analgesia after hand and forearm procedures with continuous infusions, but have not compared these with IV PCA or other modalities. A study by Salonen did not show a statistical difference in analgesia or need for supplemental analgesics between patients receiving ropivacaine or saline (1,7). More clinical trials are needed to investigate the efficacy of this approach (Fig. 13.4).

LOWER-EXTREMITY TECHNIQUES

Lumbar Plexus Block: Psoas Approach

Blocks

Lumbar plexus

Indications Continuous lumbar plexus blocks are indicated for postoperative pain management in patients undergoing hip, femur, or knee procedures. They can be combined with general anesthesia for surgery on the knee, thigh, or hip, or combined with a sciatic block for most surgeries on the lower extremity (8,9). They are also an effective alternative to neuraxial techniques in patients in whom an epidural or spinal would be contraindicated or technically difficult.

Technique Blockade of the lumbar plexus has been described using an anterior "three-in-one" technique or a posterior psoas compartment technique. Our preference is to use the posterior psoas compartment approach because it has been shown to provide more reliable anesthesia of the obturator and lateral femoral

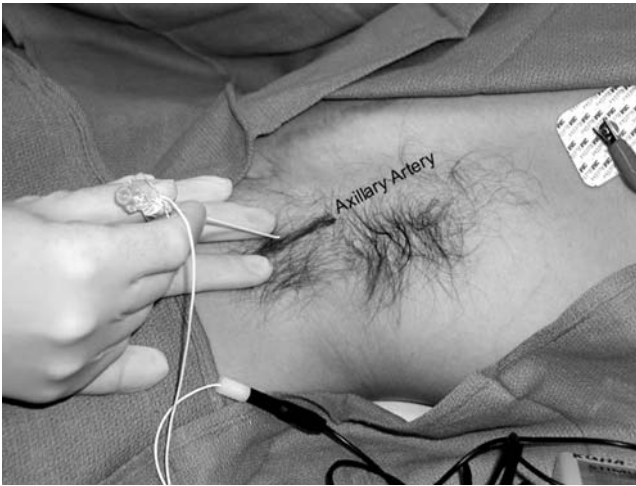


FIGURE 13.4 Axillary block.

cutaneous nerves (10,11). Another benefit of the posterior approach is that the catheter is located more distant from the surgical site.

The patient is placed in the lateral decubitus position with the side to be blocked up and the hips and knees slightly flexed. The landmarks are the same as for the single-shot technique and include the iliac crest, the spinous processes, and the posterior superior iliac spine (PSIS). Slight variations in needle positioning are described in the literature. Some sources advocate needle insertion 4 or 5 cm lateral to the interspinous line at the level of a line drawn at the posterior iliac crests (5,8). Winnie initially suggested insertion at the intersection of a line parallel to the spine passing through the PSIS and a line joining the iliac crests. Multiple studies have shown this point to be too lateral (12–16). As a result, Winnie recommended a slightly medial direction to the needle after insertion. Our preference is to use the insertion point based on research by Capdevila. This point is at the junction of the lateral third and medial two-thirds of a line between the spinous process of L4 and a line parallel to the spinal column passing through the PSIS. L4 is estimated to be 1 cm cephalad to the upper edge of the iliac crests.

A 4-in nerve stimulator needle is inserted perpendicular to the skin while the palpating hand anchors the skin and paraspinous muscles. The needle tip orientation should be cephalad (5). We attempt to contact the transverse process of L4, pull back slightly, and advance caudad to the transverse process until a quadriceps femoris twitch is elicited, as manifest by a cephalad movement of the patella. After this motor response is observed, the current is lowered to stimulate at <0.5 mA (8). Following negative aspiration for blood, 20 to 30 mL of local anesthetic is delivered. For surgical anesthesia, 30 mL is usually necessary for dense blockade of the lumbar plexus (5). If the block is used in combination with a sciatic block, the volume may be reduced to minimize the risk of local anesthetic overdose.

Evidence for continuous nerve block A retrospective case series showed that continuous lumbar plexus block with sciatic nerve block and perioperative sedation is an effective alternative to general anesthesia that provides analgesia,

adequate muscle relaxation, and postoperative pain control (9). Decreased operative blood loss was also noted (10).

A prospective, randomized study of postoperative analgesia and recovery following total knee replacement compared continuous lumbar plexus block via the psoas compartment with continuous femoral nerve block or the combination of continuous femoral and sciatic nerve catheters. The psoas block patients required less supplementary analgesia in the first 48 hours than the femoral block patients. However, continuous femoral/sciatic patients required the least supplemental analgesia. Postoperative functional outcomes at seven days and 9 to 12 months did not differ among groups (16).

A prospective, randomized trial comparing continuous psoas compartment lumbar plexus block with IV PCA reported better analgesia and higher patient satisfaction with psoas compartment block (1,17). Another prospective multicenter trial reported 94% of patients had excellent postoperative analgesia without need for additional systemic opioids when continuous psoas compartment block was used for total hip arthroplasty (12).

Caveats Differences of opinion exist on the optimal nerve stimulator current used to elicit a motor response. One source advocates not going lower than 0.5 to 1.0 mA because the needle may be in the dural sleeve if a twitch is elicited below this level (5).

The distance from the transverse process of L4 to the lumbar plexus has been extensively studied. Capdevila found this distance to be 18 mm regardless of patient gender or BMI (12). At the L4 level, motor response is usually elicited at a depth of 6 to 8 cm, but can be found anywhere between 5 and 10 cm (5,12). Some sources recommend not going beyond 9 to 10 cm depth without redirecting the needle (5,8).

The optimal depth of catheter insertion has also been debated. We advocate a distance of 5 to 7 cm (12). Some sources recommend depths of only 3 to 4 cm to minimize the risk of kinking or displacement, while others advocate up to 8 to 10 cm to prevent catheter displacement, since the skin in this region is very mobile (Figs. 13.5 and 13.6) (5,8).



FIGURE 13.5 Lumbar plexus block, psoas landmarks. *Abbreviation:* PSIS, posterior superior iliac spine.

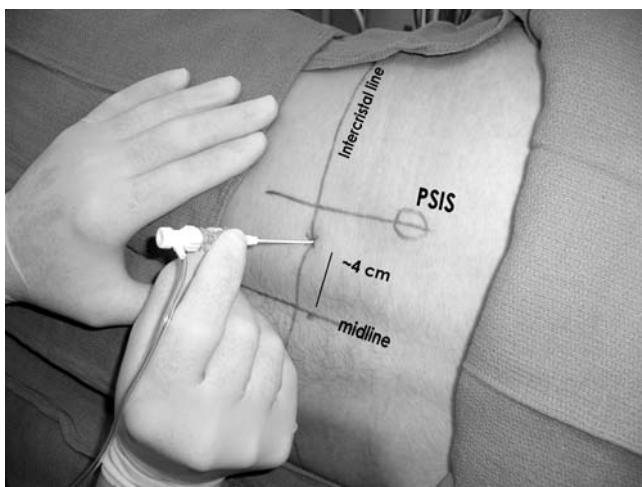


FIGURE 13.6 Lumbar plexus block, psoas insertion. *Abbreviation:* PSIS, posterior superior iliac spine.

Femoral Block

Blocks

Lumbar plexus (L2-L4)

Indications Femoral nerve block produces anesthesia of the entire anterior thigh and most of the femur and knee joint, as well as the skin on the medial lower leg. It can be used for postoperative analgesia after thigh and knee surgery or combined with sedation and a sciatic nerve block for lower-extremity surgery.

Techniques The patient should lie supine with the leg to be blocked in a neutral position. The needle insertion site is 1 cm lateral to the femoral artery in the inguinal crease. The palpating hand is used to stabilize the skin prior to needle insertion. A 2-in nerve stimulator needle is inserted and advanced at a 45° to 60° cephalad angle until a patellar twitch is elicited (5). After reducing the stimulation current to <0.5 mA, witnessing fade of motor activity and with negative aspiration for blood, 20 to 30 mL of local anesthetic is delivered. The catheter is then advanced in a cephalad direction.

The fascia iliaca approach is a modification of the femoral nerve block that may provide similar analgesia with slightly lower risk of venipuncture. A nerve stimulator is typically not required for this technique. The inguinal ligament is marked from the anterior superior iliac spine to the pubic tubercle in the supine patient. The needle insertion site is 1 cm caudal to the junction of the lateral third and the medial two thirds of this line. This site is approximately 2 to 3 cm lateral to the femoral artery. The needle is advanced at a 45° to 60° cephalad angle until two pops are felt through the fascia lata and the fascia iliaca, respectively. The angle is decreased to 30° and 20 mL of local anesthetic is injected. The catheter is advanced 15 to 20 cm cephalad past the needle tip (1).

Evidence for continuous nerve block Prospective clinical trials have shown improved analgesia and knee range of motion with a decreased incidence of nausea/vomiting when continuous femoral nerve block was compared with IV PCA (1,18,19). Analgesia and range of motion were comparable to epidural. Earlier

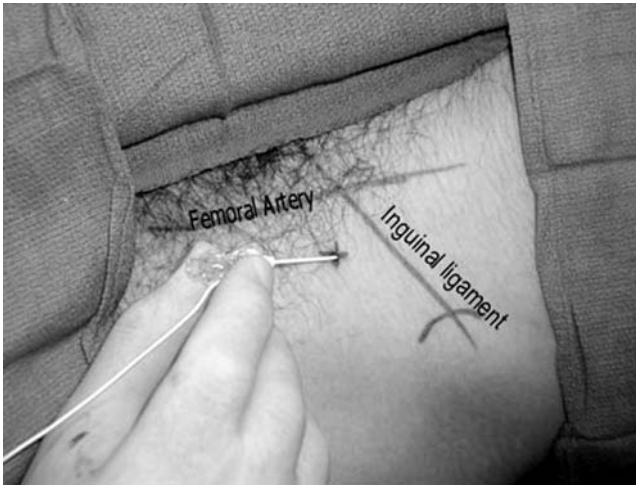


FIGURE 13.7 Femoral block.

mobilization was also achieved in continuous nerve block patients who underwent total knee arthroplasty (19,20).

A prospective, randomized trial showed that patients with continuous fascia iliaca blockade required less postoperative morphine and had improved range of motion when compared with placebo (21).

In a prospective, nonrandomized trial involving patients with total hip replacement, continuous femoral block provided comparable analgesia to IV PCA or epidural. Continuous nerve block was associated with a lower incidence of nausea, vomiting, pruritus and sedation versus IV PCA, and a lower incidence of urinary retention and hypotension than epidural (22).

Caveats Insertion of the continuous catheter 3 to 4 cm may make lateral femoral cutaneous and obturator nerve blockade more likely (Fig. 13.7) (8).

Sciatic Nerve Block: Posterior Approach (Labat)

Blocks

Sacral plexus, sciatic nerve (L4-S3)

Indications Sciatic nerve blockade produces anesthesia of the skin of the posterior thigh, the hamstring and biceps femoris muscles, part of the hip and knee joint, and the entire leg below the knee with the exception of the skin of the medial lower leg. It can be used in combination with a continuous lumbar plexus block for hip or femur surgery, or combined with a femoral or lumbar plexus block for procedures on the thigh and knee. It can also be used for amputation of the lower leg (5).

Technique The patient is positioned in the lateral decubitus position with the side to be blocked up and with a slightly forward pelvic tilt. The knees are slightly bent and the foot on the upper leg is positioned over the dependent leg so twitches can be easily observed (5). The anatomical landmarks are the greater trochanter and the PSIS. These structures are marked, and a line is drawn between them and divided in half. A perpendicular line drawn through the midpoint of this line and extending inferiorly for 4 cm identifies the needle insertion point.

It is important to infiltrate deeper tissues with local anesthetic to make advancement of the large, blunt-tipped needle more tolerable. As with all blocks, stabilization with the palpating hand is crucial for needle manipulation and catheter advancement. A 4-in nerve stimulator needle is inserted perpendicular to the skin. The bevel of the stimulating needle should be directed distally, toward the patient's foot, to aid catheter insertion. Initially, twitches of the gluteus muscle are observed. As the needle is advanced deeper, stimulation of the sciatic nerve results in twitches of the hamstrings or foot. After reducing the stimulation current to <0.5 mA, witnessing fade of motor activity along with negative aspiration for blood, 20 to 30 mL of local anesthetic is injected and the catheter is inserted.

Evidence for continuous nerve block A prospective trial demonstrated effective postoperative analgesia in patients undergoing surgical procedures on the lower leg (23).

A prospective, randomized study compared postoperative analgesia and recovery following total knee replacement with continuous lumbar plexus block via the psoas compartment with continuous femoral nerve block or the combination of continuous femoral and sciatic nerve catheters. Continuous femoral/sciatic patients required the least supplemental analgesia (16).

Caveats For patients that cannot tolerate positioning for a posterior sciatic nerve block, a high lateral approach can be used (24). With the patient supine and the leg in a neutral position, the needle insertion site is identified 3 cm caudal to the greater trochanter and 2 cm posterior to the femur. This site should be between the greater trochanter and the ischial tuberosity, which can be identified by palpating the inferior aspect of the buttock. A 4- or 6-in nerve stimulator needle is inserted perpendicular to the skin with the distal tip oriented cephalad. The femur is contacted, and the needle is withdrawn and redirected 20° posteriorly. The needle is advanced until a motor response is seen in the foot, usually at a depth of 8 to 12 cm. After reducing the stimulation current to <0.5 mA, witnessing fade of motor activity along with negative aspiration for blood, 20 to 30 mL of local anesthetic is injected and the catheter is inserted (Figs. 13.8 and 13.9).

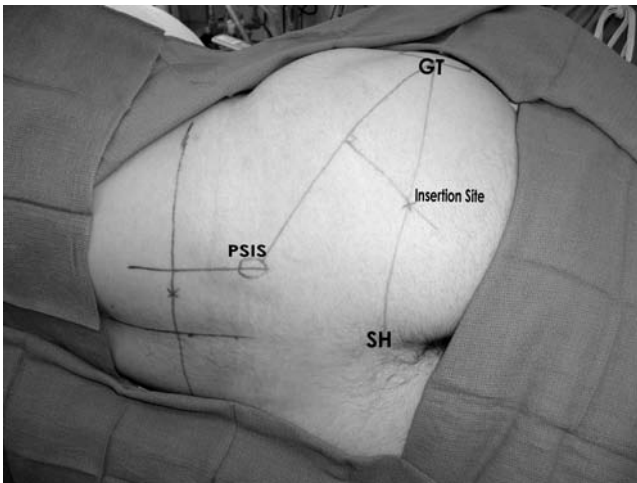


FIGURE 13.8 Sciatic block landmarks. *Abbreviations:* GT, greater trochanter; PSIS, posterior superior iliac spine; SH, sacral hiatus.

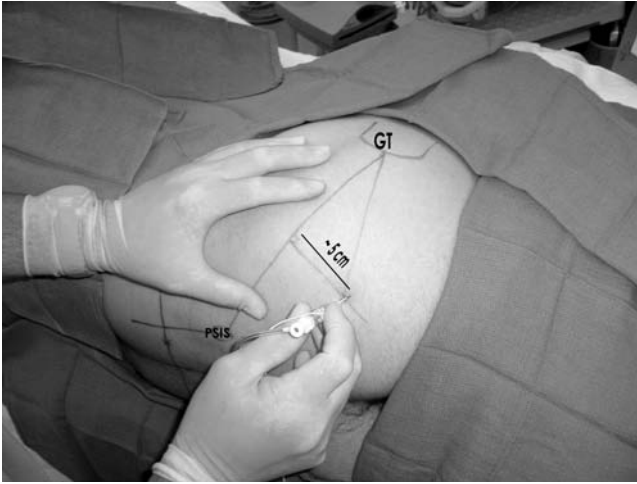


FIGURE 13.9 Sciatic block insertion. *Abbreviations:* GT, greater trochanter; PSIS, posterior superior iliac spine.

Popliteal Nerve Block: Lateral Approach

Blocks

Tibial and peroneal nerves

Indications Blockade of the branches of the sciatic nerve at the popliteal fossa provides anesthesia and analgesia for surgery on the calf, ankle, Achilles tendon, and foot. It also is effective for calf tourniquet pain. A saphenous nerve block may be combined with a popliteal nerve block to provide complete anesthesia of the lower leg.

Technique The sciatic nerve usually divides into the tibial and common peroneal nerves approximately 70 mm proximal to the popliteal fossa crease (5). The benefit of the lateral approach is that the patient can remain in the supine position, rather than having to be turned prone to perform the block via the classic posterior approach. The lateral approach also provides more secure placement of the catheter away from the mobile knee joint (1,25). The knee is slightly flexed by placing a pillow under the knee. The groove between the vastus lateralis anteriorly, and the lateral tendon of the biceps femoris posteriorly, is palpated and marked. The needle insertion site lies in this groove 8 cm proximal to the popliteal fossa crease or 10 cm proximal to the superior border of the patella (5,24).

A 4-in nerve stimulator needle is inserted with the tip oriented cephalad in a horizontal plane, perpendicular to the long axis of the leg. Once the femur is contacted, the needle is withdrawn and redirected 30° posteriorly. The needle is again advanced while watching for dorsiflexion or plantar flexion of the foot or toes. After reducing the stimulation current to <0.5 mA, witnessing fade of motor activity along with negative aspiration for blood, 30 to 40 mL of local anesthetic is injected and the catheter is inserted.

If this block is used in combination with a femoral nerve block, the bolus volume may be reduced in consideration of possible local anesthetic toxicity.

Evidence for continuous nerve block A prospective nonrandomized study with retrospective control group compared continuous popliteal nerve analgesia



FIGURE 13.10 Popliteal block, lateral approach.

versus IV PCA (1,26). This study showed that continuous nerve block provided superior analgesia, reduced postoperative morphine consumption, lowered the incidence of nausea/vomiting, and decreased urinary retention and sedation.

Two prospective randomized, controlled trials compared continuous popliteal nerve blockade with local anesthetic versus saline (27,28). Continuous nerve block patients had lower pain scores and opioid requirements, fewer opioid-related side effects, shorter lengths of hospital stay, and better sleep with fewer awakenings during the first 48 hours postoperatively (Fig. 13.10) (28).

THORACIC TECHNIQUES

Paravertebral Nerve Block

Blocks

Specific thoracic or lumbar dermatomes

Indications Thoracic paravertebral block provides selective unilateral anesthesia and analgesia for breast or other chest wall surgery (29). Lumbar paravertebral block provides anesthesia and analgesia for inguinal herniorrhaphy or analgesia following hip surgery (5). Paravertebral block can be utilized in patients in whom neuraxial techniques may be contraindicated because of coagulopathy or intolerance of the hypotension that may result from significant sympathetic blockade.

Technique The patient is positioned in the sitting or lateral decubitus position similar to that required for neuraxial anesthesia. Surface bony landmarks used to identify the correct spinal level include the spinous processes, iliac crests, and the inferior tips of the scapulae, which correspond to the T7 vertebral level. Needle insertion should be perpendicular to the skin at a point 2.5 cm lateral to the midline. The bevel of a 2-in nerve block needle is directed medially as the fingers of the palpating hand fix the skin to avoid horizontal skin movement (5). The transverse process of the vertebra should be contacted and the depth noted. The needle is then withdrawn and redirected 10° inferiorly to walk off the caudal border of the transverse process. Advance the needle 1 cm deeper than the

transverse process and inject 4 to 5 mL of local anesthetic after negative aspiration for blood. A catheter should then be advanced 3 cm past the needle tip.

Evidence for continuous nerve block A prospective randomized study on patients having breast cancer surgery comparing paravertebral nerve blocks with general anesthesia found that nerve block patients had lower visual analog scale (VAS) pain scores at rest and with activity, reduced opioid consumption, and a lower incidence of postoperative nausea and vomiting (PONV) (30). Other studies have also demonstrated the benefits of this technique for postoperative analgesia (31).

Caveats The needle should not be angled medially at insertion because of the risk of intraforaminal needle passage and nerve root or spinal cord injury (5). The depth of the transverse processes varies with patient body habitus and the level at which the block is performed. The deepest levels are at the high thoracic (T1-T2) and low lumbar levels, where contact occurs at a depth of 6 to 8 cm. The shallowest depth of contact occurs at 2 to 4 cm for the midthoracic levels (T5-T10) (5).

EQUIPMENT

Catheters

Types of catheters available for continuous peripheral nerve blockade include 20-gauge multiorifice epidural catheters, 20- or 21-gauge epidural catheters with wire stylets, or 21-gauge stimulating catheters (2). Inaccurate catheter placement is not uncommon. Some clinicians first insert the catheter and then administer a bolus of local anesthetic via the catheter in an effort to avoid this problem. The stimulating catheters deliver current to the distal tip to provide feedback on the position of the catheter tip relative to the nerve before local anesthetic injection. Although some evidence suggests this may improve accuracy of catheter placement, no investigations have yet shown definite increased accuracy of catheter placement using stimulating catheters when compared with nonstimulating catheters (32,33).

Infusion Devices

Infusion devices available for postoperative inpatient and outpatient infusions include disposable elastomeric devices, spring-powered pumps, and electronic infusion pumps. Elastomeric devices provide a more rapid than expected basal rate initially, return to their expected rate within 2 to 12 hours, and increase to a higher rate before reservoir exhaustion. These devices can provide bolus-only dosing by allowing the patient to manually release a clamp on the catheter. The risk of this method is that if the patient forgets to reclamp the tubing, the entire reservoir of local anesthetic can be delivered in less than an hour (32).

Spring-powered pumps initially provide a greater than expected basal rate, which steadily decreases to a less than expected rate by reservoir exhaustion. It is unknown whether this variability in basal rate has affected outcomes. A manually delivered bolus dose can be set with a lockout interval. Settings are preset by the manufacturer. Both spring and elastomeric pumps can be refilled (32).

Electronic infusion pumps provide the most accurate and consistent basal rates over the duration of the infusion. These pumps can be programmed by the clinician or patient and allow the patient to deliver PCA boluses electronically by pressing a button. Electronic pumps have alarms that can both notify the patient of a malfunction and sound a false alarm. Nonelectronic pumps cannot alarm. Published data on pump reliability is limited (32).

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INTRODUCTION

Of the available strategies for treatment of the patient in pain, regional anesthesia remains one of the cornerstones of therapy. While the techniques of regional anesthesia have been common knowledge for decades, there is increasing evidence of the beneficial effects of these techniques. Regional anesthesia has been shown to decrease the incidence of deep venous thrombosis, pulmonary embolism, pneumonia, transfusion requirements, respiratory depression, myocardial infarction, renal failure, and overall mortality (1). Studies have also shown that in select operations, a postoperative pain control regimen with regional anesthesia is superior in terms of pain control but also has the advantage of lower cost while sustaining improvements in morbidity and mortality (2,3).

Regional anesthesia is performed by introduction of medication around peripheral nerves or the spinal cord to prevent both afferent and efferent signal transfers. Contraindications to these procedures include patient refusal, infection at the injection site, bleeding diathesis, and specifically for neuraxial techniques, hypovolemia and left ventricular outflow obstruction (4).

Complications from regional anesthesia are rare. They range from limited neuropathies or headaches to complete paralysis. Spinal hematomas, although rare, are an especially serious complication both because of difficulty in detection and also because of the long lasting sequela produced if the condition is not recognized and corrected in an expedient fashion. The incidence of spinal hematoma ranges from 1:150,000 for epidural injections to 1:220,000 for spinal injections (5). While rare, the incidence of this complication is raised to 1:1000 with neuraxial procedures performed in the setting of anticoagulation (6). Increased recognition of this complication in the setting of anticoagulation prompted several societies to formulate guidelines for practitioners managing patients requiring regional anesthesia. Even with guidelines in place, it becomes important for the practitioner to understand the mechanism of hemostasis and the medications used to alter that process. This knowledge must be applied in determining the potential risks and benefits of pain relieving regional or neuraxial anesthetic procedures in a particular patient. This chapter will review the hemostatic process, drugs that modulate that process, and recommendations for performing regional anesthesia in patients receiving these hemostatic modulators.

