SECTION

V

THERAPEUTIC ASPECTS OF INFLAMMATORY AND SELECTED OTHER CLINICAL DISORDERS

36 Antiinflammatory and Antirheumatic Drugs

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DRUG LIST

The classical signs of inflammation are redness, swelling, heat, pain, and loss of function. The actual expression of these processes depends on the site of inflammation. For example, a skin abscess may result in the appearance of all of these features. In contrast, pneumonia, because of the inaccessibility of the lung to examination, may manifest only as loss of function (shortness of breath and hypoxia). Nevertheless, similar pathological processes occur in both sites.

Inflammation is characterized by the orderly occurrence of several processes: *initiation* of the event by a foreign substance or physical injury, *recruitment and chemoattraction* of inflammatory cells, and activation of these cells to *release inflammatory mediators* capable of damaging or killing an invading microbe or tumor. In some instances, the inflammatory response is initiated by an otherwise harmless foreign material (e.g., pollen). Inflammation can also result from an autoimmune response to the host's own tissue, as occurs in rheumatoid arthritis.

As the result of an inflammatory response, the host tissue may undergo collateral injury, since many of the inflammatory mediators are not specific for a particular tissue target. For example, many of the clinical signs (fever and labored breathing) and symptoms (shortness of breath and cough) of pneumococcal pneumonia are the result of inflammation rather than the invading microorganism. In most cases, the inflammatory response eventually subsides, but if such a self-limiting regulation does not occur, the inflammatory response will require pharmacological intervention. *The need for anti-inflammatory drugs arises when the inflammatory response is inappropriate, aberrant, sustained, or causes destruction of tissue.*

THE INFLAMMATORY PROCESS

Inflammation begins when a stimulus, such as infection, physical stress, or chemical stress, produces cellular damage (Fig. 36.1). This damage initiates the activation of transcription factors that control the expression of many inflammatory mediators. *Among the more important inflammatory mediators are the eicosanoids, biological oxidants, cytokines, adhesion factors, and digestive enzymes* (proteases, hyaluronidase, collagenase, and elastase). Only the first three of these are therapeutic targets for anti-inflammatory drugs.

The inflammatory response changes with time and can be divided into phases. The rapid phase occurs within seconds to minutes and consists of vasodilation, increased blood flow, edema, and pain. The acute phase is characterized by induction of inflammatory genes by NF-κB and other transcription factors. During this phase, moderate amounts of inflammatory mediators are produced. The chronic phase occurs over months to years and is marked by dramatically increased production of inflammatory mediators. The secondary chronic phase of inflammation occurs after years of oxidative damage has degraded blood vessels and tissues. Such chronic inflammation appears to play a role in many disease states, such as arteriosclerosis and cancer.

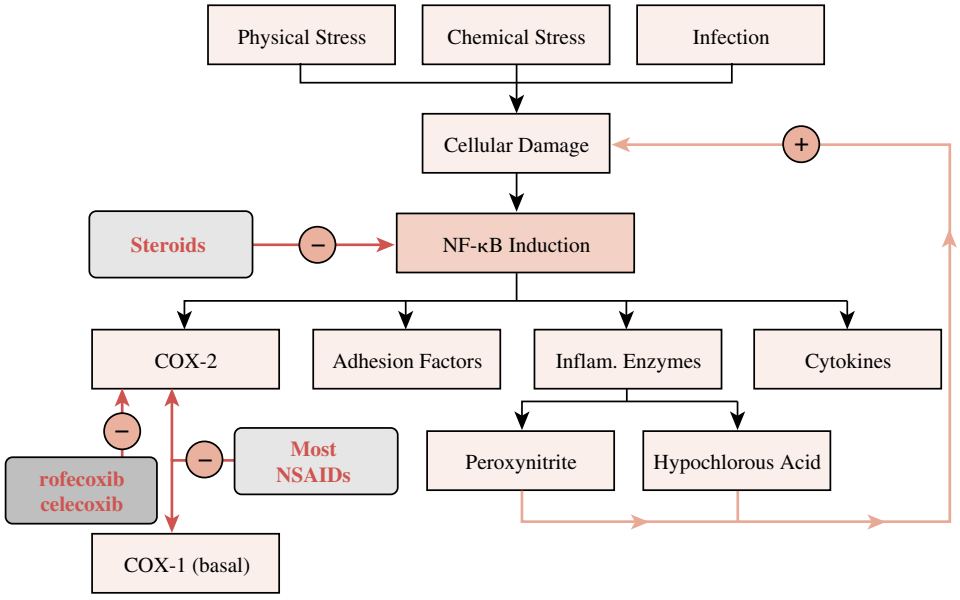

FIGURE 36.1
Overview of inflammatory processes.

Eicosanoids

The eicosanoids, so called because of their derivation from a 20-carbon unsaturated fatty acid, arachidonic acid (eicosatetraenoic acid), are obtained from membrane phospholipids and synthesized de novo at the time of cellular stimulation. Arachidonic acid is cleaved from membrane-bound phosphatidylcholine by the enzyme phospholipase A_2. Alternatively, arachidonic acid may be derived by the sequential actions of phospholipase C and diacylglyceryl lipase. Arachidonic acid can then follow either of two enzymatic pathways that result in the production of inflammatory mediators. The pathway initiated by cyclooxygenase (COX) produces prostaglandins; the lipoxygenase pathway generates leukotrienes (Fig. 36.2).

The COX enzyme exists in at least two isoforms. COX-1 is a constitutive or "housekeeping" isoform that is responsible for the basal production of prostaglandins, prostacyclins, and thromboxanes. *COX-2 is inducible by cytokines and other inflammatory stimuli and is believed to predominate during chronic inflammation.* The final product of the COX pathway is tissue specific. For example, platelets produce thromboxane A_2 (TxA_2); vascular endothelial cells produce prostacyclin (PGI_2); mast cells produce prostaglandin D_2 (PGD_2); and the vasculature, gastrointestinal (GI) tract, lung, and other tissues produce prostaglandin E_2 (PGE_2).

The biological effects of the more important eicosanoids are listed in Table 36.1. *The production of inflammatory eicosanoids is an important target of many anti-inflammatory drugs. In addition, the side effects of these drugs frequently result from their inhibition of eicosanoid production.*

A number of eicosanoids are used as therapeutic agents. In infants with congenital heart anomalies, a patent ductus arteriosus can be temporarily maintained by the PGE_1 analogue alprostadil (*Prostin VR Pediatric*) until surgical correction can be performed. In patients undergoing treatment with nonsteroidal antiinflammatory drugs, the PGE_1 analogue misoprostol (*Cytotec*) is often used to decrease gastric acid secretion, thereby inhibiting the ulceration caused by these agents. Misoprostol is also used in several non-FDA–approved applications, including the induction of labor by enhancing cervical ripening, and the induction of abortion in combination with mifepristone (RU-486). These uses of misoprostol are associated with an increased risk of uterine rupture or perforation. Dinoprostone (*Prostin E_2*), a synthetic PGE_2, causes uterine contraction and is used clinically to induce abortion during the second trimester and to empty the

