Chapter 5

Nonopioid (Nonnarcotic) Analgesics

Chapter 5 Outline

- Nonopioid (Nonnarcotic) Analgesics
  - Pain
  - Classification
  - Salicylates
  - Nonsteroidal antiinflammatory drugs
  - Acetaminophen
  - Drugs used to treat gout

Nonopioid (Nonnarcotic) Analgesics

- Haveles (p. 49)
  - Pain control is of great importance in dental practice
  - Pain is often the issue that brings a patient to the dental office
  - Conversely, pain may keep the patient from seeking dental care
  - The dental health care provider must be able to recognize and evaluate a patient's need for medication

Pain

- Haveles (p. 49)
  - Pain is the means by which the body is made urgently aware of tissue damage
  - Pain is a diagnostic symptom of an underlying pathologic condition
  - The two components of pain are perception and reaction
    - Perception: the physical component
    - Reaction: psychologic component

Classification

- Haveles (pp. 50) (Fig. 5-2)
  - Analgesic agents can be divided into two groups
    - Nonopioid, nonnarcotic, peripheral, mild, and antipyretic analgesics
    - Opioid, narcotic, central, and strong analgesics

cont’d…
Classification

- An important difference between nonopioid and opioid analgesics is the site of action
  - Nonopioid analgesics act primarily at peripheral nerve endings, although their antipyretic effect is mediated centrally
  - Opioids act primarily in the central nervous system (CNS)
- Another difference is the mechanism of action
  - Nonopioid analgesics inhibit prostaglandin synthesis
  - Opioids affect the response to pain by depressing the CNS

Salicylates

- Acetylsalicylic acid
  - Chemistry
  - Mechanism of action
  - Pharmacokinetics
  - Pharmacologic effects
  - Adverse reactions
  - Toxicity
  - Drug interactions
  - Uses
  - Dose and preparations
- Other salicylates
  - Difunisal

Chemistry

- Acetylsalicylic acid (ASA, aspirin) is broken down into acetic acid and salicylic acid
  - Acetic acid imparts the vinegar odor to a bottle of aspirin

Mechanism of Action

- Aspirin’s analgesic, antipyretic, antiinflammatory, and antiplatelet effects are related to the ability to inhibit prostaglandin synthesis
  - Aspirin inhibits cyclooxygenase (COX) to block production of prostaglandins
- Prostaglandins can sensitize pain receptors to substances such as bradykinin
  - A reduction in prostaglandins results in a reduction in pain
Pharmacokinetics

- Haveles (pp. 51-52)
  - Aspirin is rapidly and almost completely absorbed from the stomach and small intestine
  - Widely distributed into most body tissues and fluids
  - The half-life varies with the dose because a constant amount rather than constant percentage is metabolized per hour
  - This type of metabolism is called zero-order kinetics

Pharmacologic Effects

- Haveles (pp. 52-53) (Figs. 5-6, 5-7, 5-8, 5-9)
  - Analgesic: relieves mild to moderate pain
  - Antipyretic: reduces fever by inhibition of prostaglandin synthesis in hypothalamus; no effect on normal body temperature
  - Antiinflammatory: causes decreased erythema and swelling
  - Uricosuric: large doses produce uricosuric effect, small doses produce uric acid retention
  - Antiplatelet: irreversibly binds to platelets, depending on dose, can inhibit either prostacyclin (inhibit aggregation) or thromboxane A₂ (stimulates aggregation)

Adverse Reactions

- Haveles (pp. 53-54) (Table 5-1)
  - Gastrointestinal effects: may be simple dyspepsia, nausea, vomiting, or gastric bleeding
  - Bleeding: interferes with clotting mechanism by reducing platelet adhesiveness
  - Reye syndrome: in children and adolescents with either chickenpox or influenza, aspirin has been associated with Reye syndrome

- Hepatic and renal effects: rarely, aspirin can produce hepatotoxicity
  - Renal papillary necrosis and interstitial nephritis is associated with use of certain analgesics
  - Pregnancy and nursing: human studies have found only a slight positive correlation between chronic aspirin ingestion and congenital abnormalities
  - With abuse, increased risk of stillbirth, neonatal death, and decreased birth weight
  - Hypersensitivity: incidence of true allergy less than 1%, asthmatics are more likely hypersensitive
  - Aspirin hypersensitivity triad—aspirin hypersensitivity, asthma, and nasal polyps—often occur together

Toxicity

- Haveles (p. 54)
  - An overdose can produce harmful effects and even death
  - Symptoms
    - At a certain level, salicylism occurs, characterized by tinnitus, headache, nausea, vomiting, dizziness, and dimness of vision
    - At higher levels, stimulation of respiration leads to hyperventilation, producing respiratory alkalosis
    - The cause of death is usually acidosis and electrolyte imbalance

