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36 Nonsteroidal Anti-Inflammatory Drugs; Disease-Modifying Antirheumatic Drugs; Nonopioid Analgesics; Drugs Used in Gout

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THE INFLAMMATORY RESPONSE

Inflammation is commonly divided into three phases: acute inflammation, the immune response, and chronic inflammation. Acute inflammation is the initial response to tissue injury; it is mediated by the release of autacoids and usually precedes the development of the immune response. Some of the autacoids involved are listed in Table 36–1. The immune response occurs when immunologically competent cells are activated in response to foreign organisms or antigenic substances liberated during the acute or chronic inflammatory response. The outcome of the immune response for the host may be beneficial, as when it causes invading organisms to be phagocytosed or neutralized. On the other hand, the outcome may be deleterious if it leads to chronic inflammation without resolution of the underlying injurious process. Chronic inflammation involves the release of a number of mediators that are not prominent in the acute response. Some of these are listed in Table 36–2. One of the most important conditions involving these mediators is rheumatoid arthritis, in which chronic inflammation results in pain and destruction of bone and cartilage that can lead to severe disability and in which systemic changes occur that can result in shortening of life.

The cell damage associated with inflammation acts on cell membranes to cause leukocytes to release lysosomal enzymes; arachidonic acid is then liberated from precursor compounds, and various eicosanoids are synthesized (see Chapter 18).

Prostaglandins have a variety of effects on blood vessels, on nerve endings, and on cells involved in inflammation. Leukotrienes have a powerful chemotactic effect on eosinophils, neutrophils, and macrophages and promote bronchoconstriction and alterations in vascular permeability. Recent evidence suggests that the cyclooxygenase isozyme (COX II) responsible for prostaglandin production by cells involved in inflammation is not identical to the cyclooxygenase present in most other cells in the body (COX I). A selective blocker of COX II might be desirable in the treatment of inflammation since it would leave undisturbed the other functions of the prostaglandins. It has been suggested that the corticosteroids are such selective blockers (see below).

Kinins, neuropeptides, and histamine are also released at the site of tissue injury, as are complement components, cytokines, and other products of leukocytes and platelets. Stimulation of the neutrophil membranes produces oxygen-derived free radicals. Superoxide anion is formed by the reduction of molecular oxygen, which may stimulate the production of other reactive molecules such as hydrogen peroxide and hydroxyl radicals. The interaction of these substances with arachidonic acid results in the generation of chemotactic substances, thus perpetuating the inflammatory process.

THERAPEUTIC STRATEGIES

The treatment of patients with inflammation involves two primary goals: first, the relief of pain, which is often the presenting symptom and the major continuing complaint of the patient; and second, the slowing or—in theory—arrest of the tissue-damaging process. Reduction of inflammation with **nonsteroidal anti-inflammatory** drugs often results in relief of pain for significant periods. Furthermore, most of the nonopioid analgesics (aspirin, etc) also have anti-inflammatory effects, so they are appropriate for the treatment of both acute and chronic inflammatory conditions.

Table 36–1. Some properties of the mediators of acute inflammation.

Mediator	Vasodilation	Vascular Permeability	Chemotaxis	Pain
Histamine	++	↑↑↑	–	–
Serotonin	+/–	↑	–	–
Bradykinin	+++	↑	–	+++
Prostaglandins	+++	↑	+++	+
Leukotrienes	–	↑↑↑	+++	–

The **glucocorticoids** also have powerful anti-inflammatory effects and when first introduced were considered to be the ultimate answer to the treatment of inflammatory arthritis. Unfortunately, the toxicity associated with chronic corticosteroid therapy inhibits their use except in the control of acute flare-ups of joint disease. Therefore, the nonsteroidal anti-inflammatory drugs have assumed a major role in the treatment of arthritis.

Another important group of agents are characterized as **slow-acting antirheumatic drugs (SAARDs)** or **disease-modifying antirheumatic drugs (DMARDs).** Very little is known about their mechanisms of action, but they may slow the bone damage associated with rheumatoid arthritis and are thought to affect more basic inflammatory mechanisms than do the NSAIDs. Unfortunately, they are also more toxic than the nonsteroidal anti-inflammatory agents.

I. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Salicylates and other similar agents used to treat rheumatic disease share the capacity to suppress the signs and symptoms of inflammation. These drugs also exert antipyretic and analgesic effects, but it is their anti-inflammatory properties that make them most useful in the management of disorders in which pain is related to the intensity of the inflammatory process. Several of the NSAIDs are used for special indications. These include indomethacin and ketorolac. They are discussed separately.

ASPIRIN & OTHER SALICYLATES

Aspirin and all but one of the other nonsteroidal anti-inflammatory drugs (NSAIDs) (ibuprofen, naproxen, etc) are related chemically in that they are weak organic acids; nabumetone is a ketone prodrug that is metabolized to an acidic active drug. They share the important property of inhibiting prostaglandin biosynthesis. They may also decrease the production of free radicals and of superoxide and may interact with adenylyl cyclase to alter the cellular concentration of cAMP. Although these drugs effectively inhibit inflammation, there is no evidence that—in contrast to drugs such as methotrexate and gold—they alter the course of an arthritic disorder. Aspirin's long history of use and availability without prescription diminishes its glamour compared to that of the newer NSAIDs. However, because of its low cost and long history of safety, aspirin remains the initial drug of choice for treating the majority of articular and musculoskeletal disorders. Aspirin was also the standard against which all anti-inflammatory agents are measured (Table 36–3). Both ibuprofen and naproxen have joined aspirin as over-the-counter NSAIDs in the USA. Both have good to excellent safety records, and ibuprofen especially is now the usual standard against which other NSAIDs are compared.

Table 36–2. Some of the mediators of chronic inflammation, eg, in rheumatoid arthritis.

Mediator	Sources	Primary Effects
Interleukins 1, 2, and 3	Macrophages, T lymphocytes	Lymphocyte activation, prostaglandin production
GM-CSF	T lymphocytes, endothelial cells, fibroblasts	Macrophage and granulocyte activation
TNF-α	Macrophages	Prostaglandin production
Interferons	Macrophages, endothelial cells, T lymphocytes	Many
PDGF	Macrophages, endothelial cells, fibroblasts, platelets	Fibroblast chemotaxis, proliferation

GM-CSF, granulocyte-macrophage colony-stimulating factor.
TNF-α, tumor necrosis factor alpha.
PDGF, platelet-derived growth factor.

History

Quinine from cinchona bark is one of the oldest remedies for relief of mild pain and fever. Willow bark was used in folk medicine for years for similar indications. In 1763, Reverend Edmund Stone, in a letter to the president of the Royal Society, described his success in treating fever with a powdered form of the bark of the willow. He had noted that the bitterness of willow bark was reminiscent of the taste of cinchona bark, the source of quinine. The active ingredient of willow bark, salicin, which on hydrolysis yields salicylic acid, was later found in other natural sources. Acetylsalicylic acid was synthesized in 1853, but the drug was not used until 1899, when it was found to be effective in arthritis and well tolerated. The name aspirin was coined from the German word for the compound, *a*cetyl*spir*säure (*Spirea,* the genus of plants from which it was obtained, and *Säure,* the German word for acid). Because of its greater efficacy and lower cost, aspirin rapidly replaced the natural products then in use and has remained one of the most widely employed remedies for over 90 years.

Chemistry & Pharmacokinetics

Salicylic acid is a simple organic acid with a pK_a of 3.0. Aspirin (acetylsalicylic acid; ASA) has a pK_a of 3.5 (see Table 1–1). Sodium salicylate and aspirin are equally effective anti-inflammatory drugs, though aspirin may be more effective as an analgesic.

The salicylates (Figure 36–1) are rapidly absorbed from the stomach and upper small intestine, yielding a peak plasma salicylate level within 1–2 hours. The acid medium in the stomach keeps a large fraction of the salicylate in the nonionized form, promoting absorption. However, when high concentrations of salicylate enter the mucosal cell, the drug may damage the mucosal barrier. If the gastric pH is raised by a suitable buffer to 3.5 or higher, gastric irritation is decreased.

Aspirin is absorbed as such and is rapidly hydrolyzed to acetic acid and salicylate by esterases in tissue and blood. Salicylate is bound to albumin, but, as the serum concentration of salicylate increases, a greater fraction remains unbound and available to tissues. Ingested salicylate and that generated by the hydrolysis of aspirin may be excreted unchanged, but most is converted to water-soluble conjugates that are

Table 36–3. Properties of aspirin and some newer nonsteroidal anti-inflammatory drugs.

Drug	Half-life (hours)	Urinary Excretion of Unchanged Drug	Recommended Anti-inflammatory Dosage
Aspirin	0.25	< 2%	1200–1500 mg tid
Salicylate[1]	2–19	2–30%	See footnote 2
Apazone	15	62%	600 mg bid
Diclofenac	1.1	< 1%	50–75 mg qid
Diflunisal	13	3–9%	500 mg bid
Etodolac	6.5	< 1%	200–300 mg qid
Fenoprofen	2.5	30%	600 mg qid
Flurbiprofen	3.8	< 1%	300 mg tid
Ibuprofen	2	< 1%	600 mg qid
Indomethacin	4–5	16%	50–70 mg tid
Ketoprofen	1.8	< 1%	70 mg tid
Ketorolac	4–10	58%	10 mg qid[3]
Meclofenamate	3	2–4%	100 mg qid
Nabumetone[4]	26	1%	1000–2000 mg qd[5]
Naproxen	14	< 1%	375 mg bid
Oxaprozin	58	1–4%	1200–1800 mg qd[5]
Piroxicam	57	4–10%	20 mg qd[5]
Sulindac	8	7%	200 mg bid
Tolmetin	1	7%	400 mg qid

[1]Major anti-inflammatory metabolite of aspirin.
[2]Salicylate is usually given in the form of aspirin.
[3]Recommended for treatment of acute (eg, surgical) pain only.
[4]Nabumetone is a prodrug; the half-life and urinary excretion are for its active metabolite.
[5]A single daily dose is sufficient because of the long half-life.

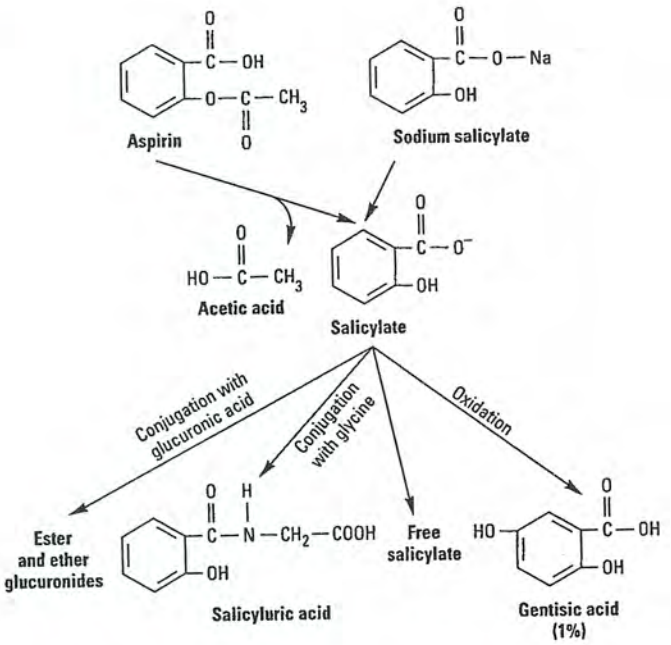

Figure 36–1. Structure and metabolism of the salicylates. (Modified and reproduced, with permission, from Meyers FH, Jawetz E, Goldfien A: *Review of Medical Pharmacology,* 7th ed. Lange, 1980.)

rapidly cleared by the kidney (Figure 36–1). When this pathway becomes saturated, a small increase in aspirin dose results in a relatively large increase in plasma levels. Alkalinization of the urine increases the rate of excretion of free salicylate. When aspirin is used in low doses (600 mg), salicylate elimination is in accordance with first-order kinetics and the serum half-life is 3–5 hours. With higher dosage, a mix of capacity-limited and first-order kinetics prevails; at anti-inflammatory dosage (≥ 4 g/d), the half-life increases to 12 hours or more.