HEMOSTASIS

The term hemostasis refers to the prevention of blood loss, but hemostasis involves much more than that. When a vessel is damaged, a process ensues resulting in interruption of that damage, temporary correction of the hemorrhage, and eventual repair. Initially when a vessel is damaged, the clotting system is activated by constriction of the damaged vessel to limit blood flow and expression of tissue

factor (TF) and von Willebrand's factor. These factors then interact with platelets to cause their activation and aggregation. Platelet activation and aggregation, in which a platelet plug is formed, is referred to as primary hemostasis. This platelet plug is then cross-linked with fibrin that is produced from the coagulation cascade. It is this coagulation cascade that results in the cleavage of fibrinogen to fibrin in a process referred to as secondary hemostasis. Once fibrin becomes cross-linked with the platelet plug, the clot stabilizes, allowing for fibrous tissue regrowth and closure of the vessel defect. While fibrin formation and cross-linking with platelets is the primary objective of coagulation, if kept unchecked the process can proceed to vessel occlusion or disseminated coagulation. The formation of thrombin and deposition of fibrin is controlled by a variety of processes that limit the coagulation cascade. Eventually, insoluble fibrin is dissolved in a process referred to as fibrinolysis or tertiary hemostasis. It is this ongoing growth, remodeling and regression of clot that characterizes the hemostatic system.

Primary Hemostasis

Platelets are plasma cells derived from progenitor megakaryocytes in the bone marrow (7). They are biconvex disks that measure $0.5 \times 3 \mu\text{m}$. Platelets are anucleated cells with a dense microtubular inner structure. This microtubular inner structure allows a conformational change to occur once platelets are activated, so as to achieve a more globular shape that aids in their adhesion and flow limiting properties (8). Platelets contain adhesive, stimulatory, and inhibitory receptors in their cell membranes as well as dense granules within their cytoplasm. These cytoplasmic granules contain the substances required for further platelet adhesion and activation such as ADP, serotonin, calcium, fibrinogen, growth factors, and cytokines (9).

While platelets are pivotal to primary hemostasis, they require activation by extrinsic factors. This activation proceeds after platelets are exposed to subendothelial collagen and von Willebrand's factor. Uncovering the subendothelial matrix exposes von Willebrand's factor to the platelet membrane receptor glycoprotein (GP) I-IX-V, forming a complex that results in initial platelet adhesion (10).

The platelet then undergoes several steps to complete the aggregation process. First, the membrane integrin receptor GP IIb/IIIa undergoes a conformational change that converts its low affinity fibrinogen receptor to one with a high affinity for fibrinogen. The cytoplasmic aspect of the receptor binds the cytoskeleton and mediates platelet spreading and clot retraction. The platelet also releases its granules containing ADP, serotonin, and thromboxane for platelet aggregation; fibronectin for adhesion; and platelet derived growth factor to allow proliferation of smooth muscle for eventual vessel remodeling (11).

Secondary Hemostasis

The central feature of secondary hemostasis is the conversion of fibrinogen to fibrin through the action of thrombin. The enzyme cascade that results in fibrinogen production is a rapid process that requires close regulation to prevent unwanted thrombosis.

The clotting cascade is typically thought to involve chain reactions of zymogens that are activated and their production amplified, the end result of which is the formation of fibrin (11). The classic teaching is that this process is initiated by one of two stimuli, committing coagulation to proceed either through the intrinsic or extrinsic pathway for the generation of thrombin (Fig. 14.1). While

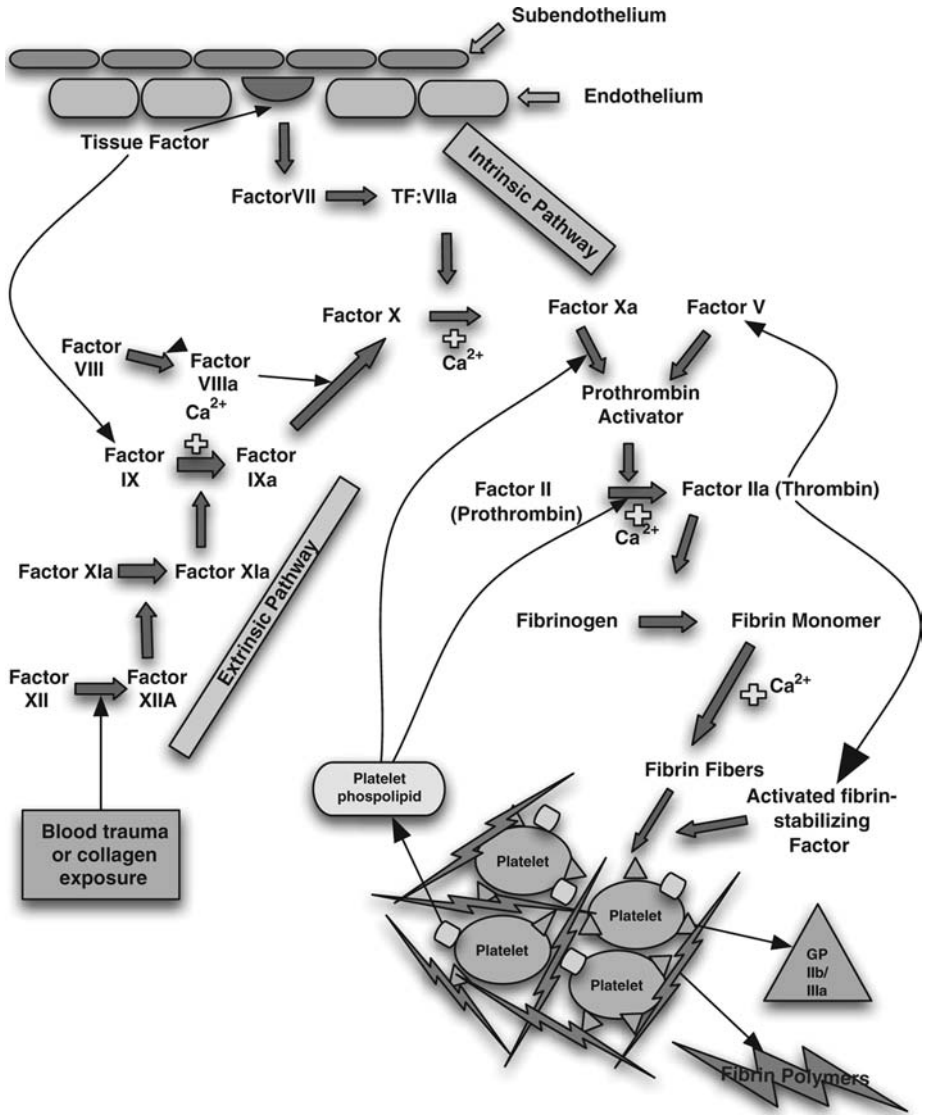


FIGURE 14.1 Coagulation cascade. Intrinsic and extrinsic components of the “tissue factor” pathway of coagulation. Note thrombin contribution for amplification of process at multiple sites.

this model has been useful in the prediction of and testing for bleeding disorders, it is not entirely correct. It is now believed that the inciting event for the coagulation cascade is factor VII’s contact with TF in the endothelium, with subsequent activation of factor VII and conversion of factor X to its activated form by factor VIIa (Fig. 14.1). Activated factor X or prothrombin then results in the cleavage of fibrinogen to fibrin monomers. These monomers eventually form fibers that adhere to platelets, increasing their tensile strength (12).

Tertiary Hemostasis

The formation of fibrin is an extremely quick and efficient reaction, which, left unchecked, would result in uncontrolled thrombosis. Fortunately, once fibrin forms, exposed lysine residues are able to bind with plasminogen, the proenzyme for clot dissolution, and become incorporated into the clot (13). The damaged vascular tissue then slowly releases a substance called tissue plasminogen activator (t-PA) from its endothelium, resulting in conversion of plasminogen to plasmin. Plasmin then digests fibrin fibers as well as procoagulants factor V, factor VII, and factor XII in a process called fibrinolysis. This is also referred to as tertiary hemostasis, in which a clot is degraded and the newly remodeled endothelium is exposed to the flow of blood (12). While the differing factors involved in clot formation and dissolution seem abstract for most clinicians, these principles of function provide the basis for drug therapy and modulation of coagulation.

PHARMACOLOGY

The categories of hemostatic modulating drugs can be divided into those agents that impact platelets, agents that inhibit the formation or action of coagulation factors, and drugs acting on the fibrinolytic system.

Antiplatelet Agents

The antiplatelet agents include nonsteroidal anti-inflammatory drugs (NSAIDs), thienopyridines, GP IIb/IIIa receptor antagonists, and dipyridamole. While all these agents inhibit the action of platelets, they each have a unique mode of action to achieve this.

Aspirin and NSAIDs

NSAIDs and aspirin achieve their antiplatelet effect by limiting thromboxane production. Thromboxane is one of the elements key to platelet aggregation and is produced by the arachidonic acid enzyme pathway. Both medications limit thromboxane production by inhibition of the enzyme cyclooxygenase, the key enzyme for the conversion of arachidonic acid to thromboxane, prostacyclin, and the prostaglandins. The cyclooxygenase system has two isoenzymes. Cyclooxygenase I (COX-1) mediates many constitutive functions in the body, while cyclooxygenase II (COX-2) is responsible for pain and inflammation (14). While inhibition of COX-2 is desired for analgesia, it is the inhibition of COX-1 that limits use of NSAIDs because of potential adverse gastrointestinal effects. COX-1 inhibition also produces an antiplatelet effect. Aspirin and the NSAIDs both have mild antiplatelet effects, though they differ in the manner in which they produce their effects. Aspirin irreversibly acetylates serine residues of COX-1, preventing arachidonic acid from binding to its active site, ultimately limiting the production of thromboxane A_2 (text box 14.1). Platelets, which lack functional nuclei, cannot produce more COX-1 and thus maintain deficient thromboxane production for the remainder of their lifespan. New COX-1 is generated when new platelets are generated 7 to 10 days after the last exposure to aspirin (15,16). NSAIDs, on the other hand, act competitively at the binding site for arachidonate on COX-1. This is a reversible reaction, which is more dependent on drug pharmacokinetics than on platelet kinetics (9). While both aspirin and NSAIDs produce antiplatelet effects, their clinical repercussions in the setting of regional anesthesia seem to be negligible.

While bleeding may be a concern when NSAIDs or aspirin are used prior to surgical procedures, the risk of spinal or perineural hematoma while receiving aspirin and NSAIDs seems to be minimal, and their use need not be discontinued prior to a neuraxial or regional anesthetic procedure (17–20). However, care should be taken in those patients taking salicylates or NSAIDs together with other hemostatic modulators, as clinically significant bleeding is difficult to predict in these situations.

Box 14.1: Aspirin and nonsteroidal anti-inflammatory drugs

No abstinence period is required for primary placement of regional anesthetic or catheter removal.

Dipyridamole

Dipyridamole [Persantine[®], Aggrenox[®] (extended release dipyridamole with aspirin)] is a vasodilator and has an antiaggregation effect on platelets. While its mechanism of action is not clearly defined, it is believed to produce its clinical effects by inhibition of nucleotide phosphodiesterase and inhibition of adenosine metabolism (21). Limited evidence exists regarding the use of this agent and the development of spinal or perineural hematomas (22). This is especially true for reports concerning neuraxial procedures and concomitant use of dipyridamole. While no studies have examined its perioperative or periprocedural use, the lack of case reports of hematomas would suggest its relative safety. Practitioners should be advised that the risk of performing regional or neuraxial anesthetic techniques in patients on combination antiplatelet agents should be evaluated on a case-by-case basis.

Thienopyridines

Thienopyridine agents work by inhibiting ADP induced platelet aggregation as well as the binding of fibrinogen to platelets (9). The prototypical drugs in this class of drugs are clopidogrel (Plavix[®]) and ticlopidine (Ticlid[®]). Both agents exhibit time and dose dependent effects on platelets. Like aspirin, both agents have a short half-life but a prolonged duration of action (text box 14.2) (23). The time required to reach steady state concentration for ticlopidine is 14 to 21 days and time to steady state for clopidogrel is 7 days (14). While intricate knowledge of initial dosing kinetics is not essential for most pain practitioners, drug labeling does recommend a drug abstinence period that mirrors the time to steady state for each agent. The abstinence period prior to surgery or neuraxial procedures for clopidogrel is recommended to be 7 days, while that for ticlopidine is 10 to 14 days. Ticlopidine also carries the recommendation of biweekly blood count monitoring for blood dyscrasias during the first 3 months of therapy and as indicated thereafter (24).

Box 14.2: Thienopyridines

An abstinence period of 7 days for clopidogrel and 14 days for ticlopidine is required for primary major neuraxial block placement.

GP IIb/IIIa Receptor Antagonists

Abciximab (ReoPro[®]), eptifibatid (Integrilin[®]), and tirofiban (Aggrastat[®]) make up a class of drugs referred to collectively as GP IIb/IIIa receptor antagonists. These agents are used widely for management of coronary thrombosis and as

prophylaxis against thrombus formation after coronary intervention. They produce their clinical effects by binding reversibly to the GP IIb/IIIa receptor on platelets to prevent von Willebrand factor binding, fibrinogen binding, and platelet-to-platelet interaction (25). Abciximab is the agent with longest half-life at 12 hours and requires 24 to 48 hours for recovery of platelet function after its discontinuation. Eptifibatide and tirofiban have more limited kinetics with restoration of platelet function in 6 to 12 hours after their cessation, as these drugs have shorter plasma half-lives and less affinity for the GP IIb/IIIa receptor (text box 14.3) (26). While no studies have examined the safety of regional anesthetics in patients receiving these agents, their use has been implicated in hematoma formation from percutaneous vascular procedures (27–29). Therapy with these agents results in prolongation of the bleeding time and activated partial thromboplastin time (aPTT), but these effects do not reflect drug concentration or degree of platelet inhibition. Platelet function testing by turbidometric assay is the most predictive means of measuring platelet inhibition (30). On the basis of available pharmacodynamic literature, regional procedures or neuraxial catheter removal should be delayed for 24 to 48 hours after last use of abciximab, or 4 to 8 hours after eptifibatide/tirofiban. Reinstitution of drug therapy should also be delayed for 2 to 4 hours after regional procedures or catheter removal to lessen the chance of hemorrhagic complications.

Box 14.3: Glycoprotein IIb/IIIa receptor antagonists

Primary placement of major neuraxial blockade or catheter removal should be delayed 24–48 hr for abciximab and 8–10 hr for eptifibatide/tirofiban. Reinstitution of antiplatelet therapy should be delayed 2–4 hr after block placement or catheter removal.

Heparins*Unfractionated Heparin*

Unfractionated heparin (UFH) is a parenterally delivered glycoaminoglycan anticoagulant used in the treatment and prophylaxis of a variety of thrombotic and thromboembolic disorders. Heparin possesses a unique pentasaccharide sequence that shows a high affinity for binding to and accelerating the action of antithrombin III (AT III) (31,32). Heparin is a heterogeneous compound with molecular weights ranging from 3000 to 30,000 d with a mean molecular weight of 15,000 daltons (33,34). Only one third of these heparin molecules contain binding sites for AT III (35–39). It is this binding to AT III that produces a conformational change in the molecule that converts it from a slow inhibitor of thrombin to a rapid one. The heparin/AT III complex inactivates factor IIa and factors Xa, IXa, and XIIa, with thrombin and Xa having the greatest sensitivity to inhibition (40).

Because of variability in size, protein binding, protein neutralization, and its narrow therapeutic window, monitoring of the anticoagulant activity of heparin is a must. Monitoring in most clinical situations is with the aPTT, with a prolongation of 1.5 times greater than control as the target for therapy (text box 14.4) (40).

Box 14.4: Unfractionated heparin IV

Normalization of activated partial thromboplastin time should occur prior to major neuraxial block placement or catheter removal.

Heparin is administered either intravenously or subcutaneously. While patients may achieve aPTT prolongation compatible with full anticoagulation after subcutaneous administration, this route of delivery is almost solely used for the purpose of thrombosis prophylaxis employing subtherapeutic doses of the drug. With intravenous administration, an immediate anticoagulant effect occurs, while there is a one- to two-hour delay with subcutaneous administration (41). Heparin clearance displays saturable binding by macrophages and endothelial cells and a slow first order nonsaturable mechanism that is largely renally dependent. This makes anticoagulant kinetics nonlinear, with disproportionate responses and prolongation of clearance at higher doses (42).

Side effects of heparin in addition to hemorrhagic complications include osteoporosis and thrombocytopenia. The mechanisms of thrombocytopenia may be a result of either weak activation of platelets by heparin or, more seriously, IgG immune mediated activation. Regardless of the cause, it is recommended that platelet counts be obtained in patients on heparin therapy for longer than 4 days because of concerns about this side effect (14,43).

Regional anesthesia for a patient being administered heparin intravenously should be withheld until resumption of normal clotting parameters has been verified with an aPTT. Patients should have platelet counts checked to rule out thrombocytopenia if the duration of heparin therapy has been greater than 4 days. While therapeutic monitoring with aPTT measurement and withholding of regional anesthetic techniques are not recommended by the American Society of Regional Anesthesia (ASRA) Consensus guidelines in patients receiving "mini dose" subcutaneous heparin (<5000 units subcutaneous every 12 hours), up to 15% of patients may show changes in aPTT with 2% to 4% demonstrating therapeutic anticoagulation (44,45). There is no safety data regarding the use of subcutaneous UFH in doses exceeding 10,000 units daily or with three times a day dosing regimens. Caution should be exercised when regional analgesia is considered under these circumstances. If epidural analgesia is to be maintained postoperatively, it is advised that three times a day dosing regimens of subcutaneous UFH be avoided and that twice a day subcutaneous UFH in conjunction with sequential compression devices be used instead (14). Catheter removal should occur two to four hours after the last dose of heparin and with confirmation of normalization of the aPTT prior to removal. Reinstitution of heparin therapy should be delayed for 1 hour in patients having neuraxial catheters removed. Heparin administration should also be delayed for 1 hour in patients undergoing primary neuraxial procedures. Consideration should be given to those patients having regional anesthetic techniques prior to procedures during which heparinization is planned if traumatic placement is experienced or if the patient is on other hemostatic modulatory agents. While the ASRA guidelines do not recommend cancellation of surgery in the event of traumatic needle placement during the performance of neuraxial anesthetic techniques, a waiting period of 6 to 12 hours is recommended by some European societies (46,47).

Low-Molecular Weight Heparin

Low-molecular weight heparins (LMWH) and the heparinoid danaparoid (Orgaran[®]) are derived from UFH by depolymerization. The LMWH include enoxaparin (Lovenox[®], Clexane[®]), dalteparin (Fragmin[®]), ardeparin (Normiflo[®]), nadroparin (Fraxiparin[®]), reviparin (Clivarin[®]), certoparin (Sandoparin[®]),

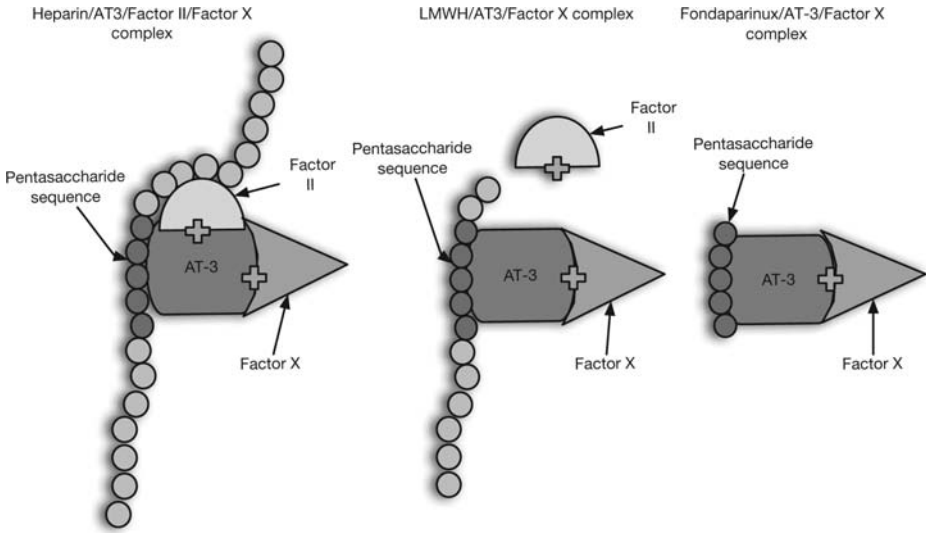


FIGURE 14.2 Inactivation of clotting enzymes by heparin, low-molecular weight heparins, and fondaparinux drugs selectivity for activation by AT III is determined by oligosaccharide chain, with specific pentasaccharide sequence required for AT III binding. Decreasing chain size results in less affinity of complex for factor II, and increased affinity AT III/factor X complex. *Abbreviation:* AT III, antithrombin III.

parnaparin (Fluxum[®]) and tinzaparin (Innohep[®], Logiparin[®]). Not all of these agents are currently available on the U.S. market, but are used in other countries. The development of LMWH led to a product with less factor IIa inhibitory action as compared with Xa inhibitory action, and more favorable pharmacokinetics, enhancing the benefit/risk ratio relative to UFH (40).

The depolymerization of UFH leads to LMWHs with mean molecular weights of 4000 to 5000 d. The lower molecular weights result in lower protein and cell binding, but also lower heparin chain binding of factor IIa with the LMWH/antithrombin/Xa complex (Fig. 14.2). The reduced protein binding produces a more predictable pharmacokinetic and pharmacodynamic profile. It also lessens unwanted effects on platelets, unlike UFH (43,48–50). The improved pharmacokinetic profile for LMWH is limited by controversy concerning dosing in obesity and renal failure, inability to monitor anticoagulant response, its increased half-life in comparison with UFH, and inability to completely reverse its anticoagulant action with protamine (text box 14.5) (51–53).

Box 14.5: Low-molecular weight heparins—DVT prophylactic dose

An abstinence period of 12 hr should be observed prior to placement of major neuraxial block or catheter removal. Reinstitution of low-molecular weight heparins anticoagulation should be delayed 2–4 hr after block or catheter removal, prior to reinstatement of anticoagulation.

Since intravascular volume is not linearly correlated with increases in total body weight (TBW), one could predict that dosing of LMWH based on TBW would lead to relative overdose and bleeding complications. Studies examining this hypothesis have not yielded the predicted response of increased bleeding complications in obese patients dosed with LMWH/TBW regimen. Likewise, small prospective studies examining fixed dose versus weight based dosing showed more favorable antifactor Xa levels in the weight based group. These studies, however, did not comment on the severely morbidly obese, and some authors would suggest attempts at routine monitoring with antifactor Xa levels to assess adequacy of therapy in patients with body mass indexes greater than 50 kg/m² (40,54–58). While studies exist that examine the relationship of weight, dose, and anticoagulant response to LMWH, few are large scale prospective studies, therefore practitioners are still cautioned to examine the risk benefit ratio in the obese patient population.

The clearance of antifactor Xa activity of LMWH is renal, and is closely correlated to the creatinine clearance. Accumulation of nadroparin and enoxaparin occurs with creatinine clearances of <50 and <20 cm³/min, respectively (59,60). While the drug used and the creatinine clearance at which accumulation occurred in different studies varied, exact cutoff values for creatinine clearance and drug dosing do not exist (40,61–64). It would seem prudent then to recommend avoidance of regional anesthesia in patients with severe renal impairment (creatinine clearances of <50 cm³/min) on LMWH unless the clinical situation would indicate that the potential benefit outweighs the risk.

Laboratory testing for the anticoagulant activity of LMWH as recommended by the American College of Pathologists has been with antifactor Xa assays (65). However, not only are antifactor Xa levels not associated with clinical outcomes, the correlation of restoration of Xa activity and assay levels is unclear. Thus, clinicians should be guided by LMWH dosing, patient comorbidities, and established guidelines to aid in the decision making process when electing regional anesthetic techniques in patients on LMWH (14,40,47,65).