- Prevention
  - Children are the primary victims of accidental poisoning
  - Education of parents regarding potential for poisoning and proper storage and childproof containers have reduced accidental poisonings in children
Toxicity

- haveles (pp. 54-55) (Box 5-3)
  - Treatment
    - Involves removing excess drug in the stomach by inducing emesis or administering activated charcoal
    - Other symptoms are treated symptomatically

Drug Interactions

- haveles (pp. 54-55) (Table 5-1)
  - Warfarin: an oral anticoagulant highly protein bound to plasma protein binding sites; aspirin can displace warfarin from binding sites increasing its anticoagulant effect
  - Probenecid: aspirin interferes with probenecid’s uricosuric effect, can cause an acute attack of gout

Drug Interactions

- Methotrexate (MTX): an antineoplastic drug used to treat certain cancers and autoimmune diseases; aspirin can displace it from protein-binding sites and interfere with clearance causing increased serum concentration and MTX toxicity
- Sulfonamide: higher doses of salicylates may produce an hypoglycemic effect
- Antihypertensives: aspirin reduces the effect of many antihypertensives including angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and thiazide and loop diuretics

Uses

- haveles (p. 55)
  - Analgesia for mild to moderate pain
  - Antipyretic effect useful to control fever but should be avoided in children (Reye syndrome)
  - Antiinflammatory action used to treat inflammatory conditions such as rheumatic fever and arthritis
  - Because of effect on platelet aggregation, used to prevent unwanted clotting

Dose and Preparations

- haveles (pp. 55-56, 62) (Tables 5-9, 5-2)
  - Usual adult dose for treatment of pain or fever is 325-650 mg every 4 hours
  - For prevention of myocardial infarction, the dose is 75-325 mg/day
  - Children’s dose is 10-15 mg/kg every 4-6 hours

Dose and Preparations

- haveles (pp. 55)
  - Regular aspirin: 325-mg tablet and 81-mg children’s tablet
    - (Bayer, Empirin, St. Joseph, Bayer; low dose)
  - Enteric coated aspirin: a coating that dissolves in the intestine rather than the stomach
    - (Ecotrin, Ecotrin; low dose)
Dose and Preparations

- **Combinations**
  - With buffer: claimed to produce fewer gastrointestinal (GI) effects (Bufferin, Ascriptin)
  - With another analgesic: combined with an opioid analgesic or acetaminophen
  - With sedatives: if anxiety is a substantial component of pain
  - With caffeine: caffeine potentiates the analgesic effect of aspirin and other analgesics (Excedrin, Anacin, Fiorinal)

Other Salicylates

- **Haveles (pp. 55-56)**
  - Sodium, choline, magnesium salicylate and salicylamide, and salsalate
  - Claim to have fewer GI side effects
  - Two advantages of these agents are that they are thought to have no effect on platelets and no cross-hypersensitivity with aspirin
  - Magnesium is contraindicated in renal disease, sodium is contraindicated in cardiovascular disease

diflunisal (Dolobid)

- **Haveles (p. 56)**
  - A salicylate classified as a NSAID
  - Can be administered before a dental procedure to delay the onset of postsurgical pain
  - Antipyretic effect is not clinically useful

Nonsteroidal Antiinflammatory Drugs

- **Haveles (p. 56)**
  - A rapidly growing group with important application in dentistry
  - Mechanism of action and many of their pharmacologic effects and adverse reactions resemble aspirin
  - Many authors agree they are the most useful drug group for treatment of dental pain
  - Currently make up only a small percentage of analgesic prescriptions

Chemical Classification

- **Haveles (p. 56)**
  - Divided into several chemical derivatives: propionic acids, acetic acids, fenamates, pyrazolones, oxicams, and others
**Examples of Nonselective Nonsteroidal Antiinflammatory Drugs**

- Propionic acid derivatives
  - ibuprofen (Motrin, Advil)
  - flurbiprofen (Ansaid-PO, Ocu fen-ophth)
  - fenoprofen (Nalfon)
  - naproxen (Naprosyn)
  - naproxen sodium (Anaprox)
  - ketoprofen (Orudis)
  - ketoprofen (Oruvail)
  - oxaprozin (Daypro)

- Acetic acid derivatives
  - indomethacin (Indocin)
  - indomethacin SR (Indocin SR)
  - sulindac (Clinoril)
  - tolmetin (Tolectin)
  - diclofenac (Cataflam)
  - diclofenac (Voltaren)
  - etodolac (Lodine)
  - etodolac (Lodine-XL)
  - ketorolac (Toradol)

- Nonacidic agent
  - nabumetone (Relafen)

