Lippincott's Illustrated Reviews:

Pharmacology

You will have learned within, those are

Chapter no. **41** to **43**

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Chapter 41

Anti-inflammatory Drugs

I. Overview

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents. Inflammation is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair. When healing is complete, the inflammatory process usually subsides. However, inappropriate activation of our immune system can result in inflammation leading to rheumatoid arthritis (RA). Normally, our immune system can differentiate between self and nonself. In RA, white blood cells (WBC) view the synovium (tissue that nourishes cartilage and bone) as nonself and initiates an inflammatory attack. WBC activation leads to activation of T lymphocytes (the cell-mediated part of our immune system), which will recruit and activate monocytes and macrophages. These will secrete proinflammatory cytokines, including tumor necrosis factor (TNF)-Î± and interleukin (IL)-1 into the synovial cavity. These cytokines will then cause 1) increased cellular infiltration into the endothelium due to release of histamines, kinins, and vasodilatory prostaglandins; 2) increased production of C-reactive protein by hepatocytes (a marker for inflammation); 3) increased production and release of proteolytic enzymes (collagenases and metalloproteinases) by chondrocytes (cells that maintain cartilage), leading to degradation of cartilage and joint space narrowing; 4) increased osteoclast activity (osteoclasts regulate bone breakdown), resulting in focal bone erosions and bone demineralization around joints; and 5) systemic manifestations in which organs such as the heart, lungs, and liver are adversely affected. In addition to T-lymphocyte activation, B lymphocytes are also involved and will produce rheumatoid factor (inflammatory marker) and other autoantibodies with the purpose of maintaining inflammation. These defensive reactions will cause progressive tissue injury, resulting in joint damage and erosions, functional disability, and significant pain and reduction in quality of life. Pharmacotherapy in the management of RA includes anti-inflammatory and/or immunosuppressive agents that will modulate/reduce the inflammatory process with the goals of reducing inflammation and pain and halting (or at least slowing) the progression of the disease. The agents to be discussed include nonsteroidal anti-inflammatory drugs (NSAIDs) and *celecoxib* (cyclooxygenase-2 inhibitor), *acetaminophen*, and disease-modifying antirheumatic drugs. Additionally, agents used for the treatment of gout will be reviewed (Figure 41.1).

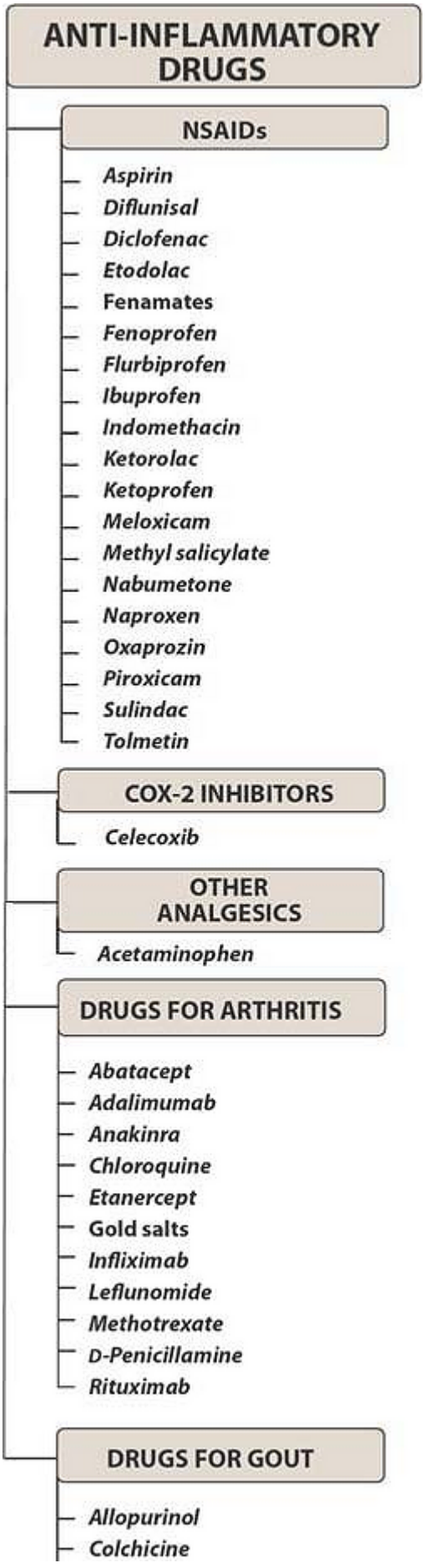

ANTI-INFLAMMATORY DRUGS
NSAIDs
Aspirin
Diflunisal
Diclofenac
Etodolac
Fenamates
Fenoprofen
Flurbiprofen
Ibuprofen
Indomethacin
Ketorolac
Ketoprofen
Meloxicam
Methyl salicylate
Nabumetone
Naproxen
Oxaprozin
Piroxicam
Sulindac
Tolmetin
COX-2 INHIBITORS
Celecoxib
OTHER ANALGESICS
Acetaminophen
DRUGS FOR ARTHRITIS
Abatacept
Adalimumab
Anakinra
Chloroquine
Etanercept
Gold salts
Infliximab
Leflunomide
Methotrexate
D-Penicillamine
Rituximab
DRUGS FOR GOUT
Allopurinol
Colchicine

Figure 41.1 Summary of anti-inflammatory drugs. NSAIDs = nonsteroidal antiinflammatory drugs; COX = cyclooxygenase.

II. Prostaglandins

All of the NSAIDs act by inhibiting the synthesis of prostaglandins. Thus, an understanding of NSAIDs requires comprehension of the actions and biosynthesis of prostaglandinsâ€"unsaturated fatty acid derivatives containing 20 carbons that include a cyclic ring structure. [Note: These compounds are sometimes referred to as eicosanoids; â€œeicosaâ€ refers to the 20 carbon atoms.]

A. Role of prostaglandins as local mediators

Prostaglandins and related compounds are produced in minute quantities by virtually all tissues. They generally act locally on the tissues in which they are synthesized, and they are rapidly metabolized to inactive products at their sites of action. Therefore, the prostaglandins do not circulate in the blood in significant concentrations. Thromboxanes, leukotrienes, and the hydroperoxyeicosatetraenoic and hydroxyeicosatetraenoic acids (HPETEs and HETEs, respectively) are related lipids, synthesized from the same precursors as the prostaglandins, and use interrelated pathways.

B. Synthesis of prostaglandins

Arachidonic acid, a 20-carbon fatty acid, is the primary precursor of the prostaglandins and related compounds. Arachidonic acid is present as a component of the phospholipids of cell membranesâ€"primarily phosphatidylinositol and other complex lipids.[1] Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A_2 and other acyl hydrolases via a process controlled by hormones and other stimuli. There are two major pathways in the synthesis of the eicosanoids from arachidonic acid.

1. **Cyclooxygenase pathway:** All eicosanoids with ring structuresâ€"that is, the prostaglandins, thromboxanes, and prostacyclinsâ€"are synthesized via the cyclooxygenase pathway. Two related isoforms of the cyclooxygenase enzymes have been described. Cyclooxygenase-1 (COX-1) is responsible for the physiologic production of prostanoids, whereas cyclooxygenase-2 (COX-2) causes the elevated production of prostanoids that occurs in sites of disease and inflammation. COX-1 is described as a â€œhousekeeping enzymeâ€ that regulates normal cellular processes, such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function. COX-2 is constitutively expressed in tissues such as the brain, kidney, and bone. Its expression at other sites is increased during states of inflammation. The two enzymes share 60 percent homology in amino acid sequence. However, the conformation for the substrate-binding sites and catalytic regions are slightly different. For example, COX-2 has a larger and more flexible substrate channel than COX-1 has, and COX-2 has a large space at the site where inhibitors bind (Figure 41.2). [Note: The structural differences between COX-1 and COX-2 permitted the development of COX-2 selective inhibitors.] Another distinguishing characteristic of COX-2 is that its expression is inhibited by glucocorticoids (Figure 41.3), which may contribute to the significant anti-inflammatory effects of these drugs.

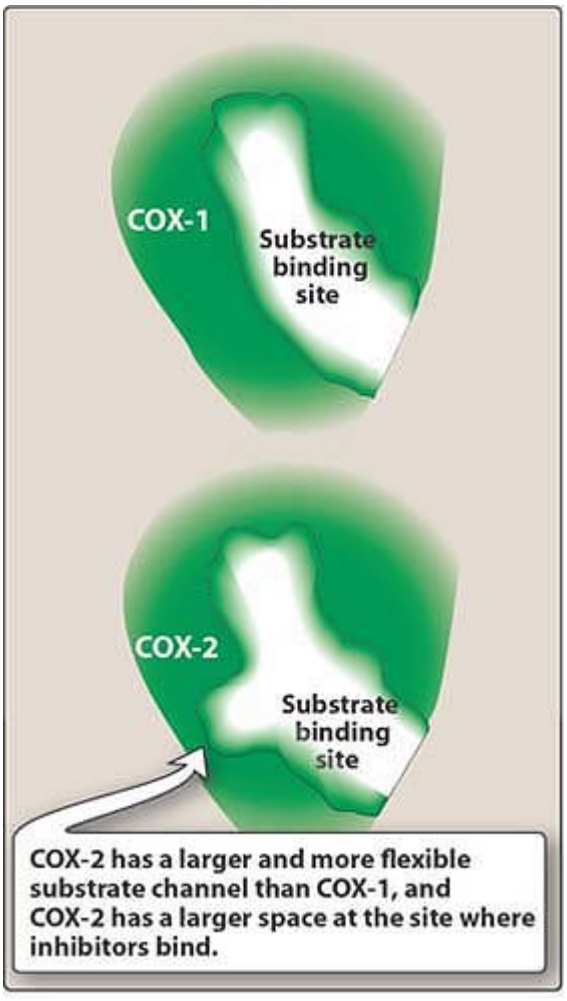


Figure 41.2 Structural differences in active sites of cyclooxygenase (COX)-1 and COX-2.

2. **Lipoxygenase pathway:** Alternatively, several lipoxygenases can act on arachidonic acid to form 5-HPETE, 12-HPETE, and 15-HPETE, which are unstable peroxidated derivatives that are converted to the corresponding hydroxylated derivatives (the HETEs) or to leukotrienes or lipoxins, depending on the tissue (see Figure 41.3).[2] Antileukotriene drugs, such as *zileuton, zafirlukast*, and *montelukast*, are useful for the treatment of moderate to severe allergic asthma (see p. 324).

C. Actions of prostaglandins

Many of the actions of prostaglandins are mediated by their binding to a wide variety of distinct cell membrane receptors that operate via G proteins, which subsequently activate or inhibit adenylyl cyclase or stimulate phospholipase C.[3] This causes an enhanced formation of diacylglycerol and inositol 1,4,5-trisphosphate. Prostaglandin $F_{2\hat{i}\pm}$ ($PGF_{2\hat{i}\pm}$), the leukotrienes, and thromboxane A_2 (TXA_2) mediate certain actions by activating phosphatidyl inositol metabolism, causing an increase of intracellular Ca^{2+}.

D. Functions in the body

Prostaglandins and their metabolites produced endogenously in tissues act as local signals that fine-tune the

response of a specific cell type. Their functions vary widely, depending on the tissue. For example, the release of TXA_2 from platelets triggers the recruitment of new platelets for aggregation (the first step in clot formation). However, in other tissues, elevated levels of TXA_2 convey a different signal; for example, in certain smooth muscles, this compound induces contraction. Prostaglandins are also among the chemical mediators that are released in allergic and inflammatory processes.

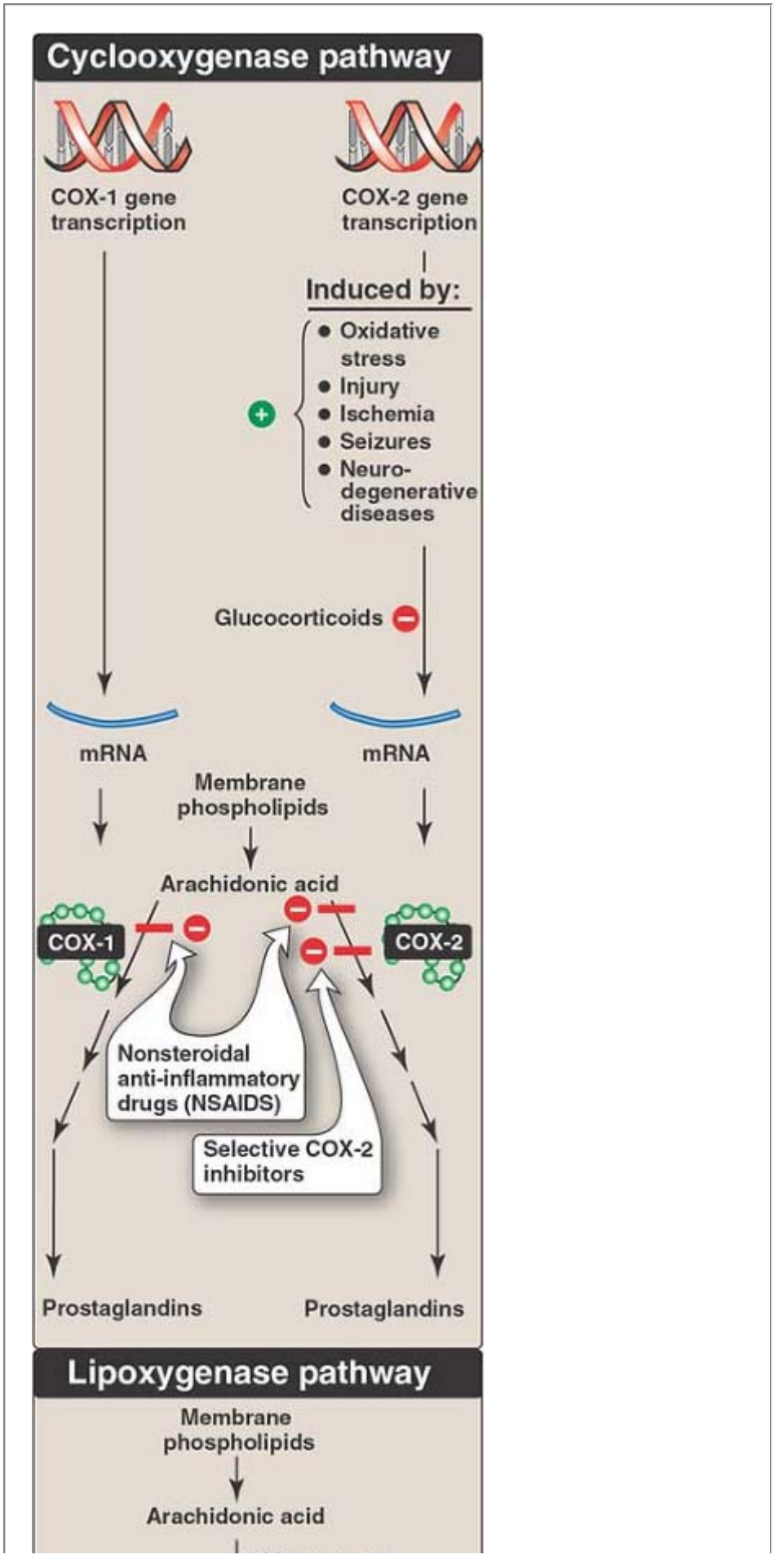

Cyclooxygenase pathway
COX-1 gene transcription
COX-2 gene transcription
Induced by:
Oxidative stress
Injury
Ischemia
Seizures
Neuro-degenerative diseases
Glucocorticoids
mRNA
mRNA
Membrane phospholipids
Arachidonic acid
COX-1
COX-2
Nonsteroidal anti-inflammatory drugs (NSAIDS)
Selective COX-2 inhibitors
Prostaglandins
Prostaglandins
Lipoxygenase pathway
Membrane phospholipids
Arachidonic acid

Figure 41.3 Synthesis of prostaglandins and leukotrienes. COX = cyclooxygenase.

III. Nonsteroidal Anti-Inflammatory Drugs

The NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities. They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoid biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects. Detection of serious cardiovascular events associated with COX-2 inhibitors have led to withdrawal of *rofecoxib* and *valdecoxib* from the market (*celecoxib* is still available for use in patients with RA). Additionally, the U.S. Food and Drug Administration (FDA) has required that the labeling of the traditional NSAIDs and *celecoxib* be updated to include the following: 1) a warning of the potential risks of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal; additionally, a warning that the risk may increase with duration of use and that patients with cardiovascular disease or risk factors may be at greater risk; 2) a warning that use is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft surgery; and 3) a notice that there is increased risk of serious gastrointestinal (GI) adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious

GI events. *Aspirin*, however, has proven to be beneficial in patients for the primary and secondary prevention of cardiovascular events and is most commonly used for this purpose rather than for pain control.

A. Aspirin and other salicylic acid derivatives

Aspirin [AS-pir-in] is the prototype of traditional NSAIDs and was officially approved by the FDA in 1939. It is the most commonly used and is the drug to which all other anti-inflammatory agents are compared.

1. **Mechanism of action:** *Aspirin* is a weak organic acid that is unique among the NSAIDs in that it irreversibly acetylates (and, thus, inactivates) cyclooxygenase (Figure 41.4). The other NSAIDs, including salicylate, are all reversible inhibitors of cyclooxygenase. *Aspirin* is rapidly deacetylated by esterases in the body producing salicylate, which has anti-inflammatory, antipyretic, and analgesic effects. The antipyretic and anti-inflammatory effects of salicylate are due primarily to the blockade of prostaglandin synthesis at the thermoregulatory centers in the hypothalamus and at peripheral target sites. Furthermore, by decreasing prostaglandin synthesis, salicylate also prevents the sensitization of pain receptors to both mechanical and chemical stimuli. *Aspirin* may also depress pain stimuli at subcortical sites (that is, the thalamus and hypothalamus).
2. **Actions:** The NSAIDs, including *aspirin*, have three major therapeutic actionsâ€”namely, they reduce inflammation (anti-inflammation), pain (analgesia), and fever (antipyrexia; Figure 41.5). However, as described later in this section, not all NSAIDs are equally potent in each of these actions.

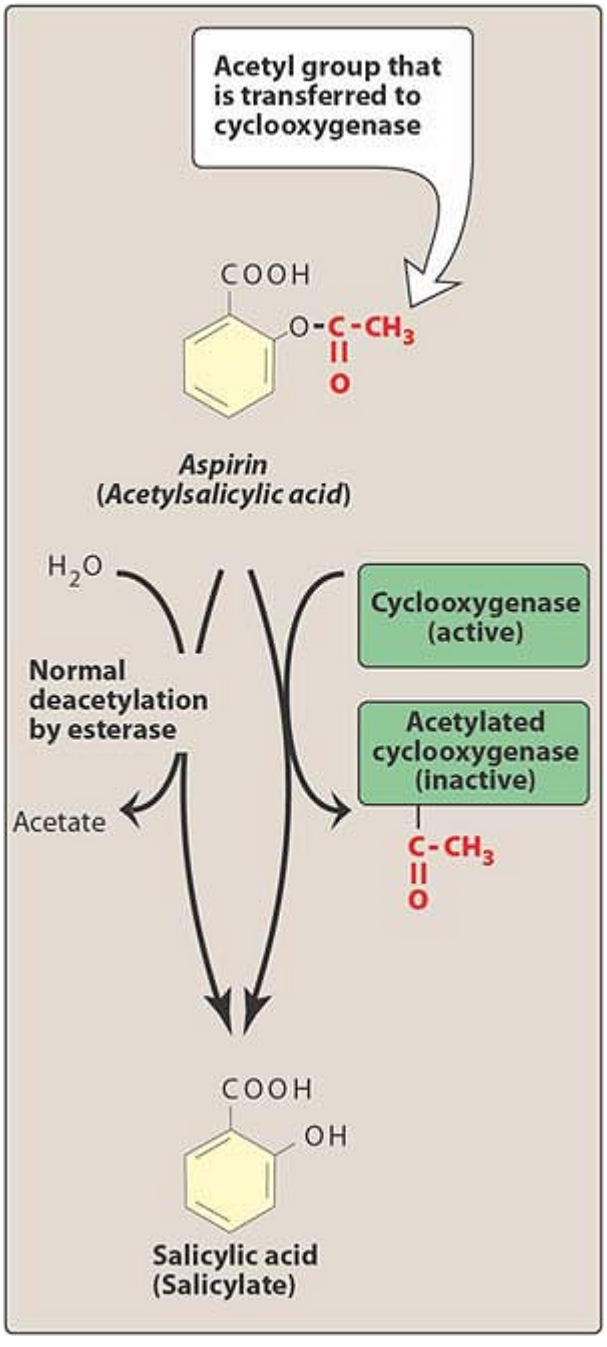


Figure 41.4 Metabolism of *aspirin* and acetylation of cyclooxygenase by *aspirin*.

a. **Anti-inflammatory actions:** Because *aspirin* inhibits cyclooxygenase activity, it diminishes the formation of prostaglandins and, thus, modulates those aspects of inflammation in which prostaglandins act as mediators. *Aspirin* inhibits inflammation in arthritis, but it neither arrests the progress of the disease nor induces remission.

b. **Analgesic action:** Prostaglandin E_2 (PGE_2) is thought to sensitize nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process. Thus, by decreasing PGE_2 synthesis, *aspirin* and other NSAIDs repress the sensation of pain. The salicylates are used mainly for

the management of pain of low to moderate intensity arising from musculoskeletal disorders rather than that arising from the viscera. Combinations of opioids and NSAIDs are effective in treating pain caused by malignancy. *Diflunisal* [dre-flu-NI-sal] is three- to four-fold more potent than *aspirin* as an analgesic and an anti-inflammatory agent, but it has no antipyretic properties.

c. **Antipyretic action:** Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated. This can be caused by PGE_2 synthesis, which is stimulated when an endogenous fever-producing agent (pyrogen), such as a cytokine, is released from white cells that are activated by infection, hypersensitivity, malignancy, or inflammation. The salicylates lower body temperature in patients with fever by impeding PGE_2 synthesis and release. *Aspirin* resets the â€œthermostatâ€ toward normal, and it rapidly lowers the body temperature of febrile

patients by increasing heat dissipation as a result of peripheral vasodilation and sweating. *Aspirin* has no effect on normal body temperature. *Diflunisal* does not reduce fever, because it does not cross the blood-brain barrier.

d. **Respiratory actions:** At therapeutic doses, *aspirin* increases alveolar ventilation. [Note: Salicylates uncouple oxidative phosphorylation, which leads to elevated CO_2 and increased respiration.] Higher doses work directly on the respiratory center in the medulla, resulting in hyperventilation and respiratory alkalosis that usually is adequately compensated for by the kidney. At toxic levels, central respiratory paralysis occurs, and respiratory acidosis ensues due to continued production of CO_2.

e. **Gastrointestinal effects:** Normally, prostacyclin (PGI_2) inhibits gastric acid secretion, whereas PGE_2 and $PGF_{2\hat{i}\pm}$ stimulate synthesis of protective mucus in both the stomach and small intestine. In the presence of *aspirin*, these prostanoids are not formed, resulting in increased gastric acid secretion and diminished mucus protection. This may cause epigastric distress, ulceration, hemorrhage, and iron-deficiency anemia. *Aspirin* doses of 1 to 4.5 g/day can produce loss of 2 to 8 mL of blood in the feces per day. Buffered and enteric-coated preparations are only marginally helpful in dealing with this problem. Agents used for the prevention of gastric and/or duodenal ulcers include the PGE_1-derivative *misoprostol* and the proton-pump inhibitors (PPIs); *esomeprazole, lansoprazole, omeprazole, pantoprazole*, and *rabeprazole*); PPIs can also be used for the treatment of an NSAID-induced ulcer and are especially appropriate if the patient will need to continue NSAID treatment. H_2-antihistamines (*cimetidine, famotidine, nizatidine*, and *ranitidine*) relieve dyspepsia due to NSAIDS, but they may mask serious GI complaints and may not be as effective as PPIs for healing and preventing ulcer formation.