Unlike UFH, LMWH is only partially neutralized by protamine. Animal studies would suggest that protamine reverses only 60% of the antifactor Xa activity of LMWH (66–68). Though case studies suggest that there is decreased bleeding in patients given protamine to reverse the action of LMWH, hemostasis is incomplete. Animal studies have also examined the role of recombinant activated factor VIIa (rVIIa) for the treatment of bleeding. Several case studies exist using LMWH in rabbits that report its effectiveness in producing hemostasis in LMWH induced hemorrhage (69–72). Clinicians experiencing unwanted bleeding during regional anesthetics should be cognizant of potential reversal agents for LMWH, though prompt neurosurgical consultation and surgical decompression still remains the cornerstone of therapy for perineural hematoma producing neurologic deficit (text box 14.6).

Box 14.6: Low–molecular weight heparins–DVT treatment doses

Insertion of major neuraxial block or catheter removal should be delayed 24 hr after last dose of low–molecular weight heparins.

While the risks of spinal anesthetics when performed in concordance with UFH and warfarin therapy have been known for decades, clinicians were faced

with new challenges after the release of LMWH. After the release of LMWH in the United States, multiple case reports of spinal hematoma were reported in patients receiving neuraxial anesthesia while on LMWH. This prompted several regional anesthesia societies to form consensus guidelines for the safe use of regional anesthesia in the patient taking hemostasis altering medications. While LMWH is used in Europe as well as the United States, differences in dosing of this drug appeared to account for the increased incidence of spinal hematoma after neuraxial anesthesia in the United States when compared with Europe (14). Formation of guidelines has helped clinicians to determine appropriate drug dosing as well as the timing of blocks and catheter removal.

Though differences in dosing of LMWH regimens between North America and Europe have been implicated in the unexpected occurrences of epidural hematoma, these different dosing regimens remain unchanged. Common dosing regimens for *thromboprophylaxis* in the United States are enoxaparin 40 mg once daily or 30 mg twice daily. Dosing may vary depending on the patient's renal function and the type of surgery performed. In patients receiving *thromboprophylactic* doses of LMWH preoperatively, performance of primary regional techniques should be delayed for 10 to 12 hours after the last dose of these medications (14). In patients receiving larger doses for *treatment* of established thrombotic disorders, delays of 24 hours should be observed. In patients undergoing catheter techniques, postoperative initiation of LMWH for *thromboprophylaxis* should be delayed for 24 hours if twice daily dosing is used. Patients who receive twice daily dosing of LMWH have an increased risk of spinal hematoma formation and should receive their first dose of LMWH no sooner than 24 hours postoperatively (14). Catheters should be discontinued prior to initiation of LMWH, or after a drug abstinence period of 24 hours. If patients are to receive once daily dosing of LMWH for *thromboprophylaxis*, initiation of therapy may begin within 6 to 8 hours postoperatively with the second dose given no sooner than 24 hours after the first dose. If a continuous catheter technique is chosen, a drug abstinence period of 10 to 12 hours should be observed prior to removal of the catheter. A time period of two to four hours should be observed prior to reinstatement of LMWH therapy in all patients having catheters removed (14). When performing neuraxial blocks, if trauma is encountered, then it is recommended to delay LMWH prophylaxis or treatment for 24 hours (14,73–75). Patients who are on LMWH and are candidates for peripheral nerve blocks should be evaluated on a case-by-case basis because of bleeding potential and accessibility to pressure should bleeding be encountered. Paraspinal techniques should follow the same recommendations as for central neuraxial techniques. Practitioners are cautioned to be more conservative with practice behaviors in patients receiving multiple medications affecting the hemostatic axis. The risk of spinal hematoma is increased when LMWH is combined with NSAIDs, aspirin, standard UFH, or dextrans. It is therefore recommended that use of these agents be avoided in conjunction with LMWH in patients receiving neuraxial catheter techniques for postoperative pain (14).

Selective Factor Xa Inhibitors

Further dissection of the LMWH pentasaccharide sequence results in a change in LMWH nonspecific inhibition of factor Xa to a new class of compounds that have specificity for only factor Xa. This new class of drugs is known as the selective factor Xa inhibitors. Like the other heparin species (UFH and LMWH), the selective

factor Xa inhibitors still retain the pentasaccharide sequence that binds and accelerates AT III. Unlike the heparins, the selective factor Xa inhibitors do not contain the additional “tail sequences” that result in the nonspecific action on other coagulation factors, and the protein binding that results in the variable kinetics and adverse effects of heparins (76). The two prototypical agents in this class of drugs are fondaparinux (Arixtra[®]) and idraparinux.

Fondaparinux is a synthetic analog of the specific antithrombin-binding pentasaccharide sequence found in heparin and LMWH. Fondaparinux, once bound to AT III, produces a conformational change in AT III that accelerates its reactivity with factor Xa. After producing this change, fondaparinux dissociates from AT III and becomes available to activate other antithrombin molecules (77–79). Fondaparinux has excellent bioavailability and a half-life of 17 hours. It is administered subcutaneously once daily with peak plasma levels occurring 2 hours after administration. Fondaparinux appears to undergo no metabolism, and is eliminated unchanged in the urine. Therefore, caution is advised when administering it to patients with renal impairment, as its clearance is lowered by 25% in individuals with creatinine clearances of 50 to 80 mL/min and by 55% in individuals with creatinine clearances <30 mL/min (80). While monitoring its effects can be achieved by measuring antifactor Xa activity, fondaparinux is not reversed by protamine, although heparinase I and recombinant factor VIIa may reverse its action (71,81–85). Armed with this information, fondaparinux poses many challenges for the pain specialist.

Idraparinux, a derivative of fondaparinux, has an even greater affinity for AT III than its parent drug and a half-life of 80 to 130 hours. This agent possesses the advantage of weekly dosing. Similar to fondaparinux, its anticoagulant activity can be monitored by obtaining antifactor Xa levels. It is not reversed with protamine or heparinase I, though recombinant factor VIIa may have some role in reversing its anticoagulant effect (71,81–85). Idraparinux is still undergoing clinical trials, and its use will likely present challenges for the performance of neuraxial and regional anesthesia. While initial experiences with these agents in the setting of regional and neuraxial anesthesia are still ongoing, implementation of these techniques should occur in accordance with guidelines set forth by clinical trials examining safety until further experience dictates changes in practice. These include the following:

- Regional anesthetics techniques should be avoided in patients on fondaparinux who have comorbid renal impairment.
- An interval of 36 hours of abstinence from fondaparinux should be observed prior to regional techniques.
- Use of techniques not requiring indwelling catheter placement is recommended.
- The next dose of fondaparinux should be delayed 12 hours after the performance of regional anesthetic techniques.
- In the setting of neuraxial techniques requiring more than one attempt, or after traumatic insertion, a different form of thromboprophylaxis should be considered (14,47,73,81).

New oral formulations of factor Xa inhibitors are undergoing study in the United States and/or have been released for use in Canada and Europe. These agents include Rivaroxaban, Apixaban, and Betrixaban. The anesthesiologist should be prepared to encounter more patients receiving these agents in the future,

as they seem to provide comparable efficacy to LMWH with a similar incidence of bleeding complications, and oral availability may make their use more appealing than LMWH (14).

Direct Thrombin Inhibitors

Thrombin is pivotal in the process of clot formation. Not only does thrombin setup the conversion of fibrinogen to fibrin, but it also activates factors V, VIII, and XI and platelets, thus favoring the formation and stabilization of blood clots (86). One potential advantage of direct thrombin inhibitors is their ability to inhibit free and clot bound thrombin. These drugs include the univalent agent argatroban (Acova[®]) and several bivalent agents. Bivalent agents [hirudan, bivalirudin (Angiomax[®], Angiox[®]), lepirudin (Refludan[®]), and desirudin (Iprivask[®], Revasc[®])] bind to thrombin's fibrinogen-binding sites in addition to thrombin's active (catalytic) site (81). While all the agents have predictable actions independent of AT III, they have different binding sites on the thrombin molecule to produce their activity (87). Currently in the United States, all direct thrombin inhibitors must be administered parenterally. Dabigatran etexilate is a univalent, orally administered direct thrombin inhibitor that is available for use in Canada and Europe and is undergoing phase III clinical trials in the United States (14). As with the orally administered factor Xa inhibitors, anesthesiologists are likely to encounter many patients in whom this agent will be selected for thromboprophylaxis once it becomes available on the U.S. market.

The class of anticoagulants known as hirudins includes hirudin, hirudin fragments (bivalirudin), and the recombinant hirudins (lepirudin and desirudin). The primary indication for these agents is anticoagulation in patients with confirmed or suspected heparin-induced thrombocytopenia and as an adjunct to angioplasty procedures, although they have also demonstrated usefulness in thromboprophylaxis after high-risk surgical procedures (14,88,89). The biologic activity of the hirudans can be monitored with the aPTT or escarin clotting time (ECT). Hirudin has a half-life of 40 minutes with intravenous injection and 120 minutes with subcutaneous injection. It undergoes little hepatic metabolism and is excreted unchanged in the urine. Dose adjustments are required in renal failure (76). Lepirudin and desirudin have half-lives of 1.3 to 2 hours, which are increased in the presence of renal impairment (81).

Bivalirudin binds to thrombin but then dissociates, leaving thrombin active after its dissociation. It has limited renal excretion, and may rely on hepatic and extra hepatic metabolism (endopeptidases) (87). Bivalirudin has a half-life of 25 to 40 minutes and has no reversal agent. Its activity is also monitored with the aPTT or ECT.

Argatroban is a small catalytic univalent molecule that binds directly to the active site of thrombin, producing its inhibition. Once associated with thrombin, it eventually loses its covalent binding, releasing thrombin to produce its biologic effect. It undergoes primarily hepatic metabolism and requires dose adjustment in the setting of hepatic dysfunction. Its half-life is 45 minutes and there is no specific reversal agent (90).

Little information is available concerning use of the direct thrombin inhibitors in the setting of regional anesthesia. On the basis of their pharmacokinetics, an abstinence period of 8 to 10 hours should be observed prior to performing a block in patients taking these drugs, and 2 to 4 hours should elapse after the block before

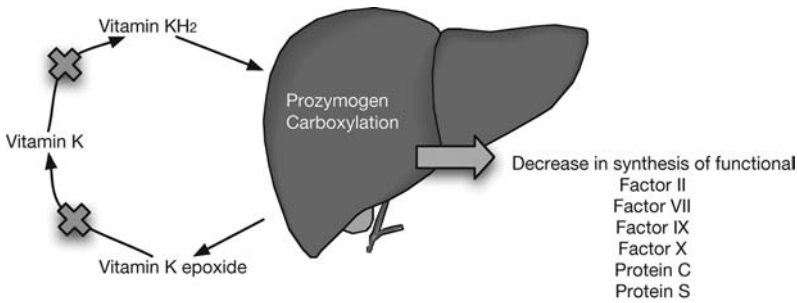


FIGURE 14.3 Hepatic action of Coumadin[®]. Coumadin's action results in an inability of factors II, VII, IX, and X and protein C and S to undergo carboxylation process, leaving them inactive. The carboxylation process enables factors to bind calcium for activation.

restarting them. Given the unproven track record with these agents and regional anesthetics, practitioners are cautioned about indwelling catheter techniques and medication management in the face of traumatic needle placement (81,91). In fact, the most recent (third edition) of the ASRA Evidence-Based Guidelines on Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy recommends that neuraxial blockade be avoided in patients receiving direct thrombin inhibitors (14).

Warfarin

Warfarin (Coumadin[®]) and the coumarin agents are vitamin K antagonists that produce their clinical effects by interfering with hydroxy conversion of vitamin K and its epoxide residue (Fig. 14.3). Vitamin K and its cofactor, once through the reductive process, are responsible for γ -carboxylation of the inactive proenzyme clotting factors II, VII, IX, and X, to their active forms (92). The effects of warfarin are indirect, and are competitive in the face of ongoing vitamin K ingestion. Normal coagulation requires the presence of vitamin K–dependent clotting factors that are complete. The degree of anticoagulation effect of warfarin is dependent on warfarin dosing, vitamin K intake, and the half-lives of existing functional coagulation factors. Clinical anticoagulant effects vary, but bleeding does not typically occur until factors are depleted to below 40% of normal values (93). Factor half-lives vary from 6 to 8 hours (factor VII), to 50 to 80 hours (factor II). This factor half-life dependent anticoagulant effect is reflected in an initial delayed effect at 8 to 12 hours and peak effect at 36 to 72 hours after initiation of warfarin administration (94). The early rise in anticoagulation is in response to loss of factor VII, with maintained levels of factors X and II, while the eventual peak effect is a reflection of the loss of all of the vitamin K–dependent clotting factors. It is the loss of factor II (prothrombin) that imparts most of the anticoagulant effect of warfarin, not the loss of factor VII or IX (95). It is this variation in rate of depletion of coagulation factors and hemostasis that produces some discrepancies in monitoring and recommendations for practitioners.

Treatment with warfarin and its derivatives is monitored by measurement of the prothrombin time (PT), and reported as the *international normalized ratio* (INR). The INR standardizes variations in prothrombin measurement due to use of

different reagents for the test among unrelated facilities. Target values for anti-coagulation with warfarin are INR prolongations of two to three times control (approximately 1.0) for most clinical situations (23). The prolongation of PT/INR is in response to loss of three of the four vitamin K-dependent clotting factors (92).

With initiation of therapy, the factor that becomes inhibited first is that with the shortest half-life (i.e., factor VII). This loss of factor VII is manifest by a gradual prolongation of the INR. With an INR of 1.4, factor VII is at 40% of normal values, which is still adequate for blood coagulation, especially considering the preserved activity of factors II and X. INR values greater than 1.4 are associated with factor VII levels less than 40% of normal, and thus may be associated with prolonged bleeding times (text box 14.7) (14).

Box 14.7: Coumadin-initiating therapy

Neuraxial block/catheter removal may be performed if international normalized ratio is 1.5 or less.

With the cessation of therapy, the converse occurs. The INR begins to normalize as the factors with the shortest half-lives regain functionality. What is different with cessation of therapy is that the INR may achieve a level of 1.5 or lower in the absence of sufficient levels of factor II (prothrombin) needed for hemostasis (23). This is caused by the relative insensitivity of PTs to loss of factor II, and its sensitivity to loss of factors VII and X. This relative discrepancy in the probability of bleeding with warfarin initiation as compared with discontinuation of therapy has resulted in two separate guidelines regarding appropriate PT/INR values for placement of regional or neuraxial blocks and catheter removal (text box 14.8).

Box 14.8: Coumadin-discontinuing therapy

Major neuraxial block or catheter removal may be performed pending normalized international normalized ratio (1.2 or less).

Regional or neuraxial anesthetics may be performed around the time of warfarin initiation if the patient's INR is 1.5 or less. Whether a catheter may be inserted will depend on the timing of regional or neuraxial anesthetic placement in relation to the initiation of warfarin and desired length of therapy. The practitioner should keep in mind that the typical time frame to observe an increase in the INR after initiation of warfarin is 24 to 36 hours. Routine screening of coagulation parameters prior to catheter removal is encouraged when catheter techniques are utilized because of the variable nature of patient responses to warfarin. With discontinuation of chronic therapy, normalization of the INR ratio (to values of 1.2 or lower) should occur before the performance of regional or neuraxial anesthetics. Once this occurs, no additional precautions are necessary for indwelling catheter techniques unless reinstatement of therapy begins prior to catheter removal. Under these circumstances, the practitioner should be guided by the recommendations for catheter management on the institution of warfarin therapy.

Fibrinolytics (Thrombolytics)

The fibrinolytics (thrombolytics) comprise a class of medications that work by accelerating plasmin formation, as with the use of recombinant t-PA, and by direct

proteolysis of clot and activation of endogenous t-PA (23). The agents in this class include streptokinase (Streptase[®], Kabikinase[®]), alteplase (t-PA[®], Activase[®], Cathflo[®]), anistreplase (APSAC[®], Eminase[®]), reteplase (Retavase[®]), tenecteplase (TNKase[®]), and urokinase (Abbokinase[®]). There is limited experience with this class of medications in the setting of regional and neuraxial anesthesia. Therefore, appropriate timing for the performance of anesthetic block procedures in patients who have received or will receive thrombolytic therapy periprocedurally remains uncertain. Package inserts for these products advise against administering them within ten days of a patient having had a surgical procedure or puncture of a noncompressible vessel. General consensus is that regional anesthesia, especially central neuraxial techniques, should be avoided in patients receiving fibrinolytic therapy, or if periprocedural use of these medications is anticipated (73). Patients who have received indwelling catheters who inadvertently receive fibrinolytics should be monitored with measurement of fibrinogen levels to determine the appropriate timing for removal of catheters (96). Patients in such situations should be followed closely for early detection of bleeding or neurologic deficits should they occur.

CONCLUSION

While regional anesthesia continues to gain notoriety for its contribution to patient care and outcomes, so does the importance of thromboembolism prophylaxis (97,98). The practitioner will likely increasingly encounter the dilemma of providing regional anesthetics around the time of administration of medications used for the prevention and treatment of thromboembolism. Negative consequences can be avoided if the practitioner is cognizant of the pharmacokinetic profiles of the medications used for thromboembolism prophylaxis and treatment, and respects appropriate time intervals for initiation of regional anesthesia and discontinuation of catheters in this setting. Likewise, proper timing for reinitiation of anticoagulant therapy after regional blocks or catheter removal must be observed. The practitioner should also develop contingency plans for alternate time frames and forms of prophylaxis in the event of traumatic needle insertion, and use caution in the event of polypharmaceutical use of agents affecting the hemostatic axis.

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INTRODUCTION

Pain serves many purposes in our busy lives—it warns us of the danger we are putting ourselves in (touching a hot stove, getting a sunburn); it warns us of impending illness or worsening of a disease process (i.e., appendicitis, sickle-cell crisis); or it may be a warning of the “danger” being imposed on us by others (i.e., surgical incisions). Pain is also perceived differently by each person on the basis of personal pain thresholds, previous experiences with pain, and emotional status at the time the pain presents itself. This chapter will provide information on the pathophysiology of pain perception in children, typical types of pain encountered in the pediatric patient, and a logic pathway toward treatment of that pain.

PAIN IN INFANTS

Pain in infants poses a major challenge for health professionals. Although infants, particularly preterm neonates, are especially vulnerable to pain and its consequences, pain is less adequately controlled in this patient population than in any other (1). Many reasons account for the undertreatment of pain in infants, most relate to a paucity of knowledge regarding the subject.

The International Association for the Study of Pain (IASP) has defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” (2). It has been suggested this definition is inappropriate for infants for a couple of reasons.

First, the interpretation of pain is subjective, and infants lack the ability of self-report in the traditional sense. This inability to verbalize pain contributes to the failure of health care professionals to recognize and treat pain aggressively in infants. It has been hypothesized that pain perception occurs in a less organized way in the preterm infant than in the child or adult. Pain is a combination of sensory (discriminative) and emotional (affective) components. Nociception incorporates the physiologic and behavioral responses of infants to a painful stimulus but not the cognitive responses that are part of pain perception (3). Consequently, health care professionals are required to rely on physiologic and behavioral responses when assessing pain in an infant. Second, the IASP definition infers that some aspects of pain may be associated with previous actual or potential tissue damage. In most neonates and infants, no opportunity has existed for gaining previous experience (2).

Development of Nociception

Health care professionals have historically believed that infants are unable to feel pain because of inadequately developed central and peripheral nervous systems. As a result, their incompletely myelinated nerves should not allow for transmission of noxious stimuli from the site of the injury to the central nervous system. An

abundance of evidence refutes these beliefs and demonstrates that the fetus has the anatomic, neurophysiologic, hormonal, and functional requirements for processing pain by mid to late gestation. By twenty weeks' gestational age, the fetal cerebral cortex has a full complement of neurons, and sensory receptors spread to all cutaneous and mucosal surfaces. At birth, the density of nociceptive nerve endings in the newborn's skin is sometimes greater than in adults (3). Lack of myelination does not support the argument that infants are incapable of perceiving pain, as even in adults 80% of fibers responsible for transmitting pain information remain unmyelinated (4). It is important to note that incomplete myelination does, in fact, affect transmission by slowing the conduction speed of pain impulses. However, the decrease in conduction speed is offset in infants by the shorter distance traveled by impulses to the central nervous system (3).

Infants born at term are equally as sensitive to pain as older children and adults, whereas preterm infants have an increased sensitivity to pain. Prenatal development of neurotransmitters in the dorsal horn of the spinal cord has been associated with nociception and increased somatosensory excitability in the immature spinal cord. In contrast, neurotransmitters contained in the descending inhibitory fibers from supraspinal centers have only been found to be present after birth. Therefore, the poorly developed inhibitory mechanisms for nociception in preterm neonates may make them more sensitive to pain (3).

ASSESSMENT OF PAIN IN THE PEDIATRIC PATIENT

Pediatric Pain Score Tools

After acknowledging that both neonates and infants experience pain, the next dilemma becomes assessing the degree of pain. If pain is inappropriately treated, then repeated painful stimuli may result in a lowering of the pain threshold and exaggerated response to various stimuli, including nonpainful stimuli.

Several behavior observational scales have been created to assess the quality and severity of pediatric pain including neonatal infant pain scale (NIPS) (5), CRIES for postoperative infants (6), FLACC for children up to age seven years (7), Children's Hospital of Eastern Ontario (CHEOPS) (8), Wong-Baker FACES scale (9), and adolescent pediatric pain tool (APPT) for adolescents (10).

The NIPS, used for infants less than one year of age, assigns a numerical score to the infant's facial expression, cry, breathing pattern, arm and leg position, and state of arousal. A score greater than three is consistent with pain (5).

CRIES is ideal for the postoperative neonatal period (6). The CRIES score is determined by crying, increased oxygen requirement, increase in vital signs (specifically heart rate and blood pressure), facial expression, and sleeplessness (6). The FLACC scale is a nonverbal pain assessment tool for patients between two months and seven years of age (7). The FLACC score depends on facial expression, leg position, activity, crying and consolability (7). Each component of the CRIES and FLACC is scored on a scale from zero to two. The five categories are then summed to give a total pain score from zero to ten, with zero being no pain and ten being the worst pain (6,7).

CHEOPS is a pain assessment tool, which may be utilized for children one to seven years of age. CHEOPS evaluates cry, facial expression, verbal complaints, torso positioning, touching the wound or affected area, and leg position (8). The various subscales differ; however, all items are scored between zero and three. A cumulative score greater than four indicates pain (8).

From ages three through six, the Wong-Baker FACES scale (9) and Oucher scale (11) are used to determine the intensity of pain. The Wong-Baker FACES scale is six cartoon character faces depicting increasing pain from left to right (9). The face starting the scale, which is on the left, is "no hurt." The scale progresses to the right with the highest possible score being five, "hurts worst" (9). The Oucher scale is scored from zero to ten, with zero being no pain and ten being the worst pain (11). Along the scale are pictures of children's faces to help demonstrate the severity of pain (11).

The APPT has been validated in children 8 to 17 years old and assesses the location, intensity, and quality of postoperative pain (10).

Once children reach the age of six or seven, they are generally able to describe the location, intensity, and severity of their pain on a numerical scale. Typically, a numerical rating scale 11 (NRS-11), or a numerical verbal scale (NVS-11) (which is also used for adults) may be employed, with zero being no pain and ten being the worst pain imaginable. A 100-mm visual analog scale (VAS) may also be utilized.

TREATMENT OF NONSURGICAL PAIN

Trauma

Despite the myriad of available pain assessment tools, pain is inappropriately evaluated and often under treated, especially in the trauma setting. The undertreatment of pediatric pain results from a combination of the following: the thought that pediatric patients do not feel pain, the myth that alleviation of the pain may hide evolving pathology, the fear of medication side effects such as hypotension and respiratory depression, and the lack of available staff to monitor the patient after a medication has been given (12).

In the pediatric population, long bone fractures are one of the most common presenting complaints in the emergency room. "Two thirds of boys and nearly half of girls can be expected to have a long bone fracture before their 15th birthday" (13). Throughout the literature, the theme of underdosing and undertreating pediatric pain persists. A study published in 2004 in *Pediatric Emergency Care* revealed, "most children with an extremity fracture and greater than one-third of children with a severe fracture [defined as a closed fracture with the presence of angulation and/or displacement] did not receive pain medication in the emergency department" (14). Long bone fractures are typically treated with nonsteroidal anti-inflammatory medications and Tylenol with codeine. In pediatric patients with musculoskeletal injuries, "ibuprofen provided the most effective relief of pain at 1 hour and was equally as effective as codeine at 4 hours, suggesting that it should be the initial drug of choice for acute analgesia" (13).

