Pre-emptive and postoperative analgesia for dentoalveolar surgery

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I. Introduction

Pain after oral surgical procedures is one of the most studied models in pharmacology and pain research. Sensory nociception in the head and oral cavity is disproportionately greater than in most other areas of the body. Because of this phenomenon, appropriate pre-emptive and postoperative pain management is critical to achieve a successful outcome. This article provides the practitioner with a brief review of the acute pain mechanism as it relates to the effects of a surgical insult. A brief understanding of the physiologic modulation of acute pain establishes a rational framework for the concept of pre-emptive and postoperative analgesia. A brief review of commonly used analgesic agents is presented. Research in pain management and new drug development is ongoing as new concepts in neurophysiology and pharmacology are being elucidated.

II. Acute pain mechanisms

When examining how to manage acute postoperative pain in the oral and maxillofacial surgery patient, it is important to review the physiologic mechanisms involved in acute postsurgical pain. Webster's dictionary describes pain as a basic bodily sensation induced by a harmful stimulus characterized by physical discomfort [1]. When tissue homeostasis is disrupted by a surgical insult, autonomic, hormonal, and chemical changes that play a role in the subjective perception of pain are observed physiologically.

This article does not address every detail involved in the acute pain mechanism. Nonetheless, a simplified understanding of the neurophysiology of acute pain is important when reviewing pharmacotherapy (Tables 1 and 2).

Peripheral pain stimuli are initially encountered at the nociceptor level on skin, joint, or end-organ surfaces, where they are processed and transmitted via first-order neurons to the dorsal horn neurons of the spinal cord. These first-order neurons vary in width and composition. These nerve fibers are classified into two general subtypes, A and C. A-fibers tend to be myelinated and fast conducting, while C-fibers tend to be unmyelinated, slower-conducting fibers. A-fibers produce a more localized sharp pain, while C-fibers produce a dull, poorly localized ache. These primary afferent fibers, through the release of specific neurotransmitters, transmit sensory information to the dorsal horn neurons of the spinal cord.

The spinal cord is composed of various laminae, numbered 1 through 10. These laminar tracts are comprised of specific types of second-order neurons, each varying in function. Examples of dorsal horn neurons include nociceptive specific cells (NS), wide dynamic range cells (WDR), complex cells, viscerosomatic cells, and others. NS cells are specific for a

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Table 1
Commonly used oral narcotic analgesics

Drug	Trade name(s)	Usual dose	Combination drug
Codeine	Empirin with codeine	30–60 mg	Aspirin (325 mg)
	Tylenol with codeine		Acetaminophen (300–650 mg)
Hydrocodone	Lortab, Norco, Vicodin, Maxidone	5, 7.5, 10 mg	Acetaminophen (500–750 mg)
Propoxyphene	Darvocet, Darvon	50–100 mg	Acetaminophen (300–650 mg)
			Aspirin (325 mg)
Hydromorphone	Dilaudid	1–4 mg	
Oxycodone	Percocet, Percodan, Roxicet,	2.25–5 mg, 7.5 mg	Acetaminophen (300–500 mg)
	Roxipirin, Tylox		Aspirin (325 mg)
Pentazocine	Talacen, Talwin	12.5–25 mg	Acetaminophen (650 mg)
			Aspirin (325 mg)
Meperidine	Demerol	50–150 mg	None

small receptive field and respond to high-threshold noxious stimuli. Conversely, WDR cells respond to a wide spectrum of stimuli, receiving mainly multi-synaptic input from both A- and C-fibers. WDR cells have a wider receptive field than NS cells. Complex, viscero-somatic, and other types of dorsal horn neurons may play excitatory and inhibitory roles on pain stimulus transmission while having various receptive field sizes and pain characteristics [2].

Depending on the afferent fiber type and the neurotransmitters involved, primary afferent stimuli are directed to specific laminae within the spinal cord, where they are processed and transmitted, via the spino-thalamic tract, to the brain. Information is transmitted to third-order neurons in the thalamus for further processing. Afferent information is then relayed to the somatotopic areas of the cerebral cortex, where conscious pain perception arises. It is at this sophisticated supraspinal level that such factors as anxiety, depression, fear, and learned behavior exert their influences on the phenomenon of perceived pain (Figs. 1 and 2).

Although pain transmission in the head is quite similar to transmission in the spinal system, some distinct differences exist. Sensory nociception is dis-

proportionately greater in the head and oral cavity when compared to other parts of the body. This amplification probably results from speech, taste, and masticatory functions. Cranial nerves V, VII, IX, and X relay sensory information to the trigeminal ganglion. The spinal nucleus of the ganglion transmits afferent sensory information through the medullary dorsal horn of the spinal cord to the thalamus [3]. This amplification in sensory distribution is what makes postsurgical dental pain one of the most studied models in pharmacology and pain research.

III. Modulation of the acute pain mechanism

Peripheral sensitization:

With the basic neuroanatomic architecture described above, the modulatory processes involved at the various levels of impulse transmission can be better understood. Free nerve endings, or nociceptors, are peripherally activated in response to tissue damage. Afferent conduction of information is transmitted through myelinated A fibers or unmyelinated C fibers to the dorsal horn neurons. At the level of the

Table 2
Properties of oral narcotic analgesics

Drug	Analgesia	Sedation	Nausea or vomiting	Constipation	Euphoria	Comment
Codeine	+	+++	++	++	+	Low potency
Hydrocodone	++	+	+	+	++	
Propoxyphene	+/−	+++	+	++	+	Rarely indicated
Hydromorphone	++	++	+	+	+++	
Oxycodone	+++	++	+	+	+++	
Pentazocine	++	+	+	+	+	CNS side effects
Meperidine	++	++	++	+	+++	Rarely indicated