Pharmacodynamics

A. Mechanism of Action: The effectiveness of aspirin is due partly to its ability to inhibit cyclooxygenase and partly to the effect of its primary metabolite, salicylate, both to inhibit cyclooxygenase and to act in other ways, eg, as an oxygen radical scavenger (see Chapter 18). Aspirin as such irreversibly blocks the enzyme cyclooxygenase (prostaglandin synthase), which catalyzes the conversion of arachidonic acid to endoperoxide compounds; at appropriate doses, the drug decreases the formation of both the prostaglandins and thromboxane A_2 but not the leukotrienes (Figure 36–2). There is no evidence that aspirin is a selective inhibitor of COX II.

B. Anti-inflammatory Effects: In addition to reducing the synthesis of eicosanoid mediators, aspirin also interferes with the chemical mediators of the kallikrein system (see Chapter 17). As a result, aspirin inhibits granulocyte adherence to damaged vasculature, stabilizes lysosomes, and inhibits the migration of polymorphonuclear leukocytes and macrophages into the site of inflammation.

C. Analgesic Effects: Aspirin is most effective in reducing pain of mild to moderate intensity. It alleviates pain of varying causes, such as that of muscular, vascular, and dental origin, postpartum states, arthritis, and bursitis. Aspirin acts peripherally through its effects on inflammation but probably also inhibits pain stimuli at a subcortical site.

D. Antipyretic Effects: Aspirin reduces elevated temperature, whereas normal body temperature is only slightly affected. The fall in temperature is related to increased dissipation of heat caused by vasodilation of superficial blood vessels. The antipyresis may be accompanied by profuse sweating.

The fever associated with infection is thought to result from two actions. The first is the production of prostaglandins in the central nervous system in response to bacterial pyrogens. The second is the effect of interleukin-1 on the hypothalamus. Interleukin-1 is produced by macrophages and is released during inflammatory responses, when its principal role is to activate lymphocytes (Table 36–2). Aspirin blocks both the pyrogen-induced production of prostaglandins and the central nervous system response to interleukin-1 and so may reset the "temperature control" in the hypothalamus, thereby facilitating heat dissipation by vasodilation.

E. Platelet Effects: Aspirin affects hemostasis. Single low doses of aspirin (about 80 mg) produce a

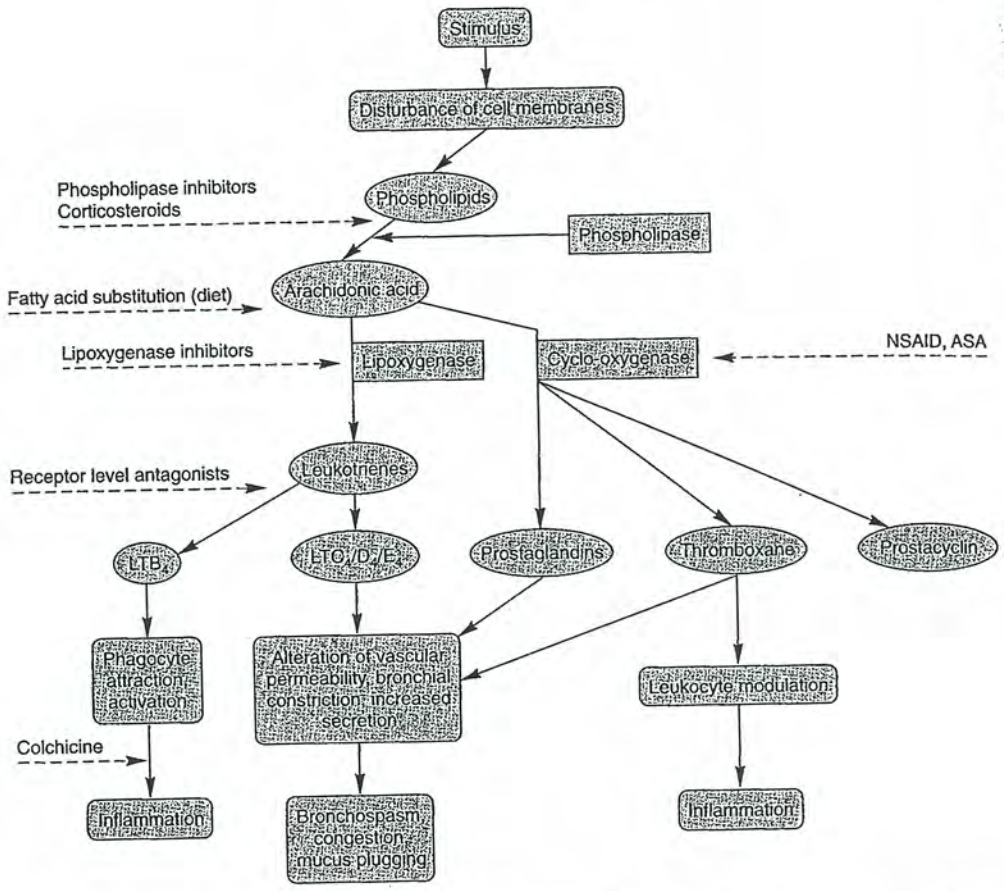

Figure 36–2. Scheme for mediators derived from arachidonic acid and sites of drug action (dashed arrows).

slightly prolonged bleeding time, which doubles if administration is continued for a week. The change is explained by the inhibition of platelet aggregation secondary to inhibition of thromboxane synthesis (see Chapter 34). Because its action is irreversible, aspirin inhibits platelet aggregation for up to 8 days—ie, until new platelets are formed. If potential bleeding complications are a concern in association with surgery, aspirin should be stopped 1 week prior to the operation.

Aspirin has a longer duration of effect than the many other compounds that inhibit platelet aggregation such as ticlopidine and dipyridamole.

Clinical Uses

A. Analgesia and Anti-inflammatory Effects: Aspirin is one of the most frequently employed drugs for relieving mild to moderate pain of varied origin. Aspirin is often combined with other mild analgesics, and over 200 such products may be purchased without prescription. These more costly combinations have never been shown to be more effective or less toxic than aspirin alone, and treating poisoning due to overdoses of such combinations is more difficult. Furthermore, the phenacetin contained in many such compounds may cause interstitial nephritis with serious renal impairment. Aspirin is not effective in the treatment of severe visceral pain such as that associated with acute abdomen, renal colic, pericarditis, or myocardial infarction. It and other NSAIDs have been combined with opioid analgesics for treatment of cancer pain. In that context, their anti-inflammatory effects act synergistically with the opioids to enhance analgesia.

The anti-inflammatory properties of salicylates in high doses are responsible for their recommendation for treatment of rheumatoid arthritis, rheumatic fever, and other inflammatory joint conditions. In mild arthritis, many patients can be managed using salicylates as their sole medication.

B. Other Indications:

1. Antipyresis–Except for a few diseases (eg, neurosyphilis, chronic brucellosis), there is no evidence that elevation of body temperature is a useful defense mechanism. On the other hand, there is rarely any great need to reduce a mild or moderate fever, es-

pecially in adults (Styrt et al, 1990). Aspirin is the best available drug for reducing fever when doing so is desirable and when there are no contraindications to its use (see below).

2. Inhibition of platelet aggregation (see also Chapter 34)–Aspirin has been shown to decrease the incidence of transient ischemic attacks and unstable angina in men and has been used as a prophylactic agent in these conditions. It may also be effective in reducing the incidence of thrombosis in coronary artery bypass grafts. The results of several clinical studies of patients at risk for or recovering from myocardial infarction have provided evidence that aspirin reduces the incidence of coronary artery thrombosis. In one large study, the ingestion of 325 mg of aspirin every other day reduced the incidence of myocardial infarction by over 40% in male physicians.

3. Other uses–Several studies have suggested that aspirin may reduce cataract formation; other studies contradict this finding (Chew et al, 1992). Other epidemiologic studies suggest that long-term use of aspirin at low dosage is associated with a lower incidence of colon cancer (Thun et al, 1991).

Dosage

The optimal analgesic or antipyretic dose of aspirin is less than the 0.6 g oral dose commonly used. Larger doses may prolong the effect. The usual dose may be repeated every 4 hours and smaller doses (0.3 g) every 3 hours. The dose for children is 50–75 mg/kg/d in divided doses.

The average anti-inflammatory dosage of 3.2–4 g daily can be tolerated by most adults. For children, 50–75 mg/kg/d usually produces adequate blood levels. Blood levels of 15–30 mg/dL are associated with anti-inflammatory effects. A simple reliable method for determining salicylate blood levels is available, and the drug can thus be titrated to the proper level. Because of the long half-lives (about 12 hours) of aspirin's active metabolites, frequent dosing is not necessary when daily doses of 4 g or more are required. A convenient method is to give the total amount divided into three doses taken after meals.

The relationship of salicylate blood levels to therapeutic effect and toxicity is illustrated in Figure 36–3.

Drug Selection

Aspirin is available from many different manufacturers, and although it may vary in texture and appearance, the content of aspirin is constant. A disintegration test is part of the official standard, and there is little evidence that differences among tablets have clinical significance. The most popular buffered aspirin does not contain sufficient alkali to modify gastric irritation, and there is no evidence that these more expensive preparations are associated with higher blood levels, greater clinical effectiveness, or a lower incidence of adverse effects. Enteric-coated aspirin may be suitable for patients in whom buffering fails to control gastritis, since the coating prevents the tablets from dissolving in the stomach and the drug is absorbed adequately in the small intestine. Therapeutic blood levels with this preparation may be similar to those achieved with the same doses of regular aspirin. Enteric coating increases the cost of aspirin, but these products are still less costly than the newer NSAIDs. The concomitant use of H_2 blockers and other drugs (except misoprostol and omeprazol) for the treatment and prevention of acid-peptic disease has not been shown to reduce the incidence of NSAID-induced gastrointestinal damage. Misoprostol, a prostaglandin E_1 derivative, has been shown to reduce NSAID-induced ulceration. Its use is complicated by its cost and some diarrhea, but misoprostol is cost-effective when NSAIDs are necessary in patients at higher risk for gastrointestinal bleeding, eg, elderly women and patients with a history of ulcers.

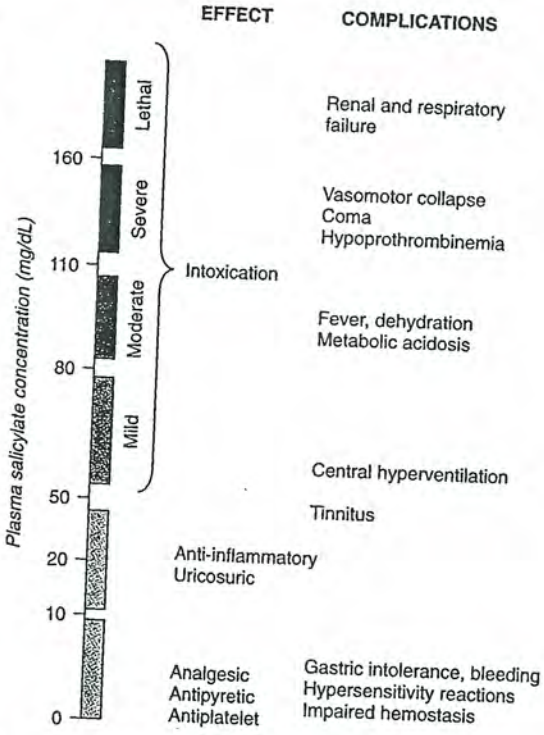

Figure 36–3. Approximate relationships of plasma salicylate levels to pharmacodynamics and complications. (Modified and reproduced, with permission, from Hollander J, McCarty D Jr: *Arthritis and Allied Conditions*. Lea & Febiger, 1972.)

