Antipyretic Analgesics: Nonsteroidals, Acetaminophen, and Phenazone Derivatives


A. Know the following about nonsteroidal anti-inflammatory drugs (NSAIDs):

1. All nonselective NSAIDs or their active metabolites are acids. These acids accumulate in inflamed tissue, the gastrointestinal (GI) tract, the kidney, and the bone marrow.
2. NSAIDs inhibit cyclooxygenases (COX-1 and COX-2), which produce prostaglandins from arachidonic acid.
3. There are two cyclooxygenase enzymes (COX-1, COX-2) with overlapping location of expression. They are both constitutive and inducible, but to differing degrees. Both COX-1 and COX-2 isoforms are involved in inflammation and in renal and GI functions.
4. Some are more COX-2 selective than others and have been deemed COX-2 inhibitors.
5. Prostaglandins sensitize nociceptors to the actions of other mediators of pain (histamine, bradykinin, and hydrogen ions) in the periphery and facilitate pain-related neuronal activities in the spinal cord.
6. NSAIDs reduce leukocyte invasion in inflamed tissue.
7. NSAIDs enhance the production of leukotrienes from arachidonic acid.
8. Leukotrienes are mediators of pseudoallergic and allergic reactions.
9. There is little difference in analgesia with nonselective and COX-2-selective drugs.
10. Dose-response and side-effect curves are not superimposable.

B. Know the characteristics of nonacidic antipyretic analgesics, i.e., acetaminophen, phenazone, propyphenazone, and dipyrone (active metabolites of 4-methylaminophenazone and others):

1. They are weak bases or neutral substances.
2. They penetrate easily into the central nervous system (CNS) and reach equally high concentrations throughout the body.
3. They are weak inhibitors of cyclooxygenases.
4. They enhance leukotriene production.
5. They exert their main actions in the CNS (inhibition of pain and fever); the mediators involved are not fully defined.
6. Dipyrone has some antispasmodic action.
7. The selective COX-2 inhibitors are non-acidic.

II. Pharmacokinetics

A. Be aware of the following properties of NSAIDs:

1. Absorption usually begins in the stomach (aspirin, hydrolyzed, and unhydrolyzed); all others are absorbed in the small intestine.
2. For some, parenteral administration is available.
3. Onset of action depends on the speed of absorption.
4. They are mostly unchanged at elimination, usually after conjugation reactions (salicylic acid, diflunisal, ketoprofen, indomethacin) or by conjugation after oxidation (diclofenac, ibuprofen, piroxicam, and most others).
5. They show different elimination half-lives: a short half-life (1–6 hours) for diclofenac, flurbiprofen, ibuprofen, and ketoprofen; intermediate half-life (about 12–24 hours) for naproxen, diflunisal, and nabumetone (active metabolite); long half-life (days) for piroxicam, phenylbutazone, tenoxicam, and oxaprozin.
6. Elimination is slowed in the elderly.
7. They have interactions with other acids in plasma protein binding and tubular excretion.
8. COX-2 inhibitors usually have intermediate to long half-lives.
9. There are sustained- or extended-release forms of short-half-life NSAIDS.

B. Be aware of the following properties of acetaminophen and phenazone derivatives:

1. They are absorbed in the small intestine (acetaminophen, dipyrone).
2. Parenteral administration is possible.
3. They are metabolized in the liver; half-life is 2 hours for acetaminophen, 5–25 hours for phenazone, and 2–10 hours for propyphenazone and dipyrone.
4. Elimination occurs by renal excretion of the metabolites.
5. Elimination is slowed in liver disease and in the elderly.

III. Know the side effects and drug interactions for these drugs (Brune and Lanz 1985; Paulus 1985; Murray and Brater 1993; Figueras et al. 1994; Langman et al. 1994; Komhoff 1997; Feinstein 2000; Fitzgerald et al. 2001; Crofford 2002; McQuay and Moore 2003; Wright 2002):

A. NSAIDs (COX-2-selective, nonselective)

1. GI tract: irritations (10%), bleeding ulcerations, perforations (1 per 10,000); serious side effects are least prominent with ibuprofen, most prominent with azapropazone and piroxicam. COX-2-selective drugs may have fewer GI side effects, but more data are needed.
2. Kidney damage: occasional (little difference between nonselective and COX-2 selective); risk of nephropathy from combination analgesics (non-phenacetin) is still unresolved.
3. Liver damage: occasional, particularly seen with aspirin (in children) and diclofenac (in adults); most likely with lipid-soluble and enterohepatic cycling drugs.
4. Bone marrow damage: aplastic anemia (most prominent with phenylbutazone).
5. Pseudoallergic reactions (10%, particularly in asthmatics, patients with neurodermatitis, and children with nasal polyposis and related conditions); sulfa allergy question (celecoxib).
6. Hypotension.
7. Occasional severe allergic reactions (Steven’s Johnson syndrome, Lyell syndrome, shock).
10. There is accumulating evidence of an increased risk of the use of COX-2 inhibitors in cardiovascular disease. Caution is advised if use of these agents is contemplated.

B. Acetaminophen, phenazone, and derivatives

1. Acetaminophen.
   a. Permanent liver damage with overdosage or chronic high dose in susceptible populations (alcoholics).
   b. Long-term effects in patients abusing combinations (analgesic nephropathy, urinary tract tumors).
2. Phenazone and derivatives.
   a. Allergic skin reactions (frequent) and pseudoallergic reactions (rare severe skin reactions).
   b. Risk of agranulocytosis low but real (1 per 100,000 weekly treatment periods for dipyrone).
   c. Shock cases occasional, as with NSAIDs.
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IV. Know the major indications for use of these drugs (Kantor 1989; McCormack and Brune 1991; Brune et al. 1992; Levy et al. 1995; Sinatra 2002):

A. NSAIDs (nonselective, COX-2 selective)
   1. Chronic intensive inflammatory pain, e.g., rheumatoid arthritis (diclofenac, indomethacin, piroxicam).
   2. Phasic intensive inflammatory pain, as in osteoarthrosis (diclofenac, ibuprofen, ketoprofen; short half-life).
   3. Acute post-traumatic or postoperative pain (diclofenac, flurbiprofen, ibuprofen, ketoprofen; short half-life).
   5. Dysmenorrhea.
   6. COX-2-selective drugs are used in all these conditions, but data are unclear on the risk-benefit ratio except during the perioperative period (minimal platelet effect) and with a history of GI bleeding. Caution should be exercised in their use.
   7. Preemptive analgesia, multimodal analgesia: use COX-2-selective or nonselective drugs?

B. Acetaminophen
   1. Some forms of headache.
   2. Fever (e.g., in children).

REFERENCES