CNS = central nervous system.
Plus and minus symbols indicate estimations of degree of negative or positive effect.
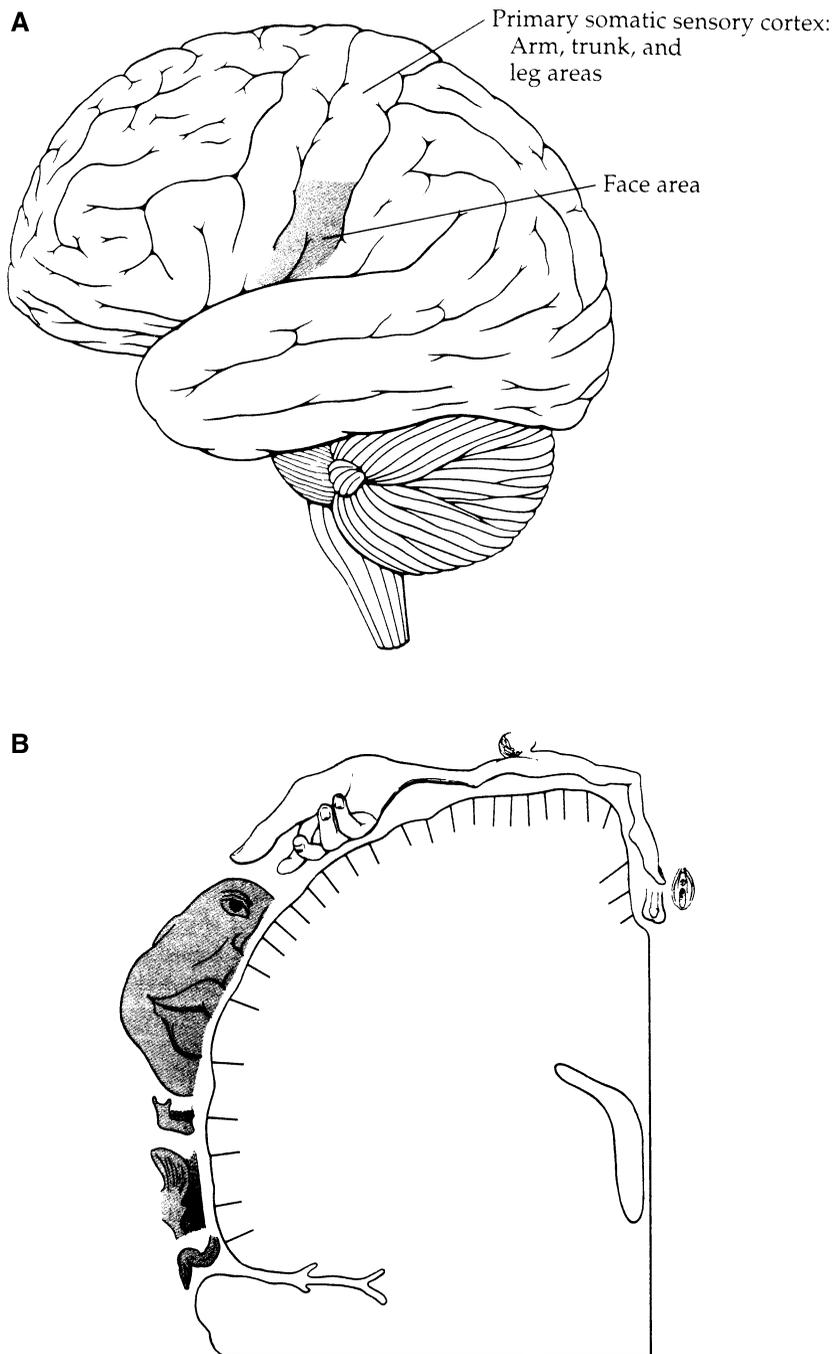
Fig. 1. (A) Primary somatic sensory cortex located in the postcentral gyrus. Note the relatively large proportional area dedicated to the facial region. (B) Schematic of Penfield and Rasmussen's homunculus [36] depicting disproportionately large areas dedicated to the face and jaw regions. (*From* Martin, JH. Neuroanatomy text and atlas. 2nd edition. Old Tappan, NJ: Appleton and Lange; 1996. p. 379; with permission.) (C) A simplified view of the ascending sensory pathway depicting first-, second-, and third-order neurons leading to the primary somatic sensory cortex. (*From* Snell, RS. Clinical neuroanatomy for medical students. 5th edition. Copyright 2001 Philadelphia: Lippincott Williams and Wilkins; 2001. p. 146; with permission.)
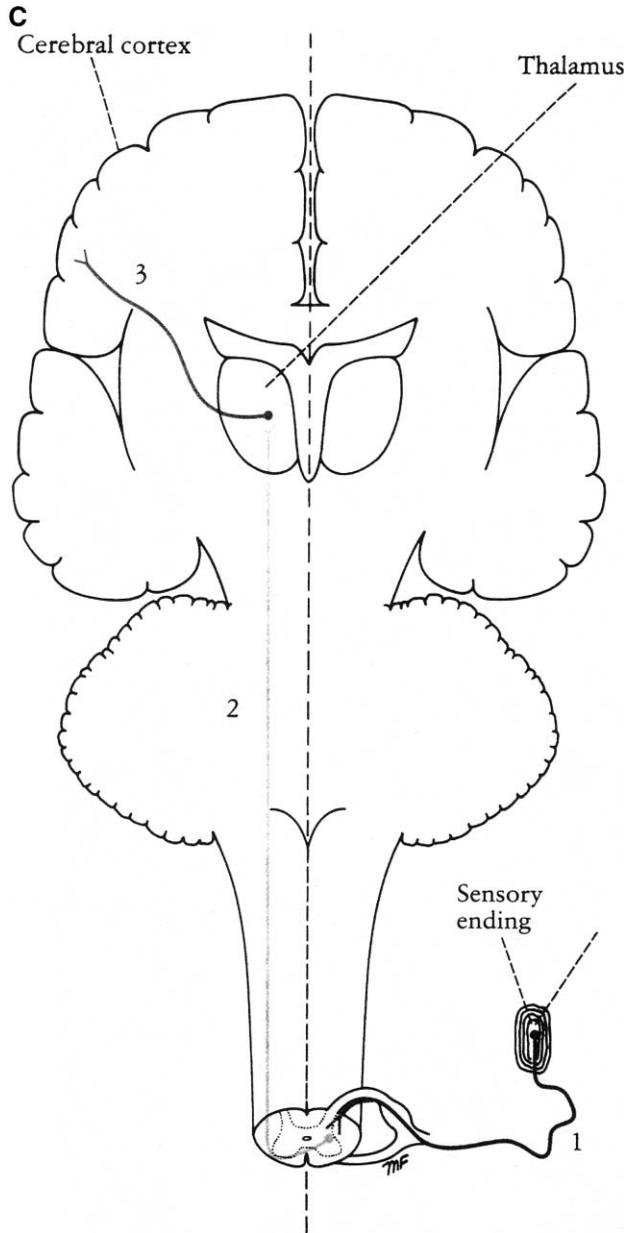
C

Cerebral cortex

Thalamus

3

2

Sensory
ending

1

Fig. 1 (*continued*).

free nerve ending, there is interplay between the various surrounding structures, including blood vessels and mast cells. This contributes to the release of "pain mediators," such as substance P, glutamate, and metabolites of arachadonic acid, among others. The release of histamine and cytokine activity in the face of mast cell degranulation can sensitize other free nerve endings in the area of insult. Plasma components, platelets, and the products of surgically damaged cells themselves all contribute to the release of neuroactive substances involved in peripheral sensitization and hyperalgesia [2,3].