When ibuprofen and/or Tylenol are not adequate, opioids are typically added to the treatment plan (Table 15.1). One of the most commonly prescribed weak opioids is codeine (typically formulated with Tylenol). Because codeine can be administered orally in a flavored suspension with less gastrointestinal upset than morphine, it is more preferable to use this opioid as long as pain can be adequately controlled. Codeine is dosed 0.5 to 1 mg/kg q4-6h. Oxycodone is an opioid analgesic medication synthesized from thebaine. Oxycodone is an effective oral (PO) medication, and it comes in preparations with and without acetaminophen. Oxycodone can be administered orally in the United States, and in other countries it is available for intranasal, intravenous (IV), intramuscular, subcutaneous or rectal (PR) use. Oxycodone is dosed 0.1 mg/kg orally every three hours (14).

TABLE 15.1 Commonly Used Drugs for Analgesia in Pediatric Patients

Analgesics	Dosing	Continuous	Mechanism (site) of action	Advantages	Disadvantages	Contraindications especially relevant to pediatric patients (<i>not inclusive</i>)	Notes
Aspirin	Intermittent 10–15 mg/kg PO/PR q4–6h (maximum 60–80 mg/kg/day)	N/A	Inhibits prostaglandin synthesis and platelet aggregation	Works both peripherally and centrally, no respiratory depression	May provoke Reye's syndrome in patients with viral illness, GI upset, irreversibly inhibits platelets, occ renal toxicity, only available PO/PR	G-6PD def, renal dz, asthma, bleeding diathesis	
Acetaminophen	10–15 mg/kg PO/PR q6–8h (maximum 90 mg/kg/day or 4 gm/day), may be given in doses of 40–60 mg/kg PR (as a one-time dose) for surgery (equivalent analgesia to morphine at this dosage)	N/A	Inhibits central cyclo-oxygenase, possibly inhibits NO formation	No respiratory depression	No anti-inflammatory activity, only available PO/PR	Hepatic disease, G-6PD def	IV formulation in phase 3 trials

(Continued)

Table 15.1 Commonly Used Drugs for Analgesia in Pediatric Patients (Continued)

Analgesics	Dosing	Mechanism (site) of action	Advantages	Disadvantages	Contraindications especially relevant to pediatric patients (<i>not inclusive</i>)	Notes	
NSAIDS Ibuprofen	5–10 mg/kg PO q6–8h (maximum 40 mg/kg/day)	N/A	Probably related to prostaglandin synthetase inhibition	No respiratory depression, fewer GI side effects than aspirin, platelet inhibition is weaker than aspirin and of short duration	occ GI upset, occ renal toxicity, only available PO	Renal dz, asthma, bleeding diathesis	Not approved for use <6 mo old
Ketorolac	0.5–1 mg/kg IV q6h (maximum 15 mg/dose) × maximum of 72 hr	N/A	Inhibits synthesis of prostaglandins	No respiratory depression, currently only IV NSAID available in the United States, comparable in efficacy to morphine in many studies, excellent for relieving bladder spasms	Inhibits platelet aggregation (potential for ↑ bleeding post operation)	Peptic ulcer dz, renal dz, asthma, dehydration	Not approved for use <2 yr old, and then only approved for single dose (however, many institutions use this drug for patients >6 mo, for maximum of 72 hr)
COX-2 inhibitors	Varies by drug, still being determined	N/A	Inhibits synthesis of prostaglandins primarily by inhibition of COX-2	Unlike other NSAIDs, should not affect platelet fxn	Not approved for use in children, dosing guidelines in literature vary, only available PO	Caution with renal dz and h/o GI bleed	

Weak opioids Tramadol	50 mg q3h if 35–55 kg, 50–100 mg q3h if >55 kg	N/A	Binding to mu receptor + weak inhibition of reuptake of norepinephrine and serotonin	Less respiratory depression than strong opioids, fewer side effects	May cause some respiratory depression, constipation, and N/V, avoid abrupt withdrawal, no IV formulation available	Caution if seizure hx	Not approved for use in children
Codeine	0.5–1 mg/kg PO q4–6h (maximum 60 mg/dose)	N/A	~10% Methylated to morphine, which binds to mu receptor	Less respiratory depression than strong opioids, fewer side effects	May cause some respiratory depression, constipation and N/V, avoid abrupt withdrawal, no IV formulation available	Frequently suspended with Tylenol, important to monitor total Tylenol dose, safe dosage has not been established under the age of 3 yr	Frequently formulated with Tylenol or ibuprofen; important to monitor total daily dosage of these medications as well. Not approved for use in children
Oxycodone	0.05–0.15 mg/kg PO q4–6h (maximum 5 mg PO q4–6h)	N/A	Precise mechanism of action unknown, believed to be similar to morphine	Less respiratory depression than strong opioids, fewer side effects	May cause some respiratory depression, constipation, and N/V, avoid abrupt withdrawal, no IV formulation available	Caution in patients with asthma	Frequently formulated with Tylenol or ibuprofen; important to monitor total daily dosage of these medications as well. Not approved for use in children

(Continued)

Table 15.1 Commonly Used Drugs for Analgesia in Pediatric Patients (Continued)

Analgesics	Dosing	Mechanism (site) of action	Advantages	Disadvantages	Contraindications especially relevant to pediatric patients (not inclusive)	Notes
Hydrocodone	~0.135 mg/kg PO q4-6h	Precise mechanism of action unknown, believed to be similar to morphine	Less respiratory depression than strong opioids, fewer side effects	May cause some respiratory depression, constipation and N/V, avoid abrupt withdrawal, no IV formulation available	Contraindications especially relevant to pediatric patients (not inclusive)	Frequently formulated with Tylenol or ibuprofen; important to monitor total daily dosage of these medications as well; not approved for use in children <2 yr old
Strong opioids Fentanyl	1-3 µg/kg IV q1-4h	Binds to mu receptor	Fast acting, potent, PO "lollipop" form available, transdermal systems available in adults	Respiratory depression, N/V, avoid abrupt withdrawal		May cause "stiff-chest" syndrome if administered too fast, usually administered only in monitored settings
Morphine	0.1-0.5 mg/kg PO q4-6h, 0.05-0.2 mg/kg IV q4h	Binds to mu receptor	Lasts longer than fentanyl, most commonly used strong narcotic (therefore health care providers comfortable with its use)	Respiratory depression, N/V, avoid abrupt withdrawal, may cause histamine release	Use with caution in patients with renal failure	

Hydromorphone	0.03–0.08 mg/kg PO q4–6h, 0.015 mg/kg IV q4–6h	0.002–0.004 mg/kg/hr	Precise mechanism of action unknown, believed to be similar to morphine	Very potent	Respiratory depression, N/V, avoid abrupt withdrawal	High abuse potential	Not approved for use in children
Meperidine	1–1.75 mg/kg PO q3–4h (maximum 100 mg/dose), 0.2–1 mg/kg IV q4h	N/A	Multiple actions similar to those of morphine	Some sympathomimetic properties	Respiratory depression, N/V, avoid abrupt withdrawal, slower elimination rate in infants and young children	h/o seizures	Rarely used in children (except sickle-cell patients) because of frequency of potentially harmful side effects
Other Ketamine	0.1–1.5 mg/kg IV, 5–10 mg/kg PO	N/A	NMDA antagonist	At low doses potentiates analgesic effect of other drugs, at higher doses acts as dissociative anesthetic/sedative; has sympathomimetic properties and maintains respiration	May cause hallucinations—administer with a benzodiazepine; causes excessive secretions—may want to also administer gycopyrrolate	Increased ICP	Frequently used with burn patients requiring repetitive debridements/dressing changes

(Continued)

Table 15.1 Commonly Used Drugs for Analgesia in Pediatric Patients (Continued)

Analgesics	Dosing	Mechanism (site) of action	Advantages	Disadvantages	Contraindications especially relevant to pediatric patients (not inclusive)	Notes
Midazolam	0.05–0.1 mg/kg IV q5min p.r.n. (maximum 2 mg/dose, total 6 mg), 0.5–1 mg/kg PO	Enhances the action of GABA	Minimal respiratory effects when used alone, potentiates narcotics, amnesia	Withdrawal may provoke seizures		
Dexmedetomidine	N/A	α_2 Agonist	Sedative effects + opioid-sparing effects	Occasionally may cause bradycardia/hypotension		Not approved for use in children
Propofol	1–3.5 mg/kg IV	Precise mechanism of action unknown, may be due to potentiation of GABA	Some antiemetic properties	Frequent apnea, burning at injection site, propofol infusion syndrome implicated in several deaths leading to recommendation that infusions be limited to <24 hr in children 12 yr old and younger		Typically only allowed for use in intubated patients or use by anesthesiologist

Abbreviations: def, deficiency; h/o, history of; hx, history; ICP, intracranial pressure; NV, nausea/vomiting; occ, occasional; PO, oral; PR, rectal.

Fentanyl, a synthetic opioid, can be administered intravenously or intramuscularly at a dose of 1 to 2 $\mu\text{g}/\text{kg}$ up to a maximal dose of 10 $\mu\text{g}/\text{kg}$. Fentanyl has an onset of action within 30 seconds to 2 minutes and a duration of action of 30 minutes to two hours depending on the route of administration. Fentanyl can be redosed every 5 to 10 minutes and titrated to effect. Fentanyl is the opioid of choice for procedural or short-term sedation. It is important to be cautious of chest wall rigidity, a potential side effect of fentanyl administration.

Morphine, a phenanthrene opioid receptor agonist, can be administered intravenously, intramuscularly, and epidurally. Morphine is given at doses of 0.05 to 0.15 mg/kg every two to four hours. The duration of action is two to seven hours. Morphine is a better choice for pediatric trauma patients who are being admitted to the hospital. Side effects associated with using opioids include respiratory depression, pruritus, and nausea and vomiting.

Meperidine is a narcotic analgesic with similar actions to morphine. Meperidine offers no additional benefit when compared with morphine for pain relief (12), and it is typically avoided because of the increased risk of seizures with repeated dosing. Ketorolac (Toradol) is rarely if ever used in pediatric trauma patients because of the increased risk of bleeding secondary to platelet inhibition.

In addition to the physical aspects of trauma pain management, psychologic factors also play a significant role. Untreated pain can result in anxiety, fear, nightmares, and sleep disturbances; behavioral and personality disturbances; and the development of vicious cycles to chronic pain. Nonpharmacologic interventions described by Michael Joseph, MD, include the following: positive reinforcement, distraction, hypnotherapy, acupuncture, massage and touch, relaxation, and lastly restraint (12). It is essential to be honest and open with pediatric trauma patients. Explain to the patient what has happened, is happening, and what is going to happen. Give the patient options whenever possible, such as where the IV line should be placed or the patient's position. Distract pediatric patients with movies, video games, music, or reading books. Encourage relaxation by challenging the patient to scream as loud as they can or take deep breaths by blowing bubbles (15).

In general, pediatric pain secondary to trauma is often not treated or is undertreated. For each patient, an individualized approach encompassing pharmacologic and nonpharmacologic methods should be employed.

Mucositis

Mucositis is defined as damage to mucosal epithelial cells, which results in an "inflammatory response and denudation of the oral mucosa by the following mechanisms (i) cytotoxic effects of chemotherapy drugs on the rapidly dividing epithelial cells of oral mucosa (ii) indirectly by bone marrow suppression" (16). As a result of the inflammation, ulcerative oral lesions develop causing pain.

The World Health Organization (WHO) published a three step ladder for cancer pain relief. When the pain initially occurs, the pain should be treated with nonopioid medications, such as acetaminophen or ibuprofen (plus or minus adjuvant analgesics). If the pain increases or persists, then an opioid-like agent such as tramadol or an opioid for mild-moderate pain, such as codeine, is added. If the pain still persists, which would be classified as moderate to severe pain, then stronger opioids for severe pain are given. The WHO recommends around the clock administration of pain medications instead of on an as needed basis. The stepwise approach is reported to be 80% to 90% effective (17).

Multiple studies have emphasized the utility and effectiveness of the WHO three step ladder. (This three-tier approach also appears to be a reasonable way to approach most forms of pain in the pediatric population.) In 1995, the WHO cancer pain relief guidelines were validated in a 10-year prospective study. Of the 2118 patients treated in this study, "good pain relief was reported in 76%, satisfactory efficacy in 12%, and inadequate efficacy in 12% of patients" (18).

In 2006, Zernikow et al. examined the inpatient treatment courses for 224 pediatric cancer patients. The pain management for these patients followed the WHO analgesic ladder. A total of 2265 cumulative treatment days occurred during the seven month study period, after which the author concluded that the WHO guidelines "provide effective analgesia for children with cancer pain" (19).

In addition, PO hygiene protocols may reduce the length and severity of pain from mucositis. Cheng et al. compared chlorhexidine versus benzydamine, antimicrobial mouth washes, to determine which was better at alleviating symptoms of oral mucositis, such as pain with eating, speaking, or swallowing. Cheng concluded that chlorhexidine was superior in "reducing ulcerative mucositis and improving mouth pain" (20). The results of this study were based on 34 subjects; therefore, further research comparing PO antimicrobial agents is essential.

In pediatric patients, limited research has been performed about alternative treatment methods, such as PO transmucosal fentanyl citrate, PO histamine gel, or palifermin, which is a recombinant human keratinocyte growth factor aimed at decreasing mucosal injury.

Sickle-Cell Disease

Sickle-cell disease is a genetic disorder affecting the red blood cells. In sickle-cell disease, when red blood cells become deoxygenated, they change shape and become crescent like. The crescent-like or sickled cells become lodged in blood vessels causing decreased blood flow and oxygen delivery to tissues downstream of the occlusion. The lack of oxygen results in ischemia or infarction, which is the source of pain in vaso-occlusive crisis.

In pediatric patients with mild sickle-cell crisis, the pain is often managed as an outpatient with acetaminophen with or without codeine or ibuprofen. Moderate or severe sickle-cell crisis pain is treated with the addition of opioids such as Morphine, 0.05 to 0.15 mg/kg, which can be given intravenously every two to four hours. It should be noted that Dampier et al. described an "eightfold range in morphine clearance values, which is consistent with the interpatient variability noted in other patient groups" (21). This difference in patient drug redistribution and metabolism may result in sickle-cell pain being inadequately treated. In addition, if the patient has been recently hospitalized or is on chronic PO opioids, tolerance may be an added factor.

Hydromorphone, another commonly used opioid, is a second opioid option; however, there is little information regarding the pharmacokinetics of hydromorphone in the pediatric patient. Hydromorphone dosing ranges from 8 µg/kg to 15 µg/kg intravenously every two to four hours. The pain of sickle-cell disease is episodic and severe; therefore, it is crucial to titrate opioids to effect on the basis of the patient's pain score and respiratory rate.

The patient's pain should be frequently assessed and reassessed by utilizing the pain scales previously discussed. Over the age of five (or even much younger in several institutions), patient- or authorized agent (nurse or caregiver)-controlled

analgesia are alternative methods for opioid administration. While treating these patients, it is important not to forget that nonsteroidal anti-inflammatory medications such as ketorolac or naproxen “have been shown to be quite effective and can lessen the requirement for parenteral administered opioids” (e.g., can be opioid sparing) (22).

Alternative/Preventative Treatments for Sickle-Cell Disease/Crisis

In 1995, Charache et al. concluded that hydroxyurea decreases the number and severity of sickle-cell crises in adults by “reactivating” fetal hemoglobin. Until 1999, limited information was available regarding the safety and efficacy of using hydroxyurea in children. In 1999, Kinney et al. performed a phase I/II trial with children ages 5 to 15 (23). Hydroxyurea was started at 15 mg/kg/d and increased to 30 mg/kg/d. “Significant hematologic changes included increases in hemoglobin concentration, mean corpuscular volume, and fetal hemoglobin parameters, and decreases in white blood cell, neutrophil, platelet, and reticulocyte count” (23). For a period of one to two years, under the supervision of a pediatric hematologist, the utilization of hydroxyurea in pediatric patients appears safe (23). Limited information is currently available regarding the use of inhaled nitric oxide for acute vaso-occlusive crisis in pediatric patients. In 2003, Weiner et al. studied 20 pediatric patients with severe vaso-occlusive crisis. At four hours, the patients who had inhaled nitric oxide reported decreased pain when compared with the placebo group. The inhaled nitric oxide group also utilized less morphine during a 24-hour period than the group receiving placebo (24); however, the difference in morphine utilization was not statistically significant.

In 2007, a case report of a four-year-old with a respiratory infection and vaso-occlusive crisis was published (25). The case report concluded that IV tramadol (currently unavailable in the United States) administered at a rate of 0.25 mg/kg/hr, when combined with other nonopioids, is “effective in relieving moderate to severe pain due to vaso-occlusive crisis and can be recommended before using morphine in a pediatric” patient (25).

Lastly, there are several nonpharmacologic treatments for sickle-cell disease including heating pads, deep tissue massage, acupuncture, and transcutaneous electrical nerve stimulation (26). Nonpharmacologic treatment methods are typically used in combination with one or several of the medications described above.

Burns

The patient’s age plays an important part in understanding and designing a treatment plan. In the preschool years, a burn injury (or any severe injury) affects the child’s self-esteem. The child may feel as though he or she is being “punished for being bad” (27). School aged children, 6 to 14 years of age, have the ability to understand different aspects of a given situation. They can be taught psychologic strategies, including guided imagery, distraction, relaxation, and reappraisal, to help with the pain (27). Adolescents have reached the age of abstract thinking and are entangled with personal and social change; they are focused on self-image and may be more prone to develop depression after a disfiguring burn injury (27).

When a patient’s initial pain is inadequately or inappropriately managed, the efficacy of analgesia for later procedures, such as wound dressing changes, could be reduced (28). Nonopioid medications are utilized to reduce the baseline discomfort from burns. Multiple institutions reported the use of acetaminophen with or without codeine as a background medication. Although limited information is available

regarding the safety of long-acting opioids in children younger than seven years of age, extended release morphine and oxycodone are also available options (29).

Opioids, primarily morphine, administered with or without benzodiazepines are the current standard of care in the acute setting. A retrospective review of the acute pediatric burn patient performed in 2001 demonstrated increased opiate usage from 44.8% in 1993 to 81.3% in 2001, and increased utilization of benzodiazepines, that is, lorazepam or midazolam, from 59.8% in 1998 to 77.5% in 2001 (30). The medication administered is titrated to effect on the basis of the situation. Pediatric patients who have a large body surface area affected typically require more pain medication. With repeated dosing, variable degrees of tolerance may develop.

For wound care and dressing changes, ketamine is used extensively, and is gaining popularity over acetaminophen. Humphries et al. compared 19 pediatric patients randomized to either an PO ketamine suspension or acetaminophen with codeine and diphenhydramine. This study revealed a 360% improvement in sedation along with improved analgesia in the ketamine group (31). Owens et al. studied 347 patients between 3 and 111 kg and reported 10 adverse outcomes requiring intervention, that is, face mask oxygen or fluid bolus. Owens recommended a stringent protocol for ketamine infusions in pediatric patients (32). Ketamine resembles phencyclidine and interacts with multiple receptors, including *N*-methyl-D-aspartate and opioid receptors. Ketamine can be administered intravenously at doses of 0.2 to 0.5 mg/kg for intense analgesia while preserving the patient's respiratory drive. Ketamine is known to produce visual and auditory hallucinations; however, these hallucinations appear to be less bothersome to children versus adults and may be minimized with the coadministration of a benzodiazepine.

For pediatric burn patients who have either developed tolerance to opioids or who are difficult to adequately sedate (i.e., during wound dressing changes), dexmedetomidine is an alternative. Dexmedetomidine is a selective α_2 -adrenoceptor agonist, which produces sedation as well as modest analgesia. After the initial loading dose of 1 μ g/kg is given over 10 minutes, an IV infusion is started at 0.2 μ g/kg/hr and titrated, if needed, to 0.7 μ g/kg/hr as appropriate. In 2006, a study performed utilizing dexmedetomidine in pediatric patients concluded that "with dexmedetomidine titration, all patients were rated adequately sedate, even though all were sedation failures with opioids and benzodiazepines" (33). The most common side effects of dexmedetomidine include hypotension, nausea, bradycardia, atrial fibrillation, and hypoxemia.

Regional anesthesia in the pediatric burn patient has been debated. Most studies concluded that regional anesthesia is safe and effective in pediatric patients; however, caution should be used with bupivacaine peripheral nerve block infusions. "Plasma protein levels may be considerably decreased in a child with extensive burns, in turn increasing the free fraction of bupivacaine" (34).

In the acute setting, it is important to develop a treatment plan with the patient and the parents shortly after arrival to the hospital. Early and adequate treatment of pain may reduce the chance of the patient developing posttraumatic stress disorder or anxiety associated with future wound care.

TREATMENT OF SURGICAL PAIN

As an ever increasing percentage of surgeries are performed on an outpatient basis, we as a profession have attempted to provide improved pain control without the side effects commonly seen with opioids (nausea and vomiting, respiratory depression, pruritus, urinary retention, ileus, etc.). Current strategies employ multimodal (also

called “balanced”) analgesia, often with multiple classes of analgesics being employed, usually in a similar fashion to the WHO three step ladder for pain relief. For more complicated or painful surgeries requiring admission, the use of opioids for severe pain may be necessary. Typical dosing follows either a q4h p.r.n. dosing or may involve the use of patient-controlled analgesia (PCA). Most patients five years of age or older can be taught to safely utilize this method, and it typically provides more consistent pain relief with improved patient satisfaction in those patients who require opioids for severe pain.

Many institutions have previously also allowed so-called “PCA by proxy” where either a nurse or caregiver (typically a parent) was empowered to push the PCA button for a patient who was unable because of incapacity from age, mental status, etc. This practice has recently been called into question on the basis of safety concerns that patients may inadvertently receive too much narcotic with resultant respiratory depression and possibly death; many hospitals are now revising these policies either to abolish this practice or to substantially modify it so that “proxy” personnel (which may include parents) receive appropriate training before being allowed to push the button for the patient.

In a Position Statement of the American Society for Pain Management Nursing (ASPMN), approved by the ASPMN Board of Directors in 2006, it was stated that “the ASPMN does not support the use of ‘PCA by proxy’ in which an unauthorized person activates the dosing mechanism of an analgesic infusion pump and delivers analgesic medication to the patient, thereby increasing the risk for potential harm.”

The ASPMN supports the use of authorized agent-controlled analgesia (AACA) in a variety of patient care settings where patients are unable to self-administer analgesia. AACA is a method of pain control in which a consistently available and competent individual is authorized by a prescriber and properly educated to activate the dosing button of an analgesic infusion pump, when a patient is unable, in response to that patient’s pain.

- Nurse-controlled analgesic (NAC): The authorized agent is the nurse responsible for the patient.
- Caregiver-controlled analgesia (CCA): The authorized agent is a nonprofessional individual (e.g., parent, significant other).

The ASPMN position statement described criteria for the use of AACA, guidelines for selection and education of the authorized agent, key prescription and monitoring recommendations during therapy, and quality improvement activities to ensure safety and effectiveness. Furthermore, in the interest of promoting optimal safety for PCA/ACCA, it appears that respiratory monitoring with oximetry and/or capnography (35), especially utilizing continuous respiratory monitoring and a smart infusion system (36), may be useful in some cases.

Besides the typical IV, PO, and PR analgesics, surgical patients enjoy the added “benefit” of quite often being candidates for some type of regional anesthesia. Although only epidural and spinal analgesia are discussed here, local anesthetic blocks for just about any part of the body have been described.

REGIONAL ANALGESIA

Regional blocks in pediatric anesthesia are primarily employed in conjunction with general anesthesia to reduce opioid requirements, opioid related side effects, and inhalation agent requirements, as well as to accelerate recovery (37) and improve postoperative pain management.