Adverse Effects

A. Gastrointestinal Effects: At the usual dosage, the main adverse effect is gastric upset (intolerance). This effect can be minimized with suitable buffering (taking aspirin with meals followed by a glass of water or antacids). The gastritis that occurs

with aspirin may be due to irritation of the gastric mucosa by the undissolved tablet, to absorption in the stomach of nonionized salicylate, or to inhibition of protective prostaglandins. In animals, ulceration can be produced by the parenteral administration of aspirin, and administration of prostaglandins has prevented aspirin-induced gastric erosions; these observations suggest that the absence of a prostaglandin may make the gastric mucosa more vulnerable. As noted above, misoprostol does reduce the frequency of recurrence of peptic ulceration in patients taking large doses of NSAIDs but causes its own toxicities.

Although aspirin has never been shown to cause peptic ulcers in humans, experimental and epidemiologic studies overwhelmingly document an increased incidence of gastric ulcers and, to a lesser extent, duodenal ulcers with heavy aspirin or newer NSAID use (Ivey, 1986). Upper gastrointestinal bleeding associated with aspirin use is usually related to erosive gastritis. A small increase in fecal blood loss is routinely associated with aspirin administration; about 1 mL of blood normally lost in the stool daily increases to about 4 mL daily in persons using ordinary aspirin doses and more for higher doses. On the other hand, with appropriate therapy, ulcers have been shown to heal while aspirin was taken concomitantly. Nevertheless, aspirin should be avoided or taken with effective buffers or prostaglandins by individuals with peptic ulcer disease.

Vomiting may occur as a result of central nervous system stimulation after absorption of large doses of aspirin.

B. Central Nervous System Effects: With higher doses, patients may experience "salicylism"—tinnitus, decreased hearing, and vertigo—reversible by reducing the dosage. Still larger doses of salicylates cause hyperpnea through a direct effect on the medulla. At low toxic salicylate levels, respiratory alkalosis may occur as a result of the increased ventilation. Later, acidosis supervenes from accumulation of salicylic acid derivatives and depression of the respiratory center.

C. Other Adverse Effects: Aspirin in a daily dose of 2 g or less usually increases serum uric acid levels, whereas doses exceeding 4 g daily decrease urate levels below 2.5 mg/dL. (See Drugs Used in Gout, below.)

Aspirin may cause mild, usually asymptomatic hepatitis, especially in patients with underlying disorders such as systemic lupus erythematosus and juvenile and adult rheumatoid arthritis.

Salicylates may cause reversible decrease of glomerular filtration rate in patients with underlying renal disease, and this may also occur (though rarely) in persons with normal kidneys.

Aspirin in usual doses has a negligible effect on glucose tolerance. Toxic amounts affect the cardiovascular system directly and may depress cardiac function and dilate peripheral blood vessels. Large doses directly affect smooth muscles.

Hypersensitivity reactions may occur after ingestion of aspirin by patients with asthma and nasal polyps and may be associated with bronchoconstriction and shock. These reactions are probably mediated by leukotrienes.

Aspirin is contraindicated in patients with hemophilia. Aspirin is not recommended for pregnant women. However, recent studies have suggested that low-dose aspirin may be valuable in certain pregnant patients with a high risk of hypertension and other complications of pregnancy (Schiff et al, 1989).

Use of aspirin in children during or immediately after a viral infection has been associated with an increase in the incidence of Reye's syndrome (Hurwitz et al, 1987; Hurwitz, 1989), and decreased aspirin use has been associated with a decreased incidence. On the other hand, the incidence of Reye's syndrome decreased in Australia *before* the use of aspirin decreased, so the direct association of Reye's syndrome with aspirin is questioned by some. In any case, acetaminophen should be used in place of aspirin in this situation.

Overdosage Toxicity

Aspirin is such a common household drug that it has been a frequent cause of poisoning in young children. Serious intoxication results when the amount ingested exceeds 150–175 mg/kg of body weight. Since the introduction of child-resistant containers, there has been a significant decrease in fatal aspirin-induced poisonings in children.

Most aspirin is sold and used without prescription. The drug must be kept out of reach of children and in the child-resistant container in which it is dispensed. Colorful, flavored, and liquid preparations should be kept in locked cabinets.

When overdosing occurs, either accidentally or with suicidal intent, gastric lavage is advised (Chapter 59). Hyperthermia may be treated with alcohol sponges or ice packs. It is important to maintain a high urine volume and to treat acid-base abnormalities. In severe toxic reactions, ventilatory assistance may be required. Sodium bicarbonate infusions may be employed to alkalinize the urine, which will increase the amount of salicylate excreted.

Drug Interactions

Drugs that enhance salicylate intoxication include acetazolamide and ammonium chloride. Alcohol increases gastrointestinal bleeding produced by salicylates. Aspirin displaces a number of drugs from protein binding sites in the blood. These include tolbutamide, chlorpropamide, nonsteroidal anti-inflammatory agents, methotrexate, phenytoin, and probenecid. Corticosteroids may decrease salicylate concentration. Aspirin reduces the pharmacologic activity of spironolactone, competes with penicillin G for renal tubular secretion, and inhibits the uricosuric effect of sulfinpyrazone and probenecid.

NONACETYLATED SALICYLATES

These drugs include **magnesium choline salicylate, sodium salicylate,** and **salicylsalicylate.** All nonacetylated salicylates are effective anti-inflammatory drugs, though they may be less effective analgesics than aspirin. Because they are much less effective than aspirin as cyclooxygenase inhibitors, they may be preferable when cyclooxygenase inhibition is undesirable—such as in patients with asthma, those with bleeding tendencies, and even (under close supervision) those with renal dysfunction.

The nonacetylated salicylates are administered in the same dosage as aspirin and can be monitored using serum salicylate measurements.

DIFLUNISAL

Diflunisal is a newer NSAID chemically derived from salicylic acid, although it is not metabolized to salicylate or salicylic acid. The drug has a plasma half-life approaching that of salicylate, and blood levels reach a steady state after several days of dosing. Like aspirin, it has analgesic and anti-inflammatory effects; unlike aspirin, it has little antipyretic activity.

The indications for use of diflunisal include pain, osteoarthritis, and rheumatoid arthritis. Adverse reactions are similar to those of other NSAIDs.

OTHER NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The adverse effects of aspirin and other salicylates—especially the gastric irritation that occurs when large doses are employed—have led to the search for alternative compounds. Starting with phenylbutazone in 1949, many drugs with aspirin-like properties (designated "newer" nonsteroidal anti-inflammatory drugs) have been approved for use in the USA for the treatment of rheumatoid arthritis or osteoarthritis (Table 36–3). In addition to their use in joint disease, several newer NSAIDs have been approved for other indications as described below.

Chemistry

The NSAIDs are grouped in several chemical classes, some of which are shown in Figure 36–4. This chemical diversity yields such a broad range of pharmacokinetic characteristics that these properties are best discussed in connection with the individual agents.

Pharmacodynamics

The anti-inflammatory activity of the newer NSAIDs is similar in mechanism to that of aspirin and is mediated chiefly through inhibition of biosynthesis of prostaglandins. Various NSAIDs have additional possible mechanisms of action, including inhibition of chemotaxis, down-regulation of interleukin-1 production, and interference with calcium-mediated intracellular events. Unlike aspirin, these drugs are reversible inhibitors of cyclooxygenase. Selectivity for COX I versus COX II is variable and incomplete. For example, in testing against the mouse enzymes, aspirin, indomethacin, piroxicam, and sulindac were considerably more effective in inhibiting COX I; ibuprofen and meclofenamate inhibited the two isozymes about equally; and the active metabolite of nabumetone was somewhat selective for COX II (Meade et al, 1993). Inhibition of lipoxygenase synthesis by the newer NSAIDs, a desirable effect for an anti-inflammatory drug, is limited but may be greater than with aspirin. Benoxaprofen, another newer NSAID, was shown to significantly inhibit leukotriene synthesis but was withdrawn because of toxicity. Of the currently available NSAIDs, indomethacin and diclofenac have been reported to reduce the synthesis of both prostaglandins and leukotrienes. It is likely that development of newer NSAIDs will continue until the clinical significance of inhibition of COX II and of lipoxygenase can be fully evaluated with more selective inhibitors.

During therapy with these drugs, inflammation is reduced by decreasing the release of mediators from granulocytes, basophils, and mast cells. The NSAIDs decrease the sensitivity of vessels to bradykinin and histamine, affect lymphokine production from T lymphocytes, and reverse vasodilation. To varying degrees, all newer NSAIDs are analgesic, anti-inflammatory, and antipyretic, and all inhibit platelet aggregation. They are all gastric irritants as well, though as a group they tend to cause less gastric irritation than aspirin. Nephrotoxicity has been observed for all of the drugs for which extensive experience has been reported, and hepatotoxicity can also occur with any NSAID.

Pharmacokinetics

Although there are many differences in the kinetics of NSAIDs, they have some general properties in common. Most of these drugs are well absorbed, and food does not substantially change their bioavailability. Most of the NSAIDs are highly metabolized, some by phase I and phase II mechanisms and others by direct glucuronidation (phase II) alone. While renal excretion is the most important route, all undergo varying degrees of biliary excretion and reabsorption (enterohepatic circulation). All of the NSAIDs are highly protein-bound (≥ 98%), usually to albumin. Some of the NSAIDs (eg, ibuprofen) are racemic mixtures, while others (eg, naproxen) are provided as a single enantiomer and a few have no chiral center (eg, diclofenac).

All NSAIDs can be found in synovial fluid after repeated dosing. Drugs with short half-lives remain in the joints longer than would be predicted from their

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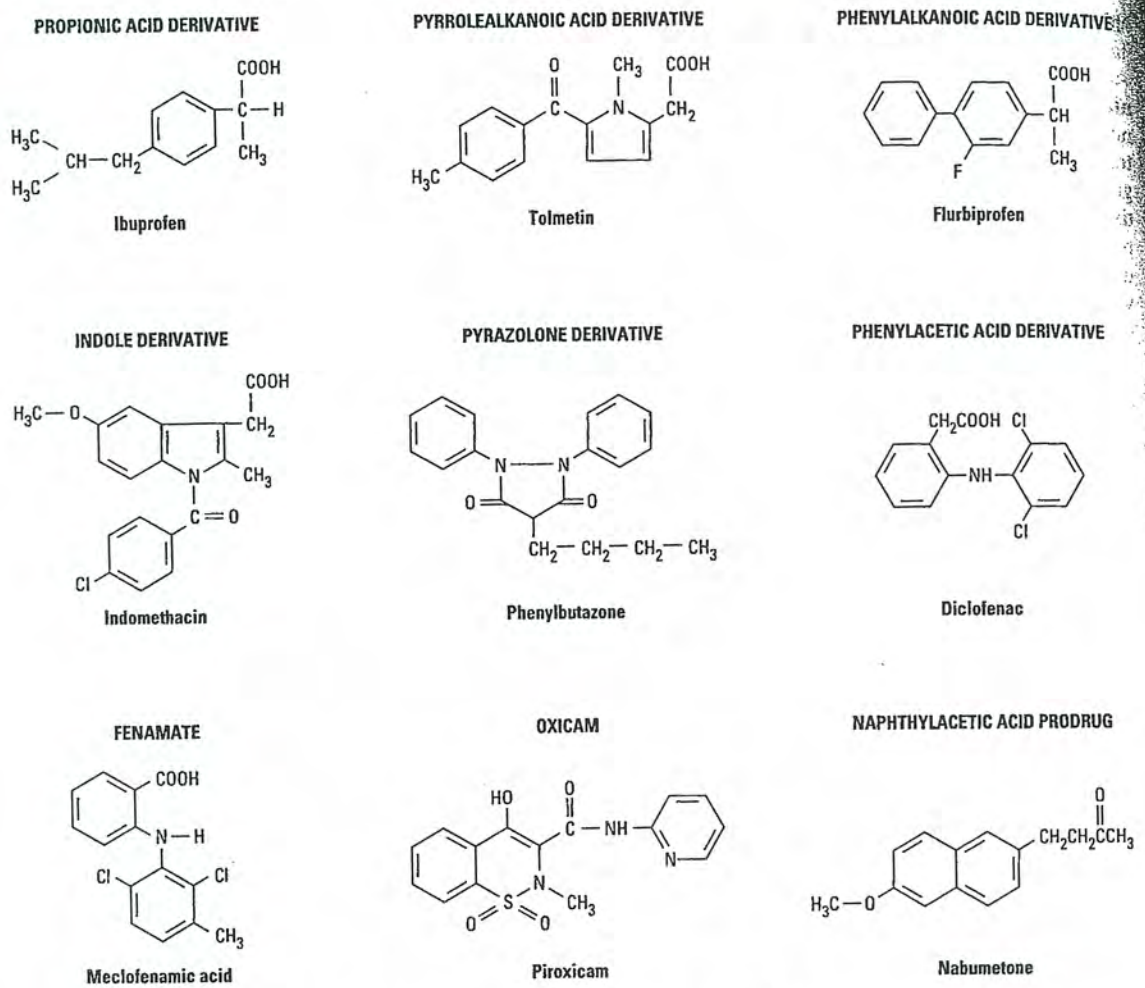


Figure 36–4. Chemical structures of some NSAIDs.

half-lives, while drugs with longer half-lives disappear from the synovial fluid at a rate proportionate to their half-lives.

