Nonopioid (Nonnarcotic) Analgesics

Chapter 5

Lesson 5.1
Analgesic Agents and Aspirin

1. Describe pain and its purpose and main components.
2. Discuss the classification of analgesic agents and the chemistry, pharmacokinetics, pharmacologic effects, adverse reactions, toxicity, drug interactions, and uses of aspirin.

Pain

- Sensation of pain: Means by which body is made urgently aware of the presence of tissue damage
- Pain: Protective reflex for self-preservation
Pain (Cont.)

- Perception is the physical component of pain
- Reaction is the psychological component of pain

Factors That Alter Pain Threshold

Salicylates, Acetylsalicylic, and Acid Chemistry

- Acetylsalicylic acid (aspirin) is broken down into:
  - Acetic acid (HA) + salicylic acid (SA)
Classification of Analgesic Agents

- Nonopioids, or nonnarcotics
  - Salicylates
    - Aspirin
    - Nonaspirin salicylates
  - Acetaminophen
- Nonsteroidal antiinflammatory drugs

- Opioids, or narcotics

Classifications of Analgesic Agents (Cont.)

- 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)
- Mechanism of action
  - Nonopioid analgesics inhibit prostaglandin synthesis
  - Opioids affect the response to pain by depressing the CNS

Acetylsalicylic Acid: Mechanism of Action

- Inhibit prostaglandin synthesis
- Enzyme cyclo-oxygenase (COX I and II)
- Prostaglandins can:
  - Sensitize pain receptors
  - Lower pain threshold to painful stimuli
  - Cause inflammation and fever
  - Affect vascular tone and permeability
Acetylsalicylic Acid: Pharmacokinetics
- Absorbed from the stomach and small intestine
- Addition of a buffer
  - Half-life of unhydrolyzed aspirin is about 15 minutes
  - Half-life of hydrolyzed aspirin is dose-dependent
- Small doses: Half-life is 2-3 hours
- Higher doses: Half-life is 15-30 hours
- Zero-order kinetics

Acetylsalicylic Acid: Pharmacologic Effects
- Analgesic effect
- Antipyretic effect
- Antiinflammatory effect
- Uricosuric effect
- Antiplatelet effect

Acetylsalicylic Acid: Adverse Reactions
- Increases bleeding
- Inhibits platelets
- Low-dose inhibition
- High-dose inhibition
- Reduces clotting
Acetylsalicylic Acid: Adverse Reactions (Cont.)
- Gastrointestinal effects
- Bleeding
- Reye's syndrome
- Hepatic and renal effects
- Pregnancy and nursing considerations
- Hypersensitivity (allergy)

Acetylsalicylic Acid: Toxicity
- Salicylism
- Tinnitus
- Headache
- Nausea
- Vomiting
- Dizziness
- Dimness of vision
- Hyperventilation > respiratory alkalosis
- Death

Acetylsalicylic Acid: Toxicity (Cont.)
- Prevention – Education of parents
- Lethal dose
  - Child: 4 gm
  - Adult: 10 to 30 gm
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Patient Education for Use of Aspirin

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Acetylsalicylic Acid: Drug Interactions

- Warfarin > Bleeding
- Probenecid > Precipitates gout attack
- Methotrexate (MTX) > Causes increased serum concentration and MTX toxicity
- Sulfonylureas > Hypoglycemia
- Antihypertensives > Reduce effects of hypertensive agents

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Acetylsalicylic Acid: Uses

- Analgesia for mild-to-moderate pain
- Antiinflammatory
- Low-dose aspirin therapy
Lesson 5.2
Nonsteroidal Antiinflammatory Drugs (NSAIDs), Acetaminophen, and Agents Used to Treat Gout

3. Define the term nonsteroidal antiinflammatory drug and discuss the chemistry, pharmacokinetics, pharmacologic effects, adverse reactions, toxicity, drug interactions, uses, and several examples of these drugs.

4. Discuss the properties, pharmacologic effects, adverse reactions, drug interactions, uses and dosing of acetaminophen.

5. Explain the disease known as gout and summarize the drugs used to treat it.

Nonsteroidal Antiinflammatory Drugs (NSAIDs)

- Chemical classification
  - Propionic acids
  - Acetic acids
  - Fenamates
  - Pyrazolones
  - Oxicams

NSAID Mechanism of Action

- Similar to aspirin
- NSAIDs inhibit the enzymes COX I and II
- Results in reduction in formation of prostaglandin precursors and thromboxanes from arachidonic acid
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**NSAID 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 by kidneys

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**NSAID Pharmacologic Effects**
- Same mechanism as aspirin – inhibition of prostaglandin synthesis by inhibiting COX
- Useful for treating dysmenorrhea
- Treatment of gout

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**Gastrointestinal Effects**
- Irritation, pain, bleeding
- Interfere with normal stomach protective mechanisms
Central Nervous System (CNS) Effects

- Sedation
- Dizziness
- Confusion
- Mental depression
- Headache
- Vertigo
- Convulsions

Other NSAID Adverse Reactions

- Blood clotting – reversibly inhibit platelet aggregation
- Cardiovascular – myocardial infarction or stroke