Neurodevelopmental Differences

Small children differ from adults not only in their size, but also in important anatomical, physiologic and pharmacologic respects. Myelination does not become complete until the 12th year of life, while ossification and fusion of vertebral arches posteriorly finishes around the 3rd to 5th year of life. Infants also have a larger volume of CSF (>4 mL/kg vs. <2 mL/kg in adults). At the sixth month of prenatal life, the terminal level of the conus medullaris (TLCM) is at the level of the S1 vertebra. A full-term neonate has the TLCM at L1-L3 and the dural sac at S3-S5 versus an adult's TLCM at T12-L2 and dural sac at S2 (38).

Safety of Placement of Neuraxial Blocks Under General Anesthesia

It is important to weigh the risks and benefits of placing a neuraxial block in a child who is awake versus a child under general anesthesia. Often the child is preverbal or uncooperative and will not be able to hold still for the procedure. Accordingly, it appears safer and more practical to perform the block under anesthesia or heavy sedation. Multiple studies have confirmed the safety of regional blocks under anesthesia or heavy sedation. The largest prospective study, conducted by The French-Language Society of Pediatric Anesthesiologists (ADARPEF) and reported in 1996, included 24,409 children. This study found a low complication rate with no serious or long-term sequelae (39).

However, a similarly sized earlier retrospective study, also done by ADARPEF in 1991 (40), reported five serious incidents. Safety precautions are suggested on the basis of this study. It appears safer to use the "loss of resistance" (LOR) technique employing normal saline instead of air in the case of neonates and infants. Consider avoiding epinephrine in the usual concentration (1:200,000), and instead use a diluted amount (1:400,000). This concentration should be sufficient for a "test dose." Also reconsider the indications for lumbar epidural in infants with incomplete myelination (about 18 months of age), especially in African-American babies.

Patient Monitoring

Monitors should be applied and functioning before performing the block, with special attention to the EKG. The P wave, QRS complex, and an upright T wave should be seen. Baseline heart rate and blood pressure should be noted. Clinically significant hypotension is very rare in children less than eight years of age. A preblock volume load, which is common practice in adults, is not necessary in pediatrics (41).

Test dosing together with careful aspiration is strongly recommended to avoid intravascular or inadvertent subarachnoid injection. These are not, however, 100% reliable, so slow incremental injections with careful monitoring of vital signs, even after a negative test dose, are recommended. The recommended test dose is 0.1 mL/kg of local anesthetic with 5 µg/mL of epinephrine to a maximum volume of 3 mL (or 2.5 µg/mL of epinephrine in the child less than 18 months old—see section "Safety of Placement of Neuraxial Blocks Under General Anesthesia"). A positive test dose is defined as an increased heart rate 10 beats/min above baseline within one minute of injection, or an increase in systolic blood pressure of 15 mmHg within two minutes of injection, and/or 25% change (increase or decrease) in T-wave amplitude (42–44).

Contraindications

Absolute contraindications to pediatric regional analgesia are lack of parental consent or infection at the potential site of injection. Relative contraindications include the following:

- Coagulopathy
- Poorly controlled seizures
- Difficult airway
- Anatomic abnormalities
- Neurologic disease (e.g., multiple sclerosis)
- VP shunt (safety of VP shunt and neuraxial block has not been studied)
- Sepsis

“Single-Shot” Caudal Block

Single-shot caudal is the most commonly used block for children, in combination with general anesthesia, to provide analgesia for surgical procedures in the T10-S5 dermatomes. It is technically simple, fast, and a reliable procedure with a failure rate less than 4% in children less than seven years of age. It is safe with a complication rate of 1 in 1000, of which most are failed blocks because of misplacement of a needle, and are without serious sequelae.

Caudal block is best performed in the lateral decubitus position after anesthetic induction, peripheral IV placement, and intubation with American Society of Anesthesiology (ASA) standard monitoring in place. After sterile preparation, the sacral cornua are palpated and the sacrococcygeal membrane is perforated with a small needle (we use a 20- or 22-gauge IV catheter at our institution), and a specific “give” or “pop” is detected. After negative aspiration and test dose, the local anesthetic is slowly given in increments. For surgeries lasting more than three hours, we commonly repeat the block with 0.75 mL/kg of 0.125% bupivacaine with epinephrine 1:200,000.

Alternatively, the block may be placed at the conclusion of surgery. One potential disadvantage is the increased risk of respiratory depression postoperatively if the patient received any opioids intra and postoperatively prior to the onset of the block.

Adding opioids, fentanyl 1 to 2 $\mu\text{g}/\text{kg}$ (45) or morphine 50 $\mu\text{g}/\text{kg}$, increases the risk of respiratory depression, requires obligatory respiratory monitoring 24 hours postoperatively, and may cause urinary retention. Clonidine 1 to 2 $\mu\text{g}/\text{kg}$ (46) may increase the rate of postoperative nausea and vomiting (PONV) and sedation, ketamine 0.5 mg/kg causes behavioral changes, neostigmine 2 $\mu\text{g}/\text{kg}$ (47) and tramadol may increase PONV, and midazolam may increase sedation. All additives (if used) must be sterilized and preservative free.

Continuous Caudal Catheter

There are several types and sizes of caudal catheters available on the market. At our institution we are using a Kimberly-Clark styletted 24-gauge caudal catheter, which is placed through a standard 20-gauge IV catheter. Proper depth of insertion can be crudely predetermined by measuring along the spinous processes of the child from the desired dermatome down to the insertion site. Successful caudal insertion of catheters as high as the thoracic dermatomes is frequently reported, especially in neonates. This is most likely due to very loose epidural fat at this age (and possibly the absence of septae, which may form in the epidural space as we

age) that allows for relatively free cephalad passage of the catheter. It is recommended to discontinue the catheter after 72 hours (48 hours in neonates), or if the dressing becomes soiled.

Epidural Block

In children, a line drawn between the two iliac crests passes over the fifth lumbar vertebra, although in the neonate it may pass lower over the L5-S1 interspace (48), versus directly over the spinous process of L4 in the adult patient. Thus, developmental changes in the position of the spinal cord and dural sac are an important consideration. The distance between the skin and the epidural space increases with age. In a 10-kg child, for example, the distance from the skin to the lumbar epidural space would be only 1.5 to 2 cm.

During placement, the anesthetized or sedated patient is usually placed in the lateral decubitus position and the spine is arched to open the interspinous space and enlarge the interlaminar space. A midline approach and LOR technique is used.

Whether air or saline should be used in the syringe for LOR technique has been debated (49). Air has been available, reliable, and simple to use. But severe complications with its use have been reported, including paraplegia (50), air embolism in children (51), and possibly death. This led to a recommendation by some to replace the air-LOR technique with the saline-LOR technique. Saline, however, is not as reliable, may cause dilution of local anesthetic, and it may be difficult to distinguish CSF from saline. In general the risk-benefit ratio seems to favor the use of saline, especially in small children.

Dosing (for All Epidural Catheters)

A common dose (and what we use at our institution) for continuous infusions is 0.1 to 0.3 mL/kg/hr of 0.07% bupivacaine for neonates and 0.2 to 0.4 mL/kg/hr of 0.1% bupivacaine in older children. Infants younger than one month are prone to accumulation of local anesthetic metabolites (which may also be active metabolites), so the infusion should be discontinued after 48 hours to avoid toxicity. Fentanyl 2 µg/mL or hydromorphone 3 µg/mL are frequently added to the local anesthetic to provide additional analgesia.

Complications

Some possible complications of epidural catheter placement include intrathecal and intravascular injection, epidural hematoma formation (which appears to be even rarer in children than in adults), spinal headache, possible spinal cord/nerve root trauma, infection, bleeding, or block failure (usually from misplacement of the needle or the catheter). Unilateral block can result from catheter migration into the spinal foramina. Migration of the catheter into an epidural vein can cause loss of analgesia, increased sedation if opioids are used, and potentially systemic toxicity from local anesthetics. All opioids can cause nausea, pruritus, and urinary retention. The possibility of air embolism or spinal cord injuries is extremely rare, as discussed previously.

CONCLUSION

Pain in pediatric patients is frequently poorly recognized and often undertreated because of fear of complications from the drugs we have available for use in this patient population. As well, there may be an underappreciation of the potentially

harmful effects of untreated pediatric pain and/or the beneficial effects of effective pediatric analgesia. A thorough understanding of available analgesics, as well as an appreciation for the pain processes that we are treating, will hopefully allow us to synthesize a pain management plan that allows maximal control of pain with minimal potential side effects and maximum patient satisfaction (52–54).

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INTRODUCTION

Trauma is a leading cause of death, disability, and human suffering worldwide. Each year approximately 100,000 people die of traumatic causes in the United States alone. Traumatic injuries are responsible for more than half of deaths in the age group 15 to 24 and the fourth most common cause of mortality across all age groups. When considering medical expenses, lost wages/productivity and other related expenditures, the cost of trauma to the American public totals hundreds of billions of dollars. These statistics help shed light on the demographics and financial impact of trauma, but do little to help us understand and quantify the individual pain and suffering experienced by trauma patients. Aggressive pain management early in the course of treatment facilitates rehabilitation and may help prevent permanent disability due to chronic pain syndromes.

OVERVIEW

Pain management of the trauma patient is complicated by several important factors. Assessment of pain is made more difficult when communication with the patient is limited because of the age of the patient and/or the nature of the injuries. Many health care providers view trauma patients' complaints of pain as an important initial diagnostic tool to evaluate the location and extent of their injuries. When central or peripheral neurologic injury is present, the sedation associated with potent analgesics or the motor blockade associated with local anesthetics may impair the assessment of neurologic function. Lastly, pain management may be constrained because of hemodynamic instability or limited cardiopulmonary reserve. Clearly, after the health care team has performed initial assessment, diagnostics, and stabilization, pain should be viewed as detrimental to the emotional and physiologic welfare of the patient and a comprehensive approach to control it should begin, whenever possible.

INITIATION OF ANALGESIA IN THE TRAUMATIZED PATIENT

Pain can be severe immediately post injury, and early analgesia is justified in patients who are neurologically intact and have stable vital signs, particularly with isolated injuries such as extremity fractures.

Pain Control During Transport

Published data on the use of prehospital analgesia in traumatized patients is scant, although the available literature suggests considerable variation in its use. Evidence suggests that prehospital analgesia is underutilized in patients with lower-extremity fractures (1,2). Children may be less likely to receive prehospital analgesia than adult trauma victims, possibly because of greater difficulty in assessing

their analgesic needs (3). Fentanyl administered via intravenous (IV) and transmucosal routes has been utilized for prehospital transport in both pediatric and adult trauma patients with good results and few side effects (4–6). In particular, hypotension and respiratory depression were not viewed as impediments to its use in this setting. Disparity between the perceptions and actual practices of paramedics and emergency medical technicians who provide initial care of the injured suggests further education and protocols are needed to optimize analgesia during the prehospital phase (3). Limited data makes firm recommendations regarding pain control in the prehospital phase of trauma management difficult. Prehospital analgesic administration will likely be in response to severe pain, therefore, potent narcotics appear to be the agents of choice. The risk of respiratory or circulatory depression can be reduced with careful IV titration. Fentanyl, with its rapid onset of action, lack of cardiovascular depression, and short to intermediate duration, may be the preferred agent.

Pain Control in the Emergency Department

Multiple studies have generated data that cause concern over the timeliness and quality of analgesia administered to trauma patients in the emergency department (ED), even when their pain has been documented to be moderate or severe (2,7,8). The initial assessment and treatment of a trauma patient in the ED can be quite hectic. Analgesic administration may be delayed by the patient interview, hemodynamic stabilization, and radiographic examinations required when assessing injuries. Studies have demonstrated earlier analgesic administration in the ED when the visual analog pain scale (VAPS) is made part of initial assessment, and pain management protocols are used (8,9).

Trauma patients with less severe injuries may be discharged straight from the ED. Typically, these are straightforward cases that can be managed with oral (PO) analgesics. Intercostal nerve blocks can be performed in the occasional patient discharged with an isolated rib fracture.

PAIN MANAGEMENT FOR THORACIC TRAUMA

Thoracic trauma is classified as either penetrating or nonpenetrating. In many cases of penetrating trauma, the damage is confined to a limited area of the thorax and effective pain management may be achieved with either PO or IV patient-controlled analgesia (PCA) opioids. Non penetrating, or blunt thoracic trauma (BTT), often the result of a motor vehicle accident or fall, is more likely to involve extensive soft-tissue and bony thorax injury and consequent pain management issues. Rib fractures are particularly common in BTT, significantly contributing to subsequent morbidity and mortality. In one review, 10% of all patients admitted to a trauma center had rib fractures demonstrated by radiographic examination (10). Pulmonary complications are a common source of morbidity in these patients, with pneumonia reported in as many as 30% of cases (10,11). Ventilatory restriction due to pain may accentuate the physiologic consequences of underlying pulmonary parenchymal contusion, causing further impairment of oxygenation. When multiple ribs are involved, flail segments may result causing mechanical impairment of ventilation. In a large retrospective study, the presence of four or more fractured ribs was an independent predictor of dramatically increased mortality (12).

Patients with significant soft-tissue injury of the thorax should be carefully evaluated for the following associated injuries that may influence the strategy of pain management.

- Pulmonary contusion
- Cardiac contusion and tamponade
- Pneumothorax and/or hemothorax
- Aortic dissection or disruption
- Spine injury
- Tracheal or bronchial disruption
- Esophageal tear
- Diaphragmatic disruption
- Orthopedic injuries such as fractures of the sternum, clavicles, or scapulae
- Hepatic or splenic injury

Nonoperative management of BTT centers around pain control, chest physiotherapy, and early mobilization (11,13). Failure of this regimen and subsequent mechanical ventilation is associated with increased patient morbidity. Techniques of pain management for BTT include the following:

- IV and/or PO narcotics
- Intercostal nerve blocks
- Intrapleural local anesthetic infusion
- Extrapleural (paravertebral) anesthetic infusion
- Epidural analgesia (EA)

According to one recent review, the most prevalent mode of pain management in BTT remains IV or PO opioids (14). However, there is convincing evidence that EA provides superior pain control with better preservation of critical pulmonary function parameters. EA has been shown to significantly reduce ventilator days, lengths of ICU and hospital stays, and the rate of tracheostomy when prospectively compared with intermittent IV narcotics in patients with BTT (15). Prominent side effects of IV and PO opiates, such as respiratory depression, somnolence, and gastrointestinal disturbance may be lessened with the use of EA. The use of EA in BTT may be impeded by common contraindications including fever, spine injury, altered mental status, and coagulopathy. A thorough, evidence-based guideline for pain management in BTT, strongly advocating EA, was recently published (16).

Epidural Analgesia

Techniques for EA include intermittent bolus or infusion of local anesthetics, opioids or a mixture of both. Available evidence does not clearly point to one superior technique for BTT. However, data from postthoracotomy patients suggests continuous infusion of a local anesthetic/narcotic mixture affords the highest quality analgesia with the least side effects (17). Addition of a dilute concentration of a local anesthetic, such as bupivacaine, to the epidural infusion allows reduction of the opioid dose. A mixture of 0.1% bupivacaine/fentanyl 1 $\mu\text{g}/\text{mL}$ is commonly used at our institution for constant infusion EA. Because of the lipophilic nature of this mixture, epidural spread is limited, and the epidural catheter should be inserted as close to the affected dermatome as possible. An initial infusion rate of 4 to 6 mL/hr will typically result in segmental analgesia extending six to eight

dermatomes from the site of catheter insertion. The local anesthetic infusion rate can be changed according to the dermatomal spread achieved and the level of analgesia.

Alternatively, morphine can be administered as a bolus, or as a continuous infusion for EA. Being less lipid soluble, morphine diffuses farther from the point of injection, allowing lumbar epidural catheters to be used for thoracic analgesia, although increased opioid side effects may result from this regimen. Morphine can be administered alone for EA with a 2- to 3-mg bolus followed by an infusion at 0.2 to 0.3 mg/hr, with titration according to the level of analgesia. Morphine is the opioid of choice for bolus EA techniques because of its long duration of action (6–24 hours), and less frequent need for redosing. Alternatively, morphine can also be combined with local anesthetic for infusion. The addition of local anesthetic may lessen opioid related side effects, but nausea, vomiting, pruritus, urinary retention, and occasional respiratory depression can still occur. Whenever patients are receiving EA with opioids, the patient should be frequently assessed for signs of excessive sedation or respiratory depression. When local anesthetics are included in the EA technique, the frequency of blood pressure monitoring may need to be increased because of the associated sympathetic block. Hypotension can be minimized by maintenance of adequate intravascular volume and avoidance of sudden postural changes. The overall morbidity of EA appears low and should not represent an impediment to its use (18).

To avoid unintentional dislodgement during mobilization of the patient, the epidural catheter should be meticulously secured with a sterile dressing. A sudden change in the level of analgesia should always prompt inspection of the catheter and infusion apparatus. The duration an epidural catheter can be safely left in place has not been adequately studied. Anecdotal evidence suggests that most catheters can remain in place for up to a week, as long as the insertion site is inspected daily via a transparent sterile dressing. Signs of local inflammation or discharge from the insertion site warrant catheter removal.

Intercostal Nerve Block

Intercostal nerve blocks have been used for decades to control pain from rib fractures. Because of significant overlap of intercostals nerves, it is necessary to block one level above and below the desired dermatome. The disadvantages of intercostal block in this setting include the need to palpate broken ribs, the need for multiple or repeated injections, technical difficulty of blocking the upper six ribs due to the overlying scapula, and the risks of pneumothorax and systemic local anesthetic toxicity. The paravertebral (extrapleural) approach to the intercostal nerves has been used in patients with BTT with satisfactory results, although experience is limited when compared with EA (19,20). The paravertebral approach, being medial to the scapula, may provide better access to the first six ribs.

Intrapleural Analgesia

Intrapleural analgesia involves infusion of a local anesthetic into the pleural space via an indwelling catheter. This results in a unilateral, gravity dependent intercostal nerve block across multiple dermatomes. Intrapleural analgesia has been used successfully in the management of BTT (21). However, there are several significant drawbacks to its use. Because distribution of the local anesthetic solution is gravity dependent, cephalic distribution may be limited when nursing the patient in an

upright position. Chest tube drainage may cause leakage of the anesthetic solution from the chest cavity. Conversely, placement of the intrapleural catheter may cause a pneumothorax.

PAIN MANAGEMENT FOR INTRA-ABDOMINAL TRAUMA

Injuries to the abdomen may be penetrating or blunt. Damage to the spleen, liver, small or large intestines, diaphragm, or great vessels are most commonly associated with the need for operation. Analgesic management of abdominal injuries, or related surgery, may be complicated by concomitant hemodynamic instability, spinal cord injury, or coagulation disorders. The negative impact of upper abdominal surgery on postoperative pulmonary mechanics has been well described. EA can provide excellent pain relief, particularly when a low thoracic catheter is utilized. IV narcotics remain the technique of choice when the PO route is unavailable or when neuraxial techniques are contraindicated. Decreased gut motility may complicate recovery when high doses of opioids are used.

PAIN MANAGEMENT FOR EXTREMITY FRACTURES

Falls in the elderly frequently result in hip fractures. From 1992 to 2000, approximately 215,000 elderly patients with the diagnosis of hip fracture were seen in the United States. EDs each year (22). Few hip fracture patients receive prehospital analgesia, and many have delayed or inadequate analgesia in the ED (1,23). Patients with cognitive decline or delirium may be particularly at risk for inadequate analgesia, as the amount of opioid administered to these patients is significantly reduced (24). Potent analgesics are often withheld from elderly patients for fear of drug-induced confusion and delirium. Evidence suggests the reverse is true. Inadequate analgesia and poor pain control may increase the risk of delirium in previously cognitively intact patients by as much as nine times (25). Current evidence supports an aggressive and comprehensive pain management protocol for patients with hip fracture.

Hip fracture patients have an increased risk of death and disability that extends years beyond the injury (26). Multiple comorbidities appear to be predictors for increased mortality in this group of patients (27). Early ambulation and mobilization decrease both the short and long term mortality and subsequent disability secondary to hip fracture (28). Adequate analgesia may permit earlier mobilization, but whether the method of pain management ultimately decreases morbidity and mortality is not known. Prospective studies on the effect of EA combined with IV morphine on rehabilitation after hip fracture surgery demonstrated superior analgesia to morphine alone (29,30). However, the enhanced analgesia did not improve functional independence or morbidity, despite patients being more comfortable with physical therapy. Preoperative cardiac events, a major source of morbidity in elderly patients awaiting surgery, may be reduced with the use of EA as compared with conventional analgesia (31). Local anesthetic nerve blocks, such as lumbar plexus blocks, have been associated with reduced perioperative narcotic needs in patients with hip fracture, but experience with them is limited.

In conclusion, techniques for pain management of hip fractures can include PO and IV narcotics, nonnarcotic analgesics, EA, lumbar plexus block, lateral femoral cutaneous, and femoral and sciatic nerve blocks. Frequent assessment of

the VAPS is necessary to determine response to therapy and possible need for multimodal therapy.

TRAUMA AND CHRONIC PAIN SYNDROMES

Complex regional pain syndrome (CRPS) types I and II are chronic, often debilitating conditions, characterized by severe pain after trauma to soft tissue, nerve, or bone, especially in the extremities. The clinical features of these syndromes are very similar and classification is made on the basis of the nature of the initial injury. CRPS type I, (formerly called reflex sympathetic dystrophy), occurs following injury to skin, soft tissue, or bone. CRPS type II, (formerly called causalgia), occurs following a peripheral nerve injury. The pathophysiology of CRPS is not fully understood, although in many cases pain responds to sympathetic blockade. Vascular injuries in the extremity often result in heightened sympathetic activity that is detrimental to tissue perfusion in the affected limb. Whenever complaints of pain in an injured limb appear out of proportion to the injury, or when nonnoxious contact is interpreted as painful (allodynia), consideration should be given to aggressive analgesia and a trial of sympathetic blockade. Continuous brachial plexus blockade utilizing a catheter and dilute solutions of a long acting local anesthetic, such as bupivacaine 0.1% to 0.15%, can provide excellent analgesia and sympathetic blockade of the arm. When motor block of the arm is undesirable, repeated stellate ganglion block of the affected side can provide sympathetic nervous system blockade. Epidural local anesthetic administration will augment analgesia and sympathetic blockade in the lower extremities. When contraindications to EA exist, block of the lumbar plexus and sciatic nerve can be considered.

Traumatic amputation of a limb can be associated with an extreme nociceptive response that can, in turn, lead to changes in the dorsal horn of the spinal cord and the development of phantom limb pain. Epidural anesthesia or analgesia has been shown to reduce the incidence and severity of phantom limb pain in some surgical patients undergoing elective lower-extremity amputation (32). However, recent reviews have questioned whether cumulative data supports clear benefit from local anesthetic nerve blocks in prevention of some chronic pain syndromes (33). Still, lack of ability to provide "preemptive" analgesia in the trauma victim should not preclude consideration of neuraxial or peripheral nerve blocks to control pain in these patients. Surgical procedures to repair or reattach severed or partially amputated digits or limbs may be complicated by intense vasoconstriction in the area. An added benefit of sympathetic block of the affected limb is improved perfusion and increased viability of tissue distal to the injury.

Anticoagulants administered for thromboprophylaxis may prevent placement of neuraxial catheters. Although prospective data is scant, most view peripheral nerve block as a safer alternative in the anticoagulated patient, although bleeding complications have been reported after lumbar plexus blocks (34). Continuous catheter techniques can provide extended analgesia and sympathetic blockade to the affected area with few side effects or complications.