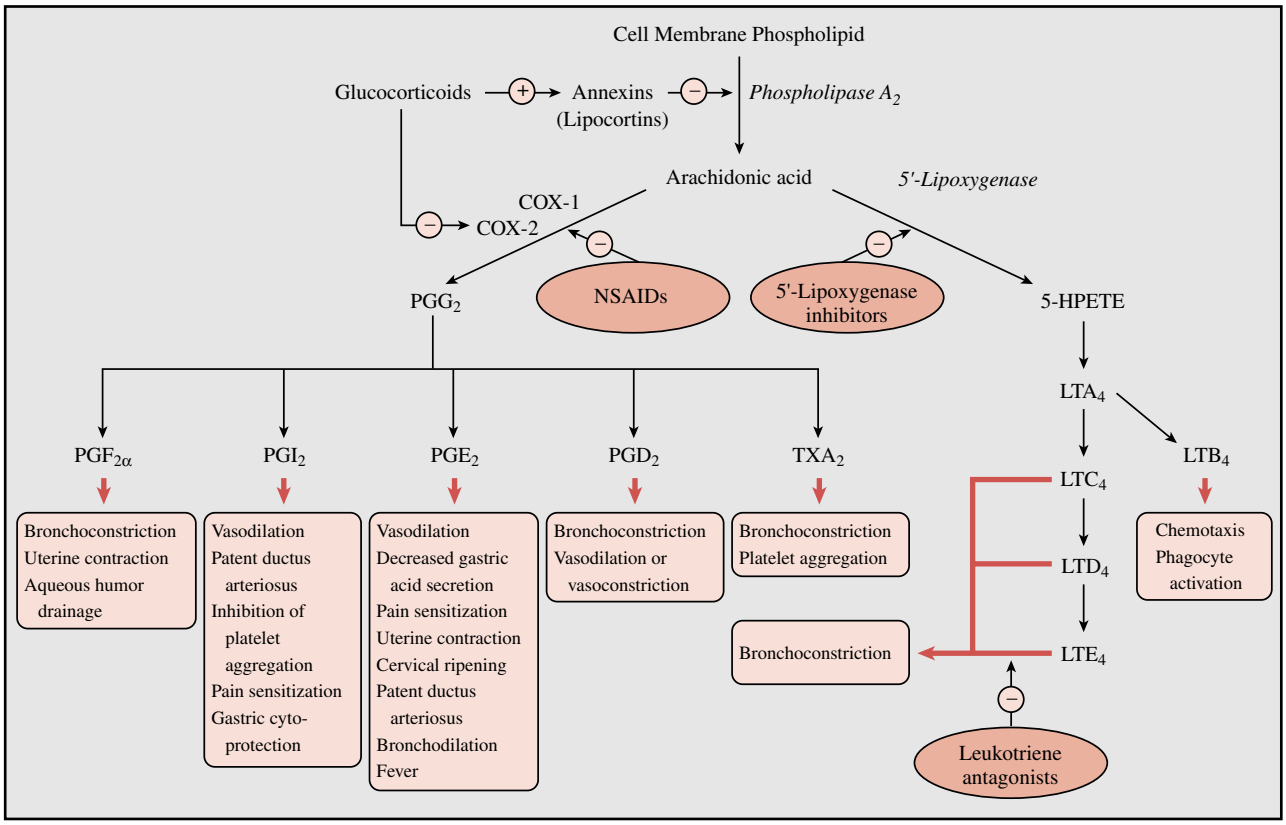

FIGURE 36.2
Eicosanoid synthesis pathway.

TABLE 36.1 Biological Effects of Eicosanoids

Eicosanoid	Primary Biological Effects
PGE_1	Vasodilation, decreased gastric acid secretion, bronchodilation
PGE_2	Vasodilation, decreased gastric acid secretion, pain sensitization, uterine contraction, cervical ripening, maintenance of patent ductus arteriosus, bronchodilation, fever
$PGF_{2\alpha}$	Bronchoconstriction, uterine contraction, increases drainage from aqueous humor
PGI_2	Vasodilation, maintenance of patent ductus arteriosus, inhibition of platelet aggregation, pain sensitization, gastric cytoprotection
TXA_2	Platelet aggregation, bronchoconstriction
LTC_4, D_4, E_4	Bronchoconstriction
LTB_4	Chemoattraction and activation of polymorphonuclear leukocytes

uterus following fetal death, missed abortion, or benign hydatidiform mole. Carboprost (*Hemabate*) is a PGF_2 analogue that can be used to terminate pregnancy or to control refractory postpartum bleeding by stimulating uterine contraction. Primary pulmonary hypertension can be treated by the synthetic PGI epoprostenol (*Flolan*). Elevated intraocular pressure may be treated with latanoprost (*Xalatan*), an analogue of PGF_2. Zafirlukast (*Accolate*) is an oral leukotriene receptor antagonist for control of the inflammatory process of asthma (see Chapter 39). Zileuton (*Zyflo*) inhibits the first enzyme in the lipoxygenase pathway and is used for the treatment of asthma.

Biological Oxidants

The biologically derived oxidants are potent bacterial killers but are also a major contributing factor in tissue injury that results from the inflammatory response. These oxidants include the superoxide anion ($\cdot O_2^-$), hydrogen peroxide (H_2O_2), nitric oxide ($\cdot NO$), peroxynitrite ($\cdot OONO^-$), hypochlorous acid (HOCl), peroxidase-generated oxidants of undefined character, probably the hydroxyl radical ($\cdot OH$), and possibly singlet oxygen ($^1O_2$). These oxidants, largely generated by phagocytic cells such as neutrophils and macrophages, induce tissue injury beyond that produced by digestive enzymes and eicosanoids. *Inhibition of production of these oxidants or inactivation of these substances by antioxidants is an important strategy for the treatment of inflammatory disorders.*

Cytokines

Numerous cytokines participate in inflammation; among the most important regulators of this process are *tumor necrosis factor-α* (TNF-α) and *interleukin 1* (IL-1). TNF-α and IL-1 are produced primarily by cells of the monocyte–macrophage lineage. They work in concert to stimulate inflammatory responses such as pain, fever, and the recruitment of lymphocytes. In addition, they induce production of many other inflammatory mediators and contribute to the tissue damage seen in chronic inflammation.

TNF-α and IL-1 are current targets of antiinflammatory drug therapy. A homotrimer of 17-kDa protein subunits whose effects include the activation of neutrophils and eosinophils, induction of COX-2, induction of proinflammatory cytokines (e.g., IL-1, IL-6), enhancement of endothelial layer permeability, induction of adhesion molecules by endothelial cells and leukocytes, stimulation of fibroblast proliferation, degradation of cartilage, and stimulation of bone reabsorption. Two receptors mediate these effects: a 55-kDa receptor (p55) and a 75-kDa receptor (p75). Each of these receptors is found in both cell surface and soluble forms. The binding of two or three cell surface receptors to TNF-α initiates an inflammatory response. Soluble p55 also acts as a signaling receptor for inflammatory responses, whereas soluble p75 acts as an antagonist.

IL-1 occurs as two polypeptides, IL-1α and IL-1β, and produces many of the same effects as TNF-α. An 80-kDa type 1 IL-1 receptor and a 68-kDa type 2 IL-1 receptor found on the surface of some cell types bind both forms of IL-1. An endogenous 17-kDa IL-1 receptor antagonist (IL-1ra) competes for binding with IL-1 and counterbalances the inflammatory response.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

The nonsteroidal anti-inflammatory drugs (NSAIDs) have a variety of clinical uses as antipyretics, analgesics, and anti-inflammatory agents. They reduce body temperature in febrile states and thus are effective antipyretics. They are also useful as analgesics, relieving mild to moderate pain (see Chapter 26) such as myalgia, dental pain, dysmenorrhea, and headache. Unlike the opioid analgesics, they do not cause neurological depression or dependence. As anti-inflammatory agents, NSAIDs are used to treat conditions such as muscle strain, tendinitis, and bursitis. They are also used to treat the chronic pain and inflammation of rheumatoid arthritis (adult onset and juvenile), osteoarthritis, and arthritic variants such as gouty arthritis and ankylosing spondylitis. While NSAIDs used to be the sole agent of choice for mild to moderate rheumatoid disease, they are now frequently used in conjunction with the *disease-modifying antirheumatic drugs* (*DMARDs*) early in the treatment of these disorders. This is because the *NSAIDs reduce pain and inflammation associated with*

rheumatoid diseases but do not delay or reverse the disease's progress.

Mechanism of Action

The anti-inflammatory actions of the NSAIDs are most likely explained by their inhibition of prostaglandin synthesis by COX-2. The COX-2 isoform is the predominant COX involved in the production of prostaglandins during inflammatory processes. Prostaglandins of the E and F series evoke some of the local and systemic manifestations of inflammation, such as vasodilation, hyperemia, increased vascular permeability, swelling, pain, and increased leukocyte migration. In addition, they intensify the effects of inflammatory mediators, such as histamine, bradykinin, and 5-hydroxytryptamine. All NSAIDs except the COX-2-selective agents inhibit both COX isoforms; the degree of inhibition of COX-1 varies from drug to drug. *No one NSAID is empirically superior for the treatment of inflammatory diseases; instead, each individual's response to and tolerance of a drug determines its therapeutic utility.*

Adverse Effects

A number of the toxicities commonly caused by the NSAIDs result from the inhibition of prostaglandin synthesis (Table 36.2). *The ability of NSAIDs to increase gastric acid secretion and inhibit blood clotting can lead to GI toxicity.* Mild reactions, such as heartburn and indigestion, may be decreased by adjusting the dosage, using antacids, or administering the drugs after meals. Occult loss of blood from the GI tract and iron deficiency anemia are also possible. More serious toxicity can result from prolonged NSAID therapy, including peptic ulceration and rarely, GI hemorrhage.