Renal Effects

- Hypertension
- Renal failure, especially in elderly
- Cystitis
- Increased incidence of urinary tract infections
- Decrease in renal blood flow
- Decrease in glomerular filtration rate
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Other NSAID Adverse Reactions
- Muscle weakness
- Ringing ears
- Hepatitis
- Hematologic problems
- Blurred vision
- Celecoxib – cholestatic jaundice

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Oral Effects and Hypersensitivity Reactions
- Oral effects
  - Ulcerative stomatitis
  - Gingival ulcerations
  - Dry mouth
- Hypersensitivity reactions
  - Hives or itching
  - Angioneurotic edema
  - Chills and fever
  - Stevens-Johnson syndrome
  - Exfoliative dermatitis
  - Epidermal necrolysis

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Pregnancy and Nursing Considerations
- Prolong gestation
- Delay parturition
- Produce dystocia – premature closing of ductus arteriosus
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Pregnancy and Nursing Considerations (Cont.)

- FDA pregnancy category B
  - Fenoprofen
  - Ibuprofen
  - Naproxen

- FDA pregnancy category C
  - Diflunisal
  - Tolmetin
  - Mefenamic acid

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NSAID Drug Interactions

- Lithium – may increase lithium toxicity
- Digoxin – may increase effect of digoxin
- Antihypertensives (diuretics, ACE inhibitors, and β-blockers) – may decrease effects
- Probenecid – may increase serum levels of NSAIDs
- Cyclosporin and MTX – increased toxicity

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NSAID Contraindications and Cautions

- Asthma
- Cardiovascular disease
- Renal disease
- Coagulopathies
- Peptic ulcer
- Ulcerative colitis
- Hypovolemic
- + ACE inhibitors, angiotensin receptor blockers
- Cardiovascular thrombotic events
- Myocardial infarction
- Stroke
- GI events
NSAID Therapeutic Uses

- Medical
  - Osteoarthritis
  - Rheumatoid arthritis
  - Gouty arthritis
  - Fever
  - Dysmenorrhea
  - Pain
  - Bursitis and tendonitis

- Dental
  - Pain
  - Equivalent in analgesic efficacy to opioid analgesics in many clinical situations

Ibuprofen (Advil, Motrin)

- Rapidly absorbed orally
- Food decreases rate but not extent of absorption
- Half-life: 2 hours
- Onset of action: ½ hour
- Duration: 4 to 6 hours
- Hepatic metabolism, excreted by kidneys

Nonsteroidal Antiinflammatory Drugs (NSAIDs)

- Naproxen (Naprosyn)
- Naproxen sodium (Anaprox)
- Naproxen Sodium OTC (Aleve)
- Propionic acid NSAIDs
  - Longer half-lives than ibuprofen
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Other NSAIDs
- Fenoprofen
- Ketorolac (Toradol)
- Diflunisal

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Nonsteroidal Antiinflammatory Drugs (NSAIDs) (Cont.)
- Cyclo-oxygenase II-specific agent
  - Fewer adverse reactions
- Celecoxib (Celebrex)
  - Less irritating to stomach
- Significantly higher incidences of GI effects
  - No real dental use

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Acetaminophen (Tylenol)
- Member of the p-aminophenols
- Analgesic & antipyretic
- Rapidly & completely absorbed from GI tract
- Peak plasma level: 1 to 3 hours
- Half-life: 1 to 4 hours
- Hepatotoxic, possibly nephrotoxic
Pharmacologic Effects of Tylenol

- Acetaminophen & aspirin:
  - = efficacious
  - = potent
- No antiinflammatory effects
- Does not produce gastric bleeding
- Does not affect platelet adhesiveness
- Does not affect uric acid excretion

Adverse Reactions of Tylenol

- Hepatic necrosis
  - N-acetyl-p-benzoquinoneimine
  - Toxic dose: 12 gm or more
  - Patients with hepatic disease should avoid acetaminophen
- Nephrotoxicity
- Alcoholics or patients who ingest three or more alcoholic beverages a day should avoid acetaminophen

Treatment of Toxicity

- Gastric lavage
- Activated charcoal
- Sulfhydryl groups – oral N-acetylcysteine
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Nephrotoxicity

- Associated with long-term consumption of acetaminophen
- Acetaminophen + aspirin or NSAIDs
  - Risk of analgesic nephropathy
  - Risk of renal papillary necrosis
  - Risk of end-stage renal disease
  - Risk of cancer of the kidney or bladder

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Skin Reactions to Tylenol

- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Acute generalized exanthematous pustulosis

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Drug Interactions of Tylenol

- Hepatotoxicity can be potentiated by agents that induce hepatic microsomal enzymes
  - Barbiturates
  - Carbamazepine
  - Phenytoin
  - Rifampin
- Chronic, large doses of alcohol
Uses of Tylenol

- Analgesic
- Antipyretic
- Patients with aspirin hypersensitivity
- Patients with aspirin-induced gastric irritation

Doses and Preparations of Tylenol

- Adult doses
  - Regular strength: 325 mg, 2 tabs every 4-6 hrs
  - Extra strength: 650 mg, 2 tabs every 6 hrs
- Infant suspension – per prescriber
- Children’s (older than 2 yr) oral suspension
- Jr. strength tabs (ages 6-11 yr)
  - 80 mg and 160 mg

Drugs Used to Treat Gout

- Colchicine
- Allopurinol (Zyloprim)
- Probenecid (Benemid)
Questions?