ABSTRACT

Pain is the leading reason for individuals to seek dental care and understanding factors in pain response assists in pain management. Some dental services, including those involving tooth preparation, can result in postprocedure discomfort leading to a recommendation for analgesic therapy following treatment. Analgesia is defined as pain relief by inhibiting specific pain pathways and drugs to relieve pain are analgesics. Over the counter agents are efficacious agents for most dental pain with ibuprofen and acetaminophen commonly recommended. Considerations for analgesic recommendations, based on the medical history, scientific evidence of efficacy, and patient preferences are discussed.

Keywords: Analgesic, Acetaminophen, Nonsteroidal anti-inflammatory agent, Neuromatrix theory of pain.

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INTRODUCTION

The most common complaint causing individuals to seek oral healthcare services is pain. Consequently, clinicians have a primary obligation to provide effective treatment and relieve associated pain. Pain is an unpleasant sensory and emotional experience associated with tissue injury or infection, resulting in cellular damage. Analgesia is defined as pain relief from inhibiting specific pain pathways and drugs to relieve pain are analgesics. Management of pain requires an understanding of its complexity, an appreciation for factors that determine its occurrence in the clinical setting, and implementation of sound clinical and pharmacological strategies.

Pathways of pain involve nociceptors, or pain receptors, which are nerve endings that respond to painful stimuli. Nociceptors are found in all tissues except the brain, but they transmit information to the brain. Nociceptors are dense in oral mucosa and in the dental pulp. Stimuli that provoke pain receptors can be mechanical, thermal or chemical. Any stimulation of the pulp is painful whether the stimulation comes from heat, cold, vibration or pressure (such as the pressure from inflammation or infection). Pain perception occurs when pain impulses travel over nerve fibers, through the spinal cord to the brain (or central nervous system). Impulses travel through the limbic system (emotional center) and ultimately to the cerebral cortex where pain is perceived and interpreted. At the same time by means of stimulation of efferent fibers from the trigeminal nerve, signal transmission is modulated to inhibit nociceptive impulses in the brain. This results in release of endogenous endorphins to cause analgesia. Endorphins are the modulators that allow an athlete to continue playing after sustaining an injury. They vary from person to person, with the result that different persons will experience different levels of pain. In 1999, a new theory of pain, consistent with the idea of the gate control theory of pain, addressed a ‘neuromatrix theory’. In this theory of pain it is proposed each person has a genetically built-in network of neurons called “body-self” neuromatrix. Just as each person is unique in physical appearance, the individual’s matrix of neurons is unique and affected by various facets of physical, psychological and cognitive make-up, including prior experience. In this theory, pain experience does not reflect a simple relationship between tissue damage and pain response. The pain experience can be divided into acute and chronic types of pain. Acute pain is described as sharp, stabbing pain while chronic pain is often dull, aching and longstanding.

During clinical dental procedures mechanically induced pain can be managed with local anesthetic agents, both topically applied and injected. This article will discuss nonprescription oral analgesic therapy considerations for pain of inflammatory origin, infection and potential post-treatment pain from clinical procedures.

PHYSIOLOGY OF PAIN OF INFLAMMATORY ORIGIN

A review of pain physiology assists understanding principles of pain management. Variation in an individual response to pain is a relevant factor to consider, also. Following tissue injury, the physiologic response stimulates macrophages, neutrophils and other cells of the immune system, to invade the damaged area and remove cellular debris. Another objective of neutrophil infiltration is to prevent or combat infection. The inflammatory process triggers the formation of prostaglandins, and other endogenous chemicals that enhance the effects of inflammation (such as substance P, histamine, bradykinin, cytokines and leukotrienes) on pain receptors. Traumatic injury provokes a sympathetic nervous system response of vasoconstriction, which decreases microcirculation in the injured tissue, producing ischemia and further amplifying pain transmission. Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and
analgesics and adjuvant drugs (Table 1). An adjuvant drug may either enhance the efficacy of an analgesic or it may have an analgesic activity of its own. For example, caffeine in doses of 65 to 200 mg enhances the analgesic effect of acetylsalicylic acid (ASA or aspirin), acetaminophen (APAP), and ibuprofen in dental and other acute pain syndromes. Hydroxyzine, an antihistamine, in doses of 25 to 50 mg enhances the analgesic effect of opioids in postoperative pain and significantly reduces the incidence of opioid-induced nausea and vomiting. Corticosteroids, through their anti-inflammatory effects, can produce analgesia in some patients with pain of inflammatory origin. These adjuvant drugs are prescribed by the dentist.