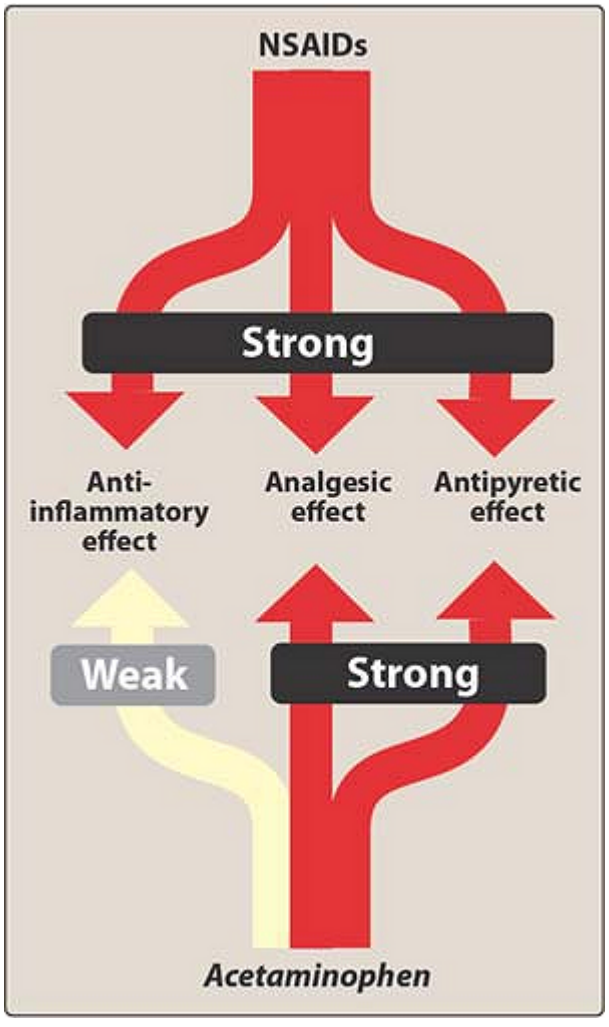


Figure 41.5 Actions of nonsteroidal antiin flammatory drugs (NSAIDs) and *acetaminophen*.

f. **Effect on platelets:** TXA_2 enhances platelet aggregation, whereas PGI_2 decreases it. Low doses (60â€“81 mg daily) of *aspirin* can irreversibly inhibit thromboxane production in platelets via acetylation of cyclooxygenase. Because platelets lack nuclei, they cannot synthesize new enzyme, and the lack of thromboxane persists for the lifetime of the platelet (3â€“7 days). As a result of the decrease in TXA_2, platelet aggregation (the first step in thrombus formation) is reduced, producing an anticoagulant effect with a prolonged bleeding time. Finally, *aspirin* also inhibits cyclooxygenase in endothelial cells, resulting in reduced PGI_2 formation; however, endothelial cells possess nuclei able to re-synthesize new cyclooxygenase. Therefore, PGI_2 is available for antiplatelet action.

g. **Actions on the kidney:** Cyclooxygenase inhibitors prevent the synthesis of PGE_2 and PGI_2â€”prostaglandins that are responsible for maintaining renal blood flow, particularly in the presence of circulating vasoconstrictors (Figure 41.6). Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema and hyperkalemia in some patients. Interstitial nephritis can also occur with all NSAIDs except *aspirin*.

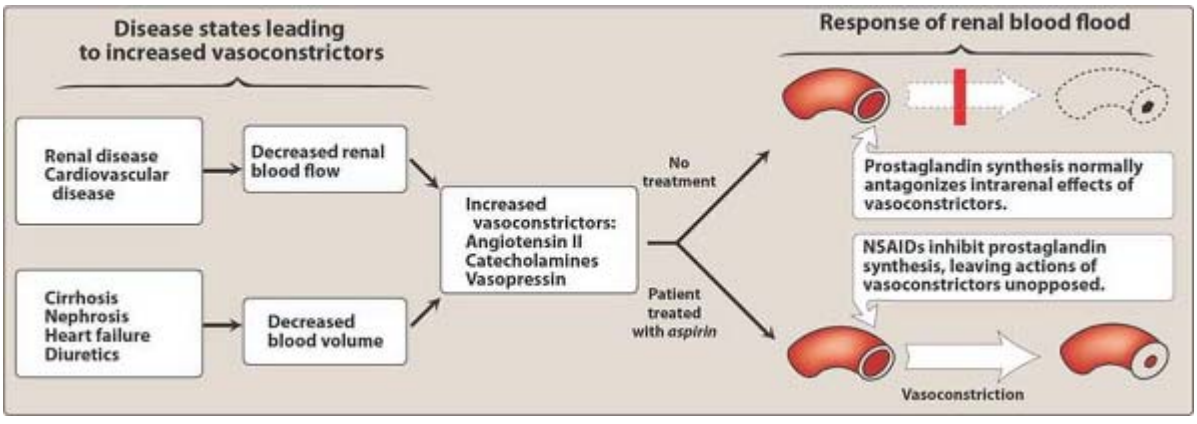


Figure 41.6 Renal effect of *aspirin* inhibition of prostaglandin synthesis. NSAIDs = nonsteroidal anti-inflammatory drugs.

3. **Therapeutic uses:**

   a. **Anti-inflammatory, antipyretic, and analgesic uses:** *The salicylic acid derivatives* are used in the treatment of gout, rheumatic fever, osteoarthritis, and RA. Commonly treated conditions requiring analgesia include headache, arthralgia, and myalgia.

   b. **External applications:** *Salicylic acid* is used topically to treat corns, calluses, and warts. *Methyl salicylate* (â€œoil of wintergreenâ€) is used externally as a cutaneous counterirritant in liniments.

   c. **Cardiovascular applications:** Aspirin is used to inhibit platelet aggregation. Low doses are used prophylactically to 1) reduce the risk of recurring transient ischemic attacks (TIAs) and stroke or death in those who have had single or multiple episodes of TIA or stroke; 2) reduce the risk of death in those having an acute myocardial infarction; 3) reduce the risk of recurrent nonfatal myocardial infarction and/or death in patients with previous myocardial infarction or unstable angina pectoris; 4) reduce the risk of myocardial infarction and sudden death in patients with chronic stable angina pectoris; 5) reduce the cardiovascular risk in patients undergoing certain revascularization procedures.

4. **Pharmacokinetics:**

   a. **Administration and distribution:** After oral administration, the un-ionized salicylates are passively absorbed from the stomach and the small intestine (dissolution of the tablets is favored at the higher pH of the gut). Rectal absorption of the salicylates is slow and unreliable, but it is a useful route for administration to vomiting children. Salicylates must be avoided in children and teenagers (<15 years old) with varicella (chickenpox) or influenza to prevent Reye's syndrome. Salicylates (except for *diflunisal*) cross both the blood-brain barrier and the placenta and are absorbed through intact skin (especially *methyl salicylate*).

   b. **Dosage:** The salicylates exhibit analgesic activity at low doses; only at higher doses do these drugs show anti-inflammatory activity (Figure 41.7). For example, two 325-mg *aspirin* tablets

administered four times daily produce analgesia, whereas 12 to 20 tablets per day produce both analgesic and anti-inflammatory activity. For long-term myocardial infarction prophylaxis, the dose is 81 to 162 mg/day; for those with RA or osteoarthritis, the initial dose is 3 grams/day; for stroke prophylaxis, the dose is 50 to 325 mg/day; in a patient having an acute mycardial infarction, the dose is 162 to 325 mg of nonenteric coated aspirin chewed and swallowed immediately.

c. **Fate:** At dosages of 650 mg/day, *aspirin* is hydrolyzed to salicylate and acetic acid by esterases in tissues and blood (see Figure 41.4). Salicylate is converted by the liver to water-soluble conjugates that are rapidly cleared by the kidney, resulting in elimination with first-order kinetics and a serum half-life of 3.5 hours. At anti-inflammatory dosages (>4 g/day), the hepatic metabolic pathway becomes saturated, and zero-order kinetics are observed, with the drug having a half-life of 15 hours or more (Figure 41.8). Saturation of the hepatic enzymes requires treatment for several days to 1 week. Being an organic acid, salicylate is secreted into the urine and can affect uric acid excretionâ€"namely, at low doses of *aspirin*, uric acid secretion is decreased, whereas at high doses, uric acid secretion is increased. Both hepatic and renal function should be monitored periodically in those receiving long-term, high-dose *aspirin* therapy, and *aspirin* should be avoided in patients with a creatinine clearance of less than 10 mL/min.

5. **Adverse effects:**

a. **Gastrointestinal:** The most common GI effects of the salicylates are epigastric distress, nausea, and vomiting. Microscopic GI bleeding is almost universal in patients treated with salicylates. [Note: *Aspirin* is an acid. At stomach pH, *aspirin* is uncharged; consequently, it readily crosses into mucosal cells, where it ionizes (becomes negatively charged) and becomes trapped, thus potentially causing direct damage to the cells. *Aspirin* should be taken with food and large volumes of fluids to diminish dyspepsia. Additionally, *misoprostol* or a *PPI* may be taken concurrently.]

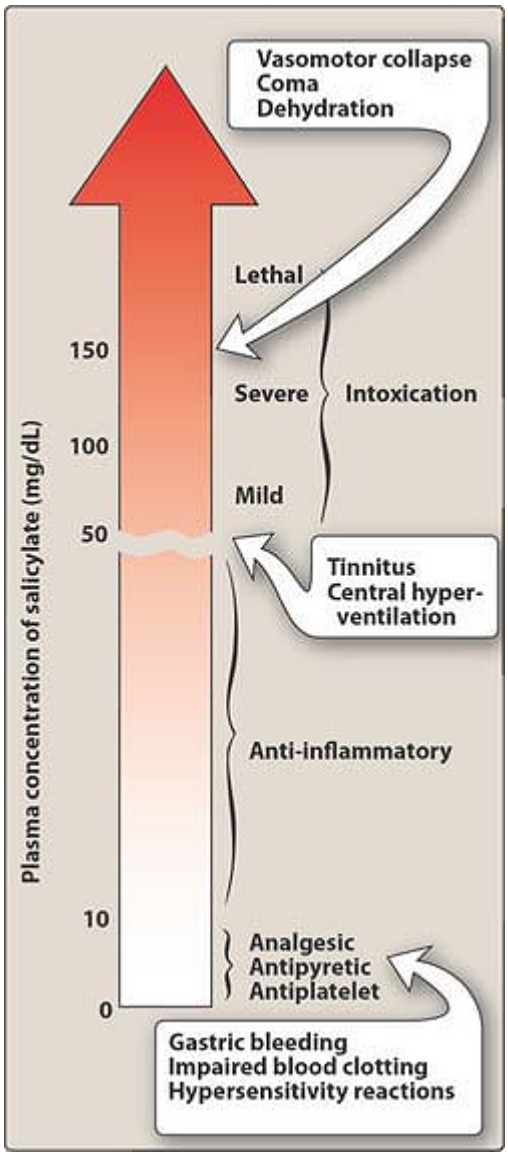


Figure 41.7 Dose-dependent effects of salicylate.

b. **Blood:** The irreversible acetylation of platelet cyclooxygenase reduces the level of platelet TXA_2, resulting in inhibition of platelet aggregation and a prolonged bleeding time. For this reason, *aspirin* should not be taken for at least 1 week prior to surgery. When salicylates are administered, anticoagulants may have to be given in reduced dosage, and careful monitoring and counseling of patients are necessary.

c. **Respiration:** In toxic doses, salicylates cause respiratory depression and a combination of uncompensated respiratory and metabolic acidosis.

d. **Metabolic processes:** Large doses of salicylates uncouple oxidative phosphorylation.[4] The energy normally used for the production of adenosine triphosphate is dissipated as heat, which explains the hyperthermia caused by salicylates when taken in toxic quantities.

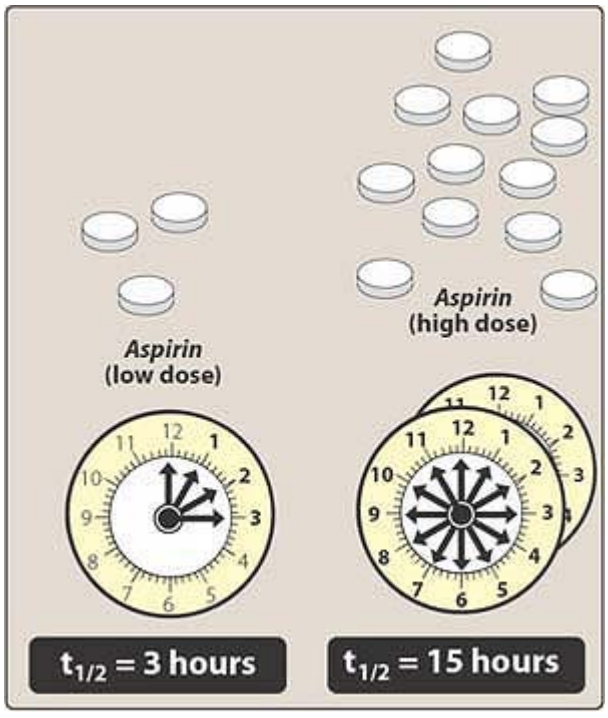


Figure 41.8 Effect of dose on the half-life of *aspirin*.

e. **Hypersensitivity:** Approximately 15 percent of patients taking *aspirin* experience hypersensitivity reactions. Symptoms of true allergy include urticaria, bronchoconstriction, or angioedema. Fatal anaphylactic shock is rare.

f. **Reye's syndrome:** *Aspirin* and other salicylates given during viral infections has been associated with an increased incidence of Reye's syndrome, which is an often fatal, fulminating hepatitis with cerebral edema. This is especially encountered in children, who therefore should be given *acetaminophen* instead of *aspirin* when such medication is required to reduce fever. *Ibuprofen* is also appropriate.

g. **Drug interactions:** Concomitant administration of salicylates with many classes of drugs may produce undesirable side effects. Because *aspirin* is found in many over-the-counter agents, patients should be counseled to read labels to verify *aspirin* content to avoid overdose. Salicylate is 90 to 95 percent protein bound and can be displaced from its protein-binding sites, resulting in increased concentration of free salicylate; alternatively, *aspirin* could displace other highly protein-bound drugs, such as *warfarin, phenytoin*, or *valproic acid*, resulting in higher free concentrations of the other agent (Figure 41.9). Chronic *aspirin* use should be avoided in patients receiving *probenecid* or *sulfinpyrazone,* because these agents cause increased renal excretion of uric acid whereas aspirin (<2 g/day) cause reduced clearance of uric acid. Concomitant use of *ketorolac* and *aspirin* is contraindicated because of increased risk of GI bleeding and platelet aggregation inhibition. Children who have received live varicella virus vaccine should avoid *aspirin* for at least 6 weeks after vaccination to prevent Reye's syndrome.

h. **In pregnancy:** *Aspirin* is classified as FDA pregnancy category C risk during Trimesters 1 and 2 and category D during Trimester 3. Because salicylates are excreted in breast milk, *aspirin* should be avoided during pregnancy and while breast-feeding.

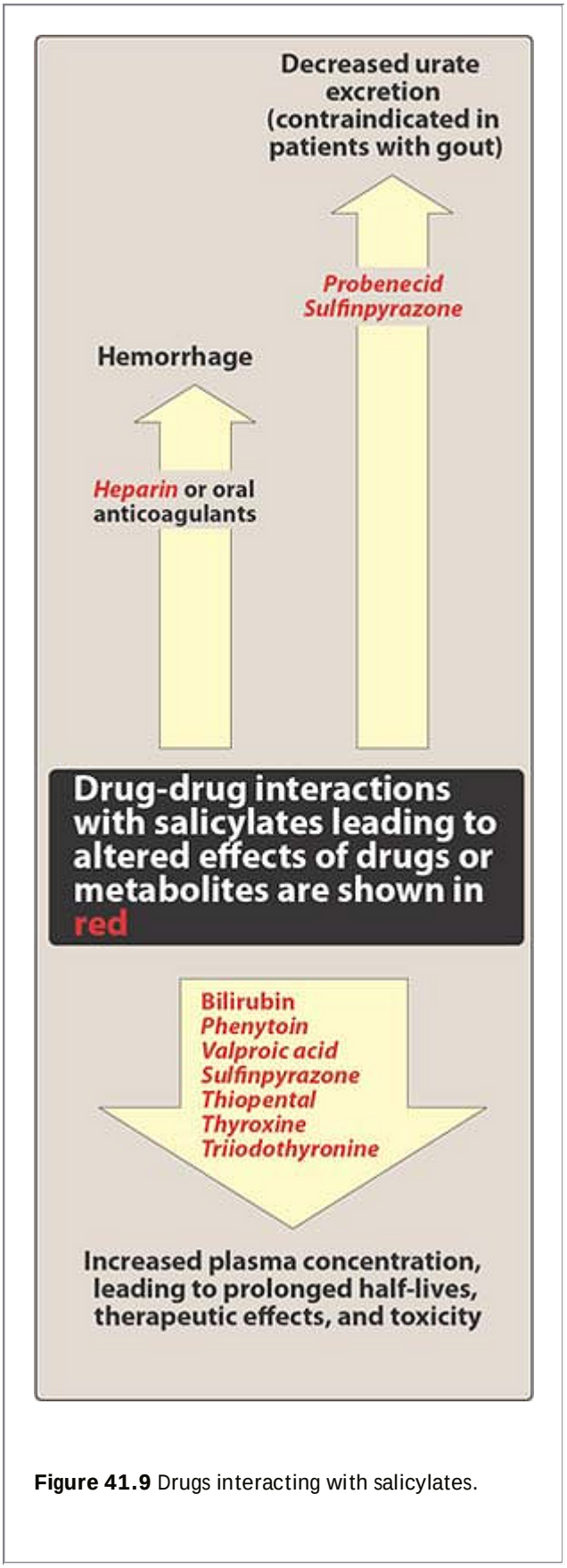


Figure 41.9 Drugs interacting with salicylates.

6. **Toxicity:** Salicylate intoxication may be mild or severe. The mild form is called salicylism and is characterized by nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears). When large doses of salicylate are administered, severe salicylate intoxication may result

(see Figure 41.7). The symptoms listed above are followed by restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure. Children are particularly prone to salicylate intoxication. Ingestion of as little as 10 g of *aspirin* (or 5 ml of *methyl salicylate*, with the latter being used as a counterirritant in liniments) can cause death in children. Treatment of salicylism should include measurement of serum salicylate concentrations and of pH to determine the best form of therapy. In mild cases, symptomatic treatment is usually sufficient. Increasing the urinary pH enhances the elimination of salicylate. In serious cases, mandatory measures include the intravenous administration of fluid, dialysis (hemodialysis or peritoneal dialysis), and the frequent assessment and correction of acid-base and electrolyte balances. [Note: *Diflunisal* does not cause salicylism.]

B. Propionic acid derivatives

Ibuprofen [eye-byoo-PROE-fen] was the first in this class of agents to become available in the United States. It has been joined by *naproxen* [nah-PROX-en], *fenoprofen* [fen-oh-PROE-fen], *ketoprofen* [key-toe-PROE-fen], *flurbiprofen* [flur-bye-PROE-fen], and *oxaprozin* [ox-ah-PROE-zin]. All these drugs possess anti-inflammatory, analgesic, and antipyretic activity; additionally, they can can alter platelet function and prolong bleeding time. They have gained wide acceptance in the chronic treatment of RA and osteoarthritis, because their GI effects are generally less intense than those of *aspirin.* These drugs are reversible inhibitors of the cyclooxygenases and, thus, like *aspirin*, inhibit the synthesis of prostaglandins but not of leukotrienes. All are well absorbed on oral administration and are almost totally bound to serum albumin. [Note: *Oxaprozin* has the longest half-life and is administered once daily.] They undergo hepatic metabolism and are excreted by the kidney. The most common adverse effects are GI, ranging from dyspepsia to bleeding. Side effects involving the central nervous system (CNS), such as headache, tinnitus, and dizziness, have also been reported.