NSAIDs can impair renal function, cause fluid retention, and provoke hypersensitivity reactions, including bronchospasm, aggravation of asthma, urticaria, nasal polyps, and rarely, anaphylactoid reactions. These reactions may occur even in those who have previously used NSAIDs without any ill effects. NSAIDs inhibit uterine contraction and can cause premature closure of the fetal ductus arteriosus.

The spectrum of toxicity produced by each NSAID is related to its inhibition of specific COX isoforms. The earliest NSAIDs inhibit both isoforms of COX. Certain of these drugs are more specific for COX-1, whereas others inhibit COX-1 and COX-2 with roughly equal potency. *More recently developed drugs selectively inhibit COX-2 and therefore do not elicit the GI and antiplatelet side effects common to drugs that inhibit COX-1.*

Adverse effects that are not unequivocally related to inhibition of prostaglandin synthesis include hepatic effects (hepatitis, hepatic necrosis, cholestatic jaundice, increased serum aminotransferases), dermal effects (photosensitivities, Stevens-Johnson syndrome, toxic epidermal necrolysis, onycholysis), central nervous system (CNS) effects (headaches, dizziness, tinnitus, deafness, drowsiness, confusion, nervousness, increased sweating, aseptic meningitis), ocular effects (toxic amblyopia, retinal disturbances), and certain renal effects (acute interstitial nephritis, acute papillary necrosis).

Contraindications and Drug Interactions

Co-morbid factors that increase the risk of NSAID-induced GI bleeding include history of ulcer disease, advanced age, poor health status, treatment with certain drugs (discussed later), long duration of NSAID therapy, smoking, and heavy alcohol use. Because of their renal effects, NSAIDs must be used with caution in

TABLE 36.2 Adverse Effects of NSAIDs – Relationship to Prostaglandin Synthesis Inhibition and Cyclooxygenase Isoforms

System Affected	Adverse Effects	Prostaglandin Effects Inhibited by NSAIDs	COX Isoforms Involved
Gastrointestinal	Erosive gastritis, peptic ulceration	PGE_2-mediated suppression of gastric acid secretion, which helps maintain mucosal barrier and regulate microcirculation	COX-1
Platelet	Prolonged bleeding time, GI blood loss	TXA_2-mediated platelet aggregation	COX-1
Renal	Decreased Na^+ and H_2O excretion, renal failure, decreased effectiveness of diuretics and antihypertensives	PGE_2- and PGI_2-induced vasodilation in juxtamedullary apparatus (increases renal blood flow, antagonizes renin, inhibits reabsorption of Na^+ and H_2O)	COX-1 COX-2
Lungs, hypersensitivity, allergic reactions	Bronchospasm, urticaria, rhinitis, nasal polyposis	All prostaglandin synthesis – when inhibited, leukotriene formation is favored	COX-1 COX-2
Uterine	Delayed parturition, dystocia	PGE_2, $PGF_{2\alpha}$, and other prostaglandins are involved cervical ripening, uterine contractions	COX-2

patients with renal impairment, heart failure, hypertension, and edema. The use of NSAIDs is contraindicated in persons who have had a hypersensitivity reaction to salicylates or any other NSAID. Asthmatics are at particular risk for these reactions. NSAIDs should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

A significant number of drug interactions are common to most of the NSAIDs. The likelihood of NSAID-induced GI toxicity is increased by concomitant treatment with corticosteroids (long term), other NSAIDs, bisphosphonates, or anticoagulants. Certain NSAIDs can also compete for protein binding sites with warfarin, compounding the risk of GI bleeding if these drugs are coprescribed. Agents that cause thrombocytopenia (e.g., myelosuppressive antineoplastic drugs) can also increase the likelihood that NSAIDs will cause bleeding. NSAIDs can decrease the clearance of methotrexate, resulting in severe hematological and GI toxicity. This does not appear to be a significant problem with low-dose methotrexate used in the treatment of rheumatoid arthritis; however, higher methotrexate doses used in the treatment of psoriasis or cancer may produce this toxicity. NSAIDs, when used in conjunction with immunosuppressive agents, can mask fever and other signs of infection.

Because NSAIDs decrease prostaglandin synthesis in the kidney, these drugs can increase the nephrotoxicity of agents such as aminoglycosides, amphotericin B, cidofovir, cisplatin, cyclosporine, foscarnet, ganciclovir, pentamidine, and vancomycin. NSAIDs can decrease the renal excretion of drugs such as lithium. NSAIDs can decrease the effectiveness of antihypertensive drugs such as β-blockers and diuretics. The elderly and those with decreased renal function are at particular risk for this interaction. Elevated hepatic enzymes and hepatic toxicity can occur with some drugs.

Specific Nonsteroidal Antiinflammatory Drugs

The acidic NSAIDs include the salicylates and an increasing number of other compounds. The latter agents, as a group, share many common properties: they may have toxicities, are highly protein bound and have the potential for interacting with other protein-bound drugs. The choice of a particular agent often depends on the reaction of the patient. Table 36.3 illustrates pharmacokinetic properties of selected NSAIDs.

Salicylates

The salicylates are also discussed in Chapter 26. Only observations that are relevant to their use as anti-inflammatory agents are discussed in this chapter.

TABLE 36.3 Pharmacokinetic Properties of Selected NSAIDs

Drug	Time to Peak Plasma Level (fasting) (hr)	Plasma Half-Life (hr)	Protein Binding (%)	Urinary Excretion (%)	Notes
Celecoxib	2–4	11	97	57	H, R
Diclofenac	2–3	1–2	99	65	F
Etodolac	1.3	7	99	84	E, H
Fenoprofen	2	2.5–3	99	95	h
Flurbiprofen	0.5–4	6	99	95	h R
Ibuprofen	1	2r	90–99	90	H
Indomethacin	1–2	1.8–2.5	90–99	60	E, h
Ketoprofen	0.5–2	2–4	99	90	h, R
Ketorolac	0.5–1	4–6	99	91	h R
Meclofenamate sodium	0.5–2	2–4	Extensive	70	h
Meloxicam	4–5	15–20	99	40	E[b]
Nabumetone[a]	2.5	24	99	80	h, R
Naproxen	2–4	14	99	90+	h, R
Oxaprozin	3–6	36–92	99.9	65	h R
Piroxicam	2–4	30–86	99	66	E, h
Rofecoxib	2–3	17	87	72	H, R
Sulindac[a]	2	16–18	98	80	E, h
Tolmetin	0.5–1	5	99	100	h

[a]Properties of the active metabolite of this drug are given.
[b]Not recommended for those with severe renal and hepatic disease. E, enterohepatic cycling; F, extensive first pass metabolism; h, dosage adjustment may be necessary in patients with hepatic impairment; H, dosage adjustment recommended for patients with hepatic impairment; R, dosage adjustment necessary for patients with renal impairment.

Among the salicylates, aspirin and sodium salicylate are by far the most commonly used.

The salicylates are useful in the treatment of minor musculoskeletal disorders such as bursitis, synovitis, tendinitis, myositis, and myalgia. They may also be used to relieve fever and headache. They can be used in the treatment of inflammatory disease, such as acute rheumatic fever, rheumatoid arthritis, osteoarthritis, and certain rheumatoid variants, such as ankylosing spondylitis, Reiter's syndrome, and psoriatic arthritis. However, other NSAIDs are usually favored for the treatment of these chronic conditions because of their lower incidence of GI side effects. Aspirin is used in the treatment and prophylaxis of myocardial infarction and ischemic stroke.