Cyclooxygenase (COX) Inhibitors

The COX-inhibiting agents—COX-1 (ASA and other nonsteroidal anti-inflammatory agents, such as ibuprofen), COX-2 [celecoxib (Celebrex)], and COX-1 variant [APAP (Tylenol)]—are considered the drugs of choice for dental pain.

Prostaglandins are endogenous fatty acid substances known to induce pain perception, influence inflammation, stimulate elevated body temperature, and affect the tone and permeability of blood vessels. Bengt Samuelsson won the Nobel Prize for Physiology in 1982 for work on providing an exact picture of how the body generates prostaglandins. Samuelsson and collaborators explained the biochemical reactions that are now used to develop painkillers and anti-inflammatory drugs with a good safety profile (fewer adverse effects). The group identified the prostaglandins tree with its branches, showing that prostaglandins are routinely synthesized when arachidonic acid, a naturally occurring chemical in the cell membrane, is acted on by COX-1 enzymes. Some prostaglandin substances produced by the enzymes are beneficial to the body, such as protective COX-1 enzymes in the mucosa of the gastrointestinal (GI) tract. These interrupt the production of other substances that can cause adverse drug effects (GI pain, GI bleeding).

When injury occurs, a chemical signal instructs macrophages and other inflammatory cells to increase activity of the COX-2 enzyme, which also acts on arachidonic acid. COX-1 is found in most tissues, including platelets, and it is thought to protect the gastric mucosa (although it inhibits clotting, thereby increasing bleeding). COX-2 is found primarily in the brain and kidneys and can be induced in other tissues (especially in association with inflammation), but it is not found in abundance in platelets (so no tendency to increase bleeding). COX-1 variant is found primarily in the CNS and causes analgesia primarily through that mechanism.
At least three COX-inhibiting isomers are known to block prostaglandin synthesis: COX-1, COX-2 and COX-1 variant. To varying degrees, ASA and nonselective NSAIDs block all COX isomers. In therapeutic doses, celecoxib selectively inhibits only the COX-2 isoenzyme. APAP is a relatively weak inhibitor of peripheral prostaglandin biosynthesis, but it is highly effective in inhibiting COX-1 variant in the CNS. COX inhibitors alter sensitivity (i.e. increase the pain threshold) to irritating stimuli, but all have a ceiling dose for the maximum analgesic effect. Most of these drugs can be found at the drug store, sold over-the-counter (OTC). When these agents do not provide adequate pain relief, opioid agents (hydrocodone, codeine derivatives) can be prescribed by the dentist.

Absorption
Cyclooxygenase (COX) inhibitors are rapidly absorbed from the stomach and the upper small intestine. Effective plasma concentrations are reached in 30 to 60 minutes and peak concentrations at about 2 to 3 hours. The rate of absorption is determined by the product formulation and pKa of the drug (the pH at which the drug is 50% ionized), the pH in the stomach, vascularity of the absorptive surface (upper small intestine), and gastric emptying time. Because absorption occurs primarily by passive diffusion of lipid-soluble molecules across the gastrointestinal mucosal membranes, the rate of absorption is decreased in an alkaline environment, such as the pH change that occurs when antacid products are taken. The presence of food can delay absorption.

Distribution
After absorption, COX inhibitors are distributed throughout most body tissues and fluids, and cross the placenta. They are metabolized in many tissues but particularly in liver endoplasmic reticulum and mitochondria. The metabolism of therapeutic doses normally follows first-order kinetics. First-order kinetics is a common biologic event where compounds rely on metabolic processes that are first-order in character and operate well below enzyme saturation concentration. However, after larger doses, the enzymes that metabolize these drugs can become saturated, leading to increased half-lives. Additional dosing in this situation can result in overdosage with serious adverse effects.

Excretion
As with most drugs, metabolites are excreted primarily by the kidneys. In the presence of kidney disease, COX-inhibitor molecules may not be excreted normally. In this situation additional dosing can lead to overdosage with serious adverse effects.