HEAD TRAUMA AND POSTTRAUMATIC HEADACHE

Approximately half of patients who sustain closed head trauma will develop posttraumatic headache (PTHA). Chronic headaches can also result from "whiplash" injury. The available literature appears to support the notion that mild head

trauma is associated with more PTHA than moderate to severe head trauma, and the development of PTHA often cannot be directly correlated to CNS damage. Although the exact etiology of PTHA is unclear, it frequently has characteristic signs and symptoms resembling one or more of the commonly occurring types of chronic headache: muscle-tension headache, myofascial pain syndrome, cervicogenic headache, neuralgia, and typical vascular headache (migraine). Symptoms similar to muscle-tension headache seem to be predominant (35). Initial assessment of the patient should include consideration of the less common causes of PTHA including sinusitis, pneumocephalus, and subdural or epidural hematoma. Optimal therapy of PTHA has not been determined, but it would seem reasonable to initiate treatment on the basis of how closely the symptoms resemble existing chronic headache states. Delayed recovery may occur when initial treatment is inadequate, there is overuse of potent analgesics, or when posttraumatic stress disorder (PTSD) is a comorbidity (36). About one third of patients with PTHA meet the criteria for PTSD (37). A multimodal approach to PTHA is required. Recovery may be enhanced with use of physical therapy, exercise, cognitive behavioral therapy, antidepressants, trigger-point injections, and the judicious use of narcotic and nonnarcotic analgesics. Refractory cases of cervicogenic PTHA have responded to more aggressive therapies such as implantation of spinal cord stimulators (38).

PAIN MANAGEMENT IN THERMAL INJURY

Pain management is one of the foremost challenges of providing care in the burn unit. The initial painful stimulation of nerve endings by the burn and subsequent continued painful stimulation associated with wound care may lead to activation and amplification of peripheral and central pain pathways. The negative physiologic and psychologic effects of these changes are obstacles to patient recovery and rehabilitation. A significant number of burn patients will subsequently suffer from chronic pain (39).

Current burn pain management practices may be suboptimal because of problems such as inadequate pain assessment, analgesic related knowledge deficits, and incomplete documentation of pain (40). An integrated pain management plan consisting of initial assessment, an analgesic administration protocol, and frequent evaluation of efficacy are extremely important in the burn unit. Assessment of pain in burned patients is aided by many tools including the McGill pain questionnaire, VAPSs, and picture-based scores for children.

Analgesia for first degree and limited second degree burns can be managed on an outpatient basis by cooling, cold water application, and PO analgesics. More severe burns are likely to require hospitalization and structured pain management. It is convenient to consider pain management for severe burns as consisting of basal or background analgesia with superimposed breakthrough analgesia for incident pain, often related to therapeutic procedures. IV opioids administered via a continuous infusion, or by PCA, are the most common agents for basal analgesia in the burn patient. The addition of IV clonidine resulted in a 50% reduction of PCA fentanyl in one prospective study, although the number of burn patients treated was small (41). Additional anecdotal cases demonstrating the efficacy of clonidine have also been reported (42). The specific opioid used for baseline analgesia is reasonably guided by institutional experience and efficacy in the individual patient. If PCA is not feasible, bolus IV administration of a longer duration agent, such as morphine, is indicated.

Analgesia for breakthrough pain due to therapeutic procedures, such as wound debridement and skin grafting, can be provided by additional doses of narcotics, nonopioid agents, local anesthetic blocks or general anesthetics. PCA with IV fentanyl has proven effective in this setting. Alternatively, PCA with intranasal fentanyl has favorably compared to PO morphine with regards to efficacy and side effects when used for procedural wound care (43). Of the nonopioid agents available, ketamine has been used extensively in this setting. Ketamine has been shown superior to morphine in reducing burn-induced secondary hyperalgesia in volunteers subjected to grade 1 burns, possibly because of its action on the NMDA receptor (44). When compared with codeine, acetaminophen, and diphenhydramine elixir, administration of PO ketamine resulted in improved analgesia and sedation for wound care procedures in pediatric burn patients (45).

The use of local anesthetic blocks for procedural wound care may be limited because of the variable distribution of the burn wounds. An exception may be the pain arising from the site of split-thickness skin harvesting, typically from the thigh. Continuous fascia iliaca compartment block with ropivacaine has been shown to reduce narcotic requirements for this painful procedure and subsequent dressing changes (46). General anesthesia should be administered for especially painful therapeutic procedures, particularly in the pediatric population. Alternative methods such as relaxation techniques, cognitive behavioral therapies, and psychologic support may be useful adjuncts, but should not be substituted for potent and effective analgesics.

SUMMARY

Pain management of the trauma patient should be multimodal with emphasis on frequent documentation of the VAPS and activation of pain management protocols. Protocols should incorporate as much evidence-based practice as is currently available. Ideally, pain management specialists should be a component of any trauma team. Members of the pain management team should have expertise in all types of regional anesthesia and possess extensive experience with analgesics, sedatives and anesthetics. Analgesia should begin as soon after injury as is safely possible. Aggressive pain management can facilitate rehabilitation, help restore functionality, and possibly decrease the likelihood of a chronic pain state ensuing. The trauma team must focus not only on physiologic consequences of injury, but also on the negative physiologic and psychologic effects of pain and suffering.

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INTRODUCTION

Labor pain is the most intense pain many women will experience. Unlike other forms of acute pain, it is considered a natural and positive experience for the sufferer. To a small extent, the upbeat image of labor pain exists because many women have very tolerable pain during childbirth. Regrettably, not all women arrive at a similar conclusion. The severity of pain among parturients shows tremendous individual variation. Some women encounter pain that is tolerable, leaving them feeling empowered; others suffer relentless, excruciating pain, depriving them of the constructive aspects of parturition.

For as long as effective pain relief has been an option to women in labor, there has been a vigorous and even emotional debate. One view can be summed as follows:

“Like menstruation, childbirth naturally should be a painless process. It is only as culture advances that the labor becomes painful, for in women of primitive races pain is absent. Savages of a low degree of civilization are generally little troubled by parturientcy.”

Behan, 1914 (1)

This concept evolved in the 1950s to Dick-Read’s *Childbirth Without Fear* and the psychoprophylaxis techniques of Velvovski (which was brought to the West by Lamaze). This view holds, in brief, that the lack of social support and historical context creates fear and anxiety in the parturient; fear leads to tensing of the muscles and uterus; fear and anxiety cause a loss of focus, resulting in any sensation being incorrectly interpreted as pain.

The contrary point of view is that labor is indeed painful, although the severity of pain varies both among people and pregnancies. In 1945, Ford studied 64 primitive societies. His observations included the following:

“The popular impression of childbirth in primitive society as painless and easy is definitely contraindicated by our cases. As a matter of fact, it is often prolonged and painful” (2).

This was followed a few years later by the observations of 80 primitive groups by Freedman and Ferguson, who found that labor in primitive cultures is similar to that of American and European women (3). Further support comes from the observation of pain behavior in primates (4). The added identification of noxious pain receptors and neural pathways in both humans and animals suggests that pain is not limited to a psychologic process.

This chapter will summarize the scientific evidence for labor pain, including the distinct components, and then present the current methods for treatment of pain. It will also provide information on options for management of nonobstetric pain in the pregnant patient.

LABOR DEFINED

The processes of labor that lead to the birth of the neonate, namely repeated uterine contraction and fetal movement through the birth canal, stimulate visceral and mechanical pain receptors. These pain receptors then transmit signals to the spinal cord, which leads to several hormonal and physiologic responses. A thorough description of pain during labor and delivery requires an understanding of the underlying process that provides the stimulus—labor.

Normal Labor

Normal labor is defined as uterine contractions that produce cervical dilation and delivery of the neonate. Although this process takes many forms, Friedman described the ideal patterns for nulliparas (first delivery) and multiparas (at least one previous birth) in 1955 and 1956 (5,6). Labor is divided into two distinct stages. The first stage consists of continual contractions of the uterine muscle that dilates the cervix to 10 cm. This stage is further divided into two phases, based both on the rate of dilation of the cervix and the descent of the fetus. The initial phase is termed the “latent phase.” During the latent phase, the uterine contractions are less potent and may be less rhythmic than is expected in later stages. The contractions are usually mild and go unnoticed in many women. These contractions lead to slow cervical dilation to roughly 3 to 4 cm. The duration of latent phase is variable, lasting 8 to 16 hours in most women. A prolonged latent phase is not unusual with a duration of 24 to 36 hours.

The end of latent phase is identified by an acceleration of the rate of cervical dilation and an increase in the strength of contractions. In this phase, termed the “active phase” of labor, the rate of cervical dilation increases significantly. Although there is great variability, the expected rate of dilation is 1 cm/hr in nulliparas and 1.5 cm/hr in multiparas. As the dilation of the cervix reaches about 7 cm, the rate of dilation slows and the fetus begins to descend. This period is termed transition, and is often described as the initiation of somatic pain in labor. At full cervical dilation (10 cm), the first stage of labor ends and the second stage begins. The second stage of labor consists of fetal descent through the pelvic canal until delivery. In the second stage of labor, the somatic pain of fetal passage tends to overwhelm the sensation of uterine contractions such that many parturients will report a decrease in abdominal pain. The third stage of labor consists of the period from the birth of the neonate until the delivery of the placenta. Although this period may carry risk to the mother, it is usually not painful.

Anatomy of Pain Transmission

Common to all birth processes are two discreet sources of painful stimulation. The first is a result of the rhythmic uterine contractions, and the second from the passage of the fetus. While most women describe significant pain from one of these processes, the peak of labor pain is usually felt during the period of transition, when both stimuli are at their greatest.

Uterine Contraction Pain

The contractions of the myometrium cause the intrauterine pressure to rise. This leads to stretching of the cervix and lower uterine segment, which will eventually allow the passage of the fetus. Nociceptors sensing pressure and stretch are located

in the cervix and the lateral wall and fornices of the uterus. These nociceptive signals are transmitted by A_δ- and C-fibers that travel with the sympathetic efferent nerves. These fibers then traverse the paracervical region, passing through, in sequence, the uterine plexus, pelvic plexus (also termed the inferior hypogastric plexus), middle hypogastric, superior hypogastric, and finally to the lower thoracic and lumbar sympathetic chain. The white rami communicantes then enter the spinal cord along with the T₁₀ to L₁ spinal nerves.

The mild to moderate pain of early labor is usually felt in the T₁₁ and T₁₂ dermatomes (the region between the umbilicus and the pubic symphysis). Similar to other pain caused by abdominal and pelvic organ stimulation, the pain of uterine contractions is usually described as visceral in nature; that is, slow, diffuse, and cramping in nature. But as the uterine contraction strength increases, the nociceptive field expands to include a wider area of referred pain. Distention of the cervix in nonpregnant women leads to pain similar in nature to that felt with contractions during labor (7). Also, the pressure generated by uterine contraction correlates with the amount of abdominal pain reported by parturients. The peak intensity of uterine contraction, the duration of the contraction, and the area under the curve all have been found to be predictors of the degree of pain (8).

Fetal Descent

As the intrauterine pressure increases and the cervix and lower uterine segment dilate, the fetus begins its passage through the birth canal. As stated earlier, this process usually begins when the cervix is dilated to 7 cm. The descent of the fetus causes mechanical pressure on the cervix and perineum, and often leads to stretching and tearing of tissues. Furthermore, pressure on other pelvic structures, including the lumbosacral plexus, bladder, rectum, intrapelvic muscles, and bony anatomy are often noted with passage of the fetus. This noxious stimulation activates somatic receptors in the pelvic floor, which are mainly carried by the pudendal nerve to the spinal cord, but also through the lower lumbar and sacral nerves of the pelvis. The pudendal nerve, of course, enters the dorsal horn of the spinal cord at the S₂ through S₄ segments.

The pain of fetal descent and passage through the birth canal is more commonly described as somatic in nature, with sharp, localized character, and is often referred to the lumbar region, thighs, and perineum. While many women describe the pain of the second stage of labor to be the worst, it is interesting to note that investigators have found that pain scores may actually decrease during this phase (9). Clinicians often note that the active participation in fetal expulsion (bearing down and breath holding) may improve the perception of pain in some women, compared with the passive tolerance of stimulation during the first stage of labor. On the other hand, the exquisite pain of fetal crowning is often quite severe, but fortunately brief.

Other Sources of Pain

It is quite clear that the pain of uterine contractions is caused by the increase in pressure leading to stretching and dilation of the cervix and lower uterine segment. Similarly, the pain that parturients feel with the descent of the fetus is certainly caused by pressure on the pelvic floor. While the aforementioned sources of noxious stimulation are both well described and common to most parturients, several other sources of stimulation are observed in clinical practice. The most common of the atypical labor pains is back pain of labor. This pain consists of a

constant pain in the lumbar region that is often noted in nulliparous women (10). It is not clear whether this pain is associated with fetal head position (i.e., occiput posterior) or whether this has other causes. Some women describe a continuous abdominal pain that occurs throughout labor (10–12). Other examples include pain in the upper abdomen and back, sharp pain located in the groin, intense pressure in the pelvis, and neuropathic-type burning pain. Women who experience these symptoms report an increased intensity of pain with contractions; these women tend to describe their labor as intolerable.

A significant amount of evidence suggests a relationship between dysfunctional labor and the severity of labor pain (13–15). There appears to be a significant relationship between not only the character of pain, but also the severity of pain that a parturient experiences. That is, dysfunctional labor results in a greater intensity of pain than uncomplicated labor. Dysfunctional labor also significantly affects a woman's ability to cope with her labor, and this may be independent of her pain control (16,17).

Physiology of Labor Pain

Similar to other intense acute pain syndromes, childbirth creates significant physiologic responses in both mother and child. The painful stimulation affects, directly or indirectly, most major organ systems in the body.

Cardiovascular

Labor pain results in an increase in catecholamine release from the adrenal glands, leading to an increase in blood pressure and heart rate. Compared with the nonpregnant state, parturients have an increase in heart rate and cardiac output of 15% and 40%, respectively. During labor, both of these vital statistics increase, partly in response to pain, and partly because of an increase in central volume caused by uterine contraction.

Respiratory

As a result of pregnancy, women increase their minute ventilation by 40%, which is probably a result of the hormone progesterone. During labor, painful stress leads to a further increase in maternal minute ventilation. During the first and second stage, minute ventilation increases by 150% to 300%, respectively. This hyperventilation results in maternal hypocarbia. Several authors have noted that this could result in a difficult situation for the fetus; that is, with the onset of a painful contraction, the parturient hyperventilates, reducing arterial carbon dioxide. With the end of the contraction, the respiratory drive is diminished because of the lack of stimulation from carbon dioxide. Because of the high metabolic rate and oxygen demand, maternal oxygen saturation, and thus oxygen delivery, falls. This results in mild hypoxemia in the fetus. Investigators have shown that the normal fetus develops a progressive acidosis during labor, which accelerates with the onset of the second stage. This acidosis is eliminated with maternal pain relief. While this brief period of oxygen limitation may not seriously affect most fetuses, those with poor uteroplacental circulation may be at risk.

Endocrine

Similar to other acute pain states, parturition results in the release of ACTH, β -endorphins, and cortisol. The serum concentrations of these hormones increase

throughout labor and parallel the degree of pain reported by parturients (18–20). Epidural analgesia, but not parenteral opioids, has the dramatic effect of decreasing levels of β -endorphins to prelabor concentrations (20,21). Interestingly, the concentration of β -endorphins in the cerebrospinal fluid remain similar to prelabor values, suggesting that this is a response to, and not a modifier of, maternal pain and anxiety (22).

Severity of Labor Pain

Although the process of labor, namely uterine contractions and fetal passage, is common to all parturients, the pain that is felt varies widely from woman to woman and from childbirth to childbirth. Some of this variation is due to the psychologic and social aspects surrounding the event, and some is due to the individual characteristics of each woman's parturition.

As with other acute pain syndromes, the psychologic and social milieus alter the perception of pain. Numerous studies have shown that women who are unprepared for the experience, or who enter into labor without social support, tend to describe a more painful experience (23–25). Clearly, fear and anxiety may increase the perceived amount of pain; similarly, increased severity of pain may aggravate fear and anxiety (26). Unfortunately, this aspect of the literature is plagued with unreliable methods, selection bias, and inconsistency in patient populations (27). Investigations into most psychosocial factors have demonstrated positive (28), negative (29), or no effects on the severity of labor pain (26,27,30).

Several maternal and obstetric characteristics have been associated with an increase in the pain reported during labor. It is a frequent observation that nulliparas (women in their first delivery) experience a greater severity of pain (28,31). While this has been borne out by research, there is not a linear correlation between pain and the number of deliveries. That is, grand multiparas report pain that is as severe as women having their second delivery (32).

Other factors that have been associated with an increase in pain include early onset of pain, lesser maternal age, greater maternal weight, greater fetal weight, and a history of painful menstruation (28,30,31,33).

MATERNAL PAIN DURING PREGNANCY

Maternal pain is common, with nearly half of women reporting a new or worsening pain during pregnancy. Musculoskeletal pain often arises from the anatomic changes that accompany pregnancy; namely, added abdominal weight, increased lordosis and pelvic flexion, joint relaxation due to hormonal effects, and edema. Pregnancy-related pain is most often limited in duration, but may linger for weeks and months after childbirth.

Common syndromes include the following:

- Lumbo-sacral back pain
- Pelvic girdle pain
- Nerve compression pain

Lumbo-sacral Back Pain

Lumbar back pain is estimated to occur in greater than 50% of women during pregnancy (34,35). One in five pregnant women will report severe back pain, and up to one third of these women will become disabled by their pain (36). The forward tilt of the pelvis during gestation is necessary to position the pelvic canal

for passage of the fetus. This tilt, added to the additional weight of the developing fetus, causes lordosis and tension on the parturient's lumbar spine. Sacroiliac joint dysfunction is also a common cause of pain. Risk factors for the development of back pain during pregnancy include extremes of age, a prior history of backache, obesity, and lack of physical exercise. Up to one month after delivery, 45% of women will continue to report significant back pain, and 10% of women report pain after one year (37).

The treatment of back pain during pregnancy may involve use of analgesics, which will be further detailed later in this chapter. Physiotherapy and water gymnastics have also been reported to reduce pain (38).

Pelvic Girdle Pain

Pelvic girdle pain is reported in up to 30% of pregnant women, and is severe in about 10%. Women who have severe pain are at highest risk of having prolonged and severe disability (36). Typical presentations include hip pain, iliosacral pain, coccygeal pain, and pubic symphysis separation and pain. The onset of pain is often sudden and may occur with movement, but persists until after delivery. Pain may continue for up to six months in some patients, but delivery is curative in most (39). In fact, early delivery is usually performed for women with severe associated disability.

The treatment of pelvic girdle pain is analgesics, bed rest, and physical therapy. Manipulation is sometimes, but not often, effective. Support with a cane or other orthotic device is helpful.

Nerve Pain

The most common nerve-related pain during pregnancy is carpal tunnel syndrome (CTS), with an incidence of 2% to 5% (40). Interestingly, about 17% of pregnant women have electromyographic evidence of CTS (41). Edema is common in pregnancy because of the expansion of the intravascular space and increased capillary permeability. Most women with CTS who are treated conservatively will continue to experience symptoms one year after delivery, and many require surgery (42).

Other forms of nerve-related pain include sciatica, meralgia paresthetica, and femoral nerve pain. These states are most likely caused by the forward rotation of the pelvis. Compression of the sciatic nerve may be at the bony canal, or at the location of the piriformis muscle. Compression of the femoral nerve commonly occurs at the waist and is accentuated by the expanding abdomen, and results in pain in the lateral thigh (meralgia paresthetica), or in the anterior thigh. A second site of compression can occur in the interior of the pelvis where the lumbar plexus is exposed to the growing uterus. These patients often have hip and thigh pain during pregnancy, have significant pain during labor, and may have femoral neuropraxia in the postpartum period.

TREATMENT

Nonlabor Pain

When managing the pregnant patient in pain, one must take into consideration the effects of treatment on both the mother and fetus. The circulating level of progesterone increases during pregnancy and causes augmented sensitivity to all medications. This may include an increased risk of respiratory depression, systemic

toxicity, and rare adverse events. While thorough descriptions of the risks and benefits of individual medications can be found elsewhere, the general principles of use are as follows:

Acetaminophen

There are no contraindications to the use of acetaminophen during pregnancy. However, prolonged use may be associated with fetal liver toxicity.

Nonsteroidal Anti-inflammatory Drugs

There are no adverse effects on fetal development during early pregnancy with normal use of nonsteroidal anti-inflammatory drugs (NSAIDs) (43). During the third trimester, the use of NSAIDs has significant fetal effects, including constriction of the fetal ductus arteriosus and reduction in renal blood flow. Use in the third trimester should be limited or avoided, and requires frequent ultrasound evaluations fetal well-being.

Opioids

Opioids are safe for use during pregnancy. Dosing should be adjusted to account for the increased sensitivity caused by progesterone. The use of opioids is believed to pose no risk to the fetus during pregnancy. Long term use can lead to neonatal opioid withdrawal, which is a very high risk condition.

Steroids

Steroids are teratogenic during the first trimester, causing primarily orofacial defects. The risk during the second and third trimesters has not been adequately defined, but these medications are commonly used for other medical diseases (e.g., asthma, multiple sclerosis, lupus). Short courses of steroids (24–48 hours) are safely used to encourage fetal lung maturity in the premature fetus.

Local Anesthetics

Although there is no contraindication to the use of local anesthetics during pregnancy, the progesterone-induced maternal sensitivity to local anesthetics requires a reduction in dosing compared with nonpregnant adults. The toxicity threshold is reduced by 25% to 40%.

Labor Pain

When approaching the treatment of labor pain, clinicians should respect patient autonomy in the selection of analgesic therapy and should allow for flexibility to change decisions regarding analgesia as labor progresses. Some women want to experience labor free of analgesic medications; conversely, some women want labor pain relief. No woman's labor is identical to another; thus, one person's decisions should not be forced on another. Furthermore, even trained personnel are not able to accurately describe the amount of pain that a woman reports (29).

The treatment of labor pain should, ideally, be a graded response: treatment attuned to the degree of pain that a woman feels (Table 17.1). Parturients who are coping effectively and report mild degrees of pain are often well served by nonpharmacologic methods of pain relief. These include popular psychologic

TABLE 17.1 Modalities of Labor Analgesia

Nonpharmacologic	Pharmacologic	
Psychologic	Non-neuraxial	Neuraxial
Psychoprophylaxis	Inhalation	Caudal
Hypnosis	Parenteral opioids	Spinal
Continuous labor support	Intravenous opioids	Epidural
Biofeedback	Paracervical block	Combined spinal epidural
Noninvasive	Pudendal block	
Water bath	Lumbar sympathetic block	
Massage		
Reiki therapy		
Invasive		
Intradermal water injections		
Acupuncture		

Note: The trend is for greater effectiveness of pain relief as list moves down the column and to the right.

methods such as Lamaze and hypnosis, physical methods such as massage, water births, and even acupuncture. Women with severe pain often find that the nonpharmacologic methods are insufficient to control their relentless pain. In these cases, pharmacologic methods are often employed to allow for an enjoyable birth experience.

Nonpharmacologic

Without a doubt, nonpharmacologic pain control serves an important and fundamental role in most women’s labor. Many women who successfully employ these techniques feel empowered and report their labor as a positive experience. Since the 1970s, the psychoprophylactic method of Lamaze has gained considerable interest (44). This practice is based on the belief that most of the pain of childbirth is caused by maternal fears, and that preparation for the childbirth experience through education and concentration techniques could reduce or eliminate the pain of labor. Observation evaluation using the McGill Pain Questionnaire found that childbirth preparation classes reduced labor pain among nulliparous women by about 10% (28). There was no reduction among multiparas.

Techniques such as hypnosis, acupuncture, and transcutaneous electric nerve stimulation (TENS) probably work by increasing the activity of descending inhibitory pathways (45). These techniques are of value in a selected population. The evidence supporting the use of nonpharmacologic pain relief as a stand-alone solution to the pain of labor tends to suffer from significant selection bias (46).

Pharmacologic

Inhalation Inhalation analgesia was the first form of pharmacologic labor pain relief used. Effective analgesia often requires doses large enough to cause maternal anesthesia, thus limiting the usefulness of this technique (47,48). Side effects include amnesia, nausea, and uterine relaxation. More concerning is a rare, but real, incidence of gastric aspiration that can cause significant morbidity and death.