Basic Pharmacology

Aspirin is available as capsules, tablets, enteric-coated tablets (*Ecotrin*), timed-release tablets (*ZORprin*), buffered tablets (*Ascriptin, Bufferin*), and as rectal suppositories. Sodium salicylate is available generically. Other salicylates include choline salicylate (*Arthropan*), choline magnesium trisalicylate (*Trilisate*), and magnesium salicylate (*Momentum*).

Although aspirin itself is pharmacologically active, it is rapidly hydrolyzed to salicylic acid after its absorption, and *it is the salicylate anion that accounts for most of the anti-inflammatory activity* of the drug. The superior analgesic activity of aspirin compared with sodium salicylate implies that aspirin has an intrinsic activity that is not totally explainable by its conversion to salicylic acid. Aspirin inhibits COX-1 to a much greater extent than COX-2; sodium salicylate is more selective for COX-1. This, combined with the ability of aspirin to acetylate proteins, might account for some of the therapeutic and toxicological differences between aspirin and the other salicylates.

The binding of salicylic acid to plasma proteins varies with its plasma concentrations. At serum salicylic acid concentrations of less than 100 μg/mL, 90 to 95% is protein bound; at 100 to 400 μg/mL, 70 to 85% is protein bound; and at concentrations greater than 400 μg/mL, 20 to 60% is protein bound. *The plasma concentration of salicylate that is associated with anti-inflammatory activity (200–300 μg/mL) is about six times that needed to produce analgesia.* At these higher concentrations, salicylate metabolism is reduced, resulting in a longer half-life for the drug. This reaction is a consequence of the saturable enzyme systems that metabolize salicylates. The plasma half-life for salicylate has been estimated to be 3 to 6 hours at the lower (analgesic) dosage and 15 to 30 hours at the higher (anti-inflammatory) dosages. The rate of hydrolysis of aspirin to salicylic acid is not dose limited, and no differences in the absorption of aspirin have been observed between arthritic patients and normal individuals.

Adverse Effects

The most common adverse effects produced by the salicylates are GI disturbances. Occult blood loss from the GI tract, peptic ulceration, and rarely, severe GI hemorrhage can occur. Because salicylic acid is highly bound to plasma proteins, it may be displaced by other highly protein-bound drugs such as oral anticoagulants, sulfonylureas, phenytoin, penicillins, and sulfonamides. The nonacetylated salicylates have greatly reduced effects on blood loss and produce fewer adverse GI effects. In addition, they may be somewhat kidney sparing. Salicylates may provoke hypersensitivity reactions and prolonged bleeding time in some individuals. Tinnitus, hearing impairment, blurred vision, and lightheadedness are indicators of toxic dosages. *The use of aspirin in conjunction with any other NSAID is not recommended* because of the lack of evidence that such combinations increase efficacy and because of the increased potential for an adverse reaction. Salicylates are contraindicated in children with febrile viral illnesses because of a possible increased risk of Reye's syndrome.

Aryl and Heteroarylakanoic Acid–Type Drugs

The prototypes of this large class of NSAIDs are indomethacin and ibuprofen. These drugs are indicated for the relief of acute and chronic rheumatoid arthritis and osteoarthritis. In addition, a number of drugs of this class are also useful in ankylosing spondylitis, acute gouty arthritis, bursitis, and tendinitis.

Adverse reactions are common with the use of these drugs but usually do not result in serious morbidity. GI and CNS effects and prolonged bleeding may occur. Fluid retention, skin rashes, and ocular toxicity also occur, but with much lower frequency than with the salicylates. The selectivity for COX-1 and COX-2 varies from drug to drug and accounts for some of the differences in toxicity. *None of the agents seems to be clearly more efficacious than the others; however, they generally cause less GI blood loss and fewer other adverse reactions than does aspirin,* and the overall incidence of adverse reactions may be lower with these drugs.

Indomethacin

Indomethacin (*Indocin*) is used in the treatment of acute gouty arthritis, rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis. It is not recommended for use as a simple analgesic or antipyretic because of its potential for toxicity. While indomethacin inhibits both COX-1 and COX-2, it is moderately selective for COX-1. It produces more CNS side effects than most of the other NSAIDs. Severe headache occurs in 25 to 50% of patients; vertigo, confusion, and psychological disturbances occur with some regularity. GI symptoms also are more frequent and severe than with most other

NSAIDs. Hematopoietic side effects (e.g., leukopenia, hemolytic anemia, aplastic anemia, purpura, thrombocytopenia, and agranulocytosis) also may occur. Ocular effects (blurred vision, corneal deposits) have been observed in patients receiving indomethacin, and regular ophthalmological examinations are necessary when the drug is used for long periods. Hepatitis, jaundice, pancreatitis, and hypersensitivity reactions also have been noted.

Sulindac

Sulindac (*Clinoril*) is chemically related to indomethacin and is generally used for the same indications. It is a prodrug that is metabolized to an active sulfide metabolite and an inactive metabolite. The most frequently reported side effects are GI pain, nausea, diarrhea, and constipation. The incidence of these effects is lower than for indomethacin, presumably because sulindac is a prodrug and thus the active metabolite is not highly concentrated at the gastric mucosa. As with indomethacin, a rather high incidence of CNS side effects (dizziness, headache) also occurs.

Tolmetin

Tolmetin (*Tolectin*) is indicated for the relief of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and moderate pain. It is ineffective in gouty arthritis for unknown reasons. Tolmetin can inhibit both COX-1 and COX-2 but has a moderate selectivity for COX-1. The most frequently reported side effects are GI disturbance and CNS reactions (e.g., headache, asthenia, and dizziness). These effects are less frequently observed than after aspirin or indomethacin use. Blood pressure elevation, edema, and weight gain or loss have been associated with tolmetin administration. Tolmetin metabolites in urine have been found to produce pseudoproteinuria in some laboratory tests.

Ketorolac

Ketorolac (*Toradol*), an NSAID chemically related to indomethacin and tolmetin, is mainly used as an analgesic, not for the treatment of inflammatory disease. It is available in oral, parenteral, and topical formulations.

Etodolac

Etodolac (*Lodine*) is indicated for the treatment of osteoarthritis, rheumatoid arthritis, and acute pain. It inhibits COX-2 with slightly more selectivity than COX-1 and therefore produces less GI toxicity than many other NSAIDs. Common adverse effects include skin rashes and CNS effects.

Diclofenac

Diclofenac (*Voltaren, Cataflam*) is approved for use in rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, dysmenorrhea, and topically for the treatment of ocular inflammation and actinic keratosis. Diclofenac exhibits approximately equal selectivity for COX-1 and COX-2. The most common adverse reactions are GI disturbances and headache. A reversible elevation of serum transaminases occurs in 15% of patients.

Ibuprofen

Ibuprofen (*Advil, Motrin*) is used as an analgesic and antipyretic as well as a treatment for rheumatoid arthritis and degenerative joint disease. The most frequently observed side effects are nausea, heartburn, epigastric pain, rash, and dizziness. Incidence of GI side effects is lower than with indomethacin. Visual changes and cross-sensitivity to aspirin have been reported. Ibuprofen inhibits COX-1 and COX-2 about equally. It decreases platelet aggregation, but the duration is shorter and the effect quantitatively lower than with aspirin. Ibuprofen prolongs bleeding times toward high normal value and should be used with caution in patients who have coagulation deficits or are receiving anticoagulant therapy.

Fenoprofen

Fenoprofen (*Nalfon*) is chemically and pharmacologically similar to ibuprofen and is used in the treatment of rheumatoid arthritis, osteoarthritis, and mild to moderate pain. GI effects such as dyspepsia and pain are most common, although dizziness, pruritus, and palpitations may occur. GI bleeding, sometimes severe, has been reported, and interstitial nephritis has been rarely associated with this drug. Concomitant administration of aspirin decreases the biological half-life of fenoprofen by increasing the metabolic clearance of hydroxylated fenoprofen. Chronic administration of phenobarbital also decreases the drug's half-life.

Naproxen

Naproxen (*Naprosyn*) also has pharmacological properties and clinical uses similar to those of ibuprofen. It exhibits approximately equal selectivity for COX-1 and COX-2 and is better tolerated than certain NSAIDs, such as indomethacin. Adverse reactions related to the GI tract occur in about 14% of all patients, and severe GI bleeding has been reported. CNS complaints (headache, dizziness, drowsiness), dermatological effects (pruritus, skin eruptions, echinoses), tinnitus, edema, and dyspnea also occur.