Central sensitization:

Recent studies have demonstrated central sensitization of the dorsal horn neurons in the spinal cord. This concept was examined by using a surgical

Pharmacologic Interventions in Arachidonic Acid Metabolism:

Surgical Stimulus (Injury to Cell Membrane):

Membrane Phospholipids

Phospholipase A2

Corticosteroids

Arachidonic Acid

NSAIDS

Lipoxygenase

Leukotrienes
Lipoxins

Vasoconstriction/Vasodilation
Pain
Inflammation
Bronchial Constriction
Gastric Mucous Protection

Cox-2

Cox-2 Inhibitors

Inflammatory Prostanoids

Induced with tissue
injury
- *Pain and tenderness*
- *Vasodilation*
- *Fever*

Cox-1

Cytoprotective Prostanoids

Maintain normal physiology
- *Maintain healthy gastric mucosa*
- *Maintain platelet aggregation*
- *PGE2, Prostacyclin,*
Thromboxane A2
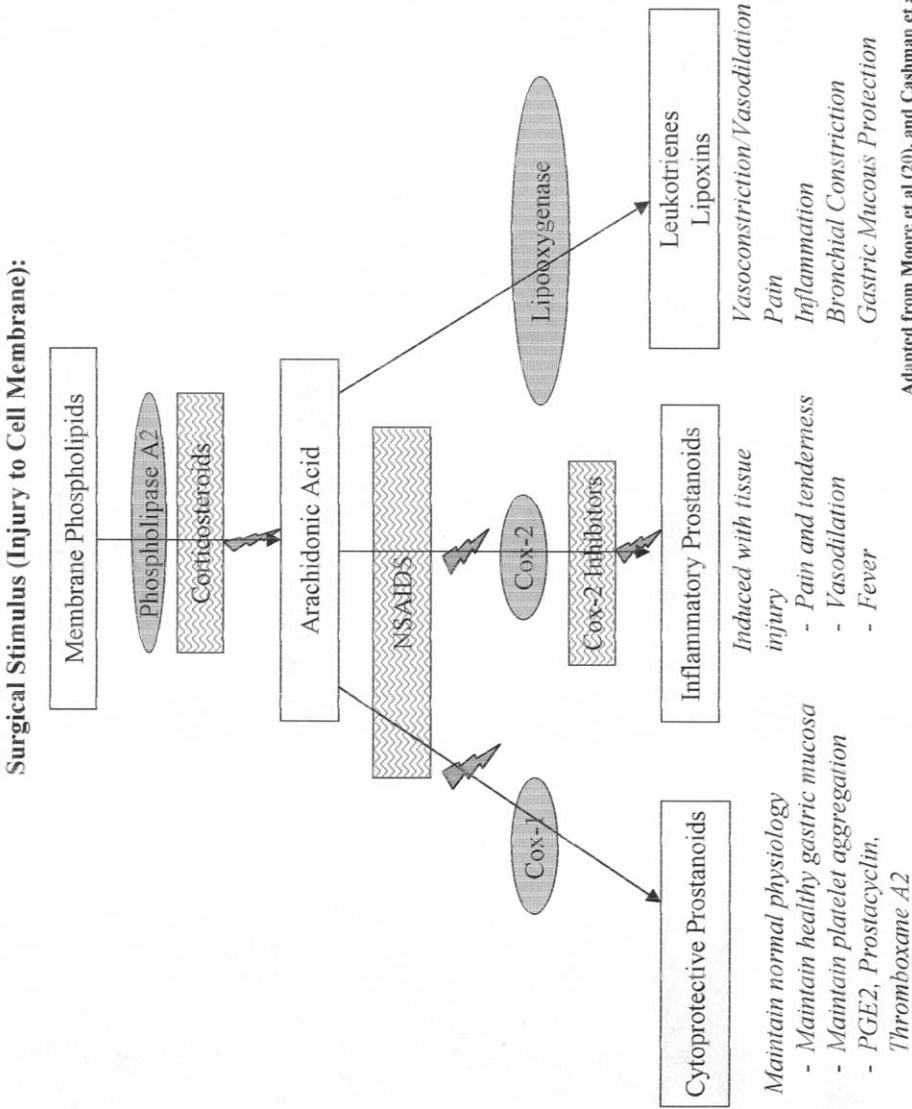
Adapted from Moore et al (20), and Cashman et al (19)

Fig. 2. Pharmacologic interventions in arachidonic acid metabolism.

incision in the rat model. Three types of dorsal horn neurons, low threshold (LT), wide dynamic range neurons (WDR), and high-threshold (HT) cells were studied after surgical incision in the root foot. Decreased withdrawal thresholds to punctate mechanical stimuli after incision was observed. The activation of various neuropeptides and excitatory amino acids up-regulate centrally mediated impulse transmission. These findings suggest central sensitization and hyperalgesia in the face of surgical insult [4]. Additional studies on the concept of central sensitization are currently underway and may have significant implications in the concept of pre-emptive and preventive analgesia.

Neuropeptide and amino acid modulators:

Research in the area of neurophysiology has elucidated the existence of specific neuropeptides and excitatory amino acids released at central and peripheral nerve terminals [2,5–7]. Examples of such neuropeptides are substance P, calcitonin, gene-related peptide, cholecystokinin (CCK), and somatostatin. These neuropeptides play a role in the modulation of transmitted afferent pain stimuli. The principle excitatory amino acid is N-methyl-D-aspartate (NMDA). Specific excitatory amino acid receptors also exist on postsynaptic dorsal horn neurons in the spinal cord. NMDA receptors are specific to A- and C-fiber stimulation [8]. These receptors, among others, have been the target of various experimental analgesic drugs.

Excitatory and inhibitory modulation was further studied at the spinal level. "Wind-up pain hyperalgesia," where repeated stimulus frequency beyond a critical threshold leads to enhancement of cellular responses, both in magnitude and duration, is thought to be a result of neurokinin excitatory modulation. Repeated stimulation of C-fibers converging on WDR cells in dorsal horn neurons is thought to elicit the release of substance P and the excitatory amino acid NMDA, leading to this clinical phenomenon [9,10]. Pharmacologic agents such as ketamine have been found to antagonize at the NMDA receptor, thus exhibiting some intrinsic analgesic properties [11]. Conversely, the release of inhibitory neuropeptides, such as γ-amino-butyric acid (GABA), from the dorsal horn neurons is associated with the inhibition of primary afferent pathways by primary afferent depolarization. It is this phenomenon that has provided the basis for dorsal spinal cord stimulation in the treatment of chronic pain patients [12]. Enhancing the activity of inhibitory GABA provides another pharmacotherapeutic approach to analgesia.

Pharmacologic agents such as barbiturates and benzodiazepines achieve their biologic effect as GABA receptor agonists.