IBUPROFEN

Ibuprofen is a simple derivative of phenylpropionic acid. In doses of about 2400 mg daily, ibuprofen is equivalent to 4 g of aspirin in anti-inflammatory effect. This drug is rapidly cleared, has a terminal half-life of 1–2 hours, and is more than 99% protein-bound. Ibuprofen is often prescribed in lower doses, at which it is analgesic (but not anti-inflammatory at less than 2400 mg/d). It is available over the counter in lower dosage under several trade names. Ibuprofen is extensively metabolized in the liver, and little is excreted unchanged. Gastrointestinal irritation and bleeding occur, though less frequently than with aspirin. The use of ibuprofen concomitantly with aspirin may decrease the total anti-inflammatory effect. The drug is contraindicated in individuals with nasal polyps, angioedema, and bronchospastic reactivity to aspirin. In addition to the gastrointestinal symptoms (which can be modified by ingestion with meals), rash, pruritus, tinnitus, dizziness, headache, aseptic meningitis particularly in patients with systemic lupus erythematosus), and fluid retention have been reported. Interaction with anticoagulants is uncommon. Rare hematologic effects include agranulocytosis and aplastic anemia. Effects on the kidney (as with all NSAIDs) include acute renal failure, interstitial nephritis, and nephrotic syndrome, again occurring very rarely. Finally, hepatitis has been reported occasionally.

NAPROXEN & FENOPROFEN

Naproxen is a naphthylpropionic acid that binds to plasma protein and has a half-life of 12–15 hours

(Table 36–3). Antacids delay its absorption. Naproxen is excreted in the urine as an inactive glucuronide metabolite. Like ibuprofen, naproxen competes with aspirin for plasma protein binding sites. It also prolongs prothrombin time. It is available over-the-counter, attesting to its relatively good long-term safety profile, though as with other NSAIDs, dyspepsia occurs in 20–40% of patients.

Fenoprofen, another propionic acid derivative, has a half-life of 2–4 hours and is given four times daily. Of all the NSAIDs, this one is most closely associated with the (fortunately very rare) toxicity of interstitial nephritis.

Adverse effects and drug interactions of naproxen and fenoprofen are similar to those of ibuprofen, ie, nephrotoxicity, nausea, dyspepsia, peripheral edema, rash, pruritus, central nervous system and cardiovascular effects, and tinnitus. Also like ibuprofen, these effects are less common than with aspirin.

FLURBIPROFEN

Flurbiprofen is another propionic acid derivative with an intermediate half-life. It is readily absorbed and achieves good synovial concentration like other NSAIDs. Following extensive metabolic degradation, it may undergo some enterohepatic recirculation before it is excreted by the kidneys. The efficacy of flurbiprofen is comparable to that of aspirin and other NSAIDs in clinical trials for patients with rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis. It is also available in a topical ophthalmic formulation for inhibition of intraoperative miosis.

As with other NSAIDs, gastrointestinal symptoms are encountered in 15–20% of patients who take the oral preparation. No significant age-related increase in adverse reactions has been reported.

KETOPROFEN

Ketoprofen is a propionic acid derivative that has some ability to inhibit both cyclooxygenase and lipoxygenase. The drug is rapidly absorbed, and its elimination half-life is 1–3 hours. It is metabolized completely in the liver. Despite being 99% bound to plasma proteins, it does not alter warfarin or digoxin activity. In contrast, concurrent administration of probenecid elevates ketoprofen levels and prolongs its plasma half-life.

The effectiveness of ketoprofen is equivalent to that of other NSAIDs and aspirin in the treatment of rheumatoid arthritis and osteoarthritis. In spite of its dual effect on prostaglandins and leukotrienes, it has not been shown to be superior to other NSAIDs. Its major adverse effects are on the central nervous system and gastrointestinal tract.

OXAPROZIN

Oxaprozin is one of the newest of the propionic acid derivative NSAIDs. As noted in Table 36–3, its major difference from the other members of this subgroup is a very long half-life; it can be given once a day. Because of this long half-life, dosage adjustments should be made at intervals no shorter than 5 days to 2 weeks. The drug appears to have the same benefits and risks associated with other NSAIDs, although it is mildly uricosuric, making it potentially more useful in gout than some other NSAIDs.

DICLOFENAC

Diclofenac is a simple phenylacetic acid derivative that resembles both flurbiprofen and meclofenamate. It is a potent cyclooxygenase inhibitor with anti-inflammatory, analgesic, and antipyretic properties. The drug is rapidly absorbed following oral administration and has a half-life of 1–2 hours. Like flurbiprofen, it accumulates in the synovial fluid. The potency of diclofenac as a cyclooxygenase inhibitor is greater than that of naproxen. The drug is recommended for chronic inflammatory conditions such as rheumatoid arthritis and osteoarthritis and for the treatment of acute musculoskeletal pain. Adverse effects occur in approximately 20% of patients and include gastrointestinal distress, occult gastrointestinal bleeding, and gastric ulceration. Transaminitis (elevation of serum aminotransferase) may occur more commonly with this drug than with other NSAIDs.

An ophthalmic preparation is available that is recommended for prevention of postoperative ophthalmic inflammation. In Europe, diclofenac is available both as a dermatologic preparation and for intramuscular administration.

SULINDAC

Sulindac, a sulfoxide, is a prodrug. Its active metabolite is, like diclofenac, an acetic acid derivative. The drug is effective only after it is converted by liver enzymes to a sulfide, which is excreted in bile and then reabsorbed from the intestine. The enterohepatic cycling prolongs the duration of action to 12–16 hours.

The indications and adverse reactions are similar to those of other NSAIDs. Among the more severe reactions, Stevens-Johnson epidermal necrolysis syndrome, thrombocytopenia, agranulocytosis, and nephrotic syndrome have all been observed. Like diclofenac, sulindac may have some propensity to cause elevation of serum aminotransferase; it is also sometimes associated with cholestatic liver damage.

TOLMETIN

Tolmetin, a pyrroleacetic acid derivative, is similar to aspirin in effectiveness in juvenile and adult rheumatoid arthritis and osteoarthritis. The drug has a short half-life and must be given frequently. Unlike most other NSAIDs, this drug may have minimal or no enterohepatic circulation.

ETODOLAC

Etodolac is newer acetic acid derivative with an intermediate half-life (Table 36–3). Like some other NSAIDs, it is a racemic mixture of *R* and *S* forms, the *R* form being inactive. The drug is well absorbed, with a bioavailability of about 80%, and is strongly bound to plasma proteins (> 90%). There are no data to suggest that etodolac differs significantly from other NSAIDs except in its pharmacokinetic parameters, although it may have slightly less gastric toxicity in terms of ulcer disease than other NSAIDs.

NABUMETONE

Nabumetone is a prodrug. It is given as a ketone (Figure 36–4) and converted to an acetic acid derivative in the body. Its half-life of more than 24 hours (Table 36–3) permits once-daily dosing. Otherwise, its properties are very similar to those of other NSAIDs, though it, like etodolac, may be slightly less gastrotoxic than other NSAIDs when given at a dosage of 1000 mg/d.

MECLOFENAMATE & MEFENAMIC ACID

Meclofenamate, a fenamic acid derivative, reaches a peak plasma level in 30–60 minutes and has a short half-life. It is excreted in the urine, largely as the glucuronide conjugate. Although long-term experience is lacking, meclofenamate appears to have adverse effects similar to those of other newer NSAIDs and to have no advantage over them. This drug enhances the effect of oral anticoagulants. Meclofenamate is contraindicated in pregnancy; its efficacy and safety have not been established for young children.

Mefenamic acid, another fenamate, possesses analgesic properties but is probably less effective than aspirin as an anti-inflammatory agent and is clearly more toxic. It should not be used for longer than 1 week and never in children.

PIROXICAM

Piroxicam, an oxicam, is an NSAID of novel structure (Figure 36–4). It has a half-life of 42–76 hours, permitting once-daily dosing, which should favor compliance. Given its long half-life, it can probably be administered every other day, though no study documenting such a dosing regimen has been published. It is rapidly absorbed in the stomach and upper small intestine and reaches 80% of its peak plasma concentration in 1 hour. It is excreted as the glucuronide conjugate and to a small extent unchanged.

Gastrointestinal symptoms are encountered in 20% of patients. Other adverse reactions include dizziness, tinnitus, headache, and rash. When piroxicam is used in dosages higher than 20 mg/d, an increased incidence of peptic ulcer is encountered. The drug may be used in the treatment of rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.

AZAPROPAZONE & CARPROFEN

These drugs are available in many other countries but are not sold in the USA. Azapropazone, a pyrazolone derivative, is structurally related to phenylbutazone but appears less likely to cause agranulocytosis. Its half-life is 12–16 hours. In patients with decreased renal function—eg, elderly patients—its half-life may be doubled. Carprofen is a propionic acid derivative with a half-life of 10–16 hours. The indications and adverse effects of azapropazone and carprofen are similar to those of other NSAIDs.

NSAIDS FOR SPECIAL INDICATIONS

INDOMETHACIN

Indomethacin, introduced in 1963, is an indole derivative (Figure 36–4). It is slightly more toxic but in certain circumstances more effective than aspirin. In the laboratory, it is among the most potent of the inhibitors of prostaglandin synthesis. Indomethacin is well absorbed after oral administration and highly bound to plasma proteins. Metabolism occurs in the liver, and unchanged drug and inactive metabolites are excreted in bile and urine.

Clinical Uses

Indomethacin is not suggested for general use as an analgesic. Except for the treatment of patent ductus

arteriosus (discussed below), it is not usually used in children. It is useful in special situations, including acute gouty arthritis and ankylosing spondylitis, and has also been effective in extra-articular inflammatory conditions such as pericarditis and pleurisy and in Bartter's syndrome (as one would anticipate other potent cyclooxygenase inhibitors would be). In acute gout, indomethacin often replaces colchicine as the initial medication. (See Drugs Used in Gout, below.)

A special application of indomethacin is in the management of patent ductus arteriosus in premature infants. Because this structure is kept patent in the fetus by the continuous production of prostaglandins, closure can be accelerated in a premature newborn by intravenous infusion of this drug. The production of prostaglandin in this situation is not an inflammatory process and is probably dependent upon COX I rather than COX II. As noted above, indomethacin is relatively selective for COX I. In many cases, surgery can be avoided by the use of indomethacin, though renal toxicity can easily occur.