C. Acetic acid derivatives

This group of drugs includes *indomethacin* [in-doe-METH-a-sin]*, sulindac* [sul-IN-dak], and *etodolac* [eh-TOE-doh-lak]. All have anti-inflammatory, analgesic, and antipyretic activity. They act by reversibly inhibiting cyclooxygenase. They are generally not used to lower fever. Despite its potency as an anti-inflammatory agent, the toxicity of *indomethacin* limits its use to the treatment of acute gouty arthritis, ankylosing spondylitis, and osteoarthritis of the hip. *Sulindac* is an inactive prodrug that is closely related to *indomethacin*. Although the drug is less potent than *indomethacin*, it is useful in the treatment of RA, ankylosing spondylitis, osteoarthritis, and acute gout. The adverse reactions caused by *sulindac* are similar to, but less severe than, those of the other NSAIDs, including *indomethacin*. *Etodolac* has effects similar to those of the other NSAIDs. GI problems are less common.

D. Oxicam derivatives

Piroxicam [peer-OX-i-kam] and *meloxicam* [mel-OX-i-kam] are used to treat RA, ankylosing spondylitis, and osteoarthritis. They have long half-lives, which permit once-daily administration, and the parent drug as well as its metabolites are renally excreted in the urine. GI disturbances are encountered in approximately 20 percent of patients treated with *piroxicam*. *Meloxicam* inhibits both COX-1 and COX-2, with preferential binding for COX-2, and at low to moderate doses shows less GI irritation than *piroxicam*. However, at high doses, *meloxicam* is a nonselective NSAID, inhibiting both COX-1 and COX-2. *Meloxicam* excretion is predominantly in the form of metabolites and occurs equally in the urine and feces.

E. Fenamates

Mefenamic [meh-FEN-a-mick] *acid* and *meclofenamate* [meh-KLO-fen-a-mate] have no advantages over other NSAIDs as anti-inflammatory agents. Their side effects, such as diarrhea, can be severe, and they are associated with inflammation of the bowel. Cases of hemolytic anemia have been reported.

F. Heteroaryl acetic acids

Diclofenac [dye-KLO-feh-nak] and *tolmetin* [tole-MEN-tin] are approved for long-term use in the treatment of RA, osteoarthritis, and ankylosing spondylitis. *Diclofenac* is more potent than *indomethacin* or *naproxen*. An ophthalmic preparation is also available. *Diclofenac* accumulates in synovial fluid, and the primary route of excretion for the drug and its metabolites is the kidney. *Tolmetin* is an effective anti-inflammatory, antipyretic, and analgesic agent with a half-life of 5 hours. It is 99 percent bound to plasma proteins, and metabolites can be found in the urine. Toxicities of these two agents are similar to those of the other NSAIDs. *Ketorolac* [key-toe-ROLE-ak] is a potent analgesic but has moderate anti-inflammatory effects. It is available for oral administration, for intramuscular use in the treatment of postoperative pain, and for topical use for allergic conjunctivitis. *Ketorolac* undergoes hepatic metabolism, and the drug and its metabolites are eliminated via the urine. *Ketorolac* is indicated for short-term relief of moderate to severe pain for up to 5 days after the first dose is administered via IV or intramuscular dosing at the doctor's office or in a hospital. This agent is to be avoided in pediatric patients; patients with mild pain, and those with chronic conditions, the dose should not exceed 40 mg/day. *Ketorolac* can cause fatal peptic ulcers as well as GI bleeding and/or perforation of the stomach or intestines.

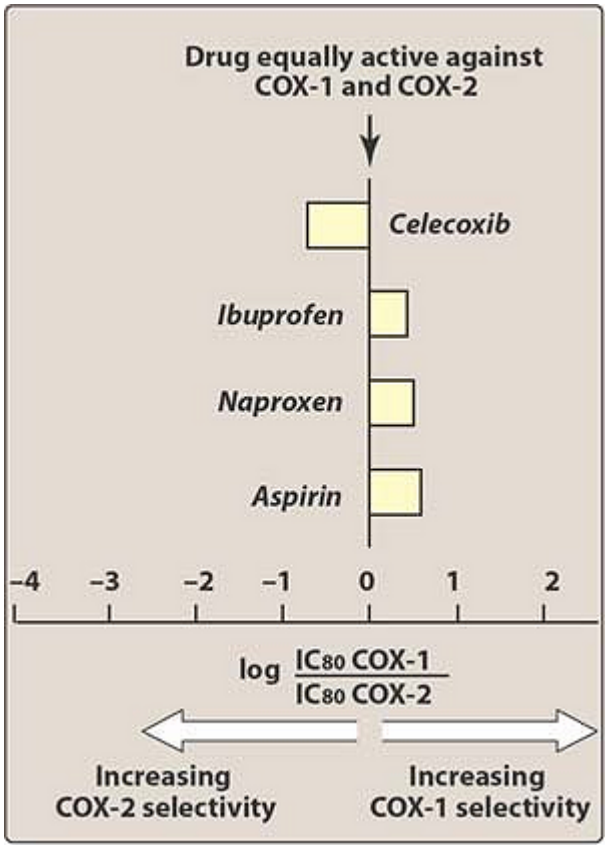


Figure 41.10 Relative selectivity of some commonly used NASAIDs. Data shown as the logarithm of their ratio of IC_{80} (drug concentration to achieve 80 percent inhibition of cyclooxygenase).

G. Nabumetone

Nabumetone [na-BYOO-meh-tone] is indicated for the treatment of RA and osteoarthritis and is associated with a low incidence of adverse effects. *Nabumetone* is hepatically metabolized by the liver to the active metabolite, which displays the anti-inflammatory, antipyretic, and analgesic activity. The active metabolite is then hepatically

metabolized to inactive metabolites with subsequent renal elimination. Therefore, cautious use of this agent in patients with hepatic impairment is warranted; additionally, the dose should be adjusted in those with creatinine clearance of less than 50 mL/min.

H. Celecoxib

Celecoxib [sel-eh-COCKS-ib] is significantly more selective for inhibition of COX-2 than of COX-1 (Figure 41.10). In fact, at concentrations achieved in vivo, *celecoxib* does not block COX-1. Unlike the inhibition of COX-1 by *aspirin* (which is rapid and irreversible), the inhibition of COX-2 is time dependent and reversible. *Celecoxib* is approved for treatment of RA, osteoarthritis, and pain. Unlike *aspirin, celecoxib* does not inhibit platelet aggregation and does not increase bleeding time. *Celecoxib* has similar efficacy to NSAIDs in the treatment of pain and the risk for cardiovascular events. *Celecoxib*, when used without concomitant *aspirin* therapy, has been shown to be associated with less GI bleeding and dyspepsia; however, this benefit is lost when *aspirin* is added to *celecoxib* therapy. In patients at high risk for ulcers (that is, history of peptic ulcer disease), use of PPIs with *celecoxib* and *aspirin* may be necessary to avoid gastric ulcers.

1. **Pharmacokinetics:** *Celecoxib* is readily absorbed, reaching a peak concentration in about 3 hours. It is extensively metabolized in the liver by cytochrome P450 (CYP2C9) and is excreted in the feces and urine. Its half-life is about 11 hours; thus, the drug is usually taken once a day but can be administered as divided doses twice daily. The daily recommended dose should be reduced by 50 percent in those with moderate hepatic impairment, and *celecoxib* should be avoided in patients with severe hepatic and renal disease.

2. **Adverse effects:** Headache, dyspepsia, diarrhea, and abdominal pain are the most common adverse effects. *Celecoxib* is contraindicated in patients who are allergic to sulfonamides. [Note: If there is a history of sulfonamide drug allergy, then use of a nonselective NSAID along with a PPI is recommended.] As with other NSAIDs, kidney toxicity may occur. *Celecoxib* should be avoided in patients with chronic renal insufficiency, severe heart disease, volume depletion, and/or hepatic failure. Patients who have had anaphylactoid reactions to *aspirin* or nonselective NSAIDs may be at risk for similar effects when challenged with *celecoxib.* Inhibitors of CYP2C9, such as *fluconazole, fluvastatin*, and *zafirlukast*, may increase serum levels of *celecoxib. Celecoxib* has the ability to inhibit CYP2D6 and, thus, could lead to elevated levels of some Î²-blockers, antidepressants, and antipsychotic drugs.

   Figure 41.11 summarizes some of the therapeutic advantages and disadvantages of members of the NSAID family.

IV. Acetaminophen

Acetaminophen [a-SEAT-a-MIN-oh-fen] inhibits prostaglandin synthesis in the CNS. This explains its antipyretic and analgesic properties. *Acetaminophen* has less effect on cyclooxygenase in peripheral tissues, which accounts for its weak anti-inflammatory activity. *Acetaminophen* does not affect platelet function or increase blood clotting time.

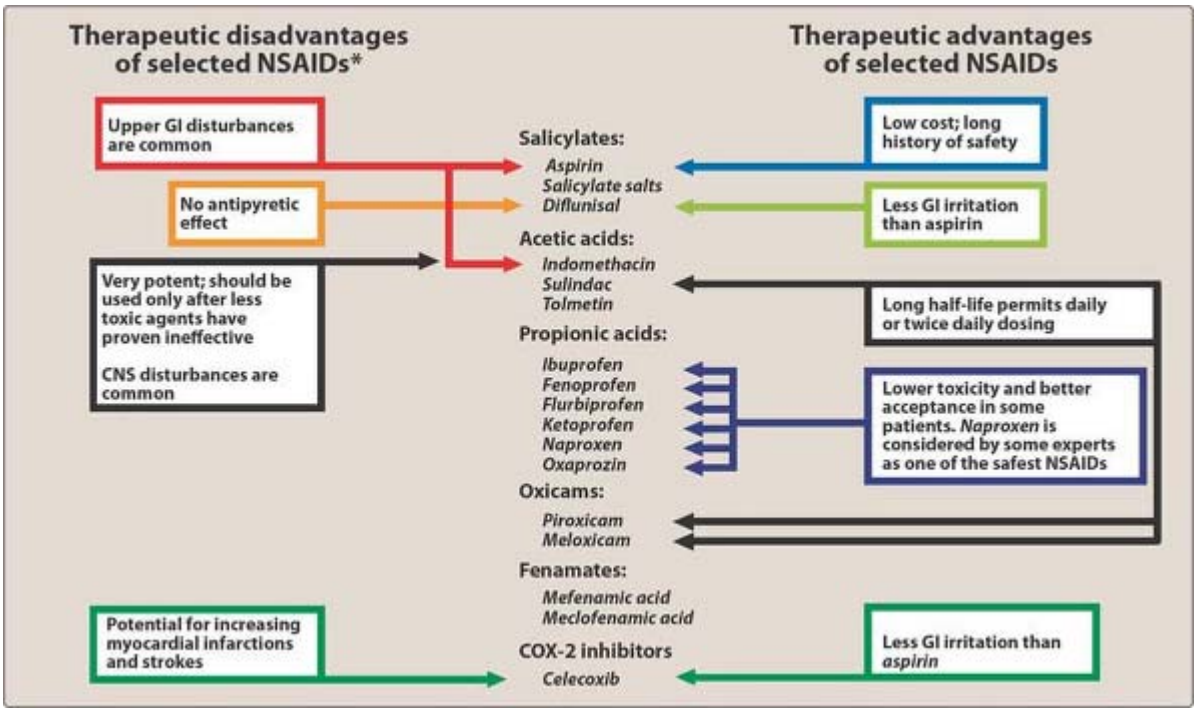


Figure 41.11 Summary of nonsteroidal anti-inflammatory agents (NSAIDs). *As a group, with the exception of *aspirin*, these drugs may have the potential to increase myocardial infarctions and strokes.

A. Therapeutic uses

Acetaminophen is a suitable substitute for the analgesic and antipyretic effects of *aspirin* for those patients with gastric complaints, those in whom prolongation of bleeding time would be a disadvantage, or those who do not require the anti-inflammatory action of *aspirin*. *Acetaminophen* is the analgesic/antipyretic of choice for children with viral infections or chickenpox (recall that *aspirin* increases the risk of Reye's syndrome). *Acetaminophen* does not antagonize the uricosuric agents *probenecid or sulfinpyrazone* and, therefore, may be used in patients with gout who are taking these drugs.

B. Pharmacokinetics

Acetaminophen is rapidly absorbed from the GI tract. A significant first-pass metabolism occurs in the luminal cells of the intestine and in the hepatocytes. Under normal circumstances, *acetaminophen* is conjugated in the liver to form inactive glucuronidated or sulfated metabolites. A portion of *acetaminophen* is hydroxylated to form N-acetylbenzoiminoquinoneâ€"a highly reactive and potentially dangerous metabolite that reacts with sulfhydryl groups. At normal doses of *acetaminophen*, the N-acetylbenzoiminoquinone reacts with the sulfhydryl group of glutathione, forming a nontoxic substance (Figure 41.12). *Acetaminophen* and its metabolites are excreted in the urine.

C. Adverse effects

With normal therapeutic doses, *acetaminophen* is virtually free of any significant adverse effects. Skin rash and minor allergic reactions occur infrequently. There may be minor alterations in the leukocyte count, but these are generally transient. Renal tubular necrosis and hypoglycemic coma are rare complications of prolonged, large-dose

therapy. With large doses of *acetaminophen,* the available glutathione in the liver becomes depleted, and N-acetylbenzoiminoquinone reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds (see Figure 41.12). Hepatic necrosis, a very serious and potentially life-threatening condition, can result. Renal tubular necrosis may also occur. [Note: Administration of N-acetylcysteine, which contains sulfhydryl groups to which the toxic metabolite can bind, can be lifesaving if administered within 10 hours of the overdose.] This agent should be avoided in patients with severe hepatic impairment. Periodic monitoring of liver enzymes tests is recommended for those on high-dose *acetaminophen*.

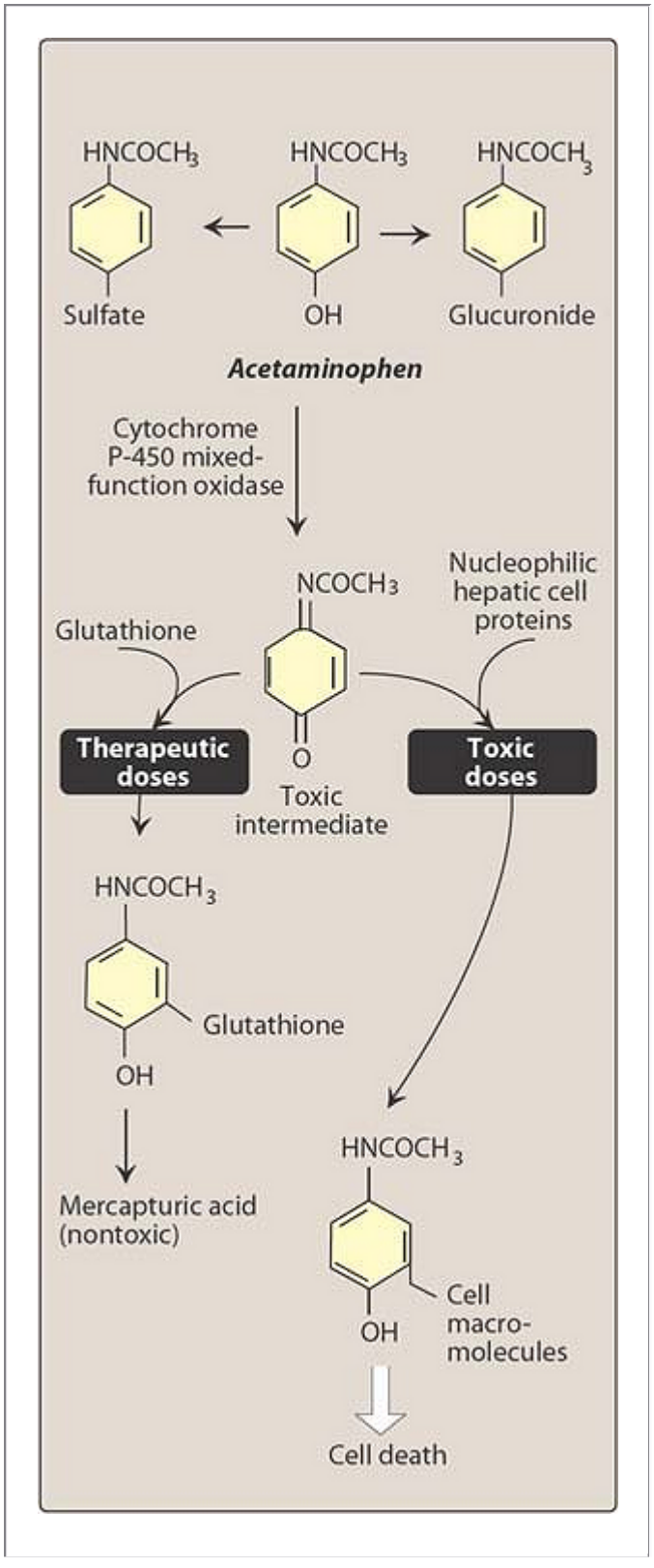


Figure 41.12 Metabolism of *acetaminophen*.

V. Disease-Modifying Antirheumatic Agents

Disease-modifying antirheumatic drugs (DMARDs) are used in the treatment of RA and have been shown to slow the course of the disease, induce remission, and prevent further destruction of the joints and involved tissues. When a patient is diagnosed with RA, the American College of Rheumatology recommends initiation of therapy with DMARDs within 3 months of diagnosis (in addition to NSAIDs, low-dose corticosteroids, physical therapy, and occupational therapy). Therapy with DMARDs is initiated rapidly to help stop the progression of the disease at the earlier stages.

A. Choice of drug

No one DMARD is efficacious and safe in every patient, and trials of several different drugs may be necessary. Most experts begin DMARD therapy with one of the traditional drugs, such as *methotrexate* or *hydroxychloroquine*. These agents are efficacious and are generally well tolerated, with well-known side-effect profiles. Inadequate response to the traditional agents may be followed by use of newer DMARDs, such as *leflunomide, anakinra,* and TNF-inhibitors *(adalimumab, etanercept*,

and *infliximab).* Combination therapies are both safe and efficacious. In most cases, *methotrexate* is combined with one of the other DMARDs. In patients who do not respond to combination therapy with *methotrexate* plus TNF inhibitors, or other combinations, treatment with *rituximab* or *abatacept* may be tried. Most of these agents are contraindicated for use in pregnant women.

B. Methotrexate

Methotrexate [meth-oh-TREX-ate], used alone or in combination therapy, has become the mainstay of treatment in patients with rheumatoid or psoriatic arthritis. *Methotrexate* slows the appearance of new erosions within involved joints on radiographs. Response to *methotrexate* occurs within 3 to 6 weeks of starting treatment. It is an immunosuppressant, and this may account for its effectiveness in an autoimmune disease. The other DMARDs can be added to *methotrexate* therapy if there is partial or no response to maximum doses of *methotrexate.* Doses of *methotrexate* required for this treatment are much lower than those needed in cancer chemotherapy and are given once a week; therefore, the adverse effects are minimized. The most common side effects observed after *methotrexate* treatment of RA are mucosal ulceration and nausea. Cytopenias (particularly depression of the WBC count), cirrhosis of the liver, and an acute pneumonia-like syndrome may occur on chronic administration. [Note: Taking *leucovorin* once daily after *methotrexate* reduces the severity of the adverse effects.] Contrary to early concerns, there have been minimal unexpected side effects after more than 20 years of surveillance, but periodic monitoring for signs of infections, complete blood counts, and liver enzymes tests are recommended.

C. Leflunomide

Leflunomide (le-FLOO-no-mide) is an immunomodulatory agent that preferentially causes cell arrest of the autoimmune lymphocytes through its action on dihydroorotate dehydrogenase (DHODH). Activated proliferating lymphocytes require constant DNA synthesis to proliferate. Pyrimidines and purines are the building blocks of DNA, and DHODH is necessary for pyrimidine synthesis. After biotransformation, *leflunomide* becomes a reversible inhibitor of DHODH (Figure 41.13). *Leflunomide* has been approved for the treatment of RA. It not only reduces pain and inflammation associated with the disease but also appears to slow the progression of structural damage. *Leflunomide* can be used in monotherapy as an alternative to *methotrexate* or as an addition to *methotrexate* in combination therapy.

1. **Pharmacokinetics:** *Leflunomide* is well absorbed after oral administration. It is extensively bound to albumin (>90 percent) and has a half-life of 14 to 18 days. [Note: Because of its long half-life, loading doses are

necessary.] *Leflunomide* is rapidly converted to the active metabolite. The metabolites are excreted in the urine and the feces. The active metabolite undergoes biliary recycling.

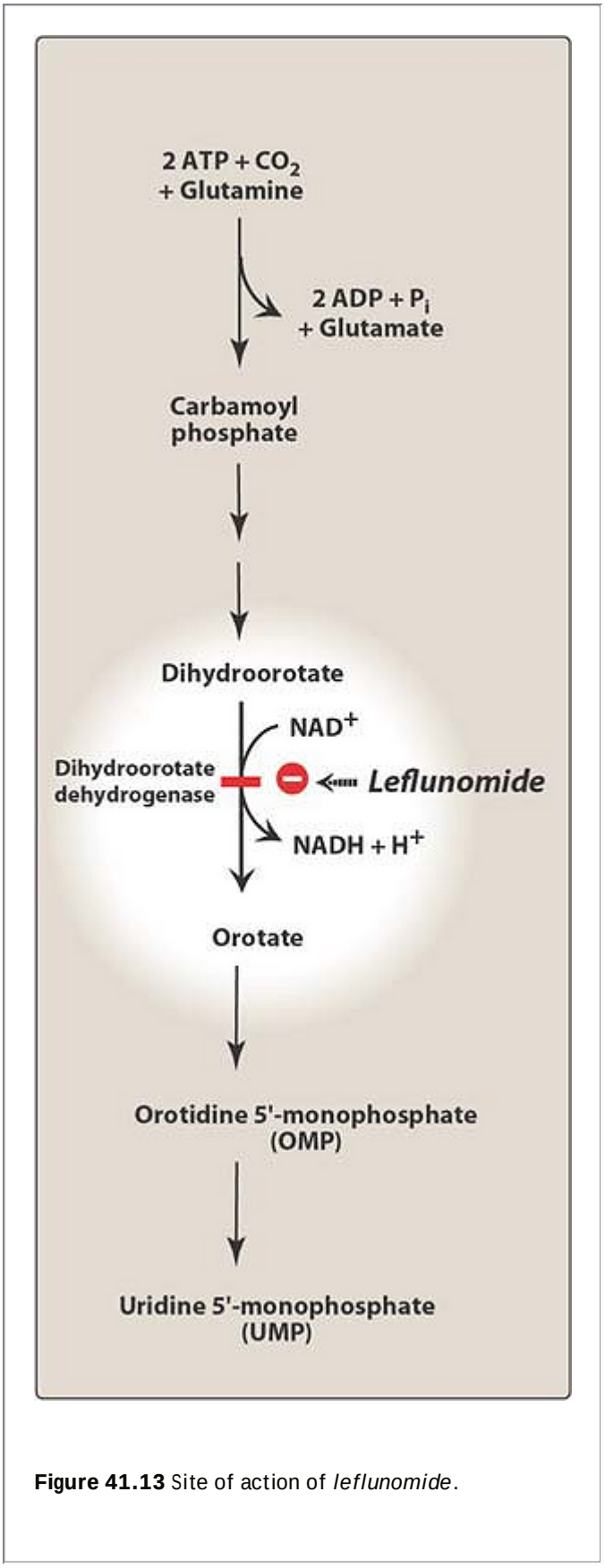


Figure 41.13 Site of action of *leflunomide*.