Supraspinal modulation:

Supraspinal modulation of impulse transmission in the thalamus and cerebral cortex is also observed. Monoamines, such as serotonin (5-HT) and norepinephrine (NE), and the release of endogenous enkephalins have been observed to down-regulate the afferent pain stimulus in the spinal cord directly or through second-messenger activation and provide excellent avenues for pharmacotherapy. Similarly, anxiolysis and patient education can modify cortical processing of pain perception [9,10]. This is extremely relevant in the ambulatory oral and maxillofacial surgery patient. Many new selective serotonin reuptake inhibitors and centrally acting analgesics such as clonidine achieve their biologic effect at this level.

IV. Pre-emptive analgesia

An understanding of the cascade of neurophysiologic events that stem from a surgical insult provides excellent rationale for attempts at pre-emptive analgesia. The oral and maxillofacial surgery patient undergoing modern ambulatory dentoalveolar surgery requires a rapid return to the activities of daily living. Unlike other surgical disciplines, inpatient hospital stays and prolonged recovery are not a tolerated outcome in most cases. It has been suggested that lessening pain during the surgical procedure itself will reduce overall postoperative analgesia requirements [13]. Pre-emptive analgesic intervention is aimed at attenuating or entirely blocking central pain sensitization, leading to reduced pain in the postoperative period. Pre-emptive goals are to attain reductions in analgesic rescue medication requirements and to hasten overall recovery.

Analgesia for postoperative dentoalveolar surgery has traditionally been approached by prescribing a particular analgesic drug of choice with instructions to "take as needed for pain." Experience with this approach dictates that many patients will wait until the onset of significant pain before starting the medication. Recent studies have demonstrated efficacy in using adjunctive analgesic measures, such as administration of long-acting local anesthesia, corticosteroids, and intraoperative nitrous oxide analgesia, with regard to reducing postoperative pain [3]. Also, the concept of using analgesic pain medication post-

operatively, before the onset of significant pain (as "preventive analgesia"), is being used [13]. Each of these modalities have lead to decreased total pain after surgery and decreased pain intensity at fixed postoperative time intervals when measured by visual analog scale [8,13].

Investigators have retrospectively explored the concept of pre-emptive blockade of central sensitization resulting from surgery [16]. In this analysis, the amount of time was measured between surgery and the first request of postoperative analgesia medication in patients who underwent a variety of surgical procedures under general anesthesia. Preoperative administration of local anesthesia delayed the postoperative request for analgesic medication by 6 hours when compared to control subjects. Preoperative opioid administration caused a 3-hour delay, and the contribution of both local anesthesia and an opioid showed additive effects on delaying the request of postoperative analgesic medications. This provided sound rationale for prospective investigational studies on pre-emptive analgesia.

Subsequent prospective studies on pre-emptive analgesia were initiated in the oral and maxillofacial ambulatory surgery model [14,15]. The preoperative use of 0.5% bupivicaine, when compared with lidocaine and saline placebo injections in patients undergoing third molar surgery under general anesthesia, lead to statistically significant decreased pain perception at 4 and 48 hours after surgery. Additional studies have suggested that the use of nonsteroidal anti-inflammatory medications before surgery, with the pre-incisional administration of long-acting local anesthesia, significantly reduced the amount of postoperative pain, as measured by visual analog scale [11]. These results support the theory that blockade of factors leading to central sensitization will have a positive effect by decreasing postoperative pain perception.

It should be pointed out that these studies support the supposition that blocking central sensitization reduces overall pain perception and pain duration. Nevertheless, the question remains: At which point is pre-emptive intervention most important, blocking the nociceptive input at surgery or blocking the postoperative pain resulting from surgery in the immediate postoperative period? A recent study indicates that whether or not the nociceptive input of surgery was blocked through the administration of long-acting local anesthesia, overall postoperative pain perception was the same [15]. This suggests the important contribution of immediate postoperative pain toward initiation of central sensitization in the ambulatory oral and maxillofacial surgical

patient. Additional studies are necessary to clarify this distinction.

When looking at the data available, for patients undergoing complex dentoalveolar surgery, it would seem prudent for the practitioner to administer a long-acting local anesthetic such as etidocaine or bupivicaine at the time of surgery or, at the latest, in the immediate postoperative period. This would pre-emptively block the initiation of central sensitization and resulting hyperalgesia. The use of nitrous oxide analgesia during surgery and corticosteroids for reduction of postoperative inflammation and local tissue injury should also lead to diminution of postoperative pain. Most recently, it has been demonstrated that pretreatment with nonsteroidal anti-inflammatory medications also lead to decreased postoperative pain and edema in the oral and maxillofacial surgery patient [11,17]. This may prove to be another effective pre-emptive analgesic approach. Further studies regarding pre-emptive analgesia in the surgical patient will undoubtedly change the standard approach to ambulatory surgical pain management.

V. Postoperative analgesic agents

The opioid drug class:

Mechanism of action:

Opioids in oral and maxillofacial surgery have long been the mainstay drug class for the management of moderate to severe postsurgical pain. References to the opium poppy can be found dating back to 300 BC in Sumarian and Egyptian culture. The opium poppy, papaver somniferum gives rise to more than 20 different alkaloids. Morphine was isolated in 1806, followed by codeine in 1832 [18]. Opioid receptors are found throughout the body, providing sites for activation of endogenously released opioid substances. Beta-endorphins, enkephalins, and dynorphin compounds have been identified as agents for endogenous central analgesia [19]. These endogenous opioid receptors provide natural targets for centrally mediated pharmacotherapy.

Opioid receptors are subdivided into delta, kappa, and mu subtypes. They are located centrally in C-fiber terminals within the dorsal horn of the spinal cord. They are also found supraspinally in nociceptive processing areas of the brain. A peripheral component of opioid analgesia has also been described at the afferent C-fiber terminals on skin and joint surfaces [9]. Current terminology has now classified delta, kappa, and mu opioid receptors as OP1, OP2, and OP3, respectively. It is primarily the

central analgesic action of opioids that makes them so effective in managing acute postsurgical pain.

Opioid receptors, neuronal pools, exogenous and endogenous ligands, routes of delivery, and dosage of various compounds have contributed immensely to our ability to effectively manage postoperative pain in the oral and maxillofacial surgery patient [19]. All opioids act on stereo-specific, saturable membrane receptors. As previously mentioned, these receptors are widely but unevenly distributed throughout the central nervous system (CNS). In addition to the three opioid receptors delta, kappa, and mu, two additional receptors, epsilon and sigma, also exist. Studies have indicated that only mu, kappa, and delta receptors (OP3, OP2, and OP1, respectively) have analgesic properties. Mu/OP3 receptors are located widely throughout the CNS and have been identified in the limbic system, thalamus, striatum, hypothalamus, and midbrain [18]. Kappa receptors are located primarily in the spinal cord and cerebral cortex. Opiate receptors are coupled with G-protein receptors, which function as positive and negative modulators of synaptic transmission via second-messenger activation. These G proteins provide amplification of physiologic activity at the receptor level. Opioid receptors differ with respect to distribution, ligand affinity, and proposed behavioral action. Research has confirmed that the mu/OP3 receptor is not only associated with analgesic properties, but is also responsible for respiratory depression. Two mu receptor subtypes have been discovered. Although a certain degree of cross-reactivity exists, mu1 is mainly responsible for analgesia and mu2 for respiratory depression. This has opened the door to research aimed at developing mu1-specific analgesic agents [19]. Pure agonists such as morphine sulfate, codeine, oxycodone, and meperidine act on the mu/OP3 receptor.