Ketoprofen

Ketoprofen (*Orudis*) is indicated for use in rheumatoid and osteoarthritis, for mild to moderate pain, and in dysmenorrhea. The most frequently reported side effects are GI (dyspepsia, nausea, abdominal pain, diarrhea, constipation, and flatulence) and CNS related (headache, excitation). Edema and increased blood

urea nitrogen have also been noted in more than 3% of patients. Ketoprofen can cause fluid retention and increases in plasma creatinine, particularly in the elderly and in patients taking diuretics.

Flurbiprofen

Flurbiprofen (*Ansaid*) is indicated for the treatment of rheumatoid arthritis and osteoarthritis. Its half-life, longer than that of many of the NSAIDs, allows for twice daily dosing. The most common adverse effects of flurbiprofen are similar to those of the other acidic NSAIDs. Flurbiprofen inhibits both COX isoforms about equally.

Oxaprozin

Oxaprozin (*Daypro*) is approved for the treatment of osteoarthritis and rheumatoid arthritis. Its long half-life allows for once daily dosing. The most frequently reported adverse effects of this drug are nausea, vomiting, and dyspepsia.

Nabumetone

Nabumetone (*Relafen*) is approved for rheumatoid arthritis, osteoarthritis, and pain management. Its long half-life allows for once-daily dosing. Although this drug is a weak inhibitor of COX, it is metabolized in the liver to 6-methoxy-2-naphthylacetic acid (6-MNA), a strong COX inhibitor that is chemically similar to naproxen. As with most NSAIDs, GI side effects are most commonly reported. The incidence of gastric ulceration is lower with nabumetone than with many other NSAIDs. This is due to its nature as a prodrug, not to COX-2 selectivity. Lower-bowel complaints, rashes, and CNS disturbances are common adverse effects.

Sulfonylphenyl Derivatives

Celecoxib (*Celebrex*) and rofecoxib (*Vioxx*) are highly selective COX-2 inhibitors. *Because of this, they produce less erosion of the GI mucosa and cause less inhibition of platelet aggregation than do the nonselective COX inhibitors.* Short-term (6 months-to a year) clinical trials have shown that celecoxib and rofecoxib produce less GI toxicity than nonselective NSAIDs. However, serious GI bleeding and ulceration have occurred in patients taking these drugs, and long-term prospective studies of their safety have yet to be completed. *Like the nonselective NSAIDs, the selective COX-2 inhibitors can produce renal side effects such as hypertension and edema.*

Celecoxib is indicated for the treatment of osteoarthritis and rheumatoid arthritis. Its use is contraindicated in individuals with hypersensitivity to sulfonamides or other NSAIDs. It should be used with caution in persons with hepatic disease. Interactions occur with other drugs that induce CYP2C9 (e.g. rifampin) or compete for metabolism by this enzyme (e.g. fluconazole, leflunomide). The most common adverse reactions to celecoxib are mild to moderate GI effects such as dyspepsia, diarrhea, and abdominal pain. Serious GI and renal effects have occurred rarely.

Rofecoxib is approved for the treatment of osteoarthritis, dysmenorrhea, and acute pain. The most common adverse reactions to rofecoxib are mild to moderate GI irritation (diarrhea, nausea, vomiting, dyspepsia, abdominal pain). Lower extremity edema and hypertension occur relatively frequently (about 3.5%). It is not metabolized by CYP2C9, so rofecoxib should not be subject to some of the interactions seen with celecoxib. However, its metabolism is increased by the coadministration of rifampin, which acts as a nonspecific inducer of hepatic metabolism.

Oxicam-Type Drugs

The oxicams are as effective as indomethacin, and their long half-life allows for once-daily dosing. Piroxicam (*Feldene*) is indicated for the treatment of rheumatoid arthritis and osteoarthritis. Piroxicam is a nonspecific COX inhibitor that has a much higher affinity for COX-1 than COX-2. This may account for the large proportion (over 30%) of patients receiving long-term therapy who have reported side effects. Adverse GI reactions have been the most frequently reported side effect, but edema, dizziness, headache, rash, and changes in hematological parameters have also occurred in 1 to 6% of patients. *Piroxicam can cause serious GI bleeding, ulceration, and perforation, particularly in the elderly,* if the recommended dosage is exceeded or if aspirin is being taken concurrently.

Meloxicam (*Mobic*), recently introduced for the treatment of osteoarthritis, is also used for rheumatoid arthritis and certain acute conditions. Although meloxicam is sometimes reported to be a selective COX-2 inhibitor, it is considerably less selective than celecoxib or rofecoxib. Its adverse effects are similar to those of piroxicam and other NSAIDs; however, the frequency of GI side effects is lower for meloxicam than for piroxicam and several other NSAIDs.

Fenamate-Type Drugs

Two compounds of the fenamate class of antiinflammatory drugs are marketed in the United States. Mefenamic acid (*Ponstel*) is indicated only for analgesia and primary dysmenorrhea when therapy will not exceed 1 week. Meclofenamate sodium (*Meclomen*) is prescribed for rheumatoid arthritis and osteoarthritis.

The fenamates show no clear superiority in antiinflammatory activity and may produce more adverse effects than other NSAIDs. Diarrhea may be severe enough to necessitate discontinuation of drug use. Other adverse GI reactions include nausea, vomiting,

abdominal pain, bleeding, and peptic ulceration. Decreases in the hematocrit or hemoglobin values occur in approximately one-sixth of patients taking meclofenamic acid, but these do not usually require discontinuation of therapy. Because of the rare possibility of drug-induced hemolytic anemia, hematological analyses should be performed on patients receiving long-term therapy if anemia is suspected.

Phenylbutazone-Type Drugs

The phenylbutazone-type drugs include phenylbutazone, oxyphenbutazone, antipyrine, dipyrone, and aminopyrine. The use of these drugs has decreased because of their propensity to cause blood dyscrasias. Only antipyrine, used in as otic drops with benzocaine (*Otocalm*), is available in the United States today; phenylbutazone is used in Canada, and dipyrone is used in some European countries.

Acetaminophen

Acetaminophen (*Tylenol*) is an effective antipyretic and analgesic that is well tolerated at therapeutic doses. It has only weak antiinflammatory activity; thus, it is not useful in the treatment of rheumatoid arthritis and other inflammatory conditions. The properties of acetaminophen are described in Chapter 26.

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

While NSAIDs alleviate the pain and inflammation of rheumatoid arthritis, they do nothing to halt the loss of bone associated with this disease. The DMARDs are a chemically diverse class of agents, all of which have varying capacities to slow the progression of joint erosion. Their actions manifest over the course of weeks to months; they are usually employed in combination with NSAIDs and sometimes other DMARDs. Until the mid-1990s, DMARDs were reserved for treatment of the later stages of the disease in which significant joint erosion had already occurred. These agents were added individually, in slow succession (more than 6 months), as the disease progressed. More recent therapies employ certain DMARDs early in the treatment of disease, since they are effective in slowing the joint deterioration that occurs at this stage.

Methotrexate

Of the DMARDs, methotrexate (*Rheumatrex*) is the most widely prescribed. It is indicated for the treatment of rheumatoid arthritis and psoriasis; it is also used for psoriatic arthritis, systemic lupus erythematosus, and sarcoidosis. It is generally as efficacious as the other agents, with a low incidence of serious side effects when prescribed on a low-dose weekly schedule. Additional uses of methotrexate as an anticancer and immunosuppressive agent are described in Chapters 56 and 57, respectively.

Basic Pharmacology

Methotrexate is a folate antimetabolite that inhibits dihydrofolate reductase and other folate-dependent enzymes in cells. The absorption, metabolism, and excretion of methotrexate are fully described in Chapter 56. When given in high doses, methotrexate exerts potent suppressing action on cellular and humoral immunity (see Chapter 57). At the low doses used in the therapy of rheumatoid arthritis, methotrexate appears to be acting more as an antiinflammatory agent than as an immunosuppressant. Methotrexate inhibits folate-dependent enzymes involved in adenosine degradation, increasing concentrations of extracellular adenosine. Adenosine acts via cell surface receptors to inhibit the production of inflammatory cytokines such as TNF-α and IFN-γ. Methotrexate also decreases the production of inflammatory prostaglandins and proteases, though a direct action on the COX enzymes has not been noted.