2. **Adverse effects:** The most common of these are headache, diarrhea, and nausea. Other untoward effects are

weight loss, allergic reactions including a flu-like syndrome, skin rash, alopecia, and hypokalemia. *Leflunomide* is teratogenic in experimental animals and, therefore, is contraindicated in pregnancy and in women of child-bearing potential. It should be used with caution in patients who have liver disease, because it is cleared by both biliary and renal

excretion. Monitoring parameters include signs of infections, complete blood counts, and liver enzymes tests.

D. Hydroxychloroquine

This agent is also used in the treatment of malaria. It is used for early, mild RA and has relatively few side effects. When used alone, it does not slow joint damage, therefore, it is often used in combination with *methotrexate.* Its mechanism of action may include inhibition of phospholipase A_2 and platelet aggregation, membrane stabilization, effects on the immune system, and antioxidant activity. It may cause renal toxicity

E. Sulfasalazine

Sulfasalazine [sull-fa-SAH-la-zeen] is also used for early, mild RA in combination with *hydroxycholoroquine* and *methotrexate*. Onset of activity is 1 to 3 months, and it is associated with leukopenia.

F. D-Penicillamine

D-Penicillamine [pen-ih-SILL-a-meen], an analog of the amino acid cysteine, slows the progression of bone destruction and RA. This agent is used as add-on therapy to existing NSAID/glucocorticoid therapy, but use in patients on DMARD therapy is avoided due to serious adverse events (for example, blood dyscrasias or renal impairment). Prolonged treatment with *penicillamine* has serious side effects, ranging from dermatologic problems to nephritis and aplastic anemia. [Note: *D-Penicillamine* is used as a chelating agent in the treatment of poisoning by heavy metals. It is also of benefit in treating cystinuria.]

G. Gold salts

Gold compounds, like the other drugs in this group, cannot repair existing damage. They can only prevent further injury. The currently available gold preparation is *auranofin* for oral administration. This agent is taken up by macrophages and will suppress phagocytosis and lysosomal enzyme activity. This mechanism retards the progression of bone and articular destruction, and beneficial effects may be seen in 3 to 6 months. The gold compounds are being used infrequently by rheumatologists because of the need for meticulous monitoring for serious toxicity (for example, myelosuppression) and the costs of monitoring.

VI. Biologic Therapies in Rheumatoid Arthritis

Interleukin-1b and TNF-Î± are proinflammatory cytokines involved in the pathogenesis of RA. When secreted by synovial macrophages, IL-1b and TNF-Î± stimulate synovial cells to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglycan synthesis. The TNF inhibitors (*etanercept, adalimumab*, and *infliximab*) have been shown to decrease signs and symptoms of RA, reduce progression of structural damage, and improve physical function; clinical response can be seen within 2 weeks of therapy. If a patient has failed therapy with one TNF inhibitor, a trial with a different TNF inhibitor is appropriate. Many experts propose that a TNF inhibitor plus *methotrexate* be considered as standard therapy for patients with rheumatoid and psoriatic arthritis. Indeed, TNF inhibitors can be administered with any of the other DMARDs, except for *anakinra*, an IL-1 receptor antagonist. Patients receiving TNF inhibitors are at increased risk for infections (tuberculosis, and sepsis), fungal opportunistic infections, and pancytopenia. Live vaccinations should

not be administered while on TNF-inhibitor therapy. These agents should be used very cautiously in those with heart failure, because these agents can cause and worsen preexisting heart failure.

A. Etanercept

Etanercept [ee-TAN-er-cept] is a genetically engineered fusion protein that binds to TNF-Î±, thereby blocking its interaction with cell surface TNF receptors. This agent is approved for use in patients with moderate to severe RA, either alone or in combination with *methotrexate.* It is also approved for use in patients with polyarticular-course juvenile RA, psoriatic arthritis, ankylosing spondylitis, and psoriasis. The combination of *etanercept* and *methotrexate* is more effective than *methotrexate* or *etanercept* alone in retarding the disease process, improving function, and achieving remission (Figure 41.14). Upon discontinuation of *etanercept*, the symptoms of arthritis generally return within a month.

1. **Pharmacokinetics:** *Etanercept* is given subcutaneously twice a week. The time to maximum serum concentration after a single injection is about 72 hours. Its median half-life is 115 hours.
2. **Adverse effects:** *Etanercept* is well tolerated. No toxicities or antibodies have been reported. However, it can produce local inflammation at the site of injection.

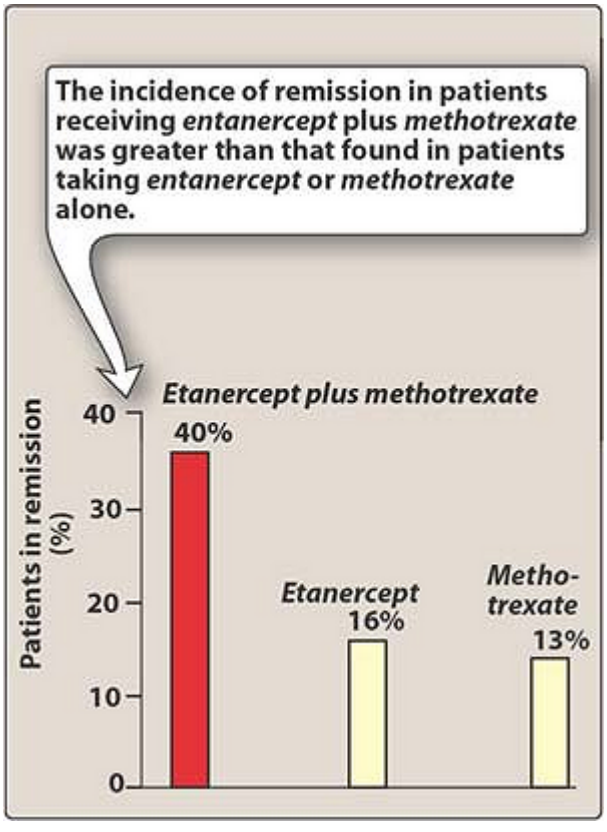


Figure 41.14 Incidence of remission from the symptoms of rheumatoid arthritis after 1 year of therapy.

B. Infliximab

Infliximab (in-FLIX-i-mab) is a chimeric IgGÎº monoclonal antibody composed of human and murine regions. The antibody binds specifically to human TNF-Î±, thereby neutralizing that cytokine. *Infliximab* is approved for use in combination with *methotrexate* in patients with RA who have had inadequate response to *methotrexate* monotherapy. This agent is not indicated for use alone, because monotherapy allows the body to develop anti-*infliximab* antibodies, with a reduction in efficacy. Additional indications include plaque psoriasis, psoriatic arthritis, ulcerative colitis, ankylosing spondylitis, and Crohn's disease for both fistulizing and nonfistulizing disease. [Note: Increased levels of TNF-Î± are found in fecal samples of patients with Crohn's disease].

1. **Pharmacokinetics:** *Infliximab* is infused IV over at least 2 hours. It distributes in the vascular compartment and has a half-life of 9.5 days. Its metabolism and elimination have not been described.

2. **Adverse effects:** Infusion reactions, such as fever, chills, pruritus, or urticaria, have occurred. Infections leading to pneumonia, cellulitis, and other conditions have also been reported. Leukopenia, neutropenia, thrombocytopenia, and pancytopenia have occurred. Whether treatment with *infliximab* predisposes to lymphoma, a condition that occurs with immunosuppressive or immune-altering drugs, remains to be established. [Note: *Infliximab* treatment does predispose to infections, which may be life-threatening.]

C. Adalimumab

Adalimumab [a-dal-AYE-mu-mab] is a recombinant monoclonal antibody that binds to human TNF-Î± receptor sites, thereby interfering with endogenous TNF-Î± activity. This agent is indicated for treatment of moderate to severe RA, either as monotherapy or in combination with *methotrexate.* It is also indicated for psoriatic arthritis, ankylosing

spondylitis, and Crohn's disease. *Adalimumab* is administered subcutaneously weekly or every other week. It may cause headache, nausea, rash, reaction at the injection site or increased risk of infection.

D. Anakinra

Interleukin-1 is induced by inflammatory stimuli and mediates a variety of immunologic responses, including degradation of cartilage and stimulation of bone resorption. *Anakinra* [an-a-KIN-ra] is an IL-1 receptor antagonist because it binds to the IL-1 receptor, thus preventing actions of IL-1. *Anakinra* treatment leads to a modest reduction in the signs and symptoms of moderately to severely active RA in adult patients who have failed one or more DMARDs. The drug may be used alone or in combination with DMARDs (other than TNF inhibitors). Patients should be monitored for signs of infection (tuberculosis and opportunistic infections have not been reported with this agent) and undergo absolute neutrophil counts, because this agent is associated with neutropenia. This agent is administered subcutaneously once a day if renal function is normal, and every other day in those with moderate to severe renal impairment.

E. Abatacept

T lymphocytes need two interactions to become activated: 1) the antigen-presenting cell (that is, macrophages or B cells) must interact with the receptor on the T cell, and 2) the CD80/CD86 protein on the antigen-presenting cell must interact with the CD28 protein on the T cell. The result is activated T lymphocytes responsible for the release of proinflammatory cytokines and maintenance of inflammation in RA. However, T lymphocytes contain another protein, CTLA4, which can bind to the CD80/86 protein found on the antigen-presenting cell; in fact, CTLA4 has higher binding affinity for CD80/86 than does CD28. Binding of CTLA4 to CD80/86 results in deactivation of the T lymphocyte. *Abatacept* [a-BAT-ah-cept] (CTLA-4Ig) is a soluble recombinant fusion protein made up of the extracellular domain of human CTLA4, and it competes with CD28 for binding on CD80/CD86 protein, thereby preventing full T-cell activation. This agent is indicated for reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderate to severe RA who have had an inadequate response to DMARDs such as *methotrexate* or TNF inhibitors. *Abatacept* can be used alone or with DMARDs other than TNF inhibitors or *anakinra.*

1. **Pharmacokinetics:** The recommended dose is based upon weight and is administered as an IV infusion over 30 minutes at Weeks 2 and 4 after the first infusion and every 4 weeks thereafter with monitoring for infusion reactions. The terminal half-life in RA patients administered multiple doses of 10 mg/kg is 13 days (range, 8â€“25 days).

2. **Adverse effects:** The most commonly reported adverse effects include headache, upper respiratory infections, nasopharyngitis, and nausea. Concurrent use with TNF inhibitors and *anakinra* is not recommended due to increased risk of serious infections.

F. Rituximab

B lymphocytes are derived from the bone marrow and are necessary for efficient immune response; however, in RA, B cells can perpetuate the

inflammatory process in the synovium by 1) activating T lymphocytes, 2) producing autoantibodies such as anti-CCP (antiâ€“cyclic citrullinated peptide antibody) and rheumatoid factor, and 3) producing pro-inflammatory cytokines such as TNF-Î± and IL-1. *Rituximab* [ri-TUK-si-mab]is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes, resulting in B-cell depletion. This agent is indicated for use in combination with *methotrexate* to reduce signs and symptoms in adult patients with moderate to severe RA who have had an inadequate response to one or more TNF-inhibitors. *Rituximab* has been shown to reduce joint erosion and joint space narrowing in these patients.

1. **Pharmacokinetics:** *Rituximab* is administered as two 1000-mg IV infusions separated by 2 weeks. To reduce the severity of infusion reactions, *methylprednisolone* at 100 mg IV or its equivalent is administered 30 minutes prior to each infusion. The mean terminal elimination half-life after the second dose is 19 days.
2. **Adverse effects:** Infusion reactions (that is, urticaria, hypotension, or angioedema) are the most common complaints with this agent and typically occur during the first infusion. The infusion may be interrupted and the patient treated with vasopressors, antihistamines, and fluids. If the infusion is to be continued, then the rate of infusion should be reduced by 50 percent after symptoms have completely resolved.

VII. Drugs Employed in the Treatment of Gout

Gout is a metabolic disorder characterized by high levels of uric acid in the blood. Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney. Hyperuricemia does not always lead to gout, but gout is always preceded by hyperuricemia. In humans, sodium urate is the end product of purine metabolism.[5] The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals (Figure 41.15). This process generates oxygen metabolites, which damage tissues, resulting in the release of lysosomal enzymes that evoke an inflammatory response. In addition, there is increased production of lactate in the synovial tissues. The resulting local decrease in pH fosters further deposition of urate crystals. The cause of hyperuricemia is an overproduction of uric acid relative to the patient's ability to excrete it. Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (<6 mg/dL), thus preventing the deposition of urate crystals. This can be accomplished by 1) interfering with uric acid synthesis with *allopurinol*, 2) increasing uric acid excretion with *probenecid* or *sulfinpyrazone*, 3) inhibiting leukocyte entry into the affected joint with *colchicine*, or 4) administration of NSAIDs.

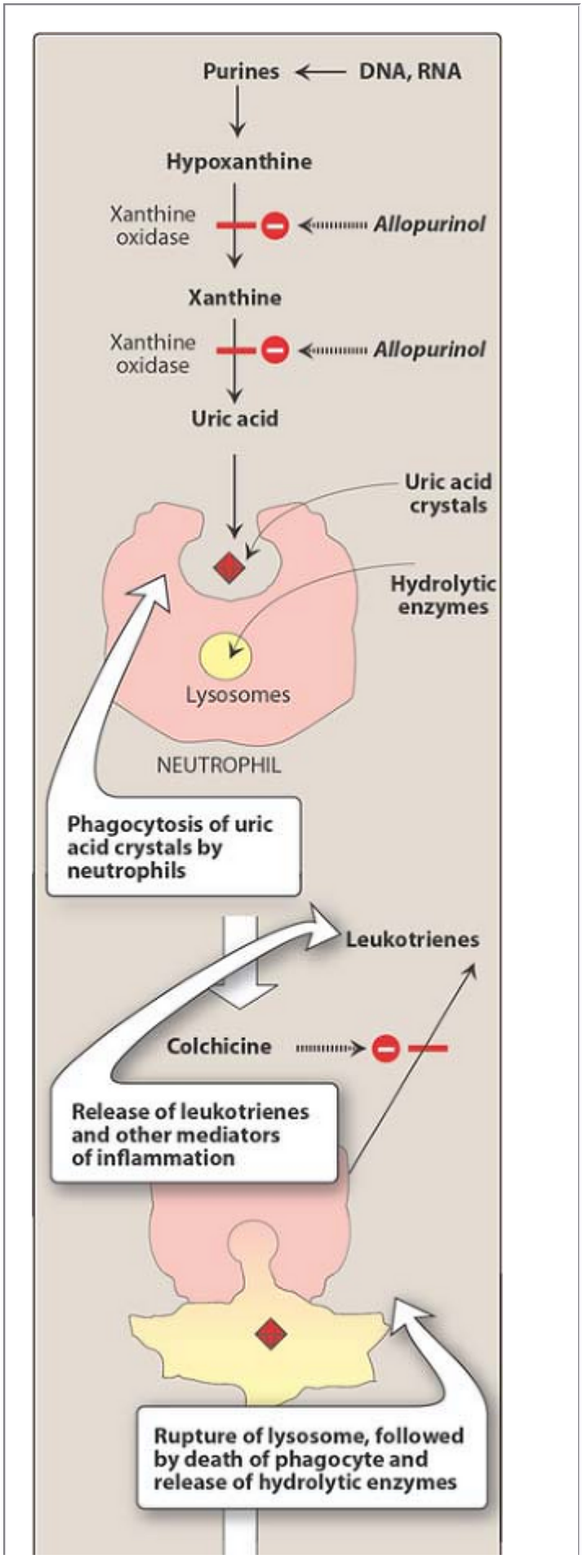

Purines
DNA, RNA
Hypoxanthine
Xanthine oxidase
Allopurinol
Xanthine
Xanthine oxidase
Allopurinol
Uric acid
Uric acid crystals
Hydrolytic enzymes
Lysosomes
NEUTROPHIL
Phagocytosis of uric acid crystals by neutrophils
Leukotrienes
Colchicine
Release of leukotrienes and other mediators of inflammation
Rupture of lysosome, followed by death of phagocyte and release of hydrolytic enzymes

Figure 41.15 Role of uric acid in the inflammation of gout.

A. Treating acute gout

Acute gouty attacks can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, or kidney disease. Acute attacks are treated with *indomethacin* to decrease movement of granulocytes into the affected area; NSAIDs other than *indomethacin*

are also effective at decreasing pain and inflammation. [Note: *Aspirin* is contraindicated, because it competes with uric acid for the organic acid secretion mechanism in the proximal tubule of the kidney.] The initial NSAID dose should be doubled within the first 24 to 48 hours (maintain recommended dosing interval per specific NSAID) and then reduced over the next few days. Intra-articular administration of glucocorticoids (when only one or two joints are affected) is also appropriate in the acute setting. Patients are candidates for prophylactic therapy if they have had more than two attacks per year, the first attack is severe or complicated with kidney stones, serum urate is greater than 10 mg/dL, or urinary urate excretion exceeds 1000 mg per 24 hours.

B. Treating chronic gout

Chronic gout can be caused by 1) a genetic defect, such as one resulting in an increase in the rate of purine synthesis; 2) renal deficiency; 3) Lesch-Nyhan syndrome;[6] or 4) excessive productionof uric acid associated with cancer chemotherapy. Treatment strategies for chronic gout include the use of uricosuric drugs that increase the excretion of uric acid, thereby reducing its concentration in plasma, and the use of *allopurinol*, which is a selective inhibitor of the terminal steps in the biosynthesis of uric acid. Uricosuric agents are first-line agents for patients with gout associated with reduced urinary excretion of uric acid. *Allopurinol* is preferred in patients with excessive uric acid synthesis, with previous histories of uric acid stones, or with renal insufficiency.

C. Colchicine

Colchicine [KOL-chi-seen], a plant alkaloid, has been used for the treatment of acute gouty attacks as well as chronic gout. It is neither a uricosuric nor an analgesic agent, although it relieves pain in acute attacks of gout. *Colchicine* does not prevent the progression of gout to acute gouty arthritis, but it does have a suppressive, prophylactic effect that reduces the frequency of acute attacks and relieves pain.

1. **Mechanism of action:** *Colchicine* binds to tubulin, a microtubular protein, causing its depolymerization. This disrupts cellular functions, such as the mobility of granulocytes, thus decreasing their migration into the affected area. Furthermore, *colchicine* blocks cell division by binding to mitotic spindles. *Colchicine* also inhibits the synthesis and release of the leukotrienes (see Figure 41.15).
2. **Therapeutic uses:** The anti-inflammatory activity of *colchicine* is specific for gout, usually alleviating the pain of acute gout within 12 hours. (Note: *Colchicine* must be administered within 24 to 48 hours of onset of attack to be effective). NSAIDs have largely replaced *colchicine* in the treatment of acute gouty attacks. *Colchicine* is currently used for prophylaxis of recurrent attacks and will prevent attacks in more than 80 percent of patients.
3. **Pharmacokinetics:** *Colchicine* is administered orally, followed by rapid absorption from the GI tract. It is also available combined with *probenecid* (see below). *Colchicine* is recycled in the bile and is excreted unchanged in the feces or urine. Use should be avoided in patients with a creatinine clearance of less than 50 mL/min.

4. **Adverse effects:** *Colchicine* treatment may cause nausea, vomiting, abdominal pain, and diarrhea (Figure 41.16). Chronic administration may lead to myopathy, neutropenia, aplastic anemia, and alopecia. The drug

should not be used in pregnancy, and it should be used with caution in patients with hepatic, renal, or cardiovascular disease. The fatal dose has been reprted as low as 7 to 10 mg.

D. Allopurinol

Allopurinol [al-oh-PURE-i-nole] is a purine analog. It reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase (see Figure 41.15). [Note: Uric acid is less water soluble than its precursors. When xanthine oxidase is inhibited, the circulating purine derivatives (xanthine and hypoxanthine) are more soluble and, therefore, are less likely to precipitate.]

1. **Therapeutic uses:** *Allopurinol* is effective in the treatment of primary hyperuricemia of gout and hyperuricemia secondary to other conditions, such as that associated with certain malignancies (those in which large amounts of purines are produced, particularly after treatment with chemotherapeutic agents) or in renal disease. This agent is the drug of choice in those with a history of kidney stones or if the creatinine clearance is less than 50 mL/day.

2. **Pharmacokinetics:** *Allopurinol* is completely absorbed after oral administration. The primary metabolite is alloxanthine (oxypurinol), which is also a xanthine oxidase inhibitor with a half-life of 15 to 18 hours; the half-life of *allopurinol* is 2 hours. Thus, effective inhibition of xanthine oxidase can be maintained with once-daily dosage. The drug and its active metabolite are excreted in the feces and urine.

3. **Adverse effects:** *Allopurinol* is well tolerated by most patients. Hypersensitivity reactions, especially skin rashes, are the most common adverse reactions, occurring in approximately three percent of patients. The reactions may occur even after months or years of chronic administration, and *allopurinol* therapy should be discontinued. Acute attacks of gout may occur more frequently during the first several weeks of therapy; therefore, *colchicine* or NSAIDs should be administered concurrently. GI side effects, such as nausea and diarrhea, are common. *Allopurinol* interferes with the metabolism of the anticancer agent *6-mercaptopurine* and the immunosuppressant *azathioprine*, requiring a reduction in dosage of these drugs.