Primary Line of Treatment
Aspirin (ASA) is the standard for the comparison and evaluation of orally effective analgesics. APAP is as effective as ASA with similar potency and time-effect curve. ASA, at a dose of 650 mg, and APAP, at a dose of 650 mg, are equianalgesic to 200 mg of ibuprofen. Ibuprofen 200 mg, is equianalgesic to 220 mg of naproxen sodium (Aleve). Consequently, OTC formulations of ASA, APAP, ibuprofen, or naproxen sodium are the drugs of choice for the management of mild odontogenic pain.

Aspirin
Despite its proven efficacy, ASA has gained a poor reputation with many clinicians and patients. This reputation, however, seems to be based more on an exaggerated notion of the drug’s potential adverse effects than on its pharmacological properties. The traditional adult single dose of ASA is 650 mg every 4 hours. Single doses larger than 1300 mg are above the ceiling dose, do not increase pain relief and may prove toxic. For children, the appropriate dosage is 81 to 165 mg, supplied as a chewable tablet, elixir, or drops; given in 4 to 6 doses, not to exceed 1200 mg/day. For adults, the daily dose should not exceed 4000 mg.

Acetaminophen
At ceiling doses, APAP is equal in analgesia with ASA for the relief of mild-to-moderate odontogenic pain. It is only a weak anti-inflammatory agent, but appears to be more effective against COX effects in the CNS. This fact may account for its ability to reduce fever and relieve pain, with minimal effect on peripheral inflammation. The frequency of adverse reactions to therapeutic doses is somewhat less than that associated with ASA. The main danger is primarily with APAP overdose. The maximum dose of APAP is 4 gm per day. Overdose of APAP is currently a problem in the United States.

Toxicity of Acetaminophen
The Food and Drug Administration (FDA) issued a final ruling on April 24, 2009 to require manufacturers of OTC pain relievers, antirheumatic agents, and fever reducers to revise their labeling of these analgesic products. The required labeling would include warnings about potential safety risks when taking the drugs, such as liver damage with excessive doses of APAP and internal bleeding with normal doses of NSAIDs. The FDA stated in the proposed rule that when labeled appropriately and used as directed, OTC analgesic agents are safe and effective drug products.
that benefit tens of millions of consumers every year and that these products should continue to be available to consumers in the OTC setting.9

Two reasons for APAP overdoses have been proposed.9 One theory is based on the fact that APAP tablets originally were dispensed in a 325 mg tablets. Then during the 1980s, the manufacturer produced a 1000 mg tablet. Unwary consumers may have purchased the ‘new’ product, unaware of the increased dosage per tablet, and swallowed two 1000 mg tablets in the same manner of formerly taking two 325 mg tablets. With this increased dosage, overdose could develop within a few days. Another theory involves opioid combinations with APAP as the additional drug in the combination. A patient may take the prescription analgesic and, if pain is still present, supplement that product with what the patient considers a ‘safe drug’ of APAP, thereby getting APAP from both products.9 The adverse effect occurs when a toxic, highly reactive metabolite of APAP accumulates in the liver and causes serious, irreversible and occasionally fatal liver damage.8

Dosage

The traditional adult single dose of APAP is 650 mg every 4 hours.8 However, a ceiling dose of 1000 mg is usually more effective than 650 mg.4 For children, the single dose is 80 to 120 mg, depending on the patient’s age and weight. The daily dose should not exceed 4000 mg for adults and 1200 mg for children.4

Ibuprofen, Naproxen, Celecoxib

COX-1 inhibitors alone, in combination with APAP, or in combination with codeine or hydrocodone are the drugs of choice for the management of moderate-to-severe odontogenic pain.4 In the management of acute moderate-to-severe odontogenic pain, full doses of COX-1 inhibitors (e.g. 400 mg ibuprofen, 440 mg naproxen sodium) are as effective as, or more effective than, full doses of ASA or APAP.5,7 Some also have been shown to be as effective as, or more effective than, oral opioids, such as codeine, hydrocodone, propoxyphene, and pentazocine, in combination with ASA or APAP.5 Because of this lack of efficacy (and placement of the drug as a controlled substance) propoxyphene has been removed from the US market.