Adverse Effects

In the low-dose regimen used for rheumatoid arthritis, most side effects of methotrexate are mild and can be managed by temporarily stopping the drug or reducing the dose. These include nausea, stomatitis, GI discomfort, rash, diarrhea, and headaches. Changes in liver aminotransferases and mild to moderate immunosuppression have been reported in rheumatoid arthritis patients taking methotrexate. Severe toxicity is possible but rare and may be a function of drug accumulation. These effects include hepatotoxicity progressing to cirrhosis, pneumonitis progressing to pulmonary fibrosis, and bone marrow depression with anemia, leukopenia, and thrombocytopenia. Folic acid supplementation is often used to alleviate certain side effects of methotrexate therapy (stomatitis, GI irritation, hematopoietic effects) but may also contribute to resistance to this therapy.

Contraindications and Drug Interactions

Methotrexate is teratogenic and is contraindicated during pregnancy and breast-feeding. Prior to attempting pregnancy, women should wait at least one menstrual cycle and men at least 3 months after discontinuing this drug. Additional contraindications to methotrexate administration include kidney, liver, and lung disease; moderate to high alcohol use; immunodeficiency; blood dyscrasias; and hypersensitivity. Elderly persons may be

at increased risk for toxicity because of decreased renal and hepatic function.

Methotrexate clearance can be decreased by the coadministration of NSAIDs; however, this not usually a problem with the low doses of methotrexate used to treat arthritis. Methotrexate can be displaced from plasma protein binding sites by phenylbutazone, phenytoin, sulfonylureas, and sulfonamides and certain other antibiotics. The antifolate effects of methotrexate are additive with those of other folate-inhibitory drugs, such as trimethoprim.

Sulfasalazine

Sulfasalazine (*Azulfidine*) is approved for the treatment of rheumatoid arthritis and ulcerative colitis. It is also used to treat ankylosing spondylitis and Crohn's disease. Comparisons of sulfasalazine with other DMARDs suggest that it is more effective than hydroxychloroquine, azathioprine, and oral gold compounds. It is at least as effective as intramuscular gold and penicillamine. It has a greater degree of toxicity than hydroxychloroquine but less than gold compounds and penicillamine. After 5 years, approximately 75% of patients have discontinued sulfasalazine therapy, primarily because of a lack of efficacy as opposed to intolerable side effects.

Basic Pharmacology

Sulfasalazine is a prodrug of which 70% is converted by colon bacteria to two active metabolites, sulfapyridine and 5-aminosalicylic acid (mesalamine). Sulfapyridine has antibacterial activities, and 5-aminosalicylic acid is antiinflammatory; however, these effects do not account for the ability of this drug to slow the processes of rheumatoid arthritis. Recent research suggests additional activities of sulfasalazine that may be relevant to these effects: its ability to increase adenosine levels, its inhibitory effects on IL-1 and TNF-α release, and its inhibition of NF-κB. The pharmacokinetic data for this and other DMARDs are provided in Table 36.4.

Adverse Effects

Mild to moderate side effects, including nausea, vomiting, abdominal pain, diarrhea, anorexia, and headache, occur in up to 33% of patients taking this drug. Skin rash and discoloration, fever, reversible male infertility, and liver enzyme elevation occur less frequently. Rare hematological abnormalities, such as agranulocytosis, aplastic anemia, hemolytic anemia, neutropenia, or other blood dyscrasias, can be fatal. Hypersensitivity reactions occur rarely.

Contraindications and Drug Interactions

Sulfasalazine is contraindicated in individuals with hypersensitivity to salicylates, sulfonamides, sulfonylureas, and certain diuretics (furosemide, thiazides, and carbonic anhydrase inhibitors). Because it can cause kernicterus, sulfasalazine is contraindicated in infants and children under 2 years of age. Sulfasalazine passes into breast milk and is therefore contraindicated for nursing mothers. Similarly, pregnant women near term should not use this drug, although it appears to be the safest of the DMARDs during early pregnancy.

TABLE 36.4 Pharmacokinetic Properties of Selected DMARDs

Drug	Time to Peak Plasma Level (fasting) (hr)	Plasma Half-Life	Protein Binding (%)	Urinary Excretion (%)	Notes
Anakinra	3–7	4–6 (hr)	–	–	–
Auranofin	2	26 d[a] 80 d[b]	60	60	–
Aurothioglucose	2–6	160 d–1 yr[b]	98	70	–
Etanercept	72	115	–	–	–
Hydroxychloroquine	3	32 d	45	Predominant	–
Infliximab	–	8–9.5 d	–	–	–
Leflunomide (M1 metabolite)	6–12	15 d	99	Minor	E, H, R
Sulfasalazine	SZ: 1.5–6 SP: 6–24	SZ: 5–7 (hr) SP: 6–14 (hr)	99% + –	SP: 75 Mes: 67	R –

[a]Blood
[b]Tissues
E, enterohepatic cycling; H, not recommended for patients with hepatic impairment; R, dosage adjustment necessary for patients with renal impairment; SZ, sulfasalazine; SP, sulfapyridine; Me, mesalamine.

Sulfasalazine can precipitate attacks of porphyria and should not be used by individuals with bowel or urinary obstruction.

Sulfasalazine can inhibit the absorption of cardiac glycosides and folic acid. It may displace certain drugs, including warfarin, phenytoin, methotrexate, tolbutamide, chlorpropamide, and oral sulfonylureas, from their protein binding sites. Sulfasalazine can diminish the effectiveness of penicillins and estrogen-containing oral contraceptives.

Antimalarials

Hydroxychloroquine (*Plaquenil*) and chloroquine (*Aralen*) are 4-aminoquinoline antimalarial drugs that possess modest DMARD activity. They are indicated for the treatment of rheumatoid arthritis and systemic lupus erythematosus; their use as antimalarials is detailed in Chapter 53. The onset of action of these drugs is longer than that of other DMARDs, and their side effects are relatively mild. Because of this, these agents show promise as ingredients of combination therapies for rheumatoid arthritis.

Basic Pharmacology

Hydroxychloroquine and chloroquine are similar in activity; however, hydroxychloroquine has a lower incidence of ocular side effects and is used more frequently. These drugs are weak bases that enter and interfere with the functioning of lysosomes and other subcellular compartments of T- and B-lymphocytes, monocytes, and macrophages. This in turn inhibits the ability of these cells to produce and release inflammatory cytokines and hydrolytic enzymes.

Adverse Effects

Skin rashes and pruritus are common adverse effects of the 4-aminoquinoline antimalarials, as are GI effects. The incidence of the most serious toxic reaction, irreversible retinopathy with resultant blindness, is dose related and can be minimized by maintaining a daily dose of hydroxychloroquine less than 6.5 mg/kg or chloroquine less than 4 mg/kg. Eye examinations should be performed regularly during treatment with these drugs. Severe hematological toxicity (neutropenia, thrombocytopenia, aplastic anemia) is rare. Reversible side effects observed during high-dose, long-term therapy with the aminoquinolines include lichenoid skin lesions, leukopenia, neuromyopathy, hair loss, sensitivity to sunburn, and changes in the electrocardiogram.

Contraindications and Drug Interactions

The aminoquinolines accumulate in lung, kidney, and liver; thus, any preexisting pathology in these tissues contraindicates their use. Similarly, any ocular pathology precludes their use. Psoriasis and porphyria are frequently exacerbated by the administration of the aminoquinolines.

Aminoquinolines can increase plasma concentrations of penicillamine, hence the potential for serious hematological or renal toxicity. Similarly, aminoquinolines can increase digoxin levels. Gold and an aminoquinoline probably should not be administered concurrently because of the propensity of each to produce dermatitis.

Leflunomide

Leflunomide (*Arava*) is an isoxazole derivative approved for the treatment of rheumatoid arthritis in 1998. Limited data suggest that it is comparable in efficacy to sulfasalazine and produces fewer adverse effects. It has a faster onset of action (4 weeks) than other DMARDs.