Figure 41.16 Some adverse effects of *colchicine*.

E. Uricosuric agents: Probenecid and sulfinpyrazone

The uricosuric drugs are weak organic acids that promote renal clearance of uric acid by inhibiting the urate-anion exchanger in the proximal tubule that mediates urate reabsorption. *Probenecid* [proe-BEN-e-sid], a general inhibitor of the tubular secretion of organic acids, and *sulfinpyrazone* [sul-fin-PEER-a-zone], a derivative of *phenylbutazone*, are the two most commonly used uricosuric agents. At therapeutic doses, they block proximal tubular resorption of uric acid. [Note: At low dosage, these agents block proximal tubular secretion of uric acid.] These drugs have few adverse effects, although gastric distress may force discontinuance of *sulfinpyrazone*. *Probenecid* blocks the tubular secretion of *penicillin* and is sometimes used to increase levels of the antibiotic. It also inhibits excretion of *naproxen, ketoprofen,* and *indomethacin.* These agents are appropriate for patients who have a creatinine clearance of less than 60 mL/min, undersecrete uric acid (<700 mg/day), and do not have a history of kidney stones.

Study Questions

Choose the ONE best answer.

41.1 In which one of the following conditions would aspirin be contraindicated?

A. Myalgia.

B. Fever.

C. Peptic ulcer.

D. RA.

E. Unstable angina.

View Answer

41.2 Which one of the following statements concerning COX-2 inhibitors is correct?

A. The COX-2 inhibitors show greater analgesic activity than traditional NSAIDs.

B. The COX-2 inhibitors decrease platelet function.

C. The COX-2 inhibitors do not affect the kidney.

D. The COX-2 inhibitors show anti-inflammatory activity similar to that of the traditional NSAIDs.

E. The COX-2 inhibitors are cardioprotective.

View Answer

41.3 An 8-year-old girl has a fever and muscle aches from a presumptive viral infection. Which one of the following drugs would be most appropriate to treat her symptoms?

A. Acetaminophen.

B. Aspirin.

C. Celecoxib.

D. Codeine.

E. Indomethacin.

View Answer

41.4 A 70-year-old man has a history of ulcer disease. He has recently experienced swelling and pain in the joints of his hands. His physician wants to begin therapy with an NSAID. Which one of the following drugs might also be prescribed along with the NSAID to reduce the risk of activating this patient's ulcer disease?

A. Allopurinol.

B. Colchicine.

C. Misoprostol.

D. Probenecid.

E. Sulindac.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 42

Autacoids and Autacoid Antagonists

I. Overview

Prostaglandins, histamine, and serotonin belong to a group of compounds called autacoids. These heterogeneous substances have widely differing structures and pharmacologic activities. They all have the common feature of being formed by the tissues on which they act; thus, they function as local hormones. [Note: The word autacoid comes from the Greek: autos (self) and akos (medicinal agent, or remedy).] The autacoids also differ from circulating hormones in that they are produced by many tissues rather than in specific endocrine glands. The drugs described in this chapter (Figure 42.1) are either autacoids or autacoid antagonists (compounds that inhibit the synthesis of certain autacoids or that interfere with their interactions with receptors).

II. Prostaglandins

Prostaglandins are unsaturated fatty acid derivatives that act on the tissues in which they are synthesized and are rapidly metabolized to inactive products at the site of action.[1]

A. Therapeutic uses of prostaglandins

Systemic administration of prostaglandins evokes a bewildering array of effectsâ€”a fact that limits the therapeutic usefulness of these agents.

1. **Abortion:** Several of the prostaglandins find use as abortifacients (agents causing abortions). The most effective option available involves oral administration *mifepristone* [mi-FEP-ri-stone] (RU-486, a synthetic steroid with antiprogestational effects) followed at least 24 hours later by the synthetic prostaglandin E_1 analog *misoprostol* [mye-so-PROST-ole] administered vaginally (Figure 42.2). Women can self-administer this regimen with complete abortion rates exceeding 95 percent. The overall case-fatality rate for abortion is less than one death per 100,000 procedures. Infection, hemorrhage, and retained tissue are among the more common complications.

Figure 42.1 Summary of drugs affecting the autacoids.

2. **Peptic ulcers:** *Misoprostol* is sometimes used to inhibit the secretion of gastric acid and to enhance mucosal resistance to injury in patients with gastric ulcer who are chronically taking nonsteroidal anti-inflammatory agents. Proton-pump inhibitors, such as *omeprazole*, and H_2 antihistamines also reduce the risk of gastric ulcer and are better tolerated than *misoprostol*, which induces intestinal disorders.

III. Histamine

Histamine is a chemical messenger that mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion, and neurotransmission in parts of the brain. Histamine has no clinical applications, but agents that interfere with the action of histamine (antihistamines) have important therapeutic applications.

A. Location, synthesis, and release

1. **Location:** Histamine occurs in practically all tissues, but it is unevenly distributed, with high amounts found in lung, skin, and the gastrointestinal tract (sites where the â€œinsideâ€ of the body meets the â€œoutsideâ€). It is found at high concentration in mast cells or basophils. Histamine also occurs as a component of venoms and in secretions from insect stings.

2. **Synthesis:** Histamine is an amine formed by the decarboxylation of the amino acid histidine by histidine decarboxylase,[2] an enzyme that is expressed in cells throughout the body, including central nervous system (CNS) neurons, gastric mucosa parietal cells, mast cells, and basophils (Figure 42.3). In mast cells, histamine is stored in granules as an inactive complex composed of histamine and the polysulfated anion, heparin, along with an anionic protein. If histamine is not stored, it is rapidly inactivated by amine oxidase enzymes.

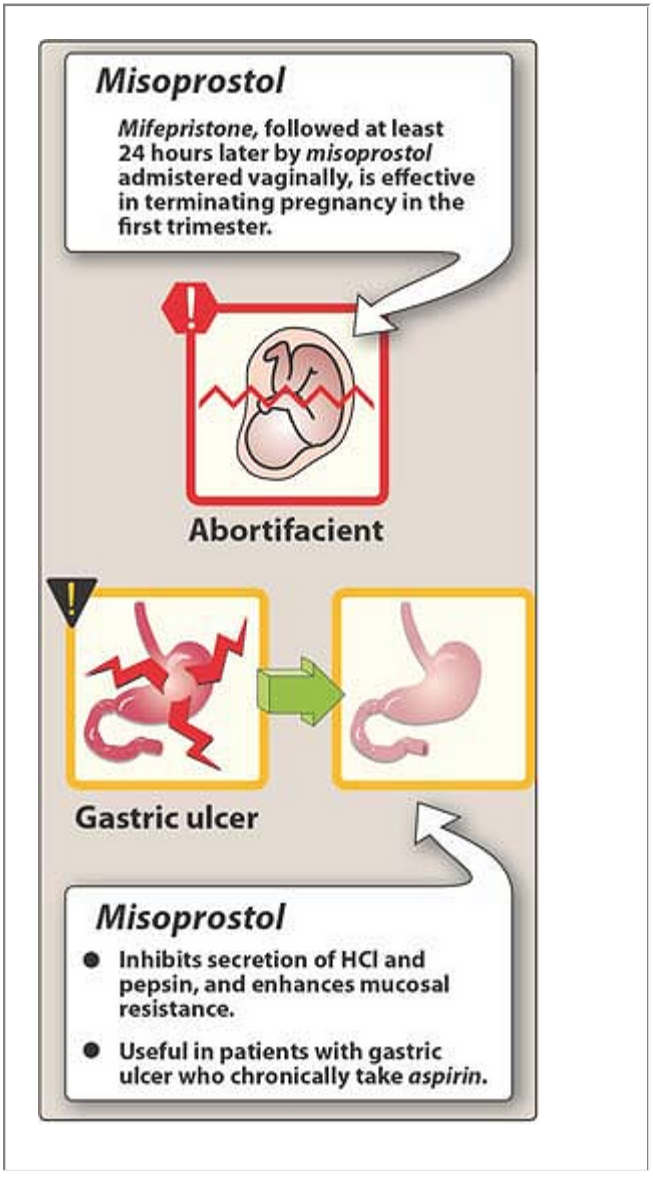


Figure 42.2 Therapeutic applications of *misoprostol*.

3. **Release of histamine:** The release of histamine may be the primary response to some stimuli, but most often, histamine is just one of several chemical mediators released. Stimuli causing the release of histamine from tissues include the destruction of cells as a result of cold, bacterial toxins, bee sting venoms, or trauma. Allergies and anaphylaxis can also trigger release of histamine.

B. Mechanism of action

Histamine released in response to various stimuli exerts its effects by binding to one or more of four types of histamine receptorsâ€"H_1, H_2, H_3, and H_4 receptors. H_1 and H_2 receptors are widely expressed and are the targets of clinically useful drugs. H_3 and H_4 receptors are expressed in only a few cell types, and their roles in drug action are unclear. All types of histamine receptors have seven transmembrane helical domains and transduce extracellular signals by way of G proteinâ€"mediated second-messenger systems. Some of histamine's wide range of pharmacologic effects are mediated by both H_1 and H_2 receptors, whereas

others are mediated by only one class. For example, the H_1 receptors are important in producing smooth muscle contraction and increasing capillary permeability (Figure 42.4). Histamine promotes vasodilation by causing vascular endothelium to release nitric oxide.[3] This chemical signal diffuses to the vascular smooth muscle, where it stimulates cyclic guanosine monophosphate production, causing vasodilation. Histamine H_2 receptors mediate gastric acid secretion. The two most common histamine receptors exert their effects by different second-messenger pathways. The actions of H_1 antihistamines occur through at least two mechanisms. Antiallergic activities of H_1 antihistamines, such as inhibition of the release of mediators from mast cells and basophils, involves stimulation of the intracellular activity of the polyphosphatidylinositol pathway.[4] Other actions of H_1 antihistamines involve the down-regulation of nuclear transcription factors that regulate the production of proinflammatory cytokines and adhesion proteins. In contrast, stimulation of H_2 receptors enhances the production of cyclic adenosine monophosphate (cAMP) by adenylyl cyclase.

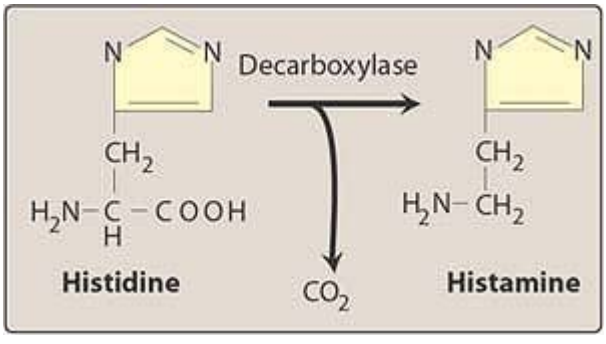


Figure 42.3 Biosynthesis of histamine.

C. Role in allergy and anaphylaxis

The symptoms resulting from intravenous injection of histamine are similar to those associated with anaphylactic

shock and allergic reactions. These include contraction of smooth muscle, stimulation of secretions, dilation and increased permeability of the capillaries, and stimulation of sensory nerve endings.

1. **Role of mediators:** Symptoms associated with allergy and anaphylactic shock result from the release of certain mediators from their storage sites. Such mediators include histamine, serotonin, leukotrienes, and the eosinophil chemotactic factor of anaphylaxis. In some cases, these cause a localized allergic reaction, producing, for example, actions on the skin or respiratory tract. Under other conditions, these mediators may cause a full-blown anaphylactic response. It is thought that the difference between these two situations results from differences in the sites from which mediators are released and in their rates of release. For example, if the release of histamine is slow enough to permit its inactivation before it enters the bloodstream, a local allergic reaction results. However, if histamine release is too fast for inactivation to be efficient, a full-blown anaphylactic reaction occurs.

IV. H_1 Antihistamines

The term antihistamine, without a modifying adjective, refers to the classic H_1-receptor blockers. These compounds do not influence the formation or release of histamine; rather, they block the receptor-mediated response of a target tissue. [Note: This contrasts with the action of *cromolyn* and *nedocromil*, which inhibit the release of histamine from mast cells and are useful in the treatment of asthma.] The H_1-receptor blockers can be divided into first- and second-generation drugs (Figure 42.5). The older first-generation drugs are still widely used because they are effective and inexpensive. However, most of these drugs penetrate the CNS and cause sedation. Furthermore, they tend to interact with other receptors, producing a variety

of unwanted adverse effects. By contrast, the second-generation agents are specific for H_1 receptors, and because they do not penetrate the blood-brain barrier, they show less CNS toxicity than the first-generation drugs. Among these agents *desloratadine* [des-lor-AH-tahdeen], *fexofenadine* [fex-oh-FEN-a-deen], and *loratadine* [lor-AT-a-deen] show the least sedation (Figure 42.6). [Note: The histamine receptors are distinct from those that bind serotonin, acetylcholine, and the catecholamines.]

H_1 Receptors

EXOCRINE EXCRETION

Increased production of nasal and bronchial mucus, resulting in respiratory symptoms.

BRONCHIAL SMOOTH MUSCLE

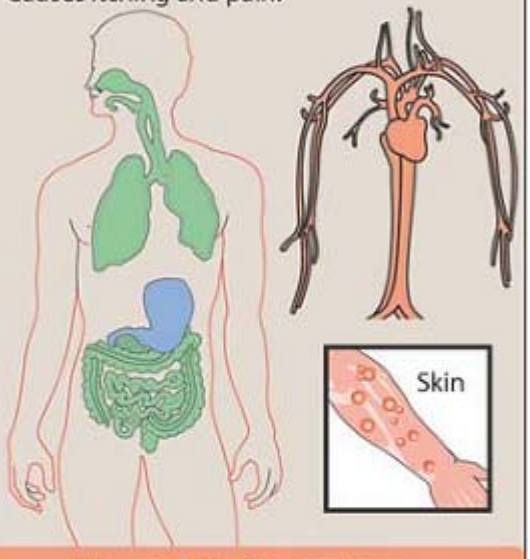
Constriction of bronchioles results in symptoms of asthma and decreased lung capacity.

INTESTINAL SMOOTH MUSCLE

Constriction results in intestinal cramps and diarrhea.

SENSORY NERVE ENDINGS

Causes itching and pain.



H_1 and H_2 Receptors

CARDIOVASCULAR SYSTEM

Lowers systemic blood pressure by reducing peripheral resistance. Causes positive chronotropism (mediated by H_2 receptors) and a positive inotropism (mediated by both H_1 and H_2 receptors).

SKIN

Dilation and increased permeability of the capillaries results in leakage of proteins and fluid into the tissues. In the skin, this results in the classic "triple response": wheal formation, reddening due to local vasodilation, and flare ("halo").

H_2 Receptors

Figure 42.4 Actions of histamine.

A. Actions

The action of all the H_1-receptor blockers is qualitatively similar. However, most of these blockers have additional effects unrelated to their blocking of H_1 receptors; these effects probably reflect binding of the H_1 antagonists to cholinergic, adrenergic, or serotonin receptors (Figure 42.7).

B. Therapeutic uses

1. **Allergic and inflammatory conditions:** H_1-receptor blockers are useful in treating allergies caused by antigens acting on immunoglobulin E antibodyâ€“sensitized mast cells. For example, antihistamines are the drugs of choice in controlling the symptoms of allergic rhinitis and urticaria, because histamine is the principal mediator. However, the H_1-receptor blockers are ineffective in treating bronchial asthma, because histamine is only one of several mediators of that condition. [Note: *Epinephrine* has actions on smooth muscle that are opposite to those of histamine, and it acts at different receptors. Therefore, *epinephrine* is the drug of choice in treating systemic anaphylaxis and other conditions that involve massive release of histamine.] Glucocorticoids show greater anti-inflammatory effects than the H_1 antihistamines.

2. **Motion sickness and nausea:** Along with the antimuscarinic agent *scopolamine*, certain H_1-receptor blockers, such as *diphenhydramine* [dye-fen-HYE-dra-meen], *dimenhydrinate* [dye-men-HYE-dri-nate], *cyclizine* [SYE-kli-zeen], *meclizine* [MEK-li-zeen], and *hydroxyzine* [hye-DROX-ee-zeen] (see Figure 42.5), are the most effective agents for prevention of the symptoms of motion sickness. The antihistamines prevent or diminish vomiting and nausea mediated by both the chemoreceptor and vestibular pathways. The antiemetic action of these medications seems to be due to their blockade of central H_1 and muscarinic receptors.

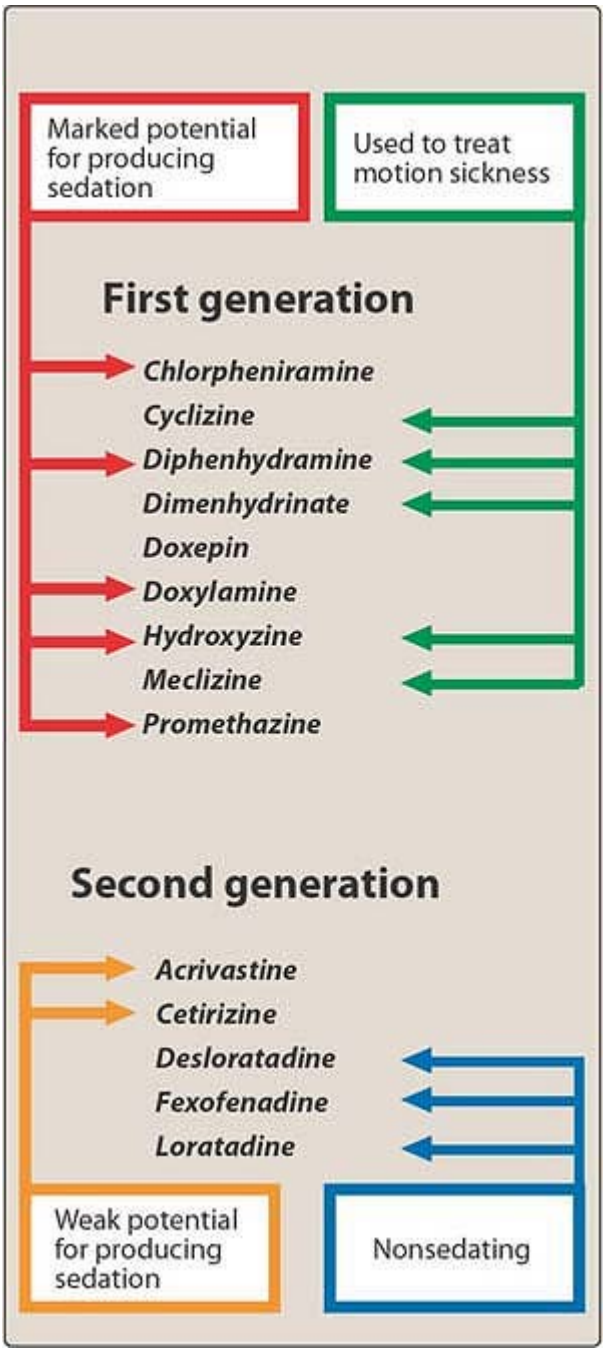


Figure 42.5 Summary of therapeutic advantages and disadvantages of some H_1 histamineâ€"receptor blocking agents.

3. **Somnifacients:** Although they are not the medication of choice, many first-generation antihistamines, such as *diphenhydramine* and *doxylamine* [dox-IL-a-meen], have strong sedative properties and are used in the treatment of insomnia (see Figure 42.5). The use of first-generation H_1 antihistamines is contraindicated in the treatment of individuals working in jobs where wakefulness is critical.

C. Pharmacokinetics

H_1-receptor blockers are well absorbed after oral administration, with maximum serum levels occurring at 1 to 2

hours. The average plasma half-life is 4 to 6 hours except for *meclizine*, which has a half-life of 12 to 24 hours. H_1-receptor blockers have high bioavailability and are distributed in all tissues, including the CNS. All first-generation H_1 antihistamines and some second-generation H_1 antihistamines, such as *desloratadine* and *loratadine*, are metabolized by the hepatic

cytochrome P450 system. *Cetirizine* [seh-TEER-ih-zeen] is excreted largely unchanged in the urine, and *fexofenadine* is excreted largely unchanged in the feces. After a single oral dose, the onset of action occurs within 1 to 3 hours. The duration of action for many oral H_1 antihistamines is at least 24 hours, facilitating once-daily dosing. They are most effective when used prophylactically before allergen exposure rather than as needed. Tolerance to the action of H_1 antihistamines has not been observed.

D. Adverse effects

First-generation H_1-receptor blockers have a low specificity; that is, they interact not only with histamine receptors but also with muscarinic cholinergic receptors, Î±-adrenergic receptors, and serotonin receptors (see Figure 42.7). The extent of interaction with these receptors and, as a result, the nature of the side effects vary with the structure of the drug. Some side effects may be undesirable, and others may have therapeutic value. Furthermore, the incidence and severity of adverse reactions for a given drug varies between individual subjects.

1. **Sedation:** First-generation H_1 antihistamines, such as *chlorpheniramine* [klor-fen-IR-a-meen], *diphenhydramine, hydroxyzine*, and *promethazine* [proe-METH-a-zeen], bind to H_1 receptors and block the neurotransmitter effect of histamine in the CNS. The most frequently observed adverse reaction is sedation (Figure 42.8). Other central actions include tinnitus, fatigue, dizziness, lassitude (a sense of weariness), uncoordination, blurred vision, and tremors. Sedation is less common with the second-generation drugs, which do not readily enter the CNS. Second-generation H_1 antihistamines are specific for H_1 receptors and penetrate the CNS poorly. They show less sedation and other CNS effects.