The nomenclature for opioid classification is based on the type and degree of receptor activation. Drugs or neurotransmitters that act on receptors and cause a biologic effect are known as agonists. Opiate agonists produce analgesia by inhibiting excitatory neurotransmission of substance P, acetylcholine, noradrenaline, and dopamine. Opiate agonists also modulate the endocrine system and immune system. They inhibit the release of vasopressin, somatostatin, insulin, and glucagon [18].

Opiate antagonists will act on receptors to reverse a biologic effect. They will occupy a receptor without eliciting a physiologic response. This has clinical significance with the use of certain narcotic-reversal agents and mixed agonist-antagonist agents. Mixed agonist-antagonist drugs can be considered for use in postoperative analgesia. These drugs have potent analgesic effects without the high potential for tolerance or dependency inherent in pure mu/OP3 agonists. The opioid agonist-antagonists have high affinity and low potency at the mu receptor while activating kappa, delta, and sigma receptors. Drugs in the agonist-antagonist class include such agents as butorphanol, pentazocine, and nalbuphine. The opioid agonist-antagonist agents have been proven effective for use in the control of moderate pain, but have not proven to be potent enough analgesics for severe postoperative pain.

The most significant adverse reaction to the opioid agonists is respiratory depression. For this reason, most opioid agents used in outpatient postsurgical pain management are formulated in combination with non-narcotic analgesics. This potentiates the analgesic effects of the individual agents within the formulation while minimizing the potentially life-threatening side effects of pure opioid administration. When these drugs are properly titrated and the recommended doses are not exceeded, the risk of respiratory depression is small because tolerance to this effect develops rapidly. Allergic reactions to opiate agonists are uncommon. Opiates can cause histamine release, resulting in pruritis. The most common gastrointestinal (GI) effects include nausea, vomiting, and constipation.

Codeine:

Codeine remains one of the most frequently prescribed narcotics to treat postoperative pain in the ambulatory surgical setting. It is also widely used for its antitussive properties. It is most commonly used in combination with acetaminophen. Codeine is closely related in structure to morphine, possessing a methyl group that protects it from rapid degradation in the liver. It is one third as potent as morphine [20]. Doses of 120 mg will produce respiratory depression similar to that resulting from 10 mg of morphine sulfate. Because of its low degradation on first pass, codeine's oral efficacy is two thirds that of its parenteral activity. Studies assessing codeine's ability to relieve postoperative oral surgical pain have been equivocal and have indicated that 60 mg of codeine is required to achieve therapeutic benefit in dental pain. The usual adult dosage is 30 to 60 mg orally every 4 to 6 hours as needed, with a maximum dose of 360 mg in 24 hours. This has led to formulations that combine codeine with other analgesics such as acetaminophen. In doing so, analgesic synergism will reduce the total dose requirements for codeine. The maximum dosage of acetaminophen should not exceed 4 g in a 24-hour period. The most common side effects are constipation, nausea, vomiting, and sedation.

A small percentage of patients have been found to be nonresponders to codeine and codeine-based derivative analgesic agents such as hydrocodone and oxycodone. These patients do not derive adequate analgesic efficacy from these types of analgesic agents. Manifestations of this phenomenon may be difficult to differentiate from drug-seeking behavior. It has been discovered that ∼ 5% to 10% of Caucasians lack functional cytochrome P450 2D6, a liver enzyme involved in the metabolism of many drugs, including codeine [21]. Assays of codeine and its metabolites have been compared to CYP2D6 phenotypic activity in human subjects, demonstrating a direct correlation between the two [22]. Although this phenomemon is still being investigated, there is a likely genetic contribution to poor codeine metabolization. Oral and maxillofacial surgery patients who do not respond to codeine-based analgesia in the immediate postoperative period may respond to alternative agents such as meperidine or propoxyphene.

Hydrocodone:

Hydrocodone was first synthesized in 1920. It is derived from the opioid alkaloid thebaine. It has antitussive and analgesic properties [23]. Hydrocodone is approximately six times more potent than codeine on a weight-per-weight basis [24]. Hydrocodone is an oral semisynthetic mu opiate receptor agonist. Structurally, hydrocodone is a ketone derivative of codeine. Equipotent doses of codeine and hydrocodone have similar efficacy and severity of adverse side effects [17]. The combination of acetaminophen and hydrocodone are used together to treat moderate to severe pain. Combination formulations of hydrocodone are available in doses of 5, 7.5, and 10 mg (such formulations include Vicodin, Vicodin E.S., Norco, and Maxidone). Hydrocodone and ibuprofen have also been combined (Vicoprofen) for the treatment of moderate to severe pain. The usual dose of 5 to 10 mg is effective for ∼ 3 hours. A 5-mg dose of hydrocodone is equipotent to 30 mg of codeine. Also, a 4-g/d ceiling dose of acetaminophen within the combination agents establishes daily dose limitations. Side effects of hydrocodone include constipation, nausea, vomiting, and sedation.

Oxycodone:

Oxycodone is an oral semisynthetic opiate agonist derived from the opioid alkaloid thebaine. It has been in clinical use since the early 1900s. Its pharmacologic action is similar to that of morphine. Oxycodone, similar to hydrocodone, is a cogener to codeine. It is ∼ 10 to 12 times more potent than codeine on a weight-per-weight basis [24]. Because of resistance to extensive

first-pass metabolism, oxycodone is an excellent orally administered narcotic analgesic agent. Similar to other narcotic combination medications, acetominaphen-oxycodone formulations (Percocet, Roxicet, Tylox) work through a synergistic effect. Combinations produce additive analgesic effects compared to the same doses of either agent alone. Similar to the hydrocodone combination agents, increased dosage of oxycodone combination agents is limited by the maximum dose and ceiling effect of acetaminophen at 4 g/d. The typical dosage of oxycodone is 5 to 10 mg. Oral administration of acetaminophen-oxycodone has an onset of analgesia in 30 minutes and a peak analgesic effect in 90 minutes. The duration of analgesia is 3 to 4 hours. The metabolism of both drugs is mediated through cytochrome P450. Administration of other drugs, which affect these isoenzymes, may affect the efficacy and incidence of adverse reactions from this formulation. As in the case of codeine, a small percentage of nonresponders may be related to decreased CYP2D6 expression. A 5-mg dose of oxycodone is equivalent to 50 to 60 mg of codeine.