Indomethacin has been recommended for use as a tocolytic in preterm labor at less than 32 weeks gestation (Morales et al, 1989); inhibition of prostaglandin synthesis reduces the frequency and strength of uterine contractions. However, others dispute this application on the basis of the recognized fetal and maternal toxicity of the drug (Norton et al, 1993). Calcium channel blockers (Chapter 12) are receiving more attention in this application.

Adverse Effects

At higher dosage levels, at least a third of patients have reactions to indomethacin requiring discontinuance of the medication. The gastrointestinal effects may include abdominal pain, diarrhea, gastrointestinal hemorrhage, and pancreatitis. Headache is experienced by 15–25% of patients and may be associated with dizziness, confusion, and depression. Rarely, psychosis with hallucinations has been reported. Hepatic abnormalities are rare. Serious hematologic reactions have been noted, including thrombocytopenia and aplastic anemia. Hyperkalemia has been reported and is related to inhibition of the synthesis of prostaglandins in the kidney. A number of interactions with other drugs have been reported (see Appendix II). Use of indomethacin, like other potent cyclooxygenase inhibitors, should be avoided in patients with nasal polyps or angioedema, in whom asthma may be precipitated. The drug is contraindicated in pregnancy and should be used with caution in persons with psychiatric disorders or peptic ulcer disease.

PHENYLBUTAZONE

Phenylbutazone, a pyrazolone derivative, rapidly gained favor after its introduction in 1949 for the treatment of rheumatoid arthritis, ankylosing spondylitis, acute gouty arthritis, and various musculoskeletal disorders. Its toxicities, particularly the hematologic effects, have resulted in its withdrawal from the North American and most European markets.

Phenylbutazone has a large number of serious adverse effects. The most serious are agranulocytosis and aplastic anemia, which have led to a number of deaths. Phenylbutazone has also caused hemolytic anemia, nephrotic syndrome, optic neuritis, deafness, serious allergic reactions, exfoliative dermatitis, and hepatic and renal tubular necrosis.

KETOROLAC

Ketorolac is an NSAID of intermediate duration of action that is promoted for systemic use mainly as a analgesic, not an anti-inflammatory drug (though it has typical NSAID properties). The drug does appear to have significant analgesic efficacy and has been used successfully to replace morphine in some situations involving mild to moderate postsurgical pain. It is most often given parenterally, but an oral dose-form is available. Longer-term use of ketorolac is associated with a significant incidence of peptic ulceration and renal compromise. This has led to its withdrawal from some European markets, though it is still available in the USA. An ophthalmic preparation is available for anti-inflammatory applications.

CLINICAL PHARMACOLOGY OF THE NSAIDS

Although aspirin is an effective drug, it is less safe than other NSAIDs (at least in the gastrointestinal tract), and it has been largely replaced by ibuprofen since the latter became an over-the-counter medication. As a group, NSAIDs tend to cause less gastric irritation, and the dosing schedule of some is simpler (one tablet once or twice daily). In choosing an agent, it is worth remembering that the cost to the patient is $30–$200 for a 60-day supply of the newer agents compared to about $10–$20 for generic over-the-counter aspirin, ibuprofen, or naproxen. A reliable method for determining salicylate blood levels is available to establish therapeutic range, which is not true for the newer drugs. The cost and follow-up advantages of aspirin must be weighed against easier dosage schedules, better compliance, and lower incidence of gastric irritation with some of the newer agents. Surveys show that most patients with inflammatory arthritis receive NSAIDs without an adequate trial of salicylates, yet none of these newer drugs have proved more effective than aspirin in controlled studies. Moreover, although less gastrointestinal irritation

has been shown for most of them, some are proving more toxic in other ways.

Because of the importance of gastric ulceration in patients taking anti-inflammatory doses of the NSAIDs, considerable effort has gone into preventing this complication or reducing its severity. The prostaglandin E_1 analog misoprostol inhibits gastric acid secretion at some doses and probably increases secretion of gastric mucosal protective factors such as bicarbonate at higher doses (see Chapters 18 and 63). Misoprostol is labeled for use with NSAIDs in patients prone to development of peptic ulcers.

The newer NSAIDs have been responsible for instances of acute renal failure and nephrotic syndrome, which develops insidiously and is neither dose-dependent nor related to duration of drug use. Patients rarely have symptoms suggestive of a hypersensitivity reaction, so the condition may go undetected until advanced.

If the decision is made to use a newer NSAID, it is important to consider adverse effects, cost, and dosing schedules. It is not possible to know which patient will respond in a specific way to which NSAID, for some patients derive benefit from one and not from another. How much of this variability of response is related to the agent per se, to individual differences in metabolism of the drug, or to a placebo effect is difficult to evaluate. When compliance is a problem, drugs such as piroxicam, naproxen, sulindac, and oxaprozin are useful because only one or two doses are required daily. If a patient is taking a hypoglycemic agent or warfarin, ibuprofen or tolmetin might be considered, since they do not potentiate the effect of the hypoglycemic drugs or warfarin. Hypersensitivity to one of the phenylpropionic or phenylacetic acids, however, should preclude use of the others in that group. Dosing schedules listed for the drugs are those recommended by the manufacturer, but it is becoming clear that some patients require and may tolerate higher doses. Until blood level assays become available, it is probably safest to use the dosages as listed.

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS)

Careful clinical and epidemiologic studies have shown that rheumatoid arthritis causes significant systemic effects that shorten life in addition to the joint disease that reduces mobility and quality of life. NSAIDs appear to offer mainly symptomatic relief; they reduce inflammation and the pain it causes and often preserve function but have little effect on the progression of bone and cartilage destruction. In recent years, therefore, interest has been renewed in treatments that might arrest—or at least slow—this progression by modifying the disease itself. The effects of disease-modifying drugs may take 6 weeks to 6 months to become evident, ie, they are slow-acting compared with NSAIDs. Members of the group include methotrexate, azathioprine, penicillamine, hydroxychloroquine and chloroquine, organic gold compounds, and sulfasalazine. Considerable controversy surrounds the long-term efficacy of these drugs. The discovery that numerous cytokines are present in joints affected by the disease process (Table 36–2) suggests that one or more of these may be useful targets of disease-modifying drug therapy.

METHOTREXATE & OTHER IMMUNOSUPPRESSIVE DRUGS

The immunosuppressive agents (see Chapter 56) have been employed for many decades in the therapy of rheumatic diseases, but their use has been largely restricted to seriously crippling disease with reversible lesions after conventional therapy has failed. Because of their toxic potential, however, immunosuppressive drugs should be employed only by physicians completely familiar with their actions. Reliable methods of selecting one drug instead of another are not available, and acceptable controlled studies demonstrating efficacy in humans are lacking for most of the drugs. However, several clinical studies suggest that of all the slow-acting antirheumatic drugs, methotrexate has the best benefit-to-risk ratio, ie, fewer patients drop out of therapy with this drug—for reasons of toxicity or lack of benefit—than with any other DMARD (Felson et al, 1990; Wolfe et al, 1990).

Immunosuppressive agents are useful in lupus nephritis, in seropositive progressive rheumatoid arthritis, and occasionally in other rheumatic diseases. They have also been shown to be effective in vasculitis syndromes, such as Wegener's granulomatosis and panarteritis. Because of the severity of toxic effects—especially the oncogenic effects, hepatotoxicity, and bone marrow depression—immunosuppressive drugs should be given only after safer agents have been tried.

Methotrexate at oncologic doses is a potent immunosuppressive drug (Chapter 56). Its principal mechanisms of action at the doses used in the rheumatic diseases probably relate to inhibition of aminoimidazolecarboxamide ribonucleotide (AICAR) transformylase and thymidylate synthase, plus enhanced adenosine release. The drug is approximately 70% absorbed after oral administration, highly polyglutaminated, and excreted in both urine (the major pathway) and bile. It is effective in rheumatoid arthritis at dosages up to 25 mg/wk, though the most common dosage is 15 mg/wk. Nausea and mucosal ulcers were the most common toxicities recorded in a large study comparing DMARDs in rheumatoid arthritis (Singh et al, 1991). Progressive

dose-related hepatotoxicity in the form of enzyme changes occur frequently, but cirrhosis is rare (less than 1%), and liver biopsy follow-up is no longer recommended routinely until the patient has taken the drug for 5 years. Some clinicians have expressed concern about a "hypersensitivity" lung reaction and a pseudolymphomatous reaction. Recent evidence suggests that methotrexate toxicity can be reduced without decreasing its efficacy in rheumatoid arthritis by giving leucovorin 24 hours after each weekly dose of methotrexate (Shiroky et al, 1993) or by the use of daily folic acid.

Other immunosuppressive drugs for which there is some experience in the treatment of arthritis include the alkylators **mechlorethamine, cyclophosphamide,** and **chlorambucil** and the purine antagonist **azathioprine,** which is FDA-approved for treatment of rheumatoid arthritis.

Azathioprine is sometimes used for rheumatoid arthritis in dosages up to 2 μg/kg/d. Neither its kinetics nor its mechanism of action in this disease is understood. Its onset of action is slow and its toxicity is considerable, making its use infrequent. Toxicities of particular concern include hematologic and hepatic damage and a slightly increased incidence of non-Hodgkin's lymphoma.

ANTIMALARIAL DRUGS (Chloroquine, Hydroxychloroquine)

The pharmacology of the 4-aminoquinoline derivatives is more fully discussed in Chapter 53. Chloroquine and hydroxychloroquine have been used in the treatment of rheumatoid arthritis and systemic lupus erythematosus since the 1950s, and their efficacy in inducing remission has been confirmed in carefully controlled studies. Rheumatoid factor, a marker for disease intensity in many patients, declines after prolonged chloroquine use; however, there is no evidence that chloroquine or hydroxychloroquine decreases the progression of erosive bone lesions.

The mechanism of anti-inflammatory action of chloroquine and hydroxychloroquine in rheumatic disorders is unclear. They suppress the responsiveness of T lymphocytes to mitogens, decrease leukocyte chemotaxis, stabilize lysosomal membranes, inhibit DNA and RNA synthesis, and trap free radicals; one or more of these effects might be relevant. The actions of these agents are not apparent until after a latent period of 12–24 weeks. The drugs are often useful as adjuncts to treatment with NSAIDs and have no adverse interactions with other antirheumatic agents.

Indications

Antimalarials are often administered to patients with rheumatoid arthritis who have not responded optimally to salicylates and NSAIDs. In addition to their use in rheumatoid arthritis, antimalarials have been used successfully for their anti-inflammatory effect in juvenile chronic arthritis, Sjögren's syndrome, and systemic lupus erythematosus (in which they have a beneficial effect on both joint and skin findings). The antimalarial drugs should not be used in psoriatic arthritis because of the possible development of exfoliative dermatitis.

Adverse Effects

These are described in detail in Chapter 53.

Dosage

Hydroxychloroquine sulfate is the preferred drug. Initial dosage is up to 6.4 mg/kg/d but not more than 400 mg daily. Once clinical improvement is established, the dose can often be decreased to 200 mg daily.

GOLD

Gold compounds were introduced for treatment of rheumatoid arthritis in the 1920s, but it was not until 1960, in a report of a large double-blind trial, that the gold salts were shown to have a useful effect. Subsequent controlled studies have generally (not universally) supported the view that parenteral gold reduces symptoms and slows progression of the disease. Some studies have demonstrated that these agents retard the progression of bone and articular destruction determined roentgenographically. Further impetus to the popularity of gold salts has been the demonstration that the drug may be continued for years, allaying earlier fears of toxicity from accumulation. A particular disadvantage of gold therapy is the high rate of discontinuance; the probability of remaining on gold therapy is less than 60% after 2 years and less than 10% after 7 years. Most of these dropouts are due to toxicity.

Introduction of an oral gold preparation (auranofin) stimulated a number of large clinical studies during the 1980s. Most of these studies suggest that the oral preparation has modest effects at best and that its benefits may not differ significantly from those of NSAIDs in some types of arthritis, though its toxicity is greater (Carette et al, 1989; Giannini et al, 1990).