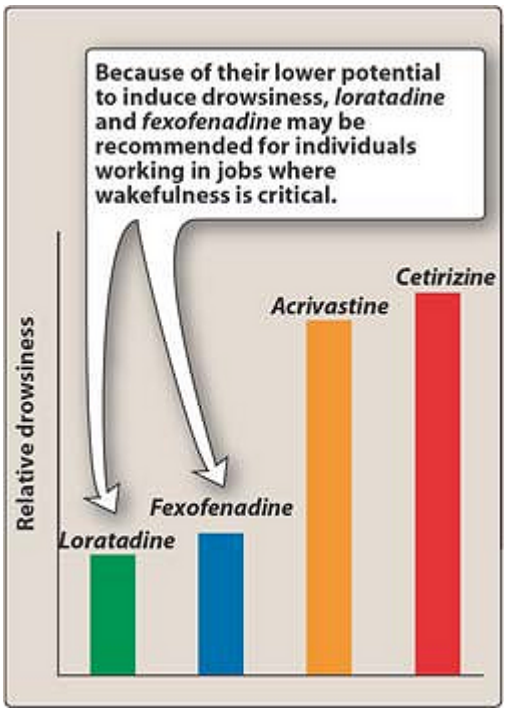


Figure 42.6 Relative potential for causing drowsiness in patients receiving second-generation H1 antihistamines.

2. **Dry mouth:** Oral antihistamines also exert weak anticholinergic effects, leading not only to a drying of the nasal passage but also to a tendency to dry the oral cavity. Blurred vision can occur as well with some drugs.

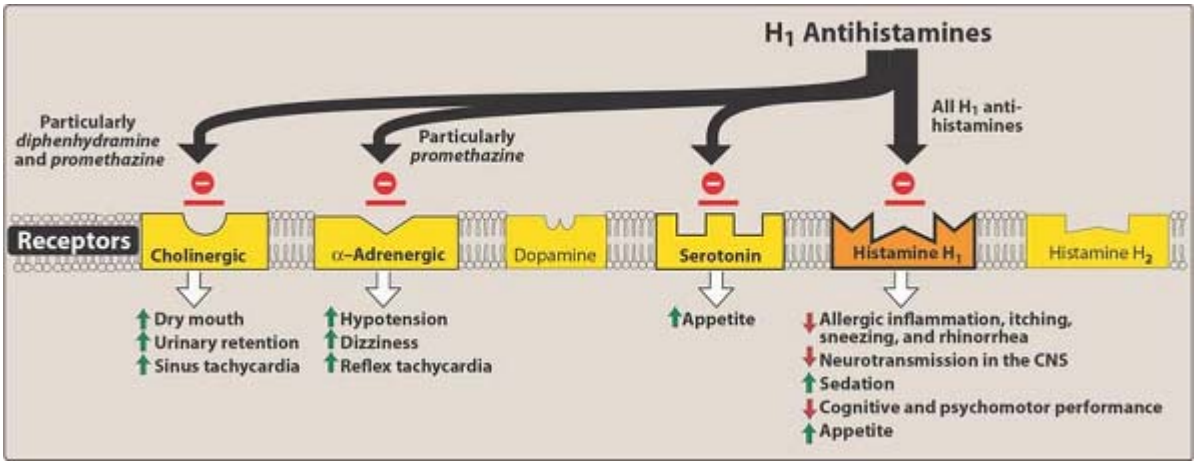


Figure 42.7 Effects of H_1 antihistamines at histamine, adrenergic, cholinergic, and serotonin-binding receptors. Many secondgeneration antihistamines do not enter the brain and, therefore, show minimal CNS effects.

3. **Drug interactions:** Interaction of H_1-receptor blockers with other drugs can cause serious consequences, such as potentiation of the effects of all other CNS depressants, including alcohol. Persons taking monoamine oxidase (MAO) inhibitors should not take antihistamines, because the MAO inhibitors can exacerbate the anticholinergic effects of the antihistamines. In addition, the first-generation antihistamines (*diphenhydramine* and others) have considerable anticholinergic (antimuscarinic) actions. These actions would decrease the effectiveness of cholinesterase inhibitors (*donepezil, rivastigmine*, and *galantamine*) in the treatment of Alzheimer's disease.

4. **Overdoses:** Although the margin of safety of H_1-receptor blockers is relatively high and chronic toxicity is rare, acute poisoning is relatively common, especially in young children. The most common and dangerous effects of acute poisoning are those on the CNS, including hallucinations, excitement, ataxia, and convulsions. If untreated, the patient may experience a deepening coma and collapse of the cardiorespiratory system.

V. Histamine H_2-Receptor Blockers

Histamine H_2-receptor blockers have little, if any, affinity for H_1 receptors. Although antagonists of the histamine H_2 receptor (H_2 antagonists) block the actions of histamine at all H_2 receptors, their chief clinical use is as inhibitors of gastric acid secretion in the treatment of ulcers and heartburn. By competitively blocking the binding of histamine to H_2 receptors, these agents reduce intracellular concentrations of cAMP and, thereby, secretion of gastric acid. The four drugs used in the United Statesâ€"*cimetidin*e, *ranitidine, famotidine*, and *nizatidine*â€"are discussed in Chapter 28.

VI. Drugs Used to Treat Migraine Headache

It has been estimated that 18 million women and 6 million men in the United States suffer from severe migraine headaches. Migraine can usually be distinguished clinically from the two other common types of headachesâ€"cluster headache and tension-type headacheâ€"by its characteristics (Figure 42.9). For example, migraines present as a pulsatile, throbbing pain; cluster headaches, as excruciating, sharp, steady pain; and tension-type headaches, as dull pain, with a persistent, tightening feeling in the head. Patients with severe migraine headaches report one to five attacks per month of moderate to severe pain, usually unilateral. The headaches affect patients for a major part of their lives and result in considerable health costs.

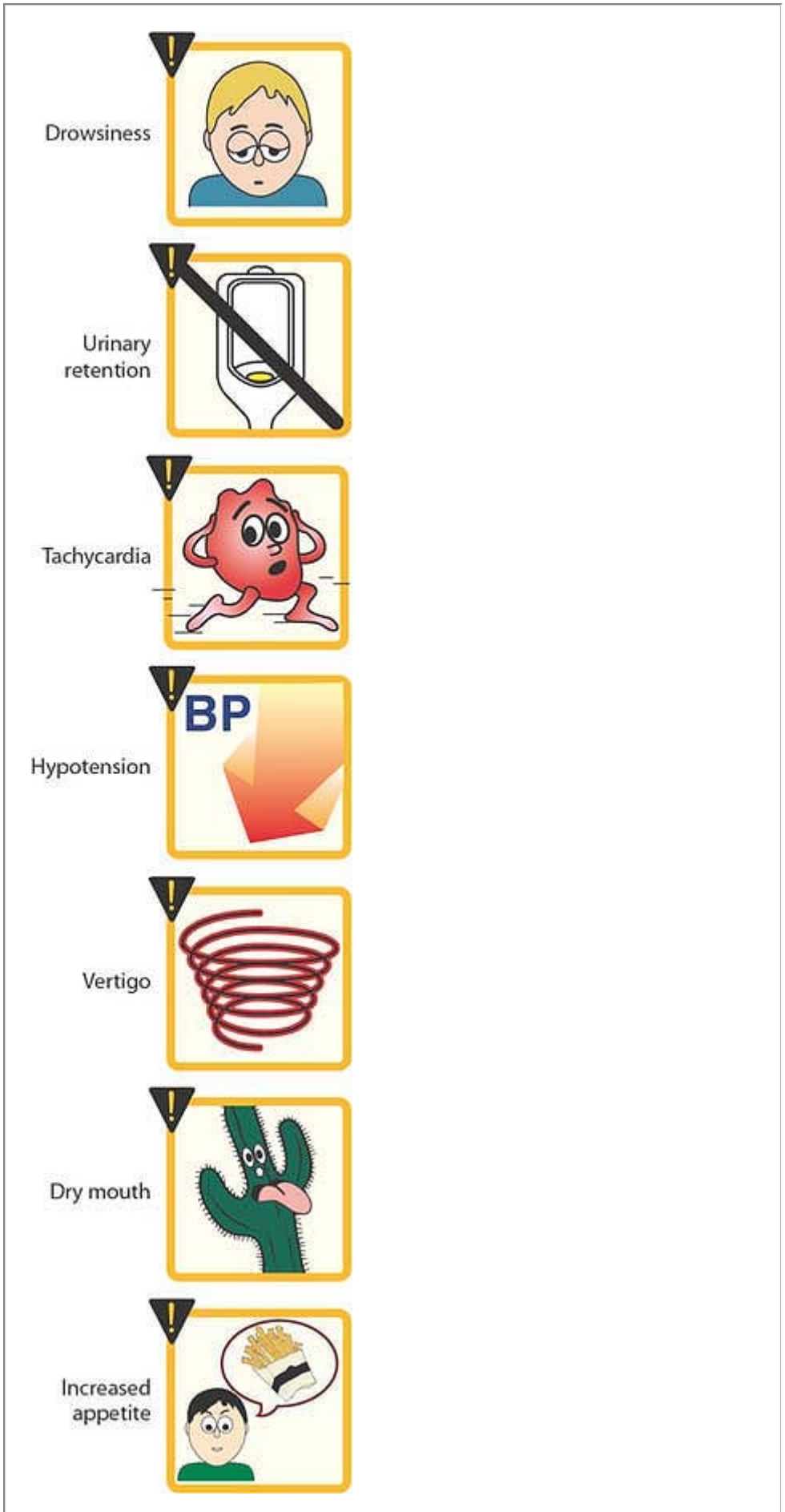

Drowsiness
Urinary retention
Tachycardia
BP
Hypotension
Vertigo
Dry mouth
Increased appetite

Figure 42.8 Some adverse effects observed with first-generation H_1 antihistamines.

A. Types of migraine

There are two main types of migraine headaches. The first, migraine without aura (previously called common migraine), is a severe, unilateral, pulsating headache that typically lasts from 2 to 72 hours. These headaches are often aggravated by physical activity and are accompanied by nausea, vomiting, photophobia (hypersensitivity to light), and phonophobia (hypersensitivity to sound). Approximately 85 percent of patients with migraine do not have aura. In the second type, migraine with aura (previously called classic migraine), the headache is preceded by neurologic symptoms called auras, which can be visual, sensory, and/or cause speech or motor disturbances. Most commonly,

these prodromal symptoms are visual, occurring approximately 20 to 40 minutes before headache pain begins. In the 15 percent of migraine patients whose headache is preceded by an aura, the aura itself allows diagnosis. The headache itself in migraines with or without auras is similar. For both types of migraines, women are three-fold more likely than men to experience either type of migraine.

	MIGRAINE	CLUSTER	TENSION TYPE
Family history	Yes	No	Yes
Sex	Females more often than males	Males more often than females	Females more often than males
Onset	Variable	During sleep	Under stress
Location	Usually unilateral	Behind or around one eye	Bilateral in band around head
Character and severity	Pulsating, throbbing	Excruciating, sharp, steady	Dull, persistent, tightening
Duration	2–72 hours per episode	15–90 minutes per episode	30 minutes to 7 days per episode
Associated symptoms	Visual auras, sensitivity to light and sound, pale facial appearance, nausea and vomiting	Unilateral or bilateral sweating, facial flushing, nasal congestion, lacrimation, pupillary changes	Mild intolerance to light and noise, anorexia

Figure 42.9 Characteristics of migraine, cluster, and tension-type headaches.

B. Biologic basis of migraine headaches

The first manifestation of migraine with aura is a spreading depression of neuronal activity accompanied by reduced blood flow in the most posterior part of the cerebral hemisphere. This hypoperfusion gradually spreads forward over the surface of the cortex to other contiguous areas of the brain. The vascular alteration is accompanied by functional changes; for example, the hypoperfused regions show an abnormal response to changes in arterial partial pressure of CO_2. The hypoperfusion persists throughout the aura and well into the headache phase, after which hyperperfusion occurs. Patients who have migraine without aura do not show hypoperfusion. However, the pain of both types of migraine may be due to extracranial and intracranial arterial dilation. This stretching leads to release of neuroactive molecules, such as substance P.

C. Symptomatic treatment of acute migraine

Acute treatments can be classified as nonspecific (symptomatic) or migraine specific. Nonspecific treatment includes analgesics, such as nonsteroidal anti-inflammatory drugs, and antiemetics, such as *prochlorperazine*, to control vomiting. Opioids are reserved as rescue medication when other treatments of a severe migraine attack are not successful. Specific migraine therapy includes triptans and *dihydroergotamine*, both of which are 5-HT_{1D} receptor agonists. It has been proposed that activation of 5-HT_{1D} receptors by these agents leads either to vasoconstriction or to inhibition of the release of proinflammatory neuropeptides. Despite their high cost, most patients prefer triptans over ergot derivatives.

1. **Triptans:** This class of drugs includes *sumatriptan* [SOO-ma-trip-tan], *naratriptan* [NAR-a-trip-tan], *rizatriptan* [rye-za-TRIP-tan], *eletriptan* [EH-leh-trip-tan], *almotriptan* [AL-moh-trip-tan], *frovatriptan* (frova-TRIP-tan), and *zolmitriptan* [zole-ma-TRIP-tan]. These agents rapidly and effectively abort or markedly reduce the severity of migraine headaches in about 70 percent of patients. The triptans are serotonin agonists, acting at a subgroup of serotonin receptors found on small, peripheral nerves that innervate the intracranial vasculature. The nausea that occurs with *dihydroergotamine* and the vasoconstriction caused by *ergotamine* (see below) are much less pronounced with the triptans, particularly *rizatriptan* and *zolmitriptan*. *Sumatriptan* is given subcutaneously, intranasally, or orally. [Note: All other agents are taken orally.] The onset of the parenteral drug (which is indicated for treatment of cluster headaches) is about 20 minutes, compared with 1 to 2 hours when the drug is administered orally. The drug has a short duration of action, with an elimination half-life of 2 hours. Headache commonly recurs within 24 to 48 hours after a single dose of drug, but in most patients, a second dose is effective in aborting the headache. *Rizatriptan* and *eletriptan* are modestly more effective than *sumatriptan*, the prototype drug, whereas *naratriptan* and *almotriptan* are better tolerated. *Frovatriptan* is the longest-acting triptan, with a half-life of more than 24 hours. Individual responses to triptans vary, and more than one drug trial may be necessary before treatment is successful. Significant elevation of blood pressure and cardiac events have been reported with triptan use. Therefore, triptans should not be administered to patients with risk factors for coronary artery disease without performing a cardiac evaluation prior to administration.
2. **Dihydroergotamine:** *Dihydroergotamine* [dye-hye-droe-er-GOT-a-meen], a derivative of *ergotamine*, is administered intravenously and has an efficacy similar to that of *sumatriptan*, but nausea is a common adverse effect.

D. Prophylaxis

Therapy to prevent migraine is indicated if the attacks occur two or more times a month and if the headaches are severe or complicated by serious neurologic signs. *Propranolol* is the drug of choice, but other Î²-blockers, particularly *nadolol*, have been shown to be effective. Other drugs that are effective for prevention of recurrent, refractory, severe migraine are shown in Figure 42.10.

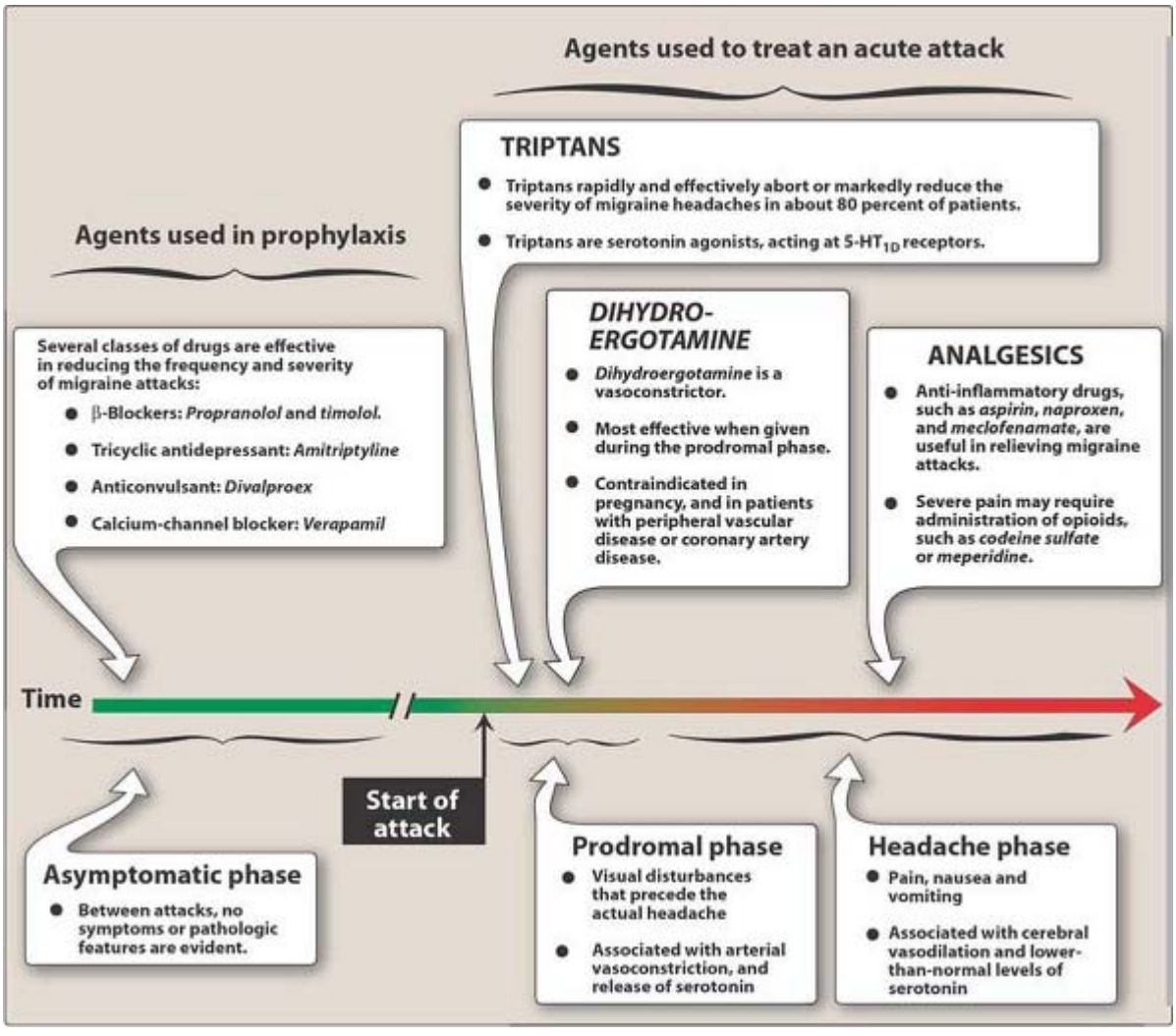


Figure 42.10 Drugs useful in the treatment and prophylaxis of migraine headaches.

P.527

P.528

Study Questions

Choose the ONE best answer.

42.1 Dihydroergotamine:

A. Causes vasodilation.

B. Exerts its actions by binding to specific ergotamine receptors.

C. Is useful in treating acute migraine headaches.

D. Is useful for maintaining uterine muscle tone during pregnancy.

E. Has actions similar to those of nitroprusside.

View Answer

42.2 A 43-year-old ship's captain complains of seasonal allergies. Which one of the following would be indicated?

A. Cyclizine.

B. Doxepin.

C. Doxylamine.

D. Hydroxyzine.

E. Fexofenadine.

View Answer

42.3 Which one of the following statements concerning H_1 antihistamines is correct?

A. Second-generation H_1 antihistamines are relatively free of adverse effects.

B. Because of the established long-term safety of first-generation H_1 antihistamines, they are the first choice for initial therapy.

C. The motor coordination involved in driving an automobile is not affected by the use of first-generation H_1 antihistamines.

D. H_1 antihistamines can be used in the treatment of acute anaphylaxis.

E. Both first- and second-generation H_1 antihistamines readily penetrate the blood-brain barrier.

View Answer

42.4 Which one of the following drugs could significantly impair the ability to drive an automobile?

A. Diphenhydramine.

B. Ergotamine.

C. Fexofenadine.

D. Ranitidine.

E. Sumatriptan.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Chapter 43

Toxicology

I. Overview

Toxicology seeks to characterize the potentially adverse effects of foreign chemicals and their doseâ€“response relationships to protect public health. Toxicology is defined as the study of the adverse effects of chemicals on living organisms. The term toxicity is defined as the inherent capacity of a chemical to cause injury. Thus, all chemicals, including drugs, have some degree of toxicity. This was first documented by the physician Paracelsus (1493â€“1541), who stated â€œAll substances are poisons: There is none which is not a poison. The right dose differentiates a poison from a remedy.â€ The adverse effects of therapeutic drugs have been discussed in previous chapters as the drugs have been presented and, therefore, will not be considered here. Instead, examples of nondrug chemicals and illicit drugs that are of public health concern, along with some basic concepts in toxicology, are presented.

II. Toxic Actions of Chemicals

Toxic chemicals from the environment may contact the skin and/or be absorbed after ingestion or inhalation. These exogenous chemicals are distributed to various organs, where they may be metabolized to products that may be more or less toxic than the administered chemical (Figure 43.1). The parent compound or its metabolites interact with target macromolecules, resulting in a toxic effect.

A. Common target tissues

Any tissue or organ within the body can potentially be affected by a chemical toxin, and indeed, most chemicals adversely affect more than one tissue. However, the lungs (â€œportal of entryâ€ for gases, vapors, and particles that can be inhaled), liver (â€œportal of entryâ€ for ingested chemicals), and tissues with a high blood flow, such as brain and kidney, are particularly vulnerable to the toxic actions of chemicals. In addition the heart is sensitive to any toxin-induced disruption in ionic gradients.

B. Nonselective actions

Exposure to some chemicals, such as corrosive compounds, leads to a local irritation and/or caustic effects that are nonselective in nature and occur wherever the site of application or exposure is located. Examples include exposure to strongly alkaline or acidic substances, which cause injury by denaturation of macromolecules, such as proteins, and cleavage of chemical bonds essential to the function of biomolecules.