Ibuprofen, 400 mg, has been shown to be more effective than ceiling doses of ASA or APAP, more effective than 60 mg of codeine, and more effective than 650 mg of ASA combined with 60 mg of codeine or 600 mg of APAP combined with 60 mg of codeine.4,5 Ibuprofen in doses between 400 and 800 mg has a longer duration of action and may have a dose-dependent increase in its analgesic and anti-inflammatory efficacy. It also has been shown that 650 mg of APAP in combination with more than 200 mg of ibuprofen is more effective than either 650 mg of APAP or 200 mg of ibuprofen alone.7 The current gold standard for the treatment of surgically induced dental pain is ibuprofen.7 The maximum adult daily dose of ibuprofen is 2400 mg.8

Naproxen sodium, 220 mg, is equi-analgesic to 650 mg of ASA, but has longer duration of action; and 550 mg of naproxen sodium is superior to 650 mg of ASA.8 Naproxen sodium, 220 and 440 mg, is equi-analgesic with 200 and 400 mg of ibuprofen respectively, but with a longer duration of action. The maximum adult daily dose of naproxen sodium is 1320 mg.8

Celecoxib is a selective COX-2 inhibitor whereas the agents discussed above are nonselective COX inhibitors. Celecoxib 200 mg, is equi-analgesic to 650 mg of ASA, and appears to have less serious GI toxicity than nonselective COX inhibitors.5 Single-dose trials have found celecoxib 200 mg more effective than placebo, but less effective than naproxen sodium 550 mg or ibuprofen 400 mg in oral surgery pain.5 The maximum adult daily dose of celecoxib is 400 mg.8

Adverse Drug Events

Intolerance to COX inhibitors is most likely to occur in individuals with a history of asthma, nasal polyps and chronic urticaria.4,5,7 A single dose of these agents can precipitate asthma in susceptible patients, probably related to the agents ability to inhibit COX, which results in increased levels of leukotrienes. A history of rhinorrhea, urticaria, angioedema, or bronchospasm occurring within 3 hours after exposure is an acceptable method of determining intolerance. APAP is usually well tolerated in recommended therapeutic dosages. However, an erythematous or urticarial skin rash may occur occasionally, sometimes accompanied by fever and mucosal lesions.7 The mechanism of intolerance to APAP is unknown. Uncommonly, COX inhibitors can cause immunoglobulin E (IgE)-dependent hypersensitivity reactions leading to hypotension and respiratory collapse.7

Therapeutic doses of ASA and other COX-1 inhibitors can cause GI distress, nausea and vomiting.4,7 They can exacerbate the symptoms of peptic ulcer disease and with chronic use, GI bleeding, ulceration and perforation can occur. Gastric bleeding induced by ASA and other COX-1 inhibitors is painless and may not be recognized by the patient. A common sign is dark stools. Bleeding in the GI tract can lead to iron-deficiency anemia. COX-2 inhibitors have been associated with abdominal pain, diarrhea and dyspepsia.7
COX-1 inhibitors impair platelet adhesion to tissue and platelet aggregation. This occurs primarily through the inhibition of thromboxane A2 synthesis. At usual therapeutic doses, ASA irreversibly inhibits platelet function for the lifetime of the platelet (about 8 to 10 days). ASA should be avoided in patients with severe liver disease, vitamin K deficiency, and hemophilia, as well as during treatment with anticoagulants, such as warfarin, because severe hemorrhage may result. In contrast to ASA, platelet inhibition with ibuprofen and naproxen is reversible and occurs only while the drug is in the patient’s system. Platelet function returns to normal when most of the drug has been eliminated from the body. However, in the presence of bleeding abnormalities (hereditary, acquired or drug-induced), the antiplatelet effect of these agents may contribute to serious bleeding. APAP appears to be a suitable substitute in patients with peptic ulcer disease, hemophilia, or other bleeding disorders, and for those individuals taking anticoagulants.

COX inhibitors decrease the synthesis of renal prostaglandins, decrease renal blood flow, cause fluid retention, and may precipitate renal failure in susceptible patients. Risk factors include old age, chronic renal insufficiency, congestive heart failure, hepatic cirrhosis and concurrent use of diuretic drugs. Renal toxicity is uncommon, even with high therapeutic doses and prolonged use of ASA. However, nephrotic syndrome, acute interstitial nephritis, and an increased incidence of end-stage renal disease have been reported in patients treated chronically with other COX-1, COX-2 and COX-1 variant inhibitors (APAP).

The only COX-2 inhibitor still available in the US is celecoxib. Selective COX-2 inhibitors may have a prothrombotic effect and other COX-2 inhibitors (rofecoxib [Vioxx], valdecoxib [Bextra]) were associated with increased cardiovascular events and taken off the US market by the FDA. Celecoxib may reduce some of the adverse effects associated with COX-1 inhibitors, however, recent evidence of potential cardiovascular events associated with COX-2 inhibitors mandates caution in the use in the oral healthcare setting.