Oxycodone is indicated for the treatment of moderate to severe postoperative pain. As a solo agent, 5 to 7.5 mg of oxycodone is administered orally every 6 hours, as needed for pain. Side effects to oxycodone are similar to all centrally acting narcotic agonists and include constipation, nausea, vomiting, and sedation. It is worthy to note that oxycodone can elicit a significant euphoric effect and carries an increased potential for abuse in both solo and combination formulations. Recent reports have shown this problem to be increasing in severity in the United States [25]. Sustained release oxycodone compounds (eg, Oxycontin) are not indicated in the management of acute pain after dentoalveolar surgery.

Meperidine (Demerol):

Meperidine hydrochloride is a synthetic opiate agonist belonging to the phenylpeperidine class. Other members of this group include alfentanil, fentanyl, loperamide, and sufentanil. Meperidine is recommended for moderate to severe acute pain and has the unique ability to interrupt postoperative shivers and chills. According to the Agency for Health Care Policy and Research Clinical Practice Guideline, for acute pain management in operative procedures, meperidine is recommended only for use in brief courses. Meperidine should be considered as a second-line agent to treat acute pain. Meperidine is metabolized to normeperidine, a compound capable of inducing seizures at high concentrations. Meperidine is available in oral and parenteral formulations and was approved for use by the FDA in 1942.

Meperidine is primarily a kappa-opiate receptor agonist and has local anesthetic effects. Its affinity for the kappa receptor is greater than that of morphine. The oral form of meperidine undergoes extensive first-pass metabolism. To treat moderate to severe pain in adults, the dose is 50 to 150 mg po or IM every 3 to 4 hours. The drug has a short analgesic effect and a significant euphoric effect [24]. The recommended IV dose is 50 to 100 mg. After oral administration, the onset of analgesia is within 15 minutes and peak effects occur in 60 to 90 minutes. Protein binding is 65%, primarily to albumin and α-1-acid glycoprotein. In patients with normal hepatic and renal function, the half-life is 3 to 5 hours. As previously mentioned, meperidine is a reasonable alternative for the rare patients who have been determined to be nonresponders to codeine-derived analgesics or those with a true allergy to the codeine class. Its use needs to be limited to 10 to 14 days, however, because of the potential buildup of toxic normeperidine byproducts. Also, meperidine is strictly contraindicated in patients taking MAO inhibitor–type antidepressants.

Pentazocine (Talwin N_x):

Pentazocine is a synthetic opiate agonist-antagonist analgesic used to treat moderate to severe pain. This drug is considered the prototype of the agonist-antagonist class of analgesics, with a potency of approximately one sixth to one third that of morphine. It was approved for use by the FDA in 1967 and reformulated to include naloxone and approved for use in 1982. At therapeutic doses, pentazocine has less respiratory depression than morphine. It does have a tendency to produce dysphoric reactions. Pentazocine is an agonist at the kappa receptor and weak antagonist at the mu receptor. Its antagonism at the mu receptor is weaker than both butorphanol and nalbuphine. It is given orally, parenterally, or intramuscularly. It is well absorbed in the GI tract, and the onset of action is 15 to 30 minutes after administration. The analgesic effect of 50 mg of pentazocine is equipotent to 60 mg of codeine. The recommended oral dose is 50 mg every 3 to 4 hours.

Butorphanol (Stadol):

Butorphanol tartrate is a synthetic parenteral and intranasal opiate agonist-antagonist. There is good GI absorption of oral butorphanol, but it undergoes extensive first-pass metabolism, making its bioavailability low. Trans-nasal administration of butorphanol has an absolute bioavailability of 60% to 70% [26]. Although it is structurally related to morphine, it is more similar in action to nalbuphine. Butorphanol is used to treat moderate to severe acute pain. Butor-

phanol injection was approved in 1978; the nasal spray was approved in 1991. Although butorphanol was not a controlled substance in the United States when it was introduced, the DEA recommended in June 1997 that both the injection and the nasal spray be classified as a controlled substance.

Butorphanol is an agonist at the kappa receptors, but is a weak antagonist at the mu receptor. A recent study indicates that butorphanol delivered trans-nasally is an effective analgesic for postoperative pain. Butorphanol is administered trans-nasally by spraying once in one nostril. Each spray is equivalent to 1 mg. In this study, the threshold dose for adequate analgesia was 1 mg . A 2-mg dose produced better analgesia, with an increased incidence in adverse events, namely dizziness and drowsiness. Butorphanol is reportedly being considered as an option for pre- and intraoperative analgesia. Additional studies will be needed to establish the exact role of butorphanol in perioperative pain management [27].

The nonsteroidal anti-inflammatory drug class (NSAIDS)

Mechanism of action:

Nonsteroidal anti-inflammatory drugs (NSAIDS) have been used since the discovery of sodium salicylate in 1875 and acetylsalicylic acid (aspirin) in 1899 for the treatment of pain, fever, and inflammation. Most recently, these drugs have become quite diverse and more specific in their mechanisms of action. The anti-inflammatory and analgesic properties of these drugs without the narcotic-related side effects of drowsiness, constipation, respiratory depression, and addiction potential make NSAIDs very popular in the ambulatory dentoalveolar surgical patient. With regard to analgesia, NSAIDs primarily act peripherally at the site of tissue injury. As previously discussed in this chapter, a cascade of events occurs at the tissue level immediately after making a surgical incision. Inflammatory mediators such as histamine, serotonin, bradykinin, platelet-activating factor, interleukin-1, and derivatives of arachadonic acid metabolism such as prostaglandins, thromboxanes, and leukotrienes are released. These mediators have been found to sensitize peripheral nociceptors, leading to inflammatory pain and hyperalgesia. NSAIDs block this cascade of events, thus leading to a reduction in inflammation and pain perception.

NSAIDs exert their effect by inhibiting the synthesis of prostaglandins within the endoperoxide pathway. Inflammation will prompt the enzyme phospholipase A2 to break down cell membrane components and yield arachadonic acid. The endoperoxide

biosynthetic pathway leads to the metabolism of arachadonic acid and the synthesis of prostaglandins. The initial step of the endoperoxide pathway is driven by the enzyme cyclooxygenase (COX). Prostaglandins have varied physiologic effects that are both beneficial and detrimental to normal physiologic homeostasis. Beneficial effects of prostaglandins include maintenance of renal blood flow through the activity of prostacyclin, gastric mucin production and mucosal protection, and maintenance of platelet function. Conversely, pain, inflammation, fever, bronchial constriction, and decreased blood flow can also be attributed to the release of prostaglandins.