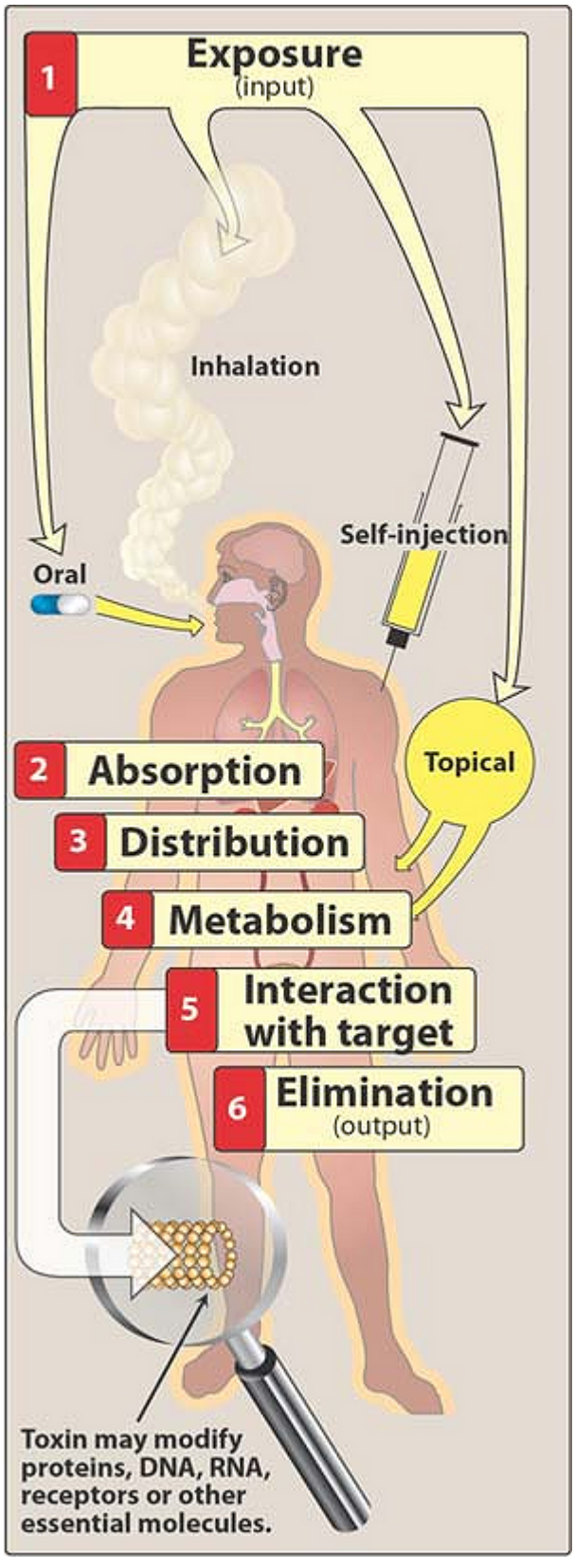


Figure 43.1 Exposure, absorption, distribution, and mode of action of toxins.

C. Selective actions

Many chemicals produce their toxic effects by interfering with the functions of specific biochemical pathways and/or macromolecules within a tissue. For example, the rodenticide *warfarin* inhibits the vitamin Kâ€“dependent posttranslational modification of certain clotting factors by the liver (see p. 240). Selective toxic actions of chemicals are usually apparent only after the chemical has been absorbed and distributed within the body, in contrast to nonselective actions, which generally occur at the exposure site.

D. Immediate and delayed actions

Many compounds have toxic actions that will quickly lead to symptoms following exposure. For example, inhibition of acetylcholinesterase by an organophosphate insecticide like malathion will rapidly lead to symptoms of excess acetylcholine at synapses and neuroeffector junctions (see p. 52). However, many chemicals exert effects that have latency periods of as long as several decadesâ€”for example, the carcinogen asbestos can lead to formation of significant pulmonary pathology, including cancer, 15 to 30 years after exposure.

III. Occupational and Specific Environmental Toxins

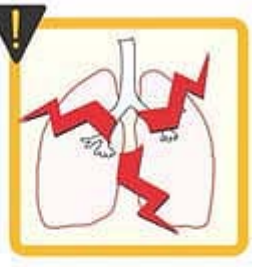
A. Halogenated hydrocarbons

Halogenated hydrocarbons are usually volatile, and exposure can be through ingestion or inhalation. They are lipid soluble and can pass through the blood-brain barrier. Most will depress the central nervous system (CNS) when acute exposures are high.

1. **Carbon tetrachloride:** Individuals can be exposed to carbon tetrachloride through consumption of contaminated drinking water. Although transient, low-level inhalation of carbon tetrachloride can produce irritation of the eyes and respiratory system. Higher levels, whether inhaled or ingested, can produce nausea, vomiting, stupor, convulsions, coma, and death from CNS depression (Figure 43.2). Carbon tetrachloride undergoes a cytochrome P450â€“mediated metabolic activation to produce free radicals that are oxidize essential cellular components. A nonlethal acute exposure can occur within a period of several hours to several days and produce liver and kidney damage.
2. **Chloroform:** The adverse effects associated with *chloroform* exposure are similar to those with carbon tetrachloride. Exposures can occur through ingestion or inhalation, and high enough levels will result in nausea, vomiting, dizziness, headaches, and stupor. *Chloroform* can also sensitize the heart to catecholamine-induced arrhythmias. *Chloroform* is hepatotoxic and nephrotoxic as a result of its metabolic activation.

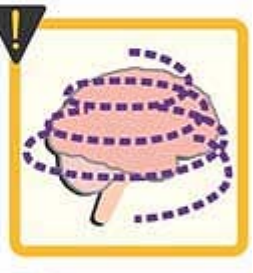
Irritation of the eyes

Irritation of respiratory system



Nausea

Dizziness



Headache

Death

Figure 43.2 Adverse effects of halogenated hydrocarbons.

B. Aromatic hydrocarbons

As with the halogenated hydrocarbons, aromatic hydrocarbons tend to be volatile, and exposure can occur through inhalation and ingestion. Large acute exposures can cause CNS depression, and lead to cardiac arrhythmias through sensitization of heart cells to catecholamines. However, other aspects of their toxicological profile can differ significantly from that of the halogenated hydrocarbons.

1. **Benzene:** Approximately half of the national exposure to benzene occurs through tobacco smoke. Chronic benzene exposure in humans produces hematopoietic toxicities, of which the most serious are agranulocytosis and leukemia, particularly acute myelogenous leukemia. Nonoccupational exposures to benzene can occur as a result of combustion of fossil fuels, including automobile gasoline, and by consumption of contaminated water.
2. **Toluene:** Automobile emissions are the principal source of exposure in ambient air, whereas indoors exposure occurs from the use of household products containing toluene-like degreasers, certain paints and primers, and furniture polish. Acute and chronic exposure to toluene can produce CNS depression, with symptoms including drowsiness, ataxia, tremors, impaired speech, hearing, and vision. Chronic exposure may also produce some damage to the liver and kidneys. Deaths have occurred at high levels of exposure.

C. Alcohols

1. **Methanol (wood alcohol) and ethylene glycol:** These primary alcohols are themselves relatively nontoxic and cause mainly CNS sedation. However, methanol and ethylene glycol are oxidized to toxic productsâ€"formic acid in the case of methanol, and glycolic, glyoxylic, and oxalic acids in the case of ethylene glycol. *Fomepizole* inhibits this oxidative pathway, preventing the formation of toxic metabolites, and allows the parent alcohols to be excreted by the kidney (Figure 43.3). Coma, seizures, hyperpnea, and hypotension all suggest that a substantial portion of the parent alcohols has been metabolized to toxic acids.
2. **Isopropanol:** This secondary alcohol is metabolized to acetone via alcohol dehydrogenase. Acetone cannot be further oxidized to a carboxylic acids and, therefore, shows only limited acidemia and toxicity.

D. Pesticides

Pesticides are a large class of chemicals designed to kill organisms that society considers to be unhealthy, a nuisance, or destructive. Although their use is often controversial, they have had a significant impact on public health through the reduction of insect-borne diseases, such as yellow fever and malaria, and they have increased crop yields in agriculture. A large variety of different pesticides are currently used throughout the world. Some of the more commonly used compounds are considered here.

1. **Organophosphosphate and carbamate insecticides**: These agents constitute two major classes of insecticides used in the United States and throughout the world. They exert their mammalian toxicity through inhibition of acetylcholinesterase, with subsequent accumulation of excess acetylcholine.

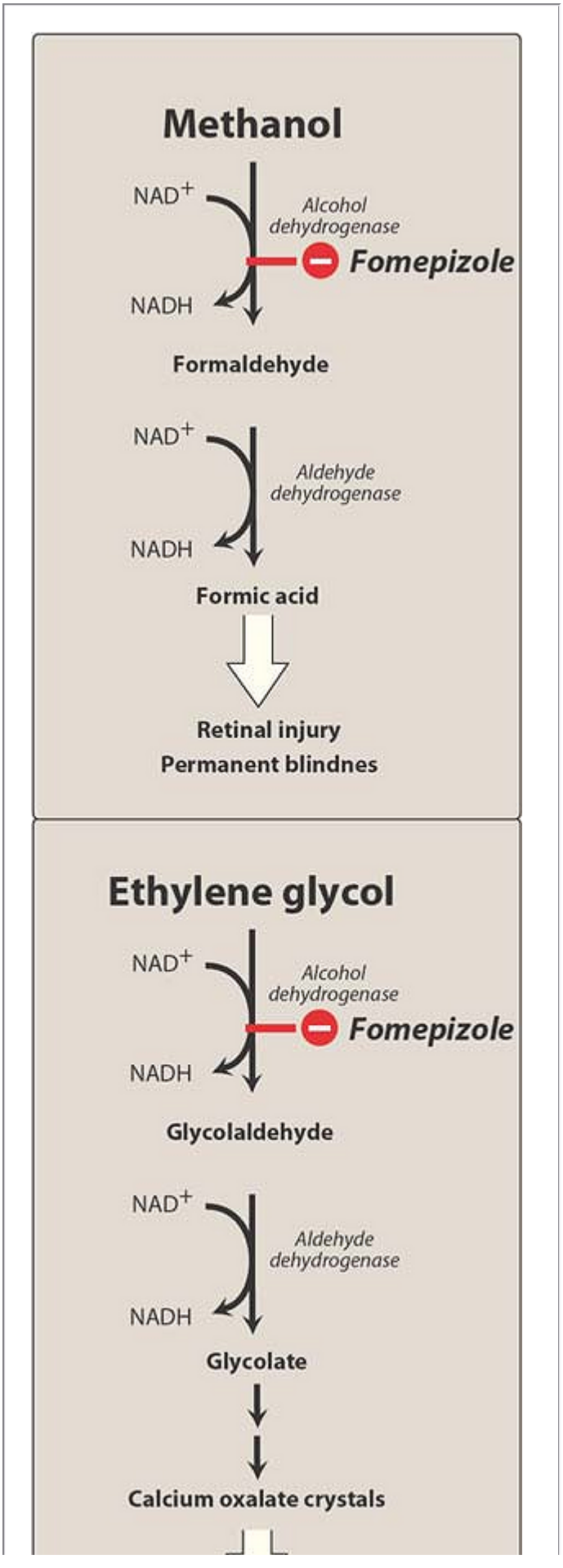

Methanol
NAD+
Alcohol dehydrogenase
Fomepizole
NADH
Formaldehyde
NAD+
Aldehyde dehydrogenase
NADH
Formic acid
Retinal injury
Permanent blindnes
Ethylene glycol
NAD+
Alcohol dehydrogenase
Fomepizole
NADH
Glycolaldehyde
NAD+
Aldehyde dehydrogenase
NADH
Glycolate
Calcium oxalate crystals

Figure 43.3 Metabolism of methanol and ethyleneglycol.

2. **Pyrethroids:** The pyrethroids exert their mammalian and insect toxicity by extending the open time of sodium channels throughout the central and peripheral nervous systems. Symptoms of toxicity include loss of coordination, tremors, convulsions, and burning and itching sensations. Pyrethroids can also act as dermal and respiratory allergens, and exposure can lead to contact dermatitis

or asthma-like symptoms. Death, when it occurs in humans, is usually due to respiratory failure. Fortunately, the pyrethroids are much more toxic to insects due to their limited ability to eliminate these compounds.

3. **Rotenone:** Rotenone is used primarily as an insecticide and is applied to a wide variety of crops. It acts by inhibiting the oxidation of the reduced form of nicotinamide-adenine dinucleotide (Figure 43.4). Symptoms of poisoning include nausea and vomiting, with convulsions and death at very high exposures.

E. Rodenticides

In contrast to insecticides, which are often applied by spraying, the rodenticides are usually used in the form of solid baits ingested by rodents. Consequently, the public health threat posed is usually through the accidental or suicidal ingestion. The most commonly used rodenticides are the anticoagulants, such as *warfarin*.

F. Heavy metals

The heavy metals that are presently of most concern from a public health perspective are lead, mercury, and cadmium. They all exert their toxic effects by binding to certain functional groups on critical macromolecules within the body, thereby inactivating their function. These functional groups include hydroxyl groups, carboxylic acid groups, sulfhydryl groups, and amino groups. Heavy metal intoxication can be treated by drugs termed chelators (see p. 536), which form complexes with the metals and prevent and/or reverse their binding to the endogenous macromolecules. Acute exposures to high levels of heavy metals are rare in the United States and are usually confined to occupational exposures. Such high exposures often result in nonselective corrosive effects. Of much greater public health concern are the more widespread chronic exposures to low levels of these toxic elements.

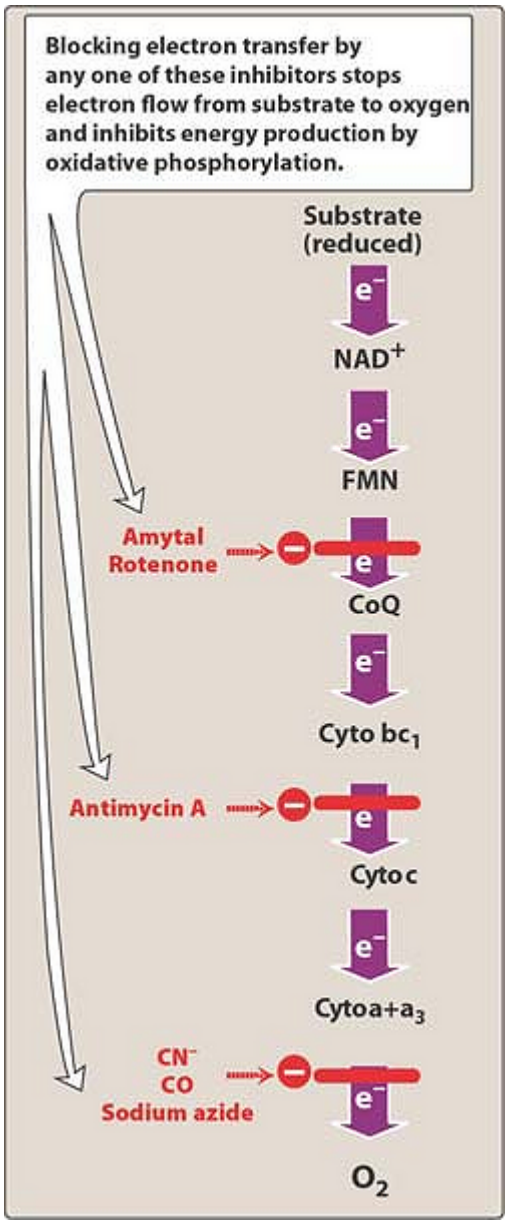


Figure 43.4 Site-specific inhibitors of electron transport.

1. **Lead:** Lead is ubiquitous in the environment, with sources of exposure including old paint, drinking water, industrial pollution, food, and contaminated dust. However, with the elimination of tetraethyl lead in gasoline during the mid-1980s in the United States, environmental exposure to organic lead has been reduced, and most chronic exposure to lead occurs with inorganic lead salts, such as those in paint used in housing constructed prior to 1978. Age-dependent differences in the absorption of ingested lead are known to occur. Adults absorb about 10 percent of an ingested dose, whereas children absorb about 40 percent. Inorganic forms of lead are initially distributed to the soft tissues and more slowly redistribute to bone, teeth, and hair. Most lead will eventually make its way to bone, where it can be detected by x-ray examination. Lead has an apparent blood half life of about 1 to 2 months, whereas its half-life from bone is 20 to 30 years. Chronic exposure to lead can have serious effects on several tissues.

    a. **Central nervous system:** The CNS effects of lead have often been termed lead encephalopathy. Symptoms

include headaches, confusion, clumsiness, insomnia, fatigue, and impaired concentration. As the disease progresses, clonic convulsions and coma can occur. Death is rare given the ability to treat lead intoxication with chelation therapy. Children are more susceptible

than adults to the CNS effects of lead. Furthermore, blood levels of 5 to 20 Âµg/dL in children have been shown to lower IQ in the absence of other symptoms. It has been estimated that as many as nine percent of the children in the United States may have blood lead levels greater than 10 Âµg/dL.

b. **Gastrointestinal system:** The actions of lead on the gastrointestinal tract are varied and often lead subjects to seek medical help. Early symptoms can include discomfort and constipation (and, occasionally, diarrhea), whereas higher exposures can produce painful intestinal spasms (Figure 43.5). Calcium gluconate infusion is effective for relief of pain.

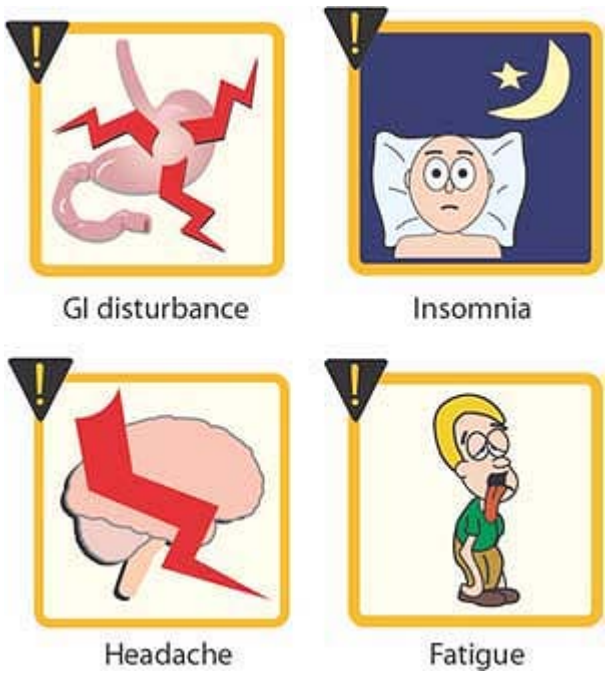


Figure 43.5 Adverse effects of lead poisoning.

c. **Blood:** Lead has complex effects on the constituents of blood, leading to hypochromic, microcytic anemia as a result of a shortened erythrocyte life span and through disruption of heme synthesis. Lead inhibits several enzymes involved in the synthesis of heme, thereby leading to increased blood levels of protoporphyrin IX and aminolevulinic acid, as well as increased urinary excretion of aminolevulinic acid and coproporphyrinogen (Figure 43.6). Elevated blood and urinary levels of these intermediates can be used diagnostically for lead intoxication, provided that blood lead levels are greater than about 25 Âµg/dL. Below that, elevated levels of heme intermediates cannot be observed, even though IQ effects can be observed in children.

2. **Mercury:** Potential exposure to mercury constitutes a significant health concern, because various forms of mercury are released into the human environment by industry, by natural release from the oceans and the earth's crust, and through the burning of fossil fuels. Human exposure to three different forms of mercury can occur.

   a. **Elemental mercury:** Toxic exposures to elemental mercury are usually occupational, in which the vapors are

inhaled. Symptoms of elemental mercury toxicity include tremors, depression, memory loss, decreased verbal skills, and inflammation of the kidneys. High concentrations of elemental mercury are corrosive and cause nonselective toxicity within the pulmonary system.

b. **Inorganic mercury salts:** Exposures to inorganic salts of mercury, such as mercuric chloride, that lead to adverse health effects are usually occupational in nature. Inorganic salts are often corrosive and can destroy the mucosa of the mouth if ingested. Renal damage can also be observed several hours after exposure. Hazardous exposures of the public to inorganic forms of mercury are uncommon.

c. **Organic mercury:** Any form of mercury that contains at least one covalent bond to a carbon atom is considered to be organic mercury. Organic forms of mercury tend to be more lipid soluble than the inorganic salts, as well as much less corrosive. Therefore, significant absorption results after ingestion, which occurs primarily from consumption of foods, particularly fish, contaminated with methylmercury. Symptoms of high levels of organic mercury can appear several days to several weeks after ingestion and are primarily neurologic in nature. These symptoms include visual disturbances, paresthesias, ataxia,

hearing loss, mental deterioration, muscle tremors, movement disorders, and with severe exposure, paralysis and death. Organic mercury poisoning in the elderly is sometimes misdiagnosed as Parkinson's disease or Alzheimer's disease. Although all forms of mercury are toxic to the fetus, organic mercury is the most dangerous, because its lipid solubility allows passage through the placenta.

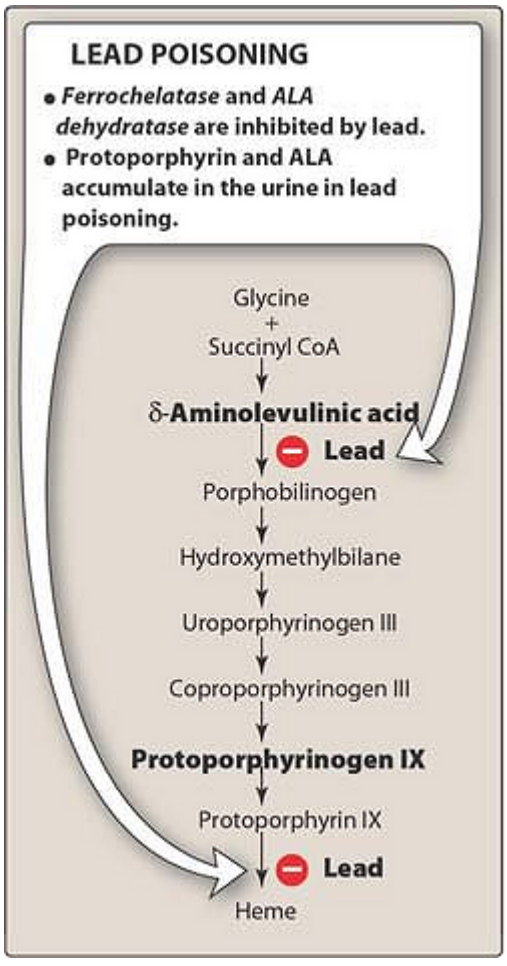


Figure 43.6 Adverse effect of lead poisoning on heme biosynthesis.