Chemistry

The parenterally administered gold preparations available in North America are **aurothiomalate** and **aurothioglucose.** Both are administered intramuscularly as water-soluble gold salts containing 50% elemental gold. **Auranofin** is a substituted gold thioglucose derivative (29% gold) that can be given by mouth.

Pharmacokinetics

Gold salts are approximately 95% bound to plasma protein during transport by the blood. Although they

tend to concentrate in synovial membranes, gold salts are also concentrated in the liver, kidney, spleen, adrenal glands, lymph nodes, and bone marrow. Following intramuscular injection of the parenteral forms, peak serum levels are reached in 2–6 hours; 40% is excreted within a week—about two-thirds in the urine and one-third in the feces. One month after intramuscular injection of 50 mg, 75–80% of the drug has been eliminated from the serum. The total body half-life of intramuscular gold, however, approaches 1 year. After oral administration of auranofin, only about 25% is absorbed. Certain tissue compartments such as the epithelial cells of the renal tubules, which have a particular affinity for gold, show its presence many years after therapy has ceased. Most studies have failed to show a correlation between serum gold concentration and either therapeutic effect or toxicity.

Pharmacodynamics

The precise manner in which gold salts produce their beneficial effects in patients with rheumatoid arthritis and allied disorders is unknown. Gold alters the morphology and functional capabilities of human macrophages; this may be its major mode of action. Other effects ascribed to gold include inhibition of lysosomal enzyme activity, reduction of histamine release from mast cells, inactivation of the first component of complement, suppression of phagocytic activity of the polymorphonuclear leukocytes, inhibition of macrophage function, and inhibition of the Shwartzman phenomenon. In addition, aurothiomalate reduces the number of circulating lymphocytes, and auranofin inhibits the release of prostaglandin E_2 from synovial cells and the release of leukotrienes B_4 and C_4 from polymorphonuclear leukocytes.

Indications & Contraindications

Gold therapy is indicated for active rheumatoid arthritis. Patients who later in the course of their disease show active inflammation and erosive changes are also candidates for gold. Patients with rheumatoid arthritis in the presence of Sjögren's syndrome and those with juvenile rheumatoid arthritis may also be considered, whereas the usefulness of gold in the treatment of psoriatic arthritis is less clear.

The major contraindications to gold are a confirmed history of previous toxicity from the drug, pregnancy, serious impairment of liver or renal function, and blood dyscrasias.

Adverse Effects

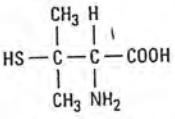
Approximately one-third of patients receiving gold salts experience some form of toxicity. Dermatitis, which is usually pruritic, is the most common adverse effect, occurring in 15–20% of patients. Eosinophilia may precede or be associated with cutaneous lesions. Hematologic abnormalities, including thrombocytopenia, leukopenia, and pancytopenia, occur in 1–10% of patients. Aplastic anemia, although rare, may be fatal. About 8–10% of patients develop proteinuria that may progress to nephrotic syndrome in a few cases. Other adverse effects include stomatitis, a metallic taste in the mouth, skin pigmentation, enterocolitis, cholestatic jaundice, peripheral neuropathy, pulmonary infiltrates, and corneal deposition of gold. Nitritoid reactions (sweating, faintness, flushing, and headaches) may occur, especially with gold thiomalate, and are presumably due to the vehicle rather than the gold salts themselves. Transient aggravation of arthritis symptoms may occur after injections of gold. Gastrointestinal disturbances (especially diarrhea) and dermatitis are the most common adverse effects of oral gold therapy.

Dosage

Parenteral gold is usually given as a 50 mg dose intramuscularly weekly until a total of 1000 mg has been injected (unless there is no response by the time 600–700 mg has been given, in which case the drug can be stopped). If 1 g is given without serious adverse effects and a favorable response is observed, the drug can be continued indefinitely in lengthening intervals of 2, 3, then 4 weeks. Oral gold is given as a 6 mg dose daily, increasing to 9 mg/d if a response is not seen after 3 months. Clinical response usually requires a few months to become evident and may be delayed for as long as 4 months. Careful clinical and laboratory monitoring is mandatory.

PENICILLAMINE

Penicillamine, a metabolite of penicillin, is an analog of the amino acid cysteine. The drug can be resolved into D and L isomers; the D form is used clinically.



Penicillamine

Pharmacokinetics

About half of an orally administered dose of penicillamine is absorbed. Absorption is enhanced if the drug is administered 1.5 hours after meals. Free penicillamine and its metabolites may be found in urine and feces. About 60% of the drug is excreted in 24 hours. No satisfactory method is available for determining blood levels.

Pharmacodynamics

The mechanism of penicillamine's action in rheumatoid arthritis is unclear. The drug suppresses

arthropathy in experimental animal models and has been shown to interact with lymphocyte membrane receptors. It may interfere with the synthesis of DNA, collagen, and mucopolysaccharides. Rheumatoid factor titer falls following administration of drug, probably reflecting disruption of disulfide bonds of macroglobulins but perhaps also reflecting a basic action of the drug on the immune system. Penicillamine is similar to gold in its latency period (3–4 months) and in its anti-inflammatory properties.

Indications

Penicillamine is reserved for patients with active, progressive erosive rheumatoid disease not controlled by conservative therapy. Penicillamine is usually prescribed for patients who have not responded to gold therapy. Penicillamine is not useful in seronegative arthropathies. Caution is required when administering other drugs simultaneously, because penicillamine impedes absorption of many drugs and prevents them from reaching therapeutic levels.

Adverse Effects

The toxic effects of penicillamine limit its usefulness. Animal studies have shown inhibition of wound healing and evidence of muscle and blood vessel damage. In humans, adverse effects are reduced by giving lower doses and by slow progression to maintenance dosages. Proteinuria is encountered in 20% of patients. Immune complex nephritis has been seen in 4% of patients; it is often reversible when the drug is withdrawn. Leukopenia and thrombocytopenia may occur at any time and may herald aplastic anemia. Most deaths related to penicillamine are due to aplastic anemia. Skin and mucous membrane reactions, the most common adverse effects, may occur at any time during therapy and may respond to lowering the dose. Drug fever, which may be seen as an early response to penicillamine, is often associated with cutaneous eruptions.

A variety of autoimmune diseases, including myasthenia gravis, Goodpasture's syndrome, lupus erythematosus, hemolytic anemia, and thyroiditis may be seen. The drug must be discontinued permanently when any of these conditions is encountered.

Loss of taste perception or a metallic taste may develop. The blunting of taste perception relates to zinc chelation. Anorexia, nausea, and vomiting occur. Mammary hyperplasia, alopecia, and psychologic changes have also been observed.

Penicillamine is contraindicated in pregnancy and in the presence of renal insufficiency and should not be given in combination with gold, cytotoxic drugs, or phenylbutazone.

Adverse effects necessitating cessation of the drug occur in about 40% of patients. Blood counts (including platelet count) and urinalysis are performed twice a month for 4–6 months, then monthly. The drug should be stopped if the platelet count falls below 100,000/μL or the white count below 3000/μL. A history of penicillin allergy is not a contraindication to penicillamine. Patients who develop renal involvement, drug fever, autoimmune syndromes, and hematologic problems should not be rechallenged with the drug.

Dosage

Penicillamine is taken orally 1.5 hours after meals. If clinical benefits are to occur, they should be apparent by 6 months. Treatment begins with 125 mg or 250 mg daily for 1–3 months; if no adverse effects are seen and improvement does not occur, the dose is doubled. If therapeutic effects are absent after 3–4 months, the dose is increased at monthly intervals up to 750 mg daily, which it is rarely necessary to exceed. If therapy is discontinued after improvement, most patients relapse within 6 months.

SULFASALAZINE

Sulfasalazine, originally introduced for the treatment of ulcerative colitis, has been shown to be effective in patients with rheumatoid arthritis (Felson et al, 1990). Its pharmacokinetics are somewhat complex, but its primary metabolites are 5-acetylsalicylic acid (5-ASA) and sulfapyridine. While 5-ASA is the active drug in inflammatory bowel disease, it is either the sulfapyridine alone or sulfapyridine and the parent drug that are active in rheumatoid arthritis. The mechanism of action in rheumatoid arthritis is probably *not* that of dihydrofolate inhibitor, though effects on B cell function may be important. Activity in rheumatoid arthritis has been proved, and the drug is approved by the FDA in the USA; it is already a frequently used drug in Europe.

Toxicity, which occurs more frequently in patients with rheumatoid arthritis than in those with ulcerative colitis, includes rashes, gastrointestinal upset, dizziness, and photosensitivity. Rarely, neutropenia may require discontinuation of the drug, and hypersensitivity pneumonitis and sterility have also occurred.

The usual dosage is 2 g/d, given in four divided doses.

GLUCOCORTICOID DRUGS

The pharmacology of corticosteroids and their other applications are discussed in Chapter 39.

The effect of prednisone and other glucocorticoids on rheumatoid arthritis is prompt and dramatic, and recent data suggest that the drug is capable of slowing the appearance of new bone erosions. Glucocorticoids are known to inhibit phospholipase A_2, the enzyme re-

sponsible for the liberation of arachidonic acid from membrane lipids (Chapter 18). In addition, glucocorticoids have recently been shown to selectively inhibit the expression of COX II (Kujubu et al, 1992; Winn et al, 1993). However, prolonged use of these drugs leads to serious, disabling toxic effects, including fractures, infections, and cataracts. In predisposed patients, diabetes, hypertension, and accelerated atherosclerotic heart disease may occur. Corticosteroids may be administered for certain serious extra-articular manifestations such as pericarditis or eye involvement or during periods of exacerbation. When prednisone is required for long-term therapy, the dosage should not exceed 10 mg daily, and gradual reduction of the dose should be encouraged. Alternate-day corticosteroid therapy is usually unsuccessful in rheumatoid arthritis, though it can be useful for some vasculitides such as subacute lupus erythematosus. Patients become symptomatic on the day they do not take the drug.

Intra-articular corticosteroids are often helpful to alleviate painful symptoms and, when successful, are preferable to increasing the dosage of systemic medication.

DIETARY MANIPULATION OF INFLAMMATION

Arachidonic acid is an eicosatetraenoic acid metabolized by the cyclooxygenase and lipoxygenase pathways. In this process arachidonic acid is released from membrane phospholipids of stimulated cells, and oxygenated, yielding several mediators. These mediators have potent effects on the development and function of smooth muscles, blood vessels, epithelial surfaces, secretory glands, leukocytes, and elements of the nervous system (Chapter 18).

It may be beneficial to alter or supplement a patient's diet to provide unsaturated fatty acids (such as eicosapentaenoic acid, which is found in marine fish) similar to arachidonic acid. This dietary change causes the alternative fatty acids to be metabolized with arachidonic acid, changing the final products of the process. For example, eicosapentaenoic acid inhibits the uptake and incorporation of arachidonic acid into membrane phospholipids of some cells, and dilutes free arachidonic acid as a substrate for oxygenation. The products of eicosapentaenoic acid oxygenation are less potent than the corresponding mediators derived from arachidonic acid (sometimes by orders of magnitude), and they diminish the activities of these mediators by competing with them for shared target-cell receptors.

Ingestion of unpurified eicosapentaenoic acid by humans causes the attenuation of platelet aggregation and decreased chemotactic activity and adherence of polymorphonuclear leukocytes evoked by leukotriene B_4. The results of clinical studies suggest that therapy with eicosapentaenoic acid decreases both morning stiffness and the number of tender joints in patients with rheumatoid arthritis and erythema associated with psoriasis. The potency of eicosapentaenoic acid approximates that of the NSAIDs. These preliminary results and the near absence of significant adverse effects suggest that dietary alteration or supplementation to provide 1–4 g/d of eicosapentaenoic acid may be a beneficial addition to conventional treatment of these conditions.

II. OTHER ANALGESICS

Acetaminophen is one of the most important drugs used for the treatment of mild to moderate pain when an anti-inflammatory effect is not necessary. Phenacetin, a prodrug that is metabolized to acetaminophen, is more toxic than its active metabolite and has no rational indications.