The enzyme cyclooxygenase (COX) has been identified as a major actor in the endoperoxide pathway. Cyclooxygenase is subdivided into two isoenzymes, COX-1 and COX-2. Physiologically, it has been determined that COX-1 is constitutively released and contributes to normal physiologic homeostasis. It provides the beneficial aspects of prostaglandin function previously mentioned. Alternatively, the isoenzyme COX-2 is released primarily after tissue injury and plays an instrumental role in tissue inflammation and pain mediation. Interleukin-1, tumor necrosis factor, lipopolysacharide, mitogens, and reactive oxygen intermediates are all mediators released after tissue injury which have been found to induce COX-2 enzyme activity [28].

NSAIDS have been designed over the years to inhibit enzymatic reactions in the endoperoxide cascade. Historically, most of the drugs were nonselective cyclooxygenase inhibitors. Sodium salicylate, aspirin, ibuprofen, and others are included in this group. During the past 10 years, COX-2 selective inhibitors have been developed. These drugs are aimed at blocking the inductive, detrimental effects of the COX-2–mediated prostaglandins while maintaining the physiologically beneficial effects of the COX-1 isoenzyme. Specific COX-2–inhibiting medications include rofecoxib (Vioxx) and celecoxib (Celebrex). These medications are slowly finding their place in the management of mild to moderate postoperative pain, with diminished side effect profiles when compared to the nonspecific cyclooxygenase inhibitors [29].

Adverse responses to NSAIDs are directly related to their mechanism of action. The most common are gastrointestinal disturbances, gastric irritation, increased bleeding time, and renal impairment. Less common effects are allergic reactions and asthma. These effects are all related to prostaglandin inhibition. Gastrointestinal adverse effects are the most common adverse reaction to NSAIDs and constitute the greatest risk of death [30]. Patients with peptic

ulcer disease and other disturbances in gastrointestinal mucosal integrity should avoid the usage of NSAIDs altogether. Increased risk of postoperative hemorrhage has been reported with the usage of NSAIDs mainly because of the drugs' antiplatelet effects. Spontaneous hemorrhage in the postoperative period is rarely the cause of NSAID use alone, but may be significant in patients with thrombocytopenia, underlying bleeding dyscrasias, or concomitant use of anticoagulant drugs [28]. It is also worthy to note that patients who are taking aspirin daily for its antithrombotic effects should discontinue use of the drug for at least 5 days before the scheduled date of surgery. Also, NSAIDs' effect on renal function is related to inhibition of renal prostacyclin, resulting in decreased renal blood flow and decreased glomerular filtration rate. This is an important issue in patients with underlying renal compromise, and the elderly who may be dependent on the vasodilatory effect of prostaglandins for baseline renal function [30]. Less commonly, aspirin and other NSAIDs can precipitate acute bronchospasm in asthmatic patients. Approximately 5% to 10% of adult asthmatics may be sensitive to NSAID administration [30]. When selecting NSAIDs for postoperative analgesia, the practitioner must evaluate not only which drug is most appropriate for a patient, but also the overall risk profile with regard to the above-mentioned issues.

Acetylsalicylic acid (aspirin):

Aspirin is the salicylic ester of acetic acid. Its uses are for analgesia, anti-inflammatory action, antipyretic action, and antithrombosis. Aspirin is the classic nonsteroidal anti-inflammatory drug. It was first introduced to medicine in 1899. It nonselectively inhibits cyclooxygenase (COX-1 and COX-2). For a long time, aspirin has been beneficial in oral and maxillofacial surgery for its anti-inflammatory action by inhibiting the formation of prostaglandin E and F subtypes. This results in decreased vasodilation, tissue permeability, edema, and leukocytic infiltration. Its analgesic activity is likely the result of prostaglandin inhibition in the periphery at the site of tissue injury. There may also be a centrally mediated analgesic component to aspirin, although this mechanism has not been clearly elucidated.

Aspirin dosing for postoperative oral surgical pain is 325 to 650 mg po every 4 hours or 1000 mg po every 6 hours, as needed for pain in the adult patient. Aspirin therapy is effective for mild to moderate pain. Aspirin has fallen out of favor as a primary drug of choice in postoperative analgesia, mainly because of its significant and permanent effect of platelet inhibi-

tion. The administration of aspirin before third molar surgery has actually been shown to increase postoperative edema. This effect is likely due to decreased platelet aggregation. It is also associated with the classic adverse effects of the NSAID drug class, such as gastroenteric irritation and ulceration, renal impairment, and the potential for hemorrhage occurrence. Besides observing standard precautions with the usage of all NSAID drugs, absolute contraindications for aspirin usage include the incidence of aspirin-induced nasal polyps, salicylate hypersensitivity, and urticaria. It should also be used with extreme caution in asthmatic patients [18].

Ibuprofen:

Ibuprofen is an oral NSAID with anti-inflammatory and antipyretic actions. It was initially approved for usage in 1974. It is most effective as an analgesic agent for mild to moderate postoperative pain. Similar to the other NSAIDs, its analgesic properties result from the peripheral inhibition of prostaglandins. Ibuprofen is a nonselective cyclooxygenase inhibitor and is associated with the classic adverse effects of the NSAID drug class, including gastroenteric irritation and ulceration, renal impairment, and alterations in platelet function.

Dosing of ibuprofen in adults and adolescents is 400 mg po every 4 to 6 hours, as needed for pain. This can be increased to 600 mg for severe pain. The half-life of ibuprofen is 2 to 5 hours. Absolute contraindications to ibuprofen are similar to other NSAIDs. They are to be avoided in asthmatic patients, aspirin-induced nasal polyps, salicylate hypersensitivity, and urticaria.

Ibuprofen provides excellent pain relief in postsurgical oral and maxillofacial surgery patients. It can be used as a transition drug after the need for pure or combination narcotic based pain control is obviated. Ibuprofen is available in combination form with hydrocodone (Vicoprofen) and provides significant relief of moderate to severe pain after third molar impaction surgery. This is accomplished by combining the centrally mediated analgesia of a narcotic with the peripherally mediated activity of an NSAID. Ibuprofen does not have the permanent effect on platelet activation that aspirin does, but nonetheless is associated with the potential for postoperative hemorrhage. This was demonstrated in a pediatric population after tonsillectomy [31]. This should be a consideration when selecting any NSAID.

Naproxen (Naprosyn):

Naproxen is an NSAID with analgesic and antipyretic activity. It is a propionic acid derivative related structurally to ibuprofen. It was approved for use by the FDA in 1976 and became available over the counter in 1994 (Aleve). Like ibuprofen, naproxen is better tolerated than aspirin with regard to NSAID-realated side effects. Naproxen is a nonselective inhibitor to the enzyme cyclooxygenase, providing peripheral analgesic properties by inhibiting the in vivo synthesis of prostaglandins. Nonspecific inhibition of the COX-1 isoenzyme contributes to this agent's adverse side effects, including decreased gastric mucosal cytoprotection, impaired renal function, and alteration in platelet function.