The most common inhalation analgesic is Entonox, a mixture of 50% nitrous oxide and 50% oxygen. Although the effectiveness of Entonox in controlling pain,

as opposed to being a useful diversion, can be questioned (one placebo-controlled randomized study demonstrated efficacy equal to that of compressed air) (49), many patients receive benefit from Entonox. This method is primarily used to reduce pain perception, or as a temporizing measure prior to epidural analgesia (50).

Parenteral Parenteral medications in labor comprise a broad spectrum of delivery routes and medications. By far, the most common form of parenteral analgesia is intramuscular injection of a long-acting opioid, commonly an agonist-antagonist. This form of pain relief is often used early in labor, especially in women who are suffering a prolonged latent phase. Sedation related to the popular combination of morphine and scopolamine has been referred to as "twilight sleep." Side effects include amnesia and sedation; the historical technique used minimal monitoring in a darkened room, leading to several cases of gastric aspiration and death.

Parenteral opioids, with adequate patient monitoring, remain a mainstay of labor pain relief. The use of parenteral opioids is most effective at temporizing pain until the patient begins active labor. Parenteral opioids are also useful in patients who have reached advanced cervical dilation but are showing signs of exhaustion. From randomized studies, a single dose of intramuscular opioid does not sufficiently reduce labor pain to any degree, but it does often allow women to rest between contractions, thereby building up their strength for second stage of labor.

For women who do not receive adequate pain control with a single administration of parenteral opioid, intravenous infusions have been described. The lipid soluble opioids are preferred because of their lower toxicity to the fetus. Use of both fentanyl and remifentanyl in patient-controlled analgesia (PCA) have been described (51,52). Despite the rapid onset of action of these medications, the intermittent boluses given at the beginning of each contraction do not work fast enough to provide adequate analgesia. Side effects include excessive sedation and loss of heart rate variability in the fetus. Up to 5% of neonates may have respiratory depression or excessive sedation at birth requiring treatment with naloxone (53).

Nerve blocks Peripheral nerve blocks can be used to control the pain of the first stage and second stage of labor. Paracervical block has been used in the past for analgesia in the first stage of labor. The majority of women (75%) describe a relief of abdominal labor pain; however, once the effect of the local anesthetic recedes, the pain of labor returns. Regrettably, bupivacaine, the long-duration local anesthetic used for this nerve block, is a potent uterotonic agent. A high rate of absorption of bupivacaine into the uterine artery can result in tonic myometrial contraction, reducing uterine blood flow and causing fetal bradycardias (up to 40%), and rarely, fetal demise. This has significantly limited the use of this easily performed block (54–56).

Bilateral pudendal nerve blocks (S₂-S₄ roots) provide analgesia for pain from the pelvic floor, including that felt during second stage of labor, and also dull the pain associated with application of forceps. The failure rate of this procedure is approximately 25%, and the dose of local anesthetic needed for bilateral blocks may approach levels that could result in maternal toxicity (57).

Lumbar sympathetic blocks have been successfully used for analgesia during the first stage of labor. This technique is technically more challenging than epidural catheterization, and is usually reserved for parturients with contraindications to neuraxial analgesia (e.g., those with extensive back surgery) (58,59).

TABLE 17.2 Types of Neuraxial Analgesia

Quality	Single spinal injection	Epidural catheter	Combined spinal epidural
Advantages	Rapid onset Very effective early in labor or for a short duration close to delivery	Continuous relief Titrated effect Surgical anesthesia	Rapid onset Prolonged duration with epidural catheter
Disadvantages	Limited duration Less effective in second stage Side effects <ul style="list-style-type: none"> • Pruritus • Nausea • Vomiting • Respiratory depression 	Slower onset Incomplete pain relief Catheter migration and dislodgement	Side effects <ul style="list-style-type: none"> • Pruritus • Nausea • Vomiting • Respiratory depression

TABLE 17.3 Contraindications to Neuraxial Analgesia

Absolute	Relative
Patient refusal	Remote infection
Inability to obtain informed consent	Thrombocytopenia
Uncorrected hypovolemia	Obstructive cardiac defect
Coagulopathy	Unstable neurologic injury
Infection at the site of insertion	Lumbar spine scoliosis correction with hardware implantation
Lack of monitoring equipment	
Lack of resuscitative equipment and medications	

Neuraxial Anesthesia

The application of neuraxial anesthesia in obstetric pain consists of a variety of techniques and medications. Until recently, the most common technique used to provide labor pain relief was a single spinal injection of long-duration opioid (e.g., morphine). However, this has now been surpassed in the United States by continuous lumbar epidural analgesia. Table 17.2 describes the common neuraxial techniques currently in use and their relative advantages and disadvantages. Regardless of the method used, neuraxial analgesia is the most effective form of labor pain relief available.

Indications As with other forms of pain relief, indications include availability, safety, and maternal request.

Contraindications Major complications from these techniques are very rare, but represent a real risk. For this reason, neuraxial analgesic techniques may only be performed where trained personnel are available to manage the potential complications. Table 17.3 details the absolute and relative contraindications of these analgesic techniques.

Side effects and complications All forms of neuraxial analgesia are associated with side effects that are a consequence of the medications being used (Table 17.4). If the

TABLE 17.4 Side Effects of Neuraxial Analgesia

Side effect	Etiology	Incidence	Treatment
Pruritus	Opioids	10–20% (labor analgesia) 70–80% (spinal opioid)	Naloxone (40 µg) Nalbuphine (3 mg) Eliminate opioids from solution
Nausea and vomiting	Opioids Hypotension	2–5% (epidural analgesia) 15–50% (spinal opioids)	Metoclopramide (10 mg) 5HT-3 antagonist Eliminate opioids Uterine displacement Intravenous fluids Vasopressors
Hypotension	Local anesthetics	5–10% (labor analgesia)	Uterine displacement Fluid administration Small doses of vasopressors may be used.
Back pain	Bruising Periosteum injury	<1%	30–40% of women have back pain after childbirth without analgesia Supportive
Extensive sensory blockade	Local anesthetics	10–30%	Reduce concentration of local anesthetic
Motor blockade	Local anesthetics	5–30%	Reduce concentration of local anesthetic

doses of medications used are minimized, these side effects are easily controlled, become tolerable, or are rare. Local anesthetic blockade of the sympathetic chain results in a reduction in blood pressure due to decreased venous return. In the parturient, treatment is by uterine displacement (relief of aortocaval compression), intravenous fluids, and small doses of vasopressors. The choice of vasopressor has been of considerable debate in the literature; both ephedrine and phenylephrine are safe in pregnancy as long as the doses are minimized and they are used judiciously. Rare complications of neuraxial analgesia include epidural hematoma or abscess formation, high spinal, nerve injury, and respiratory depression. Some of these conditions require prompt intervention to avoid permanent injury or death, and all patients receiving neuraxial analgesia should be closely monitored for their occurrence (Table 17.5).

Medications The choice of medications used for neuraxial analgesia depends on the technique selected and the parturient's stage of labor (Table 17.6). The current expectation for labor analgesia is to minimize side effects of the medications while providing adequate pain control.

Spinal analgesia In the past, several negative factors tarnished the perception of spinal analgesia. Specifically, the use of large-bore cutting needles in one of the highest risk populations resulted in an unacceptably high incidence of postdural puncture headache. Secondly, at one time, the only medications used for spinal administration were local anesthetics, which produced excessive motor and sensory blockade.

The advent of small-bore pencil-point spinal needles has dramatically altered the application of spinal anesthesia in obstetrics. Use of the current generation of 24- to 27-gauge, pencil-point needles has resulted in an incidence of postdural

TABLE 17.5 Severe Complication of Neuraxial Anesthesia

Complication	Estimated incidence	Potential result	Treatment
Epidural hematoma	1:150,000–1:250,000	Paralysis	Immediate evacuation within 4 hr of identification
Epidural abscess	1:10,000–1:30,000	Paralysis	Surgical evacuation, antibiotics
Total spinal	1:2,500	Loss of respiratory control, cardiovascular collapse	Airway support (intubation) Epinephrine, norepinephrine
Nerve injury	1:10,000–1:50,000	Pain, paresthesia, weakness	Supportive
Spinal cord injection	Isolated events	Syrinx formation, paralysis	Supportive
Cauda equina syndrome	Isolated events	Paralysis	May be due to contamination of medications, neurotoxicity from local anesthetics, investigate cause to prevent additional cases
Respiratory depression	1:2,000–1:5,000	Death	Supportive, most commonly due to sedatives added to neuraxial morphine

TABLE 17.6 A List of the Medications Commonly Used for Neuraxial Labor Analgesia

Injectate	Single spinal Injection	Epidural catheter	Combined spinal epidural
Opioids	Morphine 150–250 µg Fentanyl 12.5–25 µg	Fentanyl 2 µg/mL Sufentanil 0.25 mcg/mL	Spinal injection: Fentanyl 12.5–25 µg Sufentanil 1–5 µg Infusion: Fentanyl 1–4 µg/mL Sufentanil 0.5–1 µg/mL
Local anesthetic	Bupivacaine 1–2 mg (not commonly used)	Bupivacaine 0.04–0.125% Ropivacaine 0.07–1.5%	Spinal injection: Bupivacaine 1–2.5 mg Infusion: Bupivacaine 0.04–0.125% Ropivacaine 0.07–1.5%
Infusion rate	N/A	8–15 mL/hr	8–15 mL/hr
Duration	90–300 min	Unlimited	Unlimited

puncture headache of less than 2%. The larger of these needles (24 and 25 gauge) are excellent for the single injection technique, while the smaller bores tend to be more difficult to use in the parturient because of the difficulty in holding still during painful contractions.

The second development that revived spinal analgesia was the introduction of intrathecal opioids, including morphine, meperidine, sufentanil, and fentanyl. Intrathecal morphine proved to be effective in early labor, but had a delayed onset. Leighton et al. (60) described the combination of fentanyl (25 µg) and morphine (250 µg), which the authors found to produce rapid onset of pain relief and prolonged duration of action. This combination of medications became a widely used standard spinal injection for labor pain relief. Unfortunately, pure-opioid medications tend to be less effective and of shorter duration in advanced labor, including the second stage (61,62).

Epidural analgesia The most significant advance in the treatment of labor pain was the introduction of the epidural catheter for continuous administration of pain medications. Prior to this, epidural pain relief was provided by intermittent boluses of large volumes of local anesthetic medications. This resulted in significant side effects and complications including hypotension, high blockade, intermittent breakthrough pain, and local anesthetic toxicity. The conversion to continuous infusion allowed lower doses of local anesthetics to be used, and a stable amount of pain control to be provided.

A second advance came with the addition of opioids to the local anesthetic epidural solutions. Opioids allow for a significant reduction in the local anesthetic requirements to control labor pain. For example, the median concentration of bupivacaine required to completely ablate pain in the first stage of labor can be reduced from 0.1% to 0.05% (20 cm³ volume) with the addition of 10 µg of epidural sufentanil (63). This has led to the widespread adoption of low concentration bupivacaine solutions, which have been shown to be as effective in controlling labor pain as solutions containing high concentrations of local anesthetics (64). This, in turn, results in decreased intensity and frequency of unwanted effects of the local anesthetic (e.g., motor block, hypotension) (64). In addition, combinations of a narcotic with a local anesthetic may be more effective in relieving certain components of labor pain, such as perineal pain, than either medication alone.

Combined spinal-epidural analgesia The most recent technique developed for the treatment of labor pain is the combined spinal-epidural technique. Combined spinal-epidural analgesia is performed using a standard epidural placement technique. Once the epidural space is identified, a small-gauge spinal needle (24–27 gauge) is inserted through the epidural needle and into the subarachnoid space. After confirmation of cerebrospinal fluid return and injection of the spinal medication, the spinal needle is withdrawn and an epidural catheter is placed. This technique combines the best aspects of spinal analgesia (rapid, reliable, and profound analgesia resulting in greater maternal satisfaction), with those of epidural analgesia (namely, continuous relief with the ability to provide immediate surgical analgesia). Combined spinal-epidural analgesia produces rapid and effective analgesia, often resulting in improved maternal satisfaction (65).

The side effects of the combined spinal-epidural technique do not appear to be increased when compared with a “traditional” epidural technique. Investigators have not found an increase in the rate of inadvertent dural puncture, postdural puncture headache, failed epidural catheters, or failure of the catheter to provide surgical anesthesia (66,67). The only side effect that is likely increased is the incidence of pruritus, which is common with spinal opioid administration. The medications most often chosen for intrathecal injection are the lipid soluble opioids (sufentanil 1–2 µg and fentanyl 12.5–25 µg), with or without the addition of bupivacaine. After achieving pain relief with the spinal injection, the epidural infusion can be used to provide prolonged pain control. The epidural infusion can be started after the spinal medications have receded, or immediately after spinal injection, which prolongs the effective duration of spinal analgesia (68).

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INTRODUCTION

One of the most difficult challenges facing even the most seasoned anesthesiologist is the adequate treatment of pain in opioid-tolerant patients, who often appear to be immune to the usual effects of opioids. These opioid-resistant individuals may experience severe and escalating pain in the postoperative period, requiring above average dosing of opioids. Despite the decreased analgesic effect of opioids in these opioid-tolerant individuals, tolerance to the adverse effects of opioids may be incomplete, posing risks of respiratory compromise. However, with proper patient preparation, education, and the use of alternative therapies, a smoother analgesic course may be realized.

Patients who use opioids either legally or illegally are becoming more and more prevalent, as has opioid use among the general population. Abuse of pain prescription medication is growing and heroin use is also trending higher. The 2002 National Survey on Drug Use and Health reported that 166,000 people in the United States are active heroin users, whereas 4.4 million individuals abuse opioid analgesics (1).

In addition, adequate pain management has been receiving greater emphasis as an important goal in patient care, and the prescribing of opioids for chronic pain is growing. Between 1999 and 2003, the annual sales of outpatient opioid analgesics in the United States increased by 130% (2). Therefore, the number of patients presenting to surgery with a history of opioid use is growing. Because these patients typically manifest increased opioid dosing requirements perioperatively, the anesthesiologist must have appropriate knowledge and skills to optimally manage them.

OPIOID TOLERANCE, DEPENDENCE, AND ADDICTION

One of the reasons for the increased requirement for opioids in these patients is drug tolerance. Tolerance refers to a phenomenon whereby exposure to a drug results in the need for a higher dose to maintain the same effect previously obtained at a lower drug dose. Tolerance should not be confused with the higher drug requirements exhibited in the setting of increased pain due to a worsening pathology such as tumor growth or inflammatory changes. Specifically, tolerance refers to the changes in the body that serve to counteract the effects of the drug itself.

The most common type of tolerance is due to pharmacodynamic processes related to neural adaptation. Various theories have been postulated to explain pharmacodynamic tolerance (3). Possible mechanisms include a decrease in the number of receptors, receptor uncoupling from intracellular second messengers, and activation of alternative parallel systems with antagonistic or facilitatory effects. Other types of tolerance include "associative," which is related to learning, and "dispositional," or pharmacokinetic. Learning to behave normally despite being intoxicated is an example of associative tolerance. Dispositional or pharmacokinetic

tolerance could be due to a change in the metabolic pathway of drug elimination. Enzyme induction leads to accelerated metabolism and increased clearance. However, this type of tolerance does not appear to be as important in the opioid-tolerant population as that related to neural adaptation or pharmacodynamic tolerance. Pharmacodynamic tolerance may be due to a decrease in or desensitization of opioid receptors, although this theory has not yet been proven. Uncoupling of opioid receptors from their underlying G proteins and an upregulation of cyclic adenosine monophosphate with drug tolerance has been demonstrated in several areas of the central nervous system. Long term tolerance may involve transcription induction, spinal dynorphin synthesis, and glutaminergic activation. *N*-methyl-D-aspartate (NMDA) receptor activation also contributes by inducing calcium influx, activating protein kinase C, increasing nitric oxide production, and leading to cellular destruction and apoptosis. NMDA receptor antagonists and dynorphin antiserum have been shown to limit tolerance development.

Tolerance to the analgesic effect of opioids may develop quickly, possibly within hours (2). Unfortunately, tolerance to sedation and the respiratory depressant effects of opioids is not as pronounced. During acute opioid administration, the chronic opioid-consuming patient may show a greater degree of sedation than the opioid naïve despite higher pain scores (4).

Another important concept is that of physical dependence, which refers to the potential for withdrawal symptoms to occur when a drug dose is rapidly decreased or the drug is abruptly discontinued. With restrictions on oral intake in the perioperative patient, changes in consumption of the usual amounts of opioid may occur and predispose the patient to abstinence symptomatology. The naïve physician may falsely equate physical dependence with addiction. Physical dependence is a normal physiologic response to opioid therapy. Signs of opioid withdrawal include cardiovascular hyperactivity with hypertension and tachycardia, elevated temperature, chills, diaphoresis, piloerection, rhinorrhea, and diarrhea. Withdrawal symptoms include pain, dysphoria, and insomnia.

Addiction and psychologic dependence denote the use of a drug for the psychic effect of euphoria. Drug addiction is characterized by loss of control over drug use, craving, and continued use despite harm. Genetic predisposition to addiction behaviors relate to individual differences in neurocircuitry, which may exaggerate the reinforcing effect of a drug. The dopamine system, the body's reward system, is critically involved in the development of addiction. Dopaminergic neurons originate in the midbrain, including the nucleus accumbens, the basal forebrain, and the amygdala. Recovering addicts and alcoholics may be at risk for reactivation of addiction by drugs administered perioperatively, a phenomenon termed "cross-addiction" (5).

Pseudoaddiction is a term that describes the behavior of patients not receiving adequate pain control. Requests for more opioid medication are falsely interpreted as drug seeking. When adequate pain control is achieved, this pseudoaddictive behavior abates.

Opioid hyperalgesia is a worrisome phenomenon that may be related to tolerance. An enhanced sensitivity to pain may occur with the use of opioids. First described in the setting of opioid withdrawal, hyperalgesia has been demonstrated in both animals and humans with acute and chronic opioid administration. Both high and low doses of opioids may contribute to its development. Sharing many of the same possible developmental mechanisms as opioid tolerance, opioid hyperalgesia is conceptually different. Opioid tolerance is a right shift on the dose-effect

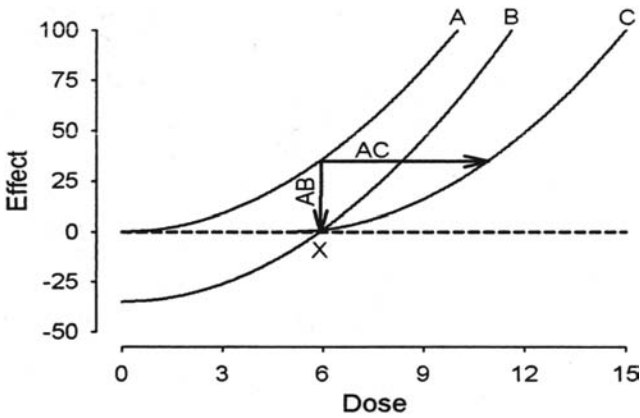


FIGURE 18.1 Possible alterations in the opioid dose versus analgesic effect relationship with chronic opioid administration are depicted. Curve A represents the relationship in opioid naïve patients, curve B represents the relationship in patients developing opioid-induced hyperalgesia, and curve C represents the relationship in patients becoming tolerant to opioid analgesia. Arrows AB and AC indicate the shift of the opioid dose versus analgesic effect relationship with the occurrence of opioid-induced hyperalgesia and tolerance.

curve, requiring an increased dose for the same effect. Opioid hyperalgesia is a decreased analgesic effect at any dose, a downward shift on the dose-effect curve (Fig. 18.1) (6). Upregulation of descending compensatory nociceptive pathways, sensitization of peripheral nerve endings and second-order neurons to nociception, and enhanced production of excitatory neurotransmitters have all been proposed as possible contributors (7). Multiple sites within the peripheral and central nervous system, including the spinal cord, are likely to be involved. Both μ - and κ -receptors have been reported to be associated with hyperalgesic effects. NMDA receptor blockade has attenuated opioid hyperalgesia. Other alternatives are to decrease the opioid amount or rotate to an alternative opioid.

PREOPERATIVE PLANNING

Patients at risk for poor pain management due to preexisting opioid use should be identified preoperatively. The consequences of poor postoperative pain management include delayed discharge and prolonged recovery, as well as pulmonary and cardiovascular compromise. With nociceptive spinal barrage, the incidence of chronic pain increases.

Preoperative assessment is critical, as it is during this period that vital information can be gleaned. The gaining of the patient's trust and cooperation is very important and will help to decrease anxiety. A preoperative plan with patient education and reassurance should be in place. If the patient is under the care of a pain management physician, consultation prior to surgery can be invaluable. The patient may be provided with a summary of possible suggestions for pain control after review of the individual's history of drug intolerances and effective opioids as well as a current list of his or her pain medications and adjuvant treatments. Early

intervention of pain management services, if available, may be helpful in dealing with patients who appear potentially challenging. Red flags for identifying these patients include a prior history of poor perioperative pain management, use of large opioid doses for chronic pain (greater than 100-mg equivalents of morphine per day), and a history of drug abuse.

During perioperative assessment of the opioid-dependent patient, alternative techniques for pain management should be explored. Regional techniques for pain management should be offered, and the patient should be reassured that these may be used in conjunction with opioid therapy to enhance the patient's pain management. Avoiding opioid withdrawal is an important goal in the perioperative management of opioid-dependent patients. Patients should be maintained on their baseline pain medications the morning of surgery, or intravenous opioid dosing equivalents should be calculated and administered. A constant infusion can be initiated if oral administration is not feasible. Continuation of the patient's opioids will help to avert a pain crisis postoperatively. This simple omission is one of the main reasons for postoperative pain consultations in this author's experience with this patient population. Recovering addicts receiving methadone or buprenorphine should be counseled to continue these on the morning of surgery with a small sip of water. However, the recovering alcoholic on disulfiram or naltrexone should discontinue these medications several days before surgery. Disulfiram should be stopped 10 days prior to surgery, while naltrexone should be discontinued 3 days before surgery (5).

If patients are deemed at risk for illegal drug use, a urine drug screen may help to identify illicit substances that may be present and may pose increased risk. In addition, liver and renal function tests, a complete blood count, and an electrocardiogram may be indicated. If benzodiazepines have been used chronically, the patient may undergo postoperative withdrawal if they are not continued through the perioperative period.

Addicts in recovery may benefit from intensifying their recovery program visits and using their individual sponsor's support during this anxiety-provoking period. A benzodiazepine can be used if clinically indicated. The care team must understand that the immediate perioperative period is not the time to attempt detoxification in patients abusing opioids. Later in the postoperative period, when pain has diminished and the patient has stabilized, this issue can be addressed.

It is anticipated that those who have been treated for chronic pain will have higher pain scores despite a higher requirement for opioids. Opioid-tolerant patients are often "pain intolerant." Chronic pain is complex with emotional, behavioral, and historical components. Cognitive behavioral techniques may decrease postoperative pain medication requirements. Patient education, relaxation techniques, and coping skills may help the patient to feel a greater sense of control over his or her experience.

Methadone therapy deserves special consideration because of the potential for significant drug interactions as well as cardiac effects. Patients may develop a prolonged QT interval on higher doses of methadone (greater than 200 mg/day), and Torsades de pointes has been reported under such circumstances (8). Perioperative use of medications that may predispose to prolonged QT syndrome may increase this risk. Such medications include chlorpromazine, erythromycin, haloperidol, and amiodarone. Other methadone drug interactions are summarized in Table 18.1.

TABLE 18.1 Drug Interactions of Methadone

Interaction	Drugs	Effect
Induce CYP3A4 activity	Carbamazepine Phenobarbital Phenytoinn	Decrease methadone levels
Inhibit hepatic enzymes	SSRIs Erythromycin Antifungal agents	Increase methadone levels
Increase AAG (α -1 acid glycoprotein) levels	Amitriptylline	Decrease methadone levels

Note: Postoperative problems may arise with discontinuance of concomitant drug. Abrupt discontinuance of erythromycin may lead to methadone withdrawal. In contrast, discontinuance of carbamazepine may lead to overdose of methadone.