3. **Cadmium:** The most frequent human exposures to cadmium occur through ingestion or inhalation. Widespread exposure to the public can occur through ingestion of food that is contaminated as a result of uptake by plants of cadmium from fertilizers and manure, and through atmospheric deposition. Large inhalational exposures are usually occupational in nature, although low-level exposure occurs from the burning of fossil fuels, which release cadmium into the environment. Cigarette smoke is also a source of cadmium. Cadmium is used heavily by a variety of industries, and environmental contamination from these sources is a major concern. Cadmium absorption upon ingestion is poor, with about five percent bioavailability. Upon inhalation, about 10 to 40 percent of the dose is absorbed. Most of the cadmium in the body will eventually distribute to the liver and kidneys, largely as a result of its binding to metallothionein. The half-life of cadmium is 10 to 30 years. Although cadmium can affect many tissues, its major toxicities are seen in the kidneys and lungs.

G. Gases and inhaled particles

Chemicals can be inhaled as gases, solids, and aerosols. Some chemicals that make their way to the alveoli can be rapidly absorbed and distributed to other tissues. Other particulates can become lodged in the alveoli and exert serious local toxicity without being absorbed into the bloodstream.

1. **Carbon monoxide:** Carbon monoxide is a gas that is colorless, odorless, and tasteless, making it impossible for individuals to detect without a carbon monoxide detector. It is a natural by-product of the combustion of

carbonaceous materials, and common sources of this gas include automobiles, poorly vented furnaces, fireplaces, wood-burning stoves, kerosene space heaters, and charcoal grills. Following inhalation, carbon monoxide rapidly binds to hemoglobin to produce carboxyhemoglobin. The binding affinity of carbon monoxide to hemoglobin is 230 to 270 times greater than that of oxygen. Consequently, even low concentrations of carbon monoxide in the air can produce significant levels of carboxyhemoglobin. In addition, bound carbon monoxide increases hemoglobin affinity for oxygen at the other oxygen-binding sites. This high-affinity binding of oxygen prevents the unloading of oxygen at the tissues, further reducing oxygen delivery (Figure 43.7). The symptoms of carbon monoxide intoxication are consistent with hypoxia, with the brain and heart showing the greatest sensitivity. Symptoms include headache, dyspnea, lethargy, confusion, and drowsiness, whereas higher exposure levels can lead to seizures, coma, and death. The management of a carbon monoxideâ€“poisoned patient includes prompt removal from the source of carbon monoxide and institution of 100 percent oxygen by nonrebreathing face mask or endotracheal tube. In patients with severe intoxication, hyperbaric oxygen therapy may be indicated.

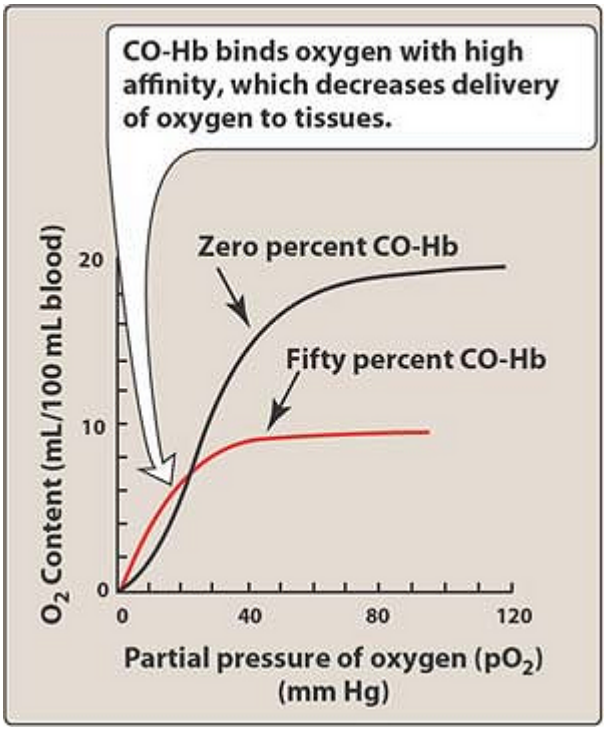


Figure 43.7 Effect of carbon monoxide on the oxygen affinity of hemoglobin. CO-Hb = carbon monoxyhemoglobin.

2. **Cyanide:** Once absorbed into the body, cyanide quickly binds to many metalloenzymes, thereby rendering them inactive. Its principal toxicity occurs as a result of the inactivation of the enzyme cytochrome oxidase (cytochrome a_3), leading to the inhibition of cellular respiration. Therefore, even in the presence of oxygen, those tissues, such as the brain and heart, which require a high oxygen demand, are adversely affected. Death can occur quickly due to respiratory arrest of central origin. Cyanide poisoning can be treated with specific antidotes (see p. 227) .

3. **Silica:** Workers in mines, foundries, construction sites, and stone cutters are at particular risk for silicosis, perhaps the oldest known occupational disease. Silicosis is a progressive lung disease that results in fibrosis and, often, emphysema. Silicosis is currently incurable, and the prognosis is often poor. However, with lower

exposures, silicosis does not always end in death or debilitation.

4. **Asbestos:** The greatest public health threat from asbestos is pulmonary in nature as a result of inhalation of the fibers, some of which stay permanently in the lung alveoli. The three diseases most commonly associated with asbestos exposure are asbestosis, mesothelioma, and lung cancer. Symptoms of these diseases may not be apparent for up to 15 to 30 years following exposure to asbestos. Asbestosis is a chronic pulmonary disease that is characterized by interstitial fibrosis in the lungs and pleural fibrosis or calcification. Initial symptoms include shortness of breath that can eventually develop into severe cough and chest pains. Asbestosis is a progressive disease with no specific treatment, and it can be fatal. Mesothelioma is a rare cancer, usually in the chest wall (although some can appear in the abdominal cavity) which seems to be caused only by asbestos. The first noticeable symptom is usually pain in the vicinity of the lesion, with dyspnea and cough developing with pleural mesothelioma. Patients usually survive no longer than 2 years after diagnosis. With all forms of asbestos-induced treatment, disease is largely symptomatic and supportive.

POISON OR SYNDROME	ANTIDOTE(S)
Acetaminophen	*N-Acetylcysteine*
Anticholinergic agents	*Physostigmine*
Benzodiazepine	*Flumazenil*
Carbon monoxide	*Oxygen (+/– hyperbaric chamber)*
Cyanide	*1) Amyl nitrite pearls 2) Sodium nitrite 3) Sodium thiosulfate*
Digitalis	*Digoxin immune Fab*
Methanol Ethylene glycol	*Fomepizole*
Heparin	*Protamine sulfate*
Lead	*Dimercapto-succinic acid*
Mercury Arsenic Gold	*Dimercaprol*
Methemo-globinemia	*Methylene blue*
Opiates	*Naloxone, nalmefene, or naltrexone*
Organo-phosphates Carbamates Nerve gases	*1) Atropine 2) Pralidoxime*

Figure 43.8 Common antidotes.

IV. Antidotes

Specific chemical antidotes for poisonings exist for only a small number of chemicals or classes of chemicals (Figure 43.8). The following are examples of strategies that form the basis for the use of specific chemical antidotes, with an example of how each can be applied.

A. Pharmacologically antagonize toxic action

Atropine is a muscarinic-receptor antagonist that is used as an antidote for intoxication by the anticholinesterases (see p. 55). It works by blocking access of excess acetylcholine to muscarinic receptors.

B. Accelerate detoxification of toxic agent

Acetaminophen at very high doses will produce liver necrosis as a result of its metabolic activation by cytochromes P450. Administration of N-acetylcysteine will serve as a substitute for glutathione by binding to and inactivating the reactive metabolites produced from *acetaminophen*. To be effective, N-acetylcysteine must be given as early as possible (within 8â€“10 hours of ingestion of acetaminophen).

C. Provide alternative target

Cyanide poisoning is treated with a two-step process. Sodium nitrite is administered to induce the oxidation of hemoglobin to methemoglobin, which has a high binding affinity for cyanide to produce cyanmethemoglobin. Amyl nitrite can also be used for this purpose. The second step in the antidotal treatment of cyanide intoxication is to accelerate its detoxification. Administration of sodium thiosulfate will accelerate the production of thiocyanate, which is much less toxic than cyanide and is also quickly excreted in the urine. In patients with smoke inhalation and cyanide toxicity, the induction of methemoglobin should be avoided unless the carboxyhemoglobin concentration is less than 10 percent. Otherwise, the oxygen-carrying capacity of blood becomes too low.

D. Reduce metabolic activation

The toxicity of methanol is thought to be mediated by formic acid, which is produced by the metabolism of methanol by alcohol dehydrogenase. *Fomepizole* is considered an antidote to methanol, because it inhibits alcohol dehydrogenase (see Figure 43.xx). Slowing the rate of methanol metabolism reduces the rate of rate formic acid production, thereby protecting the patient from the toxic effects of formic acid.

E. Restore altered target

Acetylcholinesterase that has been inhibited as a result of phosphorylation by organophosphorus compounds often can be reactivated by the antidote *pralidoxime* (see p. 52).

F. Chelators

Chelators are drugs that will form covalent bonds with cationic metals. The chelator-metal complex is then excreted in the urine, thereby greatly facilitating the excretion of the heavy metal. Unfortunately, chelators are not specific to heavy metals, and essential metals, such as zinc, often can also be chelated. Additionally, some chelators have potentially serious adverse effects themselves, and their use in treatment of heavy metal intoxication is undertaken only when the benefits of chelation therapy outweigh the associated risks.

1. **Dimercaprol:** *Dimercaprol*, also known as British Anti-Lewisite, was the first chelator utilized, having been developed during World War II as a chelator for the arsenical war gas Lewisite. *Dimercaprol* is used by itself to chelate mercury and arsenic and in combination with edetate calcium disodium to treat lead intoxication. It is not effective after oral administration and is usually given intramuscularly. Use of *dimercaprol* is often limited by its capacity to increase blood pressure and heart rate.

2. **Succimer:** *Succimer* (dimercaptosuccinic acid) is a derivative of *dimercaprol* that is effective upon oral administration. A second advantage of *succimer* over *dimercaprol* is the lack of increased blood pressure and heart rate during treatment. Some elevation of serum levels of hepatic enzymes can be observed with *succimer* treatment. *Succimer* is currently approved for treatment of lead intoxication, but may be effective in chelation of other metals as well.

3. **Edetate calcium disodium:** Edetate calcium disodium is used primarily for treatment of lead intoxication, but it can also be used for

poisoning by other metals. It is not effective after oral administration and is usually given intravenously or intramuscularly. The calcium disodium salt of EDTA must be the form utilized to prevent chelation of calcium and its depletion from the body. Edetate calcium disodium can cause renal damage that is reversible upon cessation of the drug.

V. Designer and Street Drugs

â€œDesigner drugsâ€ are synthetic derivatives of federally controlled substances, created by slightly altering the molecular structure of existing drugs and produced illegally in clandestine laboratories for illicit use. Most of these drugs have some psychoactive properties and cause visual disturbances, but they are not true hallucinogens like *lysergic acid diethylamide* (*LSD*).

A. Methylenedioxymethamphetamine

Many of the most popular designer drugs on the street today are *amphetamine* analogs. Methylenedioxymethamphetamine (MDMA) is one of the most commonly used designer drugs. Commonly known as Ecstasy, MDMA has central stimulant and psychedelic effects. Its use is popular among those attending late-night â€œraveâ€ parties, dance clubs, and rock concerts

1. **Mechanism of action:** The main effect of MDMA is on neurons that synthesize and release the neurotransmitter serotonin (5-HT). MDMA causes 5-HT release into the synaptic cleft, inhibits its synthesis, and blocks its reuptake (Figure 43.9). The effect is an increased 5-HT concentration in the synaptic cleft and a depletion of intracellular 5-HT stores. 5-HT regulates mood, appetite, and body temperature. Users of MDMA will therefore manifest more of a serotonergic effect compared with the dopaminergic effects (*amphetamine* toxicity associated with *amphetamines*; see p. 121). MDMA's effects begin within the first hour after ingestion of an oral dose and usually last 3 to 6 hours.
2. **Clinical manifestations:**
    a. **Cardiopulmonary:** Cardiopulmonary manifestations of Ecstasy use include tachycardia, tachypnea, hypertension, vasospasm, pulmonary hypertension, dysrhythmias, valvular disease, and myocardial infarction.
    b. **Neurologic:** symptoms include mydriasis, nystagmus, head jerking, hyperthermia, sexual dysfunction, seizures, cerebral infarction, dopamine and 5-HT depletion in the synapse leading to potential for irreversible neuron destruction, and 5-HT syndrome, especially in combination with other serotonergic drugs.

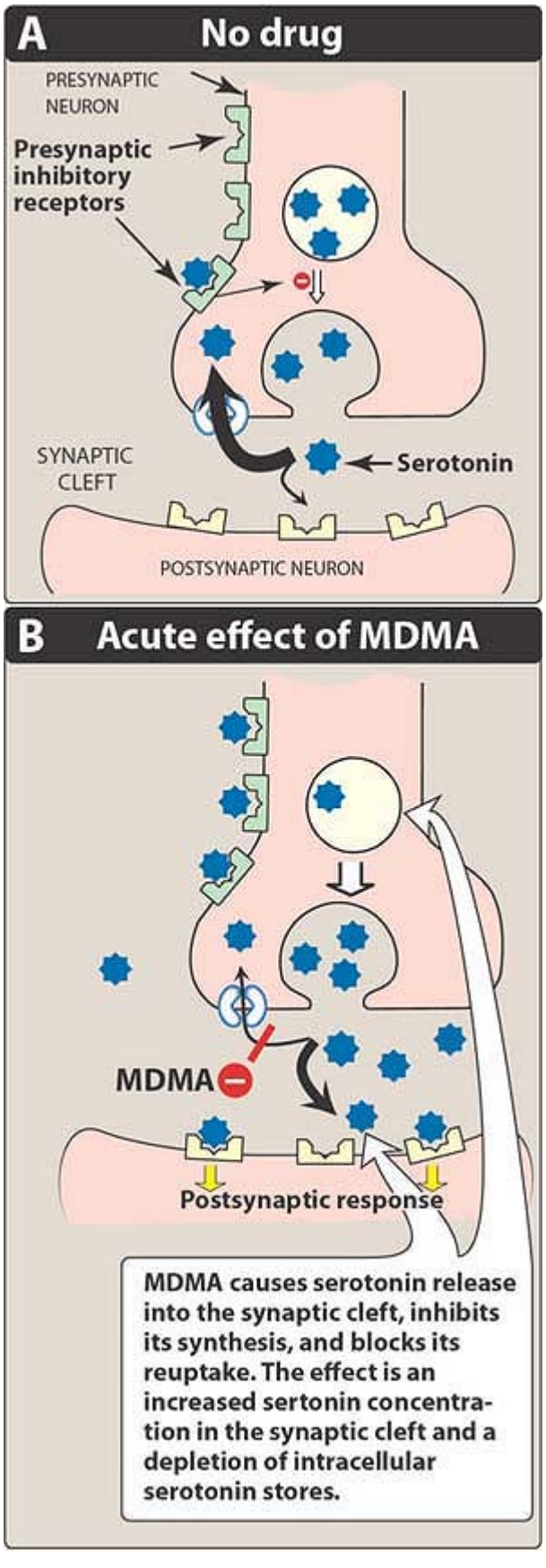

A
No drug
PRESYNAPTIC NEURON
Presynaptic inhibitory receptors
SYNAPTIC CLEFT
Serotonin
POSTSYNAPTIC NEURON
B
Acute effect of MDMA
MDMA
Postsynaptic response
MDMA causes serotonin release into the synaptic cleft, inhibits its synthesis, and blocks its reuptake. The effect is an increased sertonin concentration in the synaptic cleft and a depletion of intracellular serotonin stores.

Figure 43.9 Proposed mechanism of action of methylenedioxymethamphetamine (MDMA).

c. **Psychologic:** Most users of Ecstasy describe a sense of well-being and social interactivity as well as feelings of empathy, euphoria, agitation, visual and tactile hallucinations, and occasionally, anxiety. Chronic abuse leads to symptoms of psychosis (from dopaminergic affects) and obsessive compulsive behavior.

d. **Musculoskeletal:** Common signs and symptoms include teeth-grinding (bruxism), jaw clenching (trismus), increased muscular activity resulting in cramping, and rhabdomyolysis.

e. **Other manifestations:** Dehydration and hyperglycemia are common, as is metabolic acidosis in chronic use and overdose. Hyponatremia is of concern because, as dilution, from increased water intake, in addition to increased diuresis, secondary to inhibition of antidiuretic hormone may reduce sodium, predisposing the patient to seizures and cerebral edema.

3. **Treatment:** Treatment of isolated MDMA ingestion is supportive. Asymptomatic MDMA-induced hyponatremia is treated with fluid restriction. Refractory hypertension may be treated with *nitroprusside* or *phentolamine.* Hyperthermia is treated by aggressive external cooling with ice water, mist, and fans. Anxiety, agitation, and convulsions are treated with *diazepam*.

B. g-Hydroxybutyric acid

In the dance and â€œraveâ€ clubs, Î³-hydroxybutyric acid (GHB) has become widely abused due to its ability to rapidly produce a euphoric state. The fast and effective intoxication and the amnestic effect produced by GHB has made the drug attractive to sexual assault perpetrators. GHB is usually administered in an oral form and is rapidly and effectively absorbed by the gastrointestinal tract. The onset of action is quite rapid, with an effect usually being felt within 15 minutes and peaking anywhere between 40 and 120 minutes.

1. **Mechanism of action:** The actions of exogenous GHB are mediated primarily by the $GABA_B$ receptor. Low doses of the drug stimulate dopamine synthesis but inhibit its release, causing dopamine to concentrate in the nerve terminal. With higher doses of GHB, dopamine release is triggered. GHB also has effects through the endogenous opioid system, which may explain its euphoria-producing properties.

2. **Clinical manifestations**

   a. **Cardiopulmonary:** Chronic use of GHB can cause severe cardiopulmonary complications, such as hypoxia, bradycardia, hypotension, bradypnea, and dysrhythmia.

   b. **Central nervous system:** CNS effects are common and include euphoria in small doses, deep sleep in moderate doses, and a comatose state in large doses. Amnestic effects and loss of sexual inhibition make GHB a common drug in the commission of sexual battery. Hallucinations, agitation (especially upon arousal), seizures, myoclonus, and slurred speech are also common.

   c. **Psychologic:** Most users describe a sense of well-being and euphoria as well as being socially interactive and empathetic.

   d. **Other:** Other physiologic manifestations include salivation, vomiting, and hypothermia.

3. **Treatment:** Treatment of isolated GHB ingestion is supportive. In patients with significant CNS depression due to GHB overdose, intubation for airway protection is essential because of the high incidence of emesis. Bradycardia unresponsive to stimulation should be treated with *atropine*. *Pentobarbital* has been used successfully in the treatment of severe GHB withdrawal.

Study Questions

Choose the ONE best answer.

43.1 A 3-year-old male reports to the Emergency Department with, per the mother, continuous crying and â€œdoesn't want to play or eatâ€ for the last few days. The mom also states that the baby has not had regular bowel movements, with mostly constipation and occasional diarrhea, and frequently complains of abdominal pain. This baby now has an altered level of consciousness, is difficult to arouse, and begins to seize. The clinician rules out infection and other medical causes. Upon questioning, the mother states that the house is in an older neighborhood, that her house has not been remodeled or repainted since the 1940s, and that the paint is chipping around the windows and doors. The child is otherwise breathing on his own and urinating normally. Which toxin would you expect to be causing such severe effects in this child?

A. Mercury.

B. Lead.

C. Cadmium.

D. None of the above.

View Answer

43.2 A 41-year-old male pocket watch maker reports to the Emergency Department after he was found unconscious on the floor of the shop by a coworker. The coworker states that the patient complained of being cold this morning around 8 AM (the central heat was broken, and the outdoor temperature was 34Â°F) and that since noon, he had been complaining of headache, drowsiness, confusion, and nausea. The clinician notices that he has cherry red lips and nail beds. What is the most likely toxin causing his signs and symptoms?

A. Asbestos.

B. Cyanide.

C. Chloroform.

D. Carbon monoxide.

View Answer

43.3 A 50-year-old migrant worker comes to the Emergency Department from the field he was working in and complains of diarrhea, tearing, nausea and vomiting, and sweating. The clinician notices that he looks generally anxious and has fine fasciculations in the muscles of the upper chest as well as pinpoint pupils. Which antidote should he receive first?

A. N-Acetylcysteine.

B. Sodium nitrite.

C. Edetate calcium disodium.

D. Atropine.

View Answer

43.4 A 20-year-old female presents to the Emergency Department after being dumped in the ambulance bay with a note that said only that â€œshe was doing ecstasy at a party when she became unconscious.â€ This patient currently remains unconscious, with a heart rate of 140 bpm, temperature of 103.5Â°F, pin-point pupils, absent bowel sounds, blood pressure of 85/40 mm Hg, profuse sweating, and oxygen saturation of 86 percent on room air. Which of the following would not be a clinical manifestation of an Ecstasy patient?

A. Tachycardia.

B. Hyperthermia.

C. Pinpoint pupils.

D. Diaphoresis.

View Answer

43.5 A 23-year-old man presents to the Emergency Department unconscious with his girlfriend, who tells the clinician that they were at a rave and a couple who they met gave them what looked like water in a bottle. Her boyfriend drank about one-fourth of the bottle and suddenly collapsed. He currently is hypoxic, bradycardic, hypotensive, bradypnic, and has electrocardiographic changes. She states that they do not do drugs; they just went for the music. The urine drug screen is negative for opioids, marijuana, methadone, benzodiazepines, barbiturates, PCP, amphetamines, and cocaine. The clinician suspects GHB intoxication. GHB ingestions commonly produce which of the following?

A. Tachycardia.

B. Hyperthermia.

C. Hypertension.

D. Respiratory depression.

View Answer

POISON CONTROL CENTER: Call the nation-wide toll-free Poison Control Center number: 1-800-222-1222 and follow the instructions give by the center from the area in whch the call is made.