Naproxen is administered by mouth and has a half-life of 10 to 20 hours. It is an excellent drug of choice for mild to moderate pain, and compared to aspirin and ibuprofen, its extended half-life increases patient compliance through less frequent dosing requirements. The oral dose of naproxen sodium is initially 550 mg po, followed by 275 mg po every 6 to 8 hours, as needed. The maximum initial daily dose of naproxen sodium is 1375 mg and therefore should not exceed 1100 mg. Naproxen is available in enteric-coated and sustained-release tablets.

Ketorolac (Toradol):

Ketorolac is a NSAID that provides analgesic and anti-pyretic activity. It is similar in chemical structure to indomethacin. It was approved for parenteral usage in 1989 and oral usage in 1993. Like other NSAIDs, ketorolac is a peripheral analgesic agent. It inhibits prostaglandin synthesis through nonselective inhibition of cyclooxygenase. Ketorolac is an excellent drug for short-term post-operative pain control. Parenteral administration in the immediate postoperative period has been compared to morphine for adequacy of pain relief without the classic narcotic-related side effects [32].

Ketorolac is administered in parenteral and oral forms. Dosages are 30 mg IV or 60 mg IM in healthy adults who are greater than 50 kg in total body weight. It can be given as a single dose in the immediate postoperative period. If multiple parenteral dosing is desired, the drug can be repeated every 6 hours, with the maximum dose not to exceed 120 mg. Oral ketorolac can be administered for a maximum of 5 days postoperatively. In patients who have received IV or IM doses of ketorolac in the immediate postoperative period, 20 mg of ketorolac should be followed by 10 mg of the drug every 4 to 6 hours. The maximum oral daily dose should not exceed 40 mg.

Ketorolac has been found to be an excellent alternative to narcotics in the ambulatory surgical patient. It is best administered after completion of the

surgical procedure. Similar to the other NSAIDs, contraindications and side effects are related to the drug's nonspecific inhibition of the enzyme cyclooxygenase. Ketorolac has been found to elicit more profound adverse side effects than other classic NSAIDs, probably because of its increased potency. Absolute contraindications include asthma, breast feeding, cerebrovascular disease, dehydration and/or renal impairment, GI bleeding or peptic ulcer disease, aspirin-induced nasal polyps, urticaria, or salicylate hypersensitivity.

Cyclooxygenase 2 (COX-2) inhibitors:

The Food and Drug Administration in the United States has approved COX-2 inhibitors for the management of osteoarthritis, rheumatoid arthritis, primary dysmenorrhea, and acute pain management in adults. COX-2 inhibitors minimize the inflammatory response by inhibiting the release of the enzyme cyclooxygenase-2. COX-2 is released after tissue injury in macrophages, monocytes, synovial cells, leukocytes, and fibroblasts [29]. These COX-2 selective therapeutic agents alternatively leave the cytoprotective COX-1 enzymes intact. This provides protection against such side effects as GI tract irritation and decreased platelet aggregation, which are commonly observed with the nonselective cyclooxygenase-inhibiting agents.

Advantages of COX-2–inhibiting agents include extended half-lives, decreased frequency of dosing, and little to no effect on bleeding parameters (because of their minimal effect on platelet aggregation). COX-2 inhibitors are rapidly becoming excellent therapeutic alternatives to standard nonspecific COX inhibitors such as ibuprofen in the postsurgical and acute dental pain model. Disadvantages of the COX-2 inhibitors include the relatively high price of these drugs [29]. Continued research and drug development is being done with COX-2–inhibiting agents, and they appear to have a very promising role in the future of postoperative and pre-emptive analgesia.

Celecoxib (Celebrex):

Celecoxib (Celebrex) is a COX-2 inhibitor and has been found to be most beneficial in the management of chronic pain. It offers the advantage of having an extended half-life, allowing limitation of the dose frequency to once or twice a day. A recent study evaluating the use of celecoxib after orthopedic surgery demonstrated that 400 to 600 mg of celecoxib administered orally for 2 to 5 days after surgery was as effective as 10 mg of hydrocodone and 1 g of acetaminophen given orally 2 to 3 times daily [33]. Alternatively, other studies have shown

celecoxib to be limited in efficacy when used for the management of acute pain after third molar extraction. It is evident that additional studies will be needed to clarify this issue.

Celecoxib is administered in 200-mg daily doses or 100 mg twice daily in adults. It is used mainly in the management of chronic joint pain. As described above, higher doses have been described for the management of severe postoperative orthopedic pain; 200 mg of celecoxib has been found to be equivalent to 400 mg of ibuprofen [29]. Absolute contraindications to celecoxib include aspirin-induced nasal polyps, asthma, salicylate and sulfonamide hypersensitivity, and urticaria.

Rofecoxib (Vioxx):

Similar to celecoxib, rofecoxib (Vioxx) is a COX-2–inhibiting agent that has been found to act comparably to 400 mg of ibuprofen, but has a more profound analgesic effect in postoperative third molar patients [34]. This agent encouragingly provides measurable analgesia for up to 24 hours after surgery, whereas nonselective COX inhibitors such as ibuprofen tend to provide a maximum of 4 to 6 hours of postoperative analgesia. Studies comparing rofecoxib, celecoxib, ibuprofen, and placebo confirmed that 50 mg of rofecoxib had prolonged duration, lack of platelet inhibition, and superior analgesic efficacy [35]. For these reasons, rofecoxib has also been suggested as a good agent for pre-emptive and postoperative analgesia in the dentoalveolar surgery patient. Future studies in this area should elucidate this point further.

The recommended initial dose of rofecexib is 50 mg once a day, then 50 mg each day after surgery, as needed for pain. The effects of postoperative rofecoxib therapy beyond 5 days have not been described clearly at this point. Absolute contraindications to this medication include aspirin-induced nasal polyps, asthma, salicylate hypersensitivity, and urticaria.

VI. Summary

Oral surgical procedures provide a unique model for the study of pharmacology and pain. The role of central and peripheral sensitization and other modulating factors affecting the acute pain mechanism provide various opportunities for pharmacologic intervention in pain management. The concept of preemptive analgesia is rapidly being incorporated into the management of the ambulatory surgical patient and has lead to hastened recovery and less pain medication requirements. The modern practitioner

has access to a variety of pharmacologic agents for the treatment of acute pain. Opioids, NSAIDs, combination formulations, and new analgesic agents are constantly being put to the test in light of the many new discoveries in neurophysiology and pharmacology research. Basic knowledge of how these agents exert their effects should lead to the most appropriate selection of pharmacotherapy for each patient.

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