Pregnancy

Although there is no evidence that therapeutic doses of ASA cause fetal abnormalities other than reduced birth weight, the drug should be avoided throughout pregnancy. In addition, excessive intrapartum and postpartum maternal bleeding with a potential for life-threatening hemorrhage has been noted when ingestion has occurred within 5 days of delivery. As with ASA, an increased incidence of postpartum bleeding has been observed in patients taking other COX-1 inhibitors and they also may have potentially serious effects on the fetus. In pregnant patients, APAP is a suitable substitute for ASA and other COX-1 inhibitors in the management of mild-to-moderate pain.

Children

An association has been reported between Reye syndrome (acute hepatic necrosis) and the administration of ASA to children and teenagers with acute viral illnesses (e.g. influenza, chickenpox). For this reason APAP may be a safe alternative for elevated fever or for pain.

Alcohol Abuse

It has been suggested that in patients who abuse alcohol on a daily basis, APAP should be used at a maximum dose of 2000 mg daily. There are clinical studies which suggest alcohol abusers can use APAP on a short-term basis, and it is recommended as the best choice for the alcohol abuser with GI disease. Nonopioid analgesics, such as APAP, should be recommended for any patient who has abused narcotic substances in the past or is a current alcohol abuser.

Clinical Application of Pharmacology Principles

When drugs are prescribed dosing instructions should be explained to the patient. As well, an investigation should be completed for interactions with agents to be used in the treatment and drug effects relevant to oral procedures when medications are reported in the medical history.

Drug Prescription

Explanations to the patient should be provided on how to use a medication and on possible side effects or warnings with the drug. This includes ensuring that the patient understands the instructions on how much to take and when to take oral dose forms or instructions for applying topical dose forms. Safety issues include ensuring there are no allergy risks and no potential drug interactions with drugs currently used. The written prescription should be examined for accuracy of information to verify completeness and dose information. For example, due to a potential paradoxical sensitivity to CNS-depressant drugs in the elderly, the dose of opioids in the elderly population is advised to be 1/4th to half the adult dose.

Drug Administration

Before administering any drug, several safety issues should be considered, including a history of allergy to drugs in the
classification. In addition the drug profile on the health history should be examined for other drugs which could interact with the drug planned for use. Analyzing the medical history for medical conditions that contraindicate use of the vasoconstrictor or situations where vasoconstrictors should be used with caution, becomes paramount. Strict attention to the concentration of the vasoconstrictor in the preparation is necessary to select wisely.

The administration of many products can be understood by reading the product information, but the practitioner should always think about safety precautions, as well. For example, if peptic ulcer disease is reported on the health history, recommending ASA could cause increased GI bleeding, resulting in a serious medical issue for the patient.

**Patient Management**

Since the 1990s drug references including clinical considerations for dentistry have been available. The side-effect profile should be reviewed for relationships to appointment procedures. Some examples are:

- Low blood pressure: Incorporate strategies into the end of each appointment to prevent orthostatic hypotension.
- When xerostomia is possible, examine the mouth for evidence of caries and candidiasis and question the patient to determine, if dry mucosal tissues are a problem. If so, salivary stimulants (e.g. Salagen) can be prescribed or over-the-counter salivary moisturizer product information can be recommended.
- When vital signs might be affected, measure and evaluate blood pressure, pulse, and respiration values for normal limits and determine risk of vasoconstrictor concentrations, as well as risk for stroke.
- When antibiotic prophylaxis is indicated, question the patient about what drug was taken prior to appointment, what dosage was taken, and when it was taken in relation to the appointment time. Record this information in the treatment record to verify the issue was addressed.

**CONCLUSION**

In practice, the benefit of any particular analgesic agent in a specific patient will be determined by the degree of analgesia produced, balanced with potential adverse effects. Before recommending an OTC analgesic, clinicians should consider the degree of potential pain, the cultural and emotional characteristics of the individual, and the medical condition or age of the patient. Determining what has worked in the past may be a good ‘rule of thumb’ to follow when the patient requests advice for posttreatment pain relief. It is good practice to record drug information (generic name, dose administered) relevant to oral healthcare into the treatment record.

**REFERENCES**


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