- Fenamic acid derivatives
  - meclofenamate (Meclomen)
  - mefenamic acid (Ponstel)

- Salicylates
  - diflunisal (Dolobid)

- Oxicams
  - piroxicam (Feldene)
  - meloxicam (Mobic)

**Mechanism of Action**

- Similar to aspirin, NSAIDs inhibit the enzyme COX (prostaglandin synthase)
- Results in a reduction in the formation of prostaglandin precursors and thromboxanes from arachidonic acid

**Pharmacokinetics**

- Most NSAIDs peak in about 1-2 hours
  - Food reduces the rate but not the extent of absorption
- No effect on absorption of NSAIDs with oral antacids, except for diflunisal
- Metabolized in liver, excreted in kidneys

**Pharmacologic Effects**

- Analgesic, antipyretic, and antiinflammatory actions of NSAIDs result from same mechanism as aspirin inhibition of prostaglandin synthesis by inhibiting COX
- Useful for treating dysmenorrhea because an excess of prostaglandins in the uterine wall produces painful contractions
Adverse Reactions

- Haveles (p. 58)
  - GI effects: gastric irritation, pain, and bleeding problems leading to tarry stools can occur with all NSAIDs
  - NSAIDs can interfere with normal protective mechanisms in the stomach
  - CNS effects: dose-dependent side effects include sedation, dizziness, confusion, mental depression, headache, vertigo, and convulsions

- Blood clotting: reversibly inhibit platelet aggregation
  - In contrast to aspirin, the effect remains only as long as the drug is present in the blood
  - Renal effects: renal failure, cystitis, and increased incidence of urinary tract infections
  - Other effects: muscle weakness, ringing ears, hepatitis, hematologic problems, and blurred vision

- Oral effects: ulcerative stomatitis, gingival ulcerations, dry mouth
- Hypersensitivity reactions: can induce a wide range, including hives or itching, angioneurotic edema, chills and fever, Stevens-Johnson syndrome, exfoliative dermatitis, and epidermal necrolysis
- Pregnancy and nursing considerations: given late in pregnancy can prolong gestation, delay parturition, and produce dystocia—premature closing of ductus arteriosus

Contraindications and Cautions

- Haveles (pp. 58-59) (Box 5-4) (Table 5-5)
- Related to their adverse reactions
  - Caution for patients with asthma, cardiovascular or renal diseases with fluid retention, coagulopathies, peptic ulcer, and ulcerative colitis
  - Higher risk for adverse reactions for those with renal function impairment or history of previous hypersensitivity to aspirin or other NSAIDs and geriatric patients

Drug Interactions

- Haveles (p. 58) (Table 5-4)
- Lithium: may increase lithium toxicity in patients taking lithium for bipolar affective disorders
- Digoxin: may increase effect of digoxin used for congestive heart failure
- May decrease effect of antihypertensives, such as diuretics, ACE inhibitors, and β-blockers
- Can increase toxicity of cyclosporin and MTX

Therapeutic Uses

- Haveles (pp. 58-59) (Fig. 5-9)
- Medical: uses include osteoarthritis, rheumatoid arthritis, gouty arthritis, fever, dysmenorrhea, and pain
  - Accepted unlabeled indications include bursitis and tendonitis
- Dental: many studies find NSAIDs are equivalent in analgesic efficacy to opioid analgesics in many clinical situations
Specific Nonsteroidal Antiinflammatory Drugs

- Haveles (pp. 60-61)
  - Ibuprofen
  - Naproxen and naproxen sodium
  - Other NSAIDs
  - COX II-specific agents

Ibuprofen (Advil, Motrin)

- Haveles (pp. 59-60) (Fig. 5-9)
  - The oldest member of the NSAIDs
  - Rapidly absorbed orally, food decreases rate but not extent of absorption
  - The drug of choice for dental pain when an NSAID is indicated
  - Usual dose is 400-800 mg every 4-6 hours

naproxen and naproxen sodium (Naprosyn, Anaprox)

- Haveles (pp. 57, 60) (Fig. 5-10; Table 5-3)
  - Propionic acid NSAIDs with longer half-lives than ibuprofen
  - Can be administered on an 8- to 12-hour schedule
  - Given with a loading dose

Other Nonsteroidal Antiinflammatory Drugs

- Haveles (pp. 57, 60) (Table 5-3)
  - Fenoprofen, ketorolac, or diflunisal may be used for patients who do not respond to ibuprofen or naproxen
  - ketorolac (Toradol) is a newer NSAID
    - Oral ketorolac is indicated only as continuation therapy to intravenous or intramuscular ketorolac