ACETAMINOPHEN

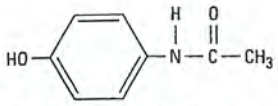
Acetaminophen is the active metabolite of phenacetin responsible for its analgesic effect. It is a weak prostaglandin inhibitor in peripheral tissues and possesses no significant anti-inflammatory effects.

Pharmacokinetics

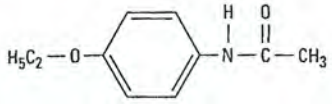
Acetaminophen is administered orally. Absorption is related to the rate of gastric emptying, and peak blood concentrations are usually reached in 30–60 minutes. Acetaminophen is slightly bound to plasma proteins and is partially metabolized by hepatic microsomal enzymes and converted to acetaminophen sulfate and glucuronide, which are pharmacologically inactive (Figure 4–4). Less than 5% is excreted unchanged. A minor but highly active metabolite (*N*-acetyl-*p*-benzoquinone) is important in large doses because of its toxicity to both liver and kidney. The half-life of acetaminophen is 2–3 hours and is relatively unaffected by renal function. With toxic quantities or liver disease, the half-life may be increased twofold or more.

Indications

Although equivalent to aspirin as an effective analgesic and antipyretic agent (Styrt et al, 1990), acetaminophen differs by its lack of anti-inflammatory properties. It does not affect uric acid levels and lacks platelet-inhibiting properties. The drug is useful in mild to moderate pain such as headache, myalgia, postpartum pain, and other circumstances in which aspirin is an effective analgesic. Acetaminophen alone is inadequate therapy for inflammatory conditions



N-Acetyl-*p*-aminophenol
(acetaminophen)



Phenacetin
(acetophenetidin)

such as rheumatoid arthritis, though it may be used as an analgesic adjunct to anti-inflammatory therapy. For mild analgesia, acetaminophen is the preferred drug in patients allergic to aspirin or when salicylates are poorly tolerated. It is preferable to aspirin in patients with hemophilia or a history of peptic ulcer and in those in whom bronchospasm is precipitated by aspirin. Unlike aspirin, acetaminophen does not antagonize the effects of uricosuric agents; it may be used concomitantly with probenecid in the treatment of gout. It is preferred to aspirin in children with viral infections.

Adverse Effects

In therapeutic doses, a mild increase in hepatic enzymes may occasionally occur in the absence of jaundice: this is reversible when the drug is withdrawn. With larger doses, dizziness, excitement, and disorientation are seen. Ingestion of 15 g of acetaminophen may be fatal, death being caused by severe hepatotoxicity with central lobular necrosis, sometimes associated with acute renal tubular necrosis (Chapters 4 and 59). Early symptoms of hepatic damage include nausea, vomiting, diarrhea, and abdominal pain. Recent data also implicate acetaminophen in rare cases of renal damage without hepatic damage. This damage has occurred even after usual doses of acetaminophen. Therapy is much less satisfactory than for aspirin overdose. In addition to supportive therapy, measures that have proved extremely useful are the provision of sulfhydryl groups to neutralize the toxic metabolites. Acetylcysteine is used for this purpose (see Chapter 59).

Hemolytic anemia and methemoglobinemia, reported with the use of phenacetin, have rarely been noted with acetaminophen. Interstitial nephritis and papillary necrosis, serious complications of phenacetin, although anticipated with widespread chronic use of acetaminophen, have not occurred despite the fact that about 80% of phenacetin is rapidly metabolized to acetaminophen. Gastrointestinal bleeding does not occur. Caution should be exercised in patients with liver disease.

Dosage

Acute pain and fever may be managed by 325–500 mg four times daily and proportionately less for children. Steady-state conditions are attained within a day.

PHENACETIN

Phenacetin can no longer be prescribed in the USA and has been removed from many over-the-counter analgesic combinations such as Anacin and Empirin Compound. However, it is still present in a number of proprietary analgesics in this country and is in common use in many other parts of the world. The association between the excessive use of analgesic combinations—especially those that contain phenacetin—and the development of renal failure has been recognized for almost 30 years. Estimates of the percentage of patients with end-stage renal disease resulting from this kind of analgesic abuse range from 5% to 15%. After prohibition of the use of phenacetin in proprietary analgesics in Finland, Scotland, and Canada, the number of new cases of analgesic nephropathies in those countries decreased significantly.

III. DRUGS USED IN GOUT

Gout is a familial metabolic disease characterized by recurrent episodes of acute arthritis due to deposits of monosodium urate in joints and cartilage. Formation of uric acid calculi in the kidneys may also occur. Gout is usually associated with high serum levels of uric acid, a poorly soluble substance that is the major end product of purine metabolism. In most mammals, uricase converts uric acid to the more soluble allantoin; this enzyme is absent in humans.

The treatment of gout is aimed at relieving the acute gouty attack and preventing recurrent gouty episodes and urate lithiasis. Therapy for an attack of acute gouty arthritis is based on our current understanding of the pathophysiologic events that occur in this disease (Figure 36–5). Urate crystals are initially phagocytosed by synoviocytes, which then release prostaglandins, lysosomal enzymes, and interleukin-1. Attracted by these chemotactic mediators, polymorphonuclear leukocytes migrate into the joint space and amplify the ongoing inflammatory process. In the later phases of the attack, increased numbers of mononuclear phagocytes (macrophages) appear, ingest the urate crystals, and release more inflammatory mediators. This sequence of events suggests that the most effective agents for the management of acute urate crystal-induced inflammation are those that suppress different phases of leukocyte activation.

Before starting chronic therapy for gout, patients in whom hyperuricemia is associated with gout and

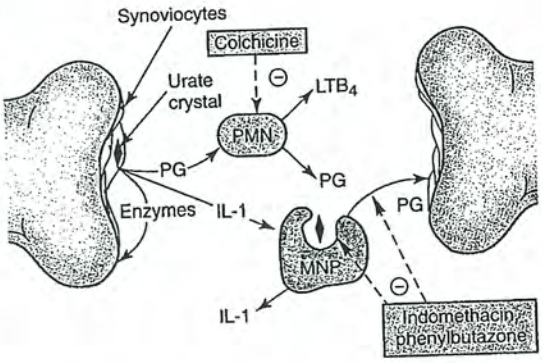


Figure 36–5. Pathophysiologic events in a gouty joint. Synoviocytes phagocytose urate crystals and then secrete inflammatory mediators, which attract and activate polymorphonuclear leukocytes (PMN) and mononuclear phagocytes (MNP) (macrophages). Drugs active in gout inhibit crystal phagocytosis and polymorphonuclear leukocyte and macrophage release of inflammatory mediators. (PG, prostaglandin; IL-1, interleukin-1; LTB_4, leukotriene B_4.)

urate lithiasis must be clearly distinguished from those who have only hyperuricemia. In an asymptomatic person with hyperuricemia, the efficacy of long-term drug treatment is unproved. Uric acid levels may be elevated up to 2 standard deviations above the mean for a lifetime without adverse consequences in some individuals.

COLCHICINE

Colchicine is an alkaloid isolated from the autumn crocus, *Colchicum autumnale.* Its structure is shown in Figure 36–6.

Pharmacokinetics

Colchicine is absorbed readily after oral administration and reaches peak plasma levels within 2 hours. Metabolites of the drug are excreted in the intestinal tract and urine.

Pharmacodynamics

Colchicine dramatically relieves the pain and inflammation of gouty arthritis in 12–24 hours without altering the metabolism or excretion of urates and without other analgesic effects. Colchicine produces its anti-inflammatory effects by binding to the intracellular protein tubulin, thereby preventing its polymerization into microtubules and leading to the inhibition of leukocyte migration and phagocytosis. It also inhibits the formation of leukotriene B_4. Several of colchicine's adverse effects are produced by its inhibition of tubulin polymerization and cell mitosis.

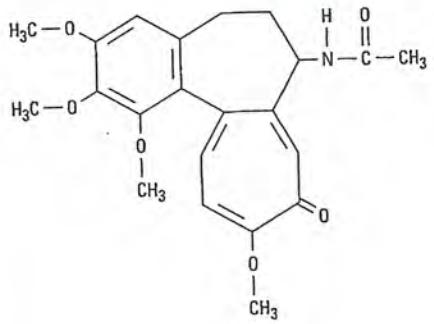
Indications

Colchicine has been the traditional drug used for alleviating the inflammation of acute gouty arthritis. Although colchicine is more specific in gout than the NSAIDs, other agents (eg, indomethacin and other NSAIDs [except aspirin]) are often employed because of the troublesome diarrhea associated with colchicine therapy. Colchicine is preferred for the prophylaxis of recurrent episodes of gouty arthritis, is effective in preventing attacks of acute Mediterranean fever, and may have a mild beneficial effect in sarcoid arthritis and in hepatic cirrhosis.

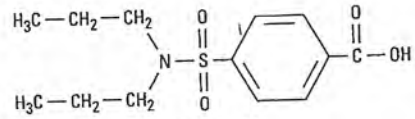
Adverse Effects

Colchicine often causes diarrhea and may occasionally cause nausea, vomiting, and abdominal pain. Colchicine may rarely cause hair loss and bone marrow depression as well as peripheral neuritis and myopathy.

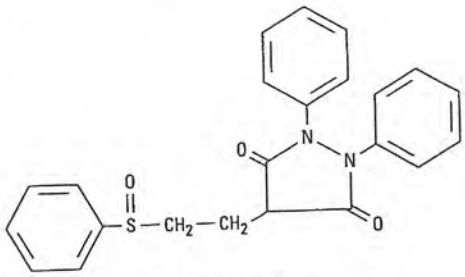
Acute intoxication after ingestion of large (nontherapeutic) doses of the alkaloid is characterized by burning throat pain, bloody diarrhea, shock, hema-



Colchicine



Probenecid



Sulfinpyrazone

Figure 36–6. Colchicine and uricosuric drugs.

turia, and oliguria. Fatal ascending central nervous system depression has been reported. Treatment is supportive.

Dosage

For terminating an attack of gout, the initial dose of colchicine is usually 0.5 or 1 mg, followed by 0.5 mg every 2 hours until pain is relieved or nausea and diarrhea appear. The total dose can be given intravenously, if necessary, but it should be remembered that as little as 8 mg in 24 hours may be fatal. The prophylactic dose of colchicine is 0.5 mg one to three times daily.

NSAIDS IN GOUT

In addition to inhibiting prostaglandin synthase, indomethacin and other NSAIDs also inhibit urate crystal phagocytosis. Indomethacin may be used as initial treatment of gout or as an alternative drug when colchicine is unsuccessful or causes too much discomfort. Indomethacin is the agent most often used today to treat acute gout. Three to four doses of 50 mg every 6 hours are given; when a response occurs the dosage is reduced to 25 mg three or four times daily for about 5 days.

Other newer NSAIDs are also being used with success in the acute episode. All other NSAIDs except aspirin, salicylates, and tolmetin have been successfully used to treat acute gouty episodes. Oxaprozin, which lowers serum uric acid, is theoretically a good NSAID to use though it should not be given to patients with uric acid stones because it increases uric acid excretion in the urine. These agents appear to be as effective and safe as the older drugs.

URICOSURIC AGENTS

Probenecid and sulfinpyrazone are uricosuric drugs employed to decrease the body pool of urate in patients with tophaceous gout or in those with increasingly frequent gouty attacks. In a patient who excretes large amounts of uric acid, the uricosuric agents should be avoided so as not to precipitate the formation of uric acid calculi.

Chemistry

Uricosuric drugs are organic acids (Figure 36–6) and, as such, act at the anionic transport sites of the renal tubule (Chapter 15). Sulfinpyrazone is a metabolite of an analog of phenylbutazone.

Pharmacokinetics

Probenecid is completely reabsorbed by the renal tubules and is metabolized very slowly. Sulfinpyrazone or its active hydroxylated derivative is rapidly excreted by the kidneys. Even so, the duration of its effect after oral administration is almost as long as that of probenecid.

Pharmacodynamics

Uric acid is freely filtered at the glomerulus. Like many other weak acids, it is also both reabsorbed and secreted in the middle segment of the proximal tubule. Uricosuric drugs—probenecid, sulfinpyrazone, and large doses of aspirin—affect these active transport sites so that net reabsorption of uric acid in the proximal tubule is decreased. Because aspirin in small (analgesic or antipyretic) doses causes net retention of uric acid by inhibiting the secretory transporter, it should not be used for analgesia in patients with gout. The secretion of other weak acids, eg, penicillin, is also reduced by uricosuric agents. Probenecid was originally developed to prolong penicillin blood levels.

As the urinary excretion of uric acid increases, the size of the urate pool decreases, although the plasma concentration may not be greatly reduced. In patients who respond favorably, tophaceous deposits of urate will be reabsorbed, with relief of arthritis and remineralization of bone. With the ensuing increase in uric acid excretion, a predisposition to the formation of renal stones is augmented rather than decreased; therefore, the urine volume should be maintained at a high level and at least early in treatment the urine pH kept above 6.0 by the administration of alkali.

Indications

Uricosuric therapy should be initiated if several acute attacks of gouty arthritis have occurred, when evidence of tophi appears, or when plasma levels of uric acid in patients with gout are so high that tissue damage is almost inevitable. Therapy should not be started until 2–3 weeks after an acute attack.

Adverse Effects

Adverse effects do not provide a basis for preferring one or the other of the uricosuric agents. Both of these organic acids cause gastrointestinal irritation, but sulfinpyrazone is more active in this regard. Probenecid is more likely to cause allergic dermatitis, but a rash may appear after the use of either compound. Nephrotic syndrome has resulted from the use of probenecid. Both sulfinpyrazone and probenecid may (though rarely) cause aplastic anemia.

Contraindications & Cautions

It is essential to maintain a large urine volume to minimize the possibility of stone formation.

Dosage

Probenecid is usually started at a dosage of 0.5 g orally daily in divided doses, progressing to 1 g daily after 1 week. Sulfinpyrazone is started at a dosage of 200 mg orally daily, progressing to 400–800 mg daily. It should be given in divided doses with food to reduce adverse gastrointestinal effects.

ALLOPURINOL

An alternative to increasing uric acid excretion in the treatment of gout is to reduce its synthesis by inhibiting xanthine oxidase with allopurinol.

Chemistry

The structure of allopurinol, an isomer of hypoxanthine, is shown in Figure 36–7.

Pharmacokinetics

Allopurinol is approximately 80% absorbed after oral administration. Like uric acid, allopurinol is itself metabolized by xanthine oxidase. The resulting compound, alloxanthine, retains the capacity to inhibit xanthine oxidase and has a long enough duration of action so that allopurinol need be given only once a day.

Pharmacodynamics

Dietary purines are not an important source of uric acid. The quantitatively important amounts of purine are formed from amino acids, formate, and carbon dioxide in the body. Those purine ribonucleotides not incorporated into nucleic acids and those derived from the degradation of nucleic acids are converted to xanthine or hypoxanthine and oxidized to uric acid (Figure 36–7). When this last step is inhibited by allopurinol, there is a fall in the plasma urate level and a decrease in the size of the urate pool with a concurrent rise in the more soluble xanthine and hypoxanthine.

Indications

Treatment of gout with allopurinol, as with uricosuric agents, is begun with the expectation that it will be continued for years if not for life. Although allopurinol is often the first urate-lowering drug used, its most rational indications are as follows: (1) in chronic tophaceous gout, in which reabsorption of tophi is more rapid than with uricosuric agents; (2) in patients with gout whose 24-hour urinary uric acid on purine-free diet exceeds 600–700 mg; (3) when probenecid or sulfinpyrazone cannot be used because of adverse effects or allergic reactions, or when they are providing less than optimal therapeutic effect; (4) for recurrent renal stones; (5) in patients with renal functional impairment; or (6) when serum urate levels are grossly elevated. One should attempt to lower serum urate levels to less than 6.5 mg/dL. Aside from gout, allopurinol is used as an antiprotozoal (Chapter 53) and is indicated to prevent the massive uricosuria following therapy of blood dyscrasias that could otherwise lead to renal calculi.

Adverse Effects

Acute attacks of gouty arthritis occur early in treatment with allopurinol when urate crystals are being withdrawn from the tissues and plasma levels are below normal. To prevent acute attacks, colchicine should be given during the initial period of therapy with allopurinol unless allopurinol is being used in combination with probenecid or sulfinpyrazone. Gastrointestinal intolerance, including nausea, vomiting, and diarrhea, may occur. Peripheral neuritis and necrotizing vasculitis, depression of bone marrow elements, and, rarely, aplastic anemia may also occur. Hepatic toxicity and interstitial nephritis have been reported. An allergic skin reaction characterized by pruritic maculopapular lesions develops in 3% of patients. Isolated cases of exfoliative dermatitis have been reported. In very rare cases, allopurinol has become bound to the lens, resulting in cataracts.

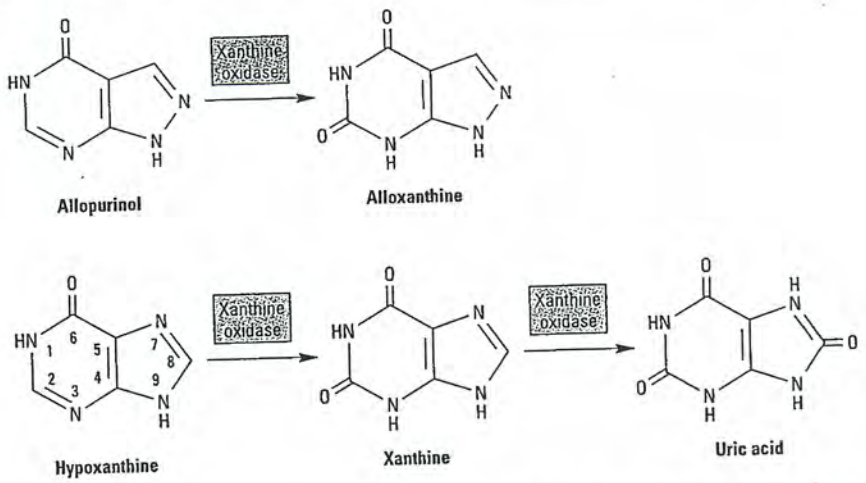


Figure 36–7. Inhibition of uric acid synthesis by allopurinol. (Modified and reproduced, with permission, from Meyers FH, Jawetz E, Goldfien A: *Review of Medical Pharmacology,* 7th ed. Lange, 1980.)

Interactions & Cautions

When chemotherapeutic mercaptopurines are being given concomitantly, their dose must be reduced to about 25%. Allopurinol may also increase the effect of cyclophosphamide. Allopurinol inhibits the metabolism of probenecid and oral anticoagulants and may increase hepatic iron concentration. Safety in children and during pregnancy has not been established.

Dosage

The initial dosage of allopurinol is 100 mg daily. It may be titrated to 300 mg/d depending on the serum uric acid response.

Colchicine or an NSAID should be given during the first weeks of allopurinol therapy to prevent the gouty arthritis episodes that sometimes occur.

PREPARATIONS AVAILABLE

Salicylates

Aspirin, acetylsalicylic acid (generic, A.S.A. Enseals, Easprin, others)
Oral (regular or enteric coated): 81, 165, 325, 500, 650, 800, 975 mg tablets; 325, 500 mg capsules; 650, 800 mg timed-release tablets
Rectal: 200, 300, 600 mg suppositories

Choline salicylate (Arthropan)
Oral: 870 mg/5 mL liquid

Diflunisal (Dolobid)
Oral: 250, 500 mg tablets

Magnesium salicylate (Doan's Pills, Magan, Mobidin)
Oral: 325, 500, 545, 600 mg tablets

Salsalate, salicylsalicylic acid (generic, Disalcid)
Oral: 500, 750 mg tablets; 500 mg capsules

Sodium salicylate (generic, Uracel 5)
Oral: 325, 650 mg enteric-coated tablets

Sodium thiosalicylate (generic, Thiocyl, Tusal)
Parenteral: 50 mg/mL for injection

Other NSAIDs

Diclofenac (Voltaren)
Oral: 25, 50, 75 mg enteric-coated tablets
Ophthalmic: 0.1% solution

Etodolac (Lodine)
Oral: 200, 300 mg capsules

Fenoprofen (generic, Nalfon)
Oral: 200, 300 mg capsules; 600 mg tablets

Flurbiprofen (Ansaid, Ocufen)
Oral: 50, 100 mg tablets
Ophthalmic: 0.03% solution

Ibuprofen (generic, Motrin, Rufen, Advil [OTC], Nuprin [OTC], others)
Oral: 50, 100, 200, 300, 400, 600, 800 mg tablets; 100 mg/5 mL suspension; 40 mg/mL drops

Indomethacin (generic, Indocin, others)
Oral: 25, 50 mg capsules; 75 mg sustained-release capsules; 25 mg/5 mL suspension
Rectal: 50 mg suppositories

Ketoprofen (Orudis, others)
Oral: 12.5, 25, 50, 75 mg capsules; 100, 150, 200 mg extended-release capsules

Ketorolac (Toradol)
Oral: 10 mg tablets
Parenteral: 15, 30 mg/mL for IM injection
Ophthalmic: 0.5% solution

Meclofenamate sodium (generic, Meclomen)
Oral: 50, 100 mg tablets and capsules

Mefenamic acid (Ponstel)
Oral: 250 mg capsules

Nabumetone (Relafen)
Oral: 500, 750 mg tablets

Naproxen (Naprosyn, Anaprox, Aleve [OTC])
Oral: 200, 250, 375, 500 mg tablets; 375, 550 mg sustained-release tablets; 125 mg/5 mL suspension

Naproxen sodium (Anaprox)
Oral: 275, 550 mg tablets (250, 500 mg base)

Oxaprozin (Daypro)
Oral: 600 mg tablets

Piroxicam (various, Feldene)
Oral: 10, 20 mg capsules

Sulindac (various, Clinoril)
Oral: 150, 200 mg tablets

Tolmetin (Tolectin)
Oral: 200, 600 mg tablets; 400 mg capsules

Disease-Modifying Antirheumatic Drugs

Auranofin (Ridaura)
Oral: 3 mg capsules

Aurothioglucose (Solganal)
Parenteral: 50 mg/mL suspension for injection

Gold sodium thiomalate (Myochrysine)
Parenteral: 25, 50 mg/mL for injection

Hydroxychloroquine (Plaquenil)
Oral: 200 mg tablets

Methotrexate (generic, Rheumatrex)
Oral: 2.5 mg tablets
Parenteral: 2.5, 25 mg/mL
Penicillamine (Cuprimine, Depen)
Oral: 125, 250 mg capsules; 250 mg tablets
Sulfasalazine (generic, Azulfidine)
Oral: 500 mg tablets, 500 mg enteric coated tablets, 250 mg/5 mL oral suspension

Drugs Used in Gout

Allopurinol (generic, Zyloprim, others)
Oral: 100, 300 mg tablets
Colchicine (generic)
Oral: 0.5, 0.6 mg tablets
Parenteral: 1 mg/2 mL for injection
Probenecid (generic, Benemid, Probalan)
Oral: 500 mg tablets
Sulfinpyrazone (generic, Anturane)
Oral: 100 mg tablets; 200 mg capsules

Acetaminophen

Acetaminophen (generic, Tylenol, Tempra, Panadol, Acephen, Acetaminophen, Uniserts, others)
Oral: 80, 160, 325, 500, 650 mg tablets; 500 mg capsules; 120, 160, 325 mg/5 mL elixir; 500 mg/15 mL elixir; 100 mg/mL solution; 120 mg/2.5 mL solution
Rectal: 120, 125, 300, 325, 650 mg suppositories

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