INTRAOPERATIVE PHASE

The patient's total basal opioid requirement should be noted by the anesthesiologist. Preoperative opioid dosing should be assessed, as maintenance of this baseline amount is necessary to avoid withdrawal. In addition, opioid dosing will be needed for the surgical stimulation. Twice the dose of the baseline opioid has been recommended for the surgical component (1). If the patient has been unable to continue his or her baseline medication preoperatively, a bolus dose of opioid should be administered early in the procedure. Thereafter, a continuous infusion of opioid intraoperatively can be useful to provide steady state levels of analgesia.

One novel approach advanced to determine opioid requirements and tolerance is the use of a large dose of fentanyl at induction, monitoring for apnea and unconsciousness after its administration (2,9). In one study, an intravenous infusion of fentanyl was initiated at 2 $\mu\text{g}/\text{kg}/\text{min}$ and titrated to unconsciousness to determine the amount of fentanyl required. Using software to simulate pharmacologic effects, the concentration needed to induce unresponsiveness was calculated in ng/mL . A safe analgesic concentration was deemed to be 25% of this value, and the appropriate infusion rate of fentanyl was determined for each individual.

Adjuvant medications such as anti-inflammatory agents and acetaminophen may provide enhanced pain control and should be administered when appropriate. Ketorolac 30 mg IV (15 mg if greater than 65 years of age) every six hours and acetaminophen 1000 mg per rectum are both useful analgesic additions.

Regional techniques should be offered and patients reassured that they will continue to receive opioids perioperatively to prevent withdrawal and maintain optimal pain control. Infiltration of the surgical site with a long-acting local anesthetic by the surgeon will decrease nociceptive activity. Neuraxial blockade with low concentrations of bupivacaine, opioid, and clonidine are excellent therapeutic options. Targeting multiple pain mechanisms will lead to improved patient recovery and minimize respiratory depression and sedation.

Intraoperative intravenous ketamine has been advocated as an adjunct to general anesthesia to improve the perioperative experience of the opioid-tolerant patient. Ketamine is a noncompetitive NMDA receptor antagonist. The NMDA excitatory glutamate receptor has been implicated in the development of neuropathic and chronic pain, as well as opioid tolerance. Previously marketed as a racemic mixture, the S (+) ketamine enantiomer is now available and demonstrates a twofold greater affinity for the NMDA receptor than its racemate. The use of

subanesthetic doses of ketamine with general anesthesia has shown promise in decreasing pathologic pain and sensitization after tissue damage, and in reducing opioid requirements after surgery (10). Ketamine may limit the development of opioid tolerance by decreasing postsynaptic density protein interaction with protein kinase C and the NMDA receptor.

A slow bolus of 0.5 mg/kg ketamine before or after induction of general anesthesia followed by repeated injections of 0.25 mg/kg every 30 minutes or an infusion of 500 µg/kg/hr is administered. Careful attention to hemodynamic changes of heart rate and blood pressure, particularly during ketamine initiation, is important.

The dysphoric mind-altering effects of ketamine may be reduced with the use of an anxiolytic sedative such as midazolam. A calm and quiet atmosphere is also helpful. Opioid-resistant patients treated with morphine and ketamine demonstrate improved oxygenation and alertness compared with those treated with morphine alone (11).

POSTOPERATIVE PERIOD

The postoperative course is often the most challenging phase of therapy in these patients. Ventilation is no longer mechanically controlled, and the opioid-tolerant patient is not immune to respiratory compromise. Indeed, these patients seem to be at increased risk of postoperative sedation compared with the opioid naïve (4). A narrowed dosing window between analgesia and respiratory depression has been described for the opioid-tolerant population. Pain scores may remain high despite an increasing risk of lethal consequences from escalation of opioid doses.

For this reason, alternative procedures and pharmacologic options in addition to opioids are recommended. Postoperative epidural analgesia is recommended for thoracic and upper abdominal surgery. Use of local anesthetic solutions without opioid may be considered in those who will be receiving large doses of perioperative opioids. Peripheral nerve blockade with continuous catheter techniques may be continued postoperatively for extremity surgery.

Intravenous patient controlled opioid analgesia with appropriately adjusted dosing is commonly used. Opioid-tolerant patients will require two to three times the usual dose administered in the opioid naïve. A continuous infusion of a background dose to cover the opioid baseline requirement may be added, but careful monitoring is critical. Continuous pulse oximetry, hourly documentation of respiratory rate, and consideration of end-tidal CO₂ monitoring may be necessary. Many of these patients report high pain scores despite high levels of sedation. Objective criteria, such as the number of demand doses, level of sedation, and respiratory rate should be considered prior to making dose changes.

When transitioning from intravenous to oral opioid dosing, the 24-hour amount used can be converted into an oral daily requirement. Administering one-half to two-thirds of this amount in a long-acting opioid formulation and allowing a sufficient amount of a short acting breakthrough opioid is an acceptable approach.

The individual who is recovering from a past history of addiction represents a unique challenge to the anesthesiologist and pain management physician. Relapse of addictive behaviors may be triggered by the administration of drugs in the perioperative period via activation of the brain's mesocorticolimbic dopamine reinforcement system. However, pain and anxiety are also potential

precipitants of relapse. These opposing forces must be weighed to determine appropriate perioperative care. Scheduled opioids are recommended, and the use of small doses of anxiolytic therapy may be useful in some patients. In addition, patients familiar with biofeedback, guided imagery, and meditation should be encouraged to practice these modalities and continue with sponsor communication.

Patients may need ongoing follow-up after discharge to avoid unnecessary future hospitalizations for inadequate pain control and opioid withdrawal when pain medications are exhausted. An outpatient pain clinic or cooperative primary care physician who is willing to manage this often challenging group of patients is invaluable. Opioid agreements and urine drug testing to ensure compliance as medications are weaned are important aspects of continuing care.

In summary, the opioid-tolerant individual represents a unique challenge to the anesthesiologist in the perioperative period. Fortunately, there are currently many more options for pain control than in years past. The anesthesiologist should draw on as many modalities and services as are appropriate for pain management in this sometimes daunting patient population.

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INTRODUCTION

With advancing age, individuals are more likely to suffer the consequences of degenerative diseases and have an increased likelihood of developing cancer. Hence, the need for operative intervention increases with age. That said, it would be simplistic to suggest that postoperative pain management techniques are dictated in a major fashion by the age of the patient. Pain relief provided to a patient undergoing a minor surgical intervention will always differ from that given to someone undergoing complex major surgery despite the age of the patient. In addition, chronological age is not always a good predictor of the physical health of the patient. We all know patients with multiorgan dysfunction who are still “young” and others of advanced years who enjoy remarkable health. Therefore, when consideration is given to estimating the risk associated with anesthesia, for example, age is often not part of the calculation process. While this chapter discusses some of the factors that can differ in elderly postoperative patients requiring pain relief, really those lessons to be learnt by such consideration should be applied to all patients whose physical health status suggests advanced age, but whose chronological age does not always match such estimates.

If we consider what factors can differ between young and “elderly” postoperative patients, these may include the following:

- The ability to communicate and sensory impairment
- The effect of aging on the peripheral and central nervous system
- Pain threshold
- Pain tolerance
- Expectation
- Complexity of surgery
- Organ impairment and associated illnesses
- Concomitant medication
- Pharmacodynamic and pharmacokinetic factors
- Social factors

COMMUNICATION AND SENSORY IMPAIRMENT

Impairment of memory is among the changes that can accompany aging. While we provide clear information to patients on how we intend to provide their postoperative analgesia, memory defects along with the cognitive consequences of general or regional anesthesia and the traumas of surgery may leave elderly patients unsure of how to obtain pain relief. We may have instructed them on the use of a patient controlled analgesia device, but as a result of issues with memory, they may not remember either what the device is or how to use it. Compounding this type of problem is that their eyesight may not be what it used to be. They may normally

wear glasses, but these may not be provided to the patient in the postoperative phase of their treatment. Further, the postoperative recovery phase may extend well beyond that which is spent in the hospital environment. It is common for patients to be discharged from the hospital while still being advised to take a variety of medications, including analgesics. With impaired memory and vision, remembering when and how to take medication, and identifying instructions on medication containers may all be less than optimal. The consequences on the quality of postoperative pain relief are obvious. Yet, it is not only issues of memory impairment that can give rise to problems. The patient may suffer from dementia, and even preoperatively be unable to communicate in any useful fashion (1–3). These patients suffer just as much pain as anyone else, but their ability to request analgesia or to explain the nature, site, and intensity of their pain may all be absent, or at least significantly diminished. Stimuli such as pain or bladder distension may precipitate inappropriate behavior in patients with dementia, and the correct treatment is not, for example, to provide sedation to the excited patient, but rather lessen the pain, drain the bladder, or reduce the cause of their excitation.

These problems of increased prevalence of sensory impairment with advancing age are symptomatic of the decrease in physiological reserve that accompanies aging. At least in the initial stages, patients may cope by establishing routines that allow them to cope with these decreased reserves. Any break in routine, as in the case of hospital admission, may be manifest by an inability to function. One result is postoperative confusion, which may be exacerbated by the prescription of sedating analgesics such as opioids. While we give them to ensure as good quality pain relief as possible, these are agents with a broad range of effects, not all of which are good.

NEURAL DIFFERENCES IN THE AGED ANIMAL

Animal studies suggest that aging has a significant effect on aspects of the morphological and functional operation of the peripheral nervous system. A decrease in the major myelin proteins contributes to a loss in myelinated and unmyelinated nerve fibers in the elderly (4). Axonal atrophy is more commonly observed, while nerve conduction and endoneural blood flow are reduced with advancing age, contributing to a reduction in peripheral nerve function (5). Even when regeneration of damaged neurons occurs, these regenerated fibers have a smaller number of terminal and collateral synapses.

In aged rats, immunochemical studies of the spinal cord reveal an increase in mRNA content of the neuropeptides tyrosine and galanin in dorsal root ganglia (DRG) neurons (6). These animals have decreased cellular content of calcitonin gene-related peptide and substance P (SP) compared with younger animals (7), while their levels of somatostatin are similar. The labeling intensity for encoding high-affinity tyrosine receptors (TrkA, TrkB, and TrkC) is decreased in the DRG neurons of the aged rats. It has also been noted that there is a progressive loss of both serotonergic and noradrenergic neurons in the superficial lamina of the spinal dorsal horn (8). These neurons are closely implicated in descending bulbospinal inhibitory control, and such loss may upset the natural endogenous pain-suppressing mechanisms.

At supraspinal levels, there is reduced neurotransmitter content expression, decreased metabolic turnover, and a loss of neurons and dendritic connections throughout the cerebral cortex, midbrain, and brainstem (9–13).

EFFECT OF AGE IN ANIMAL PAIN MODELS

It is known that levels of the neurotransmitter SP in the spinal cord are lower in very old rats when compared with those in young rats. After peripheral nerve injury, immunoreactivity to the SP receptor (neurokinin-1 or NK-1 receptor) increases in the spinal cord ipsilateral to the injury, and the increase correlates to the development of thermal hyperalgesia. After such peripheral nerve injury, aged rats develop thermal hyperalgesia and tactile allodynia more slowly than young rats, and the thermal hyperalgesia correlates to an increase in number of NK-1 receptors, which develop more slowly in the older rat (14,15).

In rats having an incision inflicted on one of their paws, the consequential mechanical sensitivity and thermal responses were tested, showing similar responses among both young and old rats to the thermal stimulus. However, younger animals appear to recover more quickly from the mechanical allodynia produced by paw incision when compared with older rats. This suggests that modulation of A-fiber-mediated sensitization differs in young and old rats (16).

Studies on isolated spinal cord neurons show that spontaneous firing rates are higher and the response to thermal stimulation is greater in aged as compared with adult rats. Furthermore, the size of the receptive field area of wide-dynamic range neurons is larger and that of low-threshold neurons smaller in aged as compared with adult rats. The increased nociceptive neuronal activity in older rats correlates with the finding that paw withdrawal latency is significantly shorter in aged as compared with adult rats following heat stimulation of the paw. This, along with the previously mentioned loss of serotonergic and noradrenergic fibers in the spinal dorsal horn of older rats, may contribute to the apparent diminution of descending inhibitory control of nociceptive processing in older animals.

Pickering and colleagues (2006) studied young, old, and senescent rats using a chronic sciatic nerve constriction model. They found that senescent animals were less sensitive to neuropathic pain than old or young rats, while these senescent animals were more sensitive to acute pain than the other groups (15). All of these findings confirm that from a physiological perspective, definite differences exist between young adult and older animals.

EXPECTATION

It would seem to many that the level of expectation from young patients is significantly higher than that of more elderly patients. Young people undergoing surgery seem to expect that the surgical experience will be uncomplicated, that the results of their procedures will be optimal, and that they can expect pain free passage through the postoperative phase of their treatment. In contrast, it seems that at least some older patients are more accepting if these high standards are not met. Indeed, it was not that long ago when patients were happy to just survive anesthesia and surgery, and were apparently less likely to complain if, for example, postoperative pain was less than ideally treated. That said, our goal is to produce the best results for our patients, and for that objective to be met with the fewest treatment related side effects. We now know that high quality postoperative pain relief does not just bring emotional benefits, but may also be rewarded by a more prompt postoperative recovery.

INTERCURRENT ILLNESS

As age advances, there is an increased chance that the patient will have other, and often multiple, illnesses. These illnesses in themselves may influence postoperative

TABLE 19.1 Preexisting Illnesses in the Elderly and Their Impact on Pain and Pain Relief

Illness	Effect on pain and its relief
Peptic ulcer disease	Caution with use of NSAIDs.
Prostatic hypertrophy	Increased risk of urinary retention with opioids.
Congestive heart failure	NSAID use may cause fluid retention and cause or exacerbate heart failure.
Obstructive airway disease	Opioids may worsen respiratory failure.
Renal impairment	NSAIDs may exacerbate renal failure.
Constipation	May be worsened by opioids.

TABLE 19.2 Drug Interactions of Potential Concern in the Elderly Postoperative Patient

Drug	Effect on pain and its relief
Diuretics	Effectiveness of diuretics is reduced with concurrent NSAID use.
Anticoagulants	Risk of gastric bleeding is increased with concomitant NSAID administration.
Opioids	Elderly patients taking opioids chronically may be tolerant to their effects when used for postoperative analgesia.

pain, however, use of intercurrent medication for these diseases can also have effects on the treatment of postoperative pain.

While the possible intercurrent illnesses and medications that may influence postoperative pain are legion, below are some examples to highlight the scope of the issues involved (Tables 19.1 and 19.2).

We should not underestimate the effect that a surgical procedure can have on an elderly patient. For example, after years of trouble, they may have regularized their bowel habits by changing their diet or taking laxatives. This routine is broken, and we administer constipating agents such as opioids, let dehydration occur, and withhold food prior to surgery. Such patients are discharged and almost inevitably get into trouble with severe constipation. We can predict this complication, and therefore should preempt it by ensuring adequate hydration, use of nonconstipating analgesics, and by additional provision of laxative to cover the postoperative period.

PAIN THRESHOLD AND PAIN TOLERANCE IN RELATION TO AGING

What differences exist between younger and older patients in terms of pain threshold and tolerance? Are older people more stoical and less likely to complain? Do they feel the same amount of pain as a younger patient having the same procedure performed? These are important questions when it comes to rationalizing postoperative pain relief in elderly patients. Gibson (2003) reported that over 50 studies have examined age-related differences in sensitivity to experimentally induced pain, and that the majority of these studies have focused on pain threshold. Of 41 studies examined, 21 reported an increase in pain threshold with advancing age, 3 showed a decrease, and 17 showed no change. When all results are examined meta-analytically, the effect size is 0.74 ($P < 0.0005$), indicating that there is definite evidence of an increase in pain threshold with advancing age (17). That said, there may well be a difference in pain threshold depending on the type of pain inflicted. Lautenbacher and colleagues (2005) studied 20 young men with an average age of 27.1 years and compared them with 20 elderly men with an average age of 71.6 years. They found that somatosensory thresholds for

non-noxious stimuli increased with age, whereas pressure pain thresholds decreased and heat pain thresholds showed no age-related changes (18). These results are confirmed by Lin and colleagues (2005), who found that there was a consistent relationship between sensory thresholds, as measured by quantitative sensory testing, and age (19).

When pain tolerance is considered, the 10 studies examining the effect of age on pain tolerance show a definite age-related decrease in willingness to endure very strong pain (20–23). The decrease in pain tolerance is estimated at -0.45 ($P < 0.001$) across the studies.

Lasch and colleagues (1997) examined the effect of intraesophageal balloon dilatation in healthy young and older adults. The volume of air inflated into the balloon before report of pain was measured. The volume was significantly higher in the older subjects. Indeed, many of the older subjects failed to report pain even after maximal balloon inflation, in marked contrast to the younger subjects (24). It certainly seems, using this experimental technique, that pain threshold does increase with age. But this study also reminds us that pain is not always an entirely negative symptom. On many occasions, it provides timely warning of impending problems. For example, if it requires a larger volume within a hollow viscus in an elderly patient before pain is experienced as compared with a younger subject, then the discomfort caused by an obstructive lesion in the bowel may also take longer to become symptomatic in an older patient, with obvious consequences on the treatment and prognosis of the causative lesion. It is also clinically apparent that the incidence of silent myocardial ischemia increases with age (25). Whether this is due to an increased pain threshold in the older patient, a pain reducing effect of concomitant medication, or the effects of an intercurrent illness is debatable, but all probably have some effect. Therefore, while our emphasis is on the management of pain in the elderly, we should not lose sight of the fact that thought must also be given to the absence of pain in these patients under circumstance where it would normally be present.

PHARMACOKINETIC ALTERATIONS

Physiological changes in older people affecting fat mass (increased), muscle mass (reduced), and body water (reduced) have important effects on drug distribution. Blood volume may also be reduced because of concomitant use of diuretics. With the reduction in relative fat mass, drugs that are highly lipophilic, such as fentanyl and lidocaine, can have an increased duration of effect, as less of them are soaked up by fat tissue. In contrast, water soluble drugs such as morphine are less efficiently distributed, and higher plasma concentrations are obtained with equivalent doses, so side effects may be more frequent (26).

Free drug availability is significantly augmented by decreases in serum albumin, particularly in those elderly patients with chronic disease and malnutrition. Such changes increase the potential for adverse effects associated with highly protein bound analgesics such as nonsteroidal anti-inflammatories (NSAIDs) and antiepileptic agents such as valproate, phenytoin, and carbamazepine. Levels of α 1-acid glycoprotein, the serum carrier for basic drugs such as meperidine, appear roughly unchanged in older people (unless inflammation/infection is present) (27).

With increased age, liver and kidney function decrease, and these organs become progressively less efficient at drug clearance. Drug half-life, a ratio of the volume of distribution to clearance, is notably increased for several benzodiazepines and tricyclic antidepressants.

Lipid-soluble drugs such as lidocaine and opioid (“narcotic”) analgesics are good examples of drugs that undergo significant first-pass metabolism during passage from the gastrointestinal tract to the liver. Peak plasma concentrations may rise, as may the potential for dose-related side effects, with decreases in liver function. This situation is further compounded when cardiac output is impaired through disease. Highly protein bound drugs are less influenced by first-pass metabolism.

It seems that hepatic phase I reactions involving oxidation, hydrolysis, and reduction appear more strongly altered by age than phase II conjugation processes (acetylation, glucuronidation, sulfation, and glycine conjugation). In general, phase I reactions diminish irrespective of which microsomal cytochrome P (CYP)450 enzyme is involved, although interindividual variation can be significant. Acetaminophen and diazepam, both processed through the CYP3A4 and CYP3A5 enzyme routes, are metabolized at equal rates irrespective of age. Carbamazepine, lidocaine, and fentanyl, in contrast, are subject to reduced metabolism by the same enzyme systems in older patients. Glucuronidation of morphine and glutathione conjugation of acetaminophen are examples of reduced and unaltered phase II reactions, respectively. Age appears to have no effect on the frequencies of slow and rapid metabolizing genetic polymorphisms.

The most important pharmacokinetic effect of age is the reduction in renal clearance. This can be compounded by illnesses, which further reduce renal function. This can lead to drug toxicity at dosing levels appropriate for a younger patient with normal renal function. Drugs with a predominant renal mode of excretion, such as gabapentin, can accumulate when kidney function fails.

PHARMACODYNAMIC CHANGES

Whether the elderly demonstrate actual changes in intrinsic sensitivity at the receptor level is controversial, both in terms of measurable alterations in receptor numbers and in the efficiency of signal transduction following receptor binding. It has been shown that in elderly rats, the number of μ - and κ -receptors falls, while δ -opioid receptor numbers remain unchanged.

One factor that is of practical concern when opioid drugs are being used is that of pain tolerance. Buntin-Mushock and colleagues (2005) performed a retrospective chart review of 206 patients who had been prescribed strong opioids. They found that younger patients reached a maximum dose of around 450 mg of oral morphine over a 15-month period, while older patients achieved a maximum dose of around 210 mg over 14 months. When discharged from their clinic, only the older patients actually demonstrated a reduction in their visual analog pain scores. They suggest that perhaps older patients have a lower chance of developing opioid tolerance (28).

From a practical perspective, declines in homeostatic counterregulatory mechanisms in older patients create a less forgiving background to drug administration, and it is clear that older patients are less able to regain their original physiological steady state after the administration of drugs. For example, tricyclic antidepressants and opioids can induce orthostatic hypotension and precipitate syncope and falls. Homeostatic changes increase the risk of gastric irritation and bleeding following exposure to NSAIDs, and statistics would suggest that the risk of gastric bleeding is four times higher in older individuals when compared with younger adults (29,30).

SOCIAL FACTORS

With advancing age, the chances of social isolation increase, as may dependency. An increasing proportion of surgery is now performed on a day stay or short stay basis, but there is a large difference between the discharge of a young person after day case surgery to a well defined family and support structure and that of an elderly patient who lives alone or whose partner has failing physical and mental ability. Postoperative pain does not end when a patient is discharged from the hospital, but rather, it usually ends when the tissue has healed. Therefore, the need for analgesia after a wide range of surgical procedures may extend well beyond hospital discharge. Thus, mechanisms to ensure that patients, in particular the elderly, receive adequate pain relief for the postoperative period in a safe and "user-friendly" manner are essential. This may involve provision of patient medication predisposed in daily containers (containing all medication that the patient needs to take on that particular day and at a particular time), or frequent home visits by support staff to ensure that postoperative recovery is progressing in an acceptable fashion.

CONCLUSION

While our aim should be to provide good quality postoperative analgesia to all patients regardless of age, this may be more problematic in elderly patients. That said, it is arguably more important that they do get optimal analgesia, as they are more likely to exhibit consequences from failing to achieve this standard. Many factors mitigate against good quality pain relief in elderly patients. They are more likely to need surgery, have preexisting pain conditions, have intercurrent health problems that complicate the postoperative recovery phase, and to be on other drugs that may interfere with those that we select as postoperative analgesics. Additionally, now days, patients are much more likely to be discharged from the hospital to an environment where support is deficient than would have been the case in the past. To some extent, we reassure ourselves that the patient is pain free, or at least comfortable, at the time of discharge after day case surgery. However, soon after discharge, local anesthetics used to infiltrate wounds wear off, the pain returns, and patients have often either not been provided with take-home analgesics, or they do not understand exactly how or when they can take the analgesics they received on discharge.

We could discuss issues of pain tolerance and threshold in elderly patients, but to an extent, these discussions lack relevance. Pain naturally accompanies trauma such as that inflicted by surgery, and therefore, we must ensure that pain relief is of the best possible quality, that it has a low risk of inducing side effects, and that it is continued for as long as is necessary.

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Handbook of Acute Pain Management

About the book

Pain is a pervasive symptom in medicine. It is imperative that physicians not only evaluate and diagnose the source of pain, but that they also recognize how to manage the actual pain symptoms with effective treatment. Addressing the latest developments in both pharmacologic and non-pharmacologic pain therapies, this text is a useful reference for all those administering to patients with acute pain.

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- Patient-controlled analgesia options
- Anticoagulation guidelines during regional and neuraxial anesthetic techniques
- Pain management issues in special populations – specifically pediatric, opioid-tolerant, obstetric, trauma, and elderly patients

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