Cyclooxygenase II-Specific Agents

- Haveles (pp. 60-61) (Table 5-6)
  - Current NSAIDs inhibit both COX I and COX II
    - COX I is an enzyme responsible for adverse reactions of NSAIDs
    - COX II is synthesized only when inflammation occurs
  - COX II-specific inhibitors, because they inhibit COX II (good) more than COX I (bad), should have fewer adverse reactions than the former NSAIDs
    - Clinically they are equivalent to nonselective NSAIDs

Cyclooxygenase II-Specific Agents

- rofecoxib (Vioxx) and valdecoxib (Bextra) were removed from the market as a result of a high incidence of cardiovascular events (heart attack) associated with these drugs
  - The theory is they may suppress prostacyclin (PGI2), which is synthesized by vascular endothelium and smooth muscle
  - Inhibition of the COX II enzyme may also inhibit the function of endothelial cells

cont'd…
Acetaminophen (Tylenol)

- Haveles (p. 61)
- Acetaminophen is the only member of the p-aminophenols currently available for clinical use
  - Used as an analgesic and antipyretic in children and in adults when aspirin is contraindicated

Pharmacokinetics

- Haveles (p. 61)
  - Rapidly and completely absorbed from the GI tract; peak plasma level in 1-3 hours
  - Metabolized by liver microsomal enzymes
  - With large doses, an intermediate metabolite is produced that is thought to be hepatotoxic and possibly nephrotoxic

Pharmacologic Effects

- Haveles (p. 61)
  - Analgesic and antipyretic effects are about the same potency as aspirin
  - Acetaminophen does not possess any clinically significant antiinflammatory effect
  - Unlike aspirin, acetaminophen does not produce gastric bleeding or affect platelet adhesiveness or uric acid excretion

Adverse Reactions

- Haveles (pp. 61-62) (Table 5-7)
  - Hepatic effects: the toxic metabolite that contributes to hepatic necrosis is N-acetyl-p-benzoquinone imine
    - Hepatic necrosis may occur after ingestion of a single dose of 20-25 grams
    - Patients with hepatic disease should avoid acetaminophen
    - Alcoholics or patients who ingest three or more alcoholic beverages a day should avoid acetaminophen

Treatment of Toxicity

- Haveles (p. 62)
  - Should begin with gastric lavage if a drug has recently been ingested
    - Administration of activated charcoal and magnesium or sodium sulfate solution should follow
**Nephrotoxicity**

- Nephrotoxicity has been associated with long-term consumption of acetaminophen
  - Primary lesion appears to be papillary necrosis with secondary interstitial nephritis
  - Concurrent chronic use of acetaminophen and aspirin or NSAIDs increases risk of analgesic nephropathy, renal papillary necrosis, end-stage renal disease, and cancer of the kidney or urinary bladder

**Drug Interactions**

- Acetaminophen is remarkably free of drug interactions at its usual therapeutic doses
  - Hepatotoxicity can be potentiated by administration of agents that induce hepatic microsomal enzymes

**Uses**

- Acetaminophen is used as an analgesic and antipyretic
  - Especially useful in patients who have aspirin hypersensitivity or in whom aspirin-induced gastric irritation would be a problem
  - Used as an analgesic instead of aspirin for young children

**Dose and Preparations**

- Available in many combinations and elixirs
  - Usual adult dose is 325-650 mg every 4-6 hours or 1000 mg three to four times a day
    - Not more than 4 grams in 24 hours should be ingested by adults
  - Various elixirs, drops, and chewable tablets are available for children
    - The elixir is 120 mg/5 ml or 160 mg/5 ml
    - Drops contain 60 mg/0.6 ml

**Drugs Used to Treat Gout**

- Both NSAIDs and colchicine are used to treat acute attacks of gout
  - Probenecid and allopurinol are available to prevent gout
**colchicine**

- Haveles (p. 63)
  - For treatment of an acute attack of gout
    - Appears to inhibit the chemotactic property of leukocytosis and interfere with the inflammatory response to urate crystals

**allopurinol**

- Haveles (p. 63)
  - Inhibits the synthesis or uric acid
    - Used to prevent excess uric acid from forming
  - Used in patients receiving either chemotherapy or irradiation for malignancy
    - The death of many cells causes release of large amounts of uric acid precursors
  - Side effects include hepatotoxicity of a hypersensitivity type

**probenecid (Benemid)**

- Haveles (pp. 53, 63) (Fig. 5-7)
  - A uricosuric agent
    - Causes increased excretion of uric acid
    - Blocks the tubular reabsorption of filtered urate, prevents new tophi and mobilizes those present
  - GI side effects and hypersensitivity may occur
    - Headaches and sore gingiva have also been reported
  - Increases the level of the NSAIDs and penicillin