Basic Pharmacology

Leflunomide is a prodrug that is converted to an active malonitrilamide metabolite, A77 1726 (M1). M1 inhibits T-cell proliferation by blocking de novo pyrimidine synthesis and inhibiting the tyrosine kinases that are associated with certain cytokine and growth factor receptors.

Adverse Effects

Diarrhea occurs in approximately one-third of patients taking this drug; indigestion, nausea, and vomiting occur in about 10%. Other common adverse effects include weight changes, headache, skin rashes, pruritus, and reversible alopecia and hepatic enzyme elevation. Although leflunomide acts as an immunosuppressive, it does not appear to cause significant bone marrow depression.

Contraindications and Drug Interactions

Leflunomide is teratogenic in animal models; it is absolutely contraindicated in pregnancy, in women who may become pregnant, and in breast-feeding women. Because of its long half-life, the M1 metabolite of leflunomide may remain in the body for up to 2 years; therefore, a drug elimination procedure using cholestyramine should be used before any attempt at pregnancy. This drug is not recommended for use in children. Caution should be used when administering this drug to individuals with renal or hepatic disease, heavy alcohol use, or immunosuppression.

The long half-life of leflunomide must be taken into account to prevent drug interactions. Hepatotoxicity is possible if leflunomide is given in conjunction with a hepatotoxic agent such as methotrexate or certain NSAIDs. Leflunomide inhibits CYP2C9, the enzyme responsible for the metabolism of numerous drugs. Rifampin induces the P450 enzyme responsible for converting leflunomide

to its M1 metabolite. Cholestyramine enhances the clearance of leflunomide and its M1 metabolite.

TNF-α Inhibitors

Two recently introduced biological therapies were designed to interfere with the inflammatory cascade initiate by TNF-α. Etanercept (*Enbrel*) is indicated for the treatment of moderate to severe rheumatoid arthritis in individuals over age 4. Infliximab in conjunction with methotrexate (*Remicade*) is approved for use by adults in the treatment of rheumatoid arthritis. It is also indicated for therapy of Crohn's disease. Over the short term, the efficacy of these drugs in the treatment of rheumatoid arthritis appears to be superior to that of methotrexate alone; however, their ability to prevent bone erosion for longer than 24 months must be further studied. The cost of both drugs is significantly higher than that of the other DMARDs.

Basic Pharmacology

Etanercept is a recombinant fusion protein produced in Chinese hamster ovary cells. It consists of the intracellular ligand-binding portion of the human p75 TNF receptor linked to the Fc portion of human immunoglobulin (Ig) G_1. Two p75 molecules are attached to each Fc molecule. Etanercept binds to soluble TNF-α and TNF-β and forms inactive complexes, effectively lowering circulating levels of these cytokines. It is administered subcutaneously, generally twice weekly.

Infliximab is a chimeric monoclonal antibody targeted against TNF-α. It consists of a human IgG_1 Fc heavy chain and partial κ-light chain fused to a murine hypervariable region. Infliximab binds to both soluble and transmembrane forms of TNF-α and inhibits their ability to bind to TNF receptors. It does not inhibit TNF-β, which binds to the same receptors as TNF-α. Infliximab is administered intravenously, usually at 4- to 8-week intervals.

Adverse Effects

The most common adverse reaction to etanercept is mild to moderate erythema, pain, or pruritus at the injection site (37%). Headaches and abdominal pain can also occur. New positive autoantibodies, such as antinuclear antibodies (ANA), anti-dsDNA antibodies, and anticardiolipin antibodies, can develop in patients treated with etanercept. Although there is so far no association between this and the development of autoimmune diseases or malignancies, long-term studies have yet to be done. Rare cases of pancytopenia may be associated with this drug. Although clinical trials showed no increased risk of infection with etanercept treatment, postmarketing reports of serious infections, sepsis, and associated fatalities exist.

Infliximab produces an acute infusion-related reaction consisting of fever and chills in approximately 20% of patients. Other common side effects include headache, nausea, and diarrhea. Persons given infliximab with methotrexate may have a greater elevation of hepatic enzyme levels than those given methotrexate alone. Because it is a human–mouse fusion protein, infliximab seems to be more immunogenic than etanercept. During infliximab treatment, autoantibodies (anti-dsDNA, ANA) and antibodies to the drug itself (human antichimeric antibodies) can develop. Concomitant therapy with methotrexate or immunosuppressive drugs decreases this risk somewhat. It is possible that infliximab may increase the incidence of autoimmune diseases and malignancies; however, long-term data are needed to determine whether this is the case. As with etanercept, a low risk of serious infection was seen in clinical trials of infliximab; however, sepsis, disseminated tuberculosis, and other potentially fatal infections have been reported in patients taking this drug.

Contraindications and Drug Interactions

Etanercept therapy should not be initiated in patients with active infection. If an infection develops in a person taking etanercept, he or she should be closely monitored. If a serious infection or sepsis occurs, the drug should be discontinued. Etanercept should be used with caution in individuals who have conditions predisposing them to serious infection (e.g., uncontrolled diabetes, hematological abnormalities). Data on drug interactions are limited. Live virus vaccines are contraindicated because of the potential for secondary transmission of the infection by the vaccine. Myelosuppressive antirheumatic agents have been associated with pancytopenia in some patients treated with etanercept.

Infliximab should not be given to individuals with known hypersensitivity to murine proteins. As with etanercept, precautions for the prevention of serious infections must be taken, and live virus vaccines are contraindicated.

Interleukin-1 Antagonists

Anakinra (*Kineret*) is the first antirheumatic agent that acts by blocking the action of IL-1. This drug was recently approved for the treatment of moderately to severely active rheumatoid arthritis in adults who have not responded to therapy with one or more DMARDs. Anakinra may be used alone or in combination with DMARDs other than the TNF antagonists. Clinical trials have shown anakinra to be more effective than placebo, either alone or in conjunction with methotrexate.

Basic Pharmacology

Anakinra is a nonglycosylated form of the human IL-1 receptor antagonist (IL-1ra). It is produced in a recombinant *Escherichia coli* expression system and has an additional methionine residue at its amino terminus. In rheumatoid arthritis patients, the amount of naturally occurring IL-1ra in the synovial fluid is not sufficient to counteract the high levels of locally produced IL-1. Anakinra acts as a competitive antagonist of the type 1 IL-1 receptor and decreases the pain and inflammation produced by IL-1. It is administered as a daily subcutaneous injection.

Adverse Effects

The most common adverse reactions to anakinra are redness, bruising, pain, and inflammation at the injection site. Neutropenia may occur, and the risk of serious infection is somewhat elevated, particularly in asthmatic patients. Antibodies to anakinra can develop with long-term therapy, but no correlation between antibody development and clinical response or adverse effects has been observed.

Contraindications and Drug Interactions

No drug interaction studies have been conducted in humans. Animal studies indicate no change in the clearance or toxicity of either methotrexate or anakinra when the two agents are administered together. Concomitant administration of a TNF blocker appears to increase the risk of serious infection. The response to vaccines may be diminished in patients taking anakinra.

Gold Compounds

Gold compounds (chrysotherapy) are the oldest of the DMARDs in use to treat rheumatoid arthritis. Parentally administered gold is generally believed to be somewhat less effective than methotrexate; oral gold is less effective than parenteral preparations. Gold compounds take several months to produce a measurable effect. Among patients who can tolerate this therapy, some benefit will be obtained in about 80%, and complete remission will be induced in 20% of cases. Remissions are maintained for varying periods after discontinuing therapy, with a relapse rate as high as 80%. Relapse is usually less severe in such patients, and a second course of gold therapy usually produces beneficial effects.

Basic Pharmacology

The gold preparations available in the United States include two preparations administered via intramuscular injection: gold sodium thiomalate (GSTM, *Myochrysine, Aurolate*) and aurothioglucose (gold sodium thioglucose, GSTG, *Solganal*), and an oral preparation, auranofin (*Ridaura*). Although called gold salts, these compounds contain monovalent gold bound to sulfur, a bond that is at least partly covalent. For this reason, these complexes are termed gold preparations or gold compounds in this chapter.

The mechanism by which gold compounds produce their antiarthritic effects is not known. Since gold therapy can suppress the increased phagocytic activity that occurs in rheumatoid arthritis, the antirheumatic activity of gold preparations may involve the inhibition of either antigen processing by macrophages or lysosomal enzyme release in the joint. Gold preparations also directly inhibit certain lysosomal enzymes found in polymorphonuclear leukocytes and macrophages.

Generally, 2 months of multiple dosing of gold compounds is required to reach steady-state levels. Auranofin therapy produces lower steady-state blood gold concentrations than does treatment with parenteral gold compounds, but it also produces a lower incidence of adverse effects.

Adverse Effects

Toxic manifestations of gold therapy are most common after a minimal total amount (200–300 mg) of gold has been administered. Serious reactions necessitating discontinuance of therapy or antidotal therapy are encountered in perhaps 5% of the patients.

Both oral and parenteral gold therapy frequently produces dermatitis, usually preceded and accompanied by pruritus. Stomatitis may accompany dermatitis, which may be preceded by a metallic taste in the mouth of the patient. Blue or gray skin discoloration can arise from gold deposition in that tissue, and photosensitivity may also occur. Unlike parenteral gold compounds, auranofin does not accumulate appreciably in the skin. Auranofin, but not the parenteral gold preparations, most frequently causes diarrhea (about 50%), abdominal pain, nausea, and anorexia.

Mild proteinuria is fairly common and does not always require discontinuance of therapy; however, severe proteinuria may indicate a toxic nephritis. The proteinuria is usually reversible when gold administration is stopped. Hepatotoxicity has also been reported. Fatalities from gold therapy have been reported, usually a consequence of a blood dyscrasia. The most common hematological abnormality is eosinophilia. Serious blood dyscrasias, such as thrombocytopenia, agranulocytosis, and hypoplastic or aplastic anemia, are rare.

To complement steroidal and other measures used in treating gold toxicity, it may be necessary to hasten the elimination of gold from the body. Appropriate chelating agents include dimercaprol and penicillamine (see Chapter 2). The proper administration of either of these agents markedly increases the excretion of gold and alleviates the signs and symptoms of gold toxicity.

Contraindications and Drug Interactions

Gold compounds are contraindicated for use in patients with systemic lupus erythematosus, Sjögren's syndrome, severe debilitation, or uncontrolled congestive heart failure or hypertension. Caution must be used in administering gold compounds to individuals who have conditions that might increase their susceptibility to gold toxicity: blood dyscrasias, immunosuppression, renal disease, hepatic disease, skin diseases, or inflammatory bowel disease. Animal studies have shown adverse effects on reproduction; gold compounds may distribute to breast milk and are therefore contraindicated for women who are breast-feeding.

Gold should be used cautiously in patients receiving drugs that can also cause nephrotoxicity. Interactions between gold compounds and penicillamine may result in severe hematological and renal side effects.

Other Drugs for Rheumatoid Arthritis Therapy

The following drugs are not commonly used as first-line treatments of rheumatoid arthritis, either because they lack the efficacy of other drugs or because they produce more serious side effects or both. They do, however, remain useful in specific clinical situations and in individuals in whom more conservative therapies have failed.

Corticosteroids

Serious adverse effects are produced by long-term, high-dose exposure to the corticosteroids; therefore, these drugs are not agents of choice for the treatment of rheumatic disease. In general, the use of low-dose corticosteroids avoids significant side effects (e.g. fluid retention, osteoporosis, GI bleeding, immunosuppression) but does not completely control the disease. However, for patients whose disease is refractory to other agents or who cannot tolerate the side effects of other DMARDs, a corticosteroid such as prednisone may be used to control symptoms. Low-dose corticosteroids may also be used as an alternative to more toxic DMARDs in pregnant, elderly, or debilitated individuals. Intraarticular injection of corticosteroids can control acute inflammation of a specific joint without causing systemic side effects. High-dose steroids can control severe systemic manifestations of autoimmune disease, such as iritis, pericarditis, nephritis, or vasculitis. Following discontinuation of corticosteroid treatment, rebound joint deterioration is common.

A detailed discussion of the pharmacodynamics, mechanism of action, and adverse effects of the corticosteroids and their role in therapeutics can be found in Chapter 60.

Immunosuppressive Drugs

The immunosuppressive drugs are used in rheumatoid arthritis and certain other autoimmune conditions that are refractory to less toxic treatments. Their pharmacology and additional clinical uses are described in Chapter 57. Azathioprine (*Imuran*) is a prodrug that is metabolized to a purine antimetabolite. Its disease-modifying activity results from the inhibition of lymphocyte proliferation and secretion of certain cytokines. This drug is used in the treatment of rheumatoid arthritis, lupus nephritis, and psoriatic arthritis. Cyclosporine (*Sandimmune, Neoral*) is used in refractory rheumatoid arthritis, psoriasis, and inflammatory bowel disease. It acts by blocking the transcriptional activation of many genes involved in the first phase of T cell activation. Cyclophosphamide (*Cytoxan*) is an alkylating agent that was used in severe rheumatoid in the past but is seldom used today because of its severe bladder toxicity, bone marrow toxicity, and carcinogenicity.

Minocycline

The tetracycline antibiotic minocycline (*Minocin*) is modestly effective in the treatment of rheumatoid arthritis and is generally well tolerated. Radiographic evidence of its efficacy as a DMARD is lacking, although clinical symptoms do abate. It can be useful in the treatment of early, mild disease. A more detailed description of the pharmacology and clinical uses of minocycline is found in Chapter 47.

Penicillamine

Penicillamine (*Cuprimine*) can be used to treat acute, severe rheumatoid arthritis, producing reductions in joint pain, edema, and stiffness. The response to penicillamine is usually delayed (4–12 weeks), and remissions can last several months after withdrawal of treatment. Radiographic evidence of this drug's efficacy is limited; thus, penicillamine is seldom used to treat rheumatoid arthritis. The mechanism of action of penicillamine is unknown, but some evidence suggests that it may involve the inhibition of angiogenesis, synovial fibroblast proliferation, or transcriptional activation. Because penicillamine can chelate copper and promote its excretion, it is used to treat Wilson's disease (hepatolenticular degeneration) and has also been used in mercury and lead intoxication.

Penicillamine is readily absorbed from the GI tract and is rapidly excreted in the urine, largely as the intact molecule. Gradually increasing its dose minimizes side effects, which necessitate discontinuance of penicillamine therapy in perhaps one-third of patients. The most common side effects are maculopapular pruritic dermatitis, GI upset, loss of taste sensation, mild to occasionally severe thrombocytopenia and leukopenia,

and mild proteinuria, which at times may progress to the nephritic syndrome. Discontinuance of therapy usually results in a rapid disappearance of side effects.

NEW APPROACHES TO THE TREATMENT OF RHEUMATOID ARTHRITIS

In previous decades, a pyramid model dominated the treatment of rheumatoid arthritis. Early in the course of the disease, salicylates were used to control pain and stiffness. If salicylates were poorly tolerated or began to lose efficacy, they were discontinued and a different NSAID was used. As the efficacy of NSAID therapy waned and joint deterioration progressed, treatment with a DMARD was added. DMARDs were employed singly and sequentially for periods of up to 6 months before clinicians could determine their efficacy and switch to a new drug if necessary.

The most recent treatment paradigm calls for earlier, more aggressive treatment of rheumatoid arthritis. DMARDs are frequently employed along with NSAIDs in the initial treatment of the disease. The COX-2 inhibitors are often used because they are less likely to cause serious GI toxicity than are the nonspecific COX inhibitors. The usual DMARD of choice for patients with mild rheumatoid arthritis is hydroxychloroquine or sulfasalazine; methotrexate is used for those with moderate to serious disease. Other DMARDs are used if these agents are poorly tolerated or do not produce sufficient response. Combination therapy of methotrexate and another agent is also used to treat disease that is not responsive to individual DMARDs.

Study Questions

1. A man aged 74 has moderate hypertension controlled with hydrochlorothiazide 12.5 mg once daily and losartan 50 mg once daily. He is prescribed rofecoxib 50 mg once daily to control osteoarthritis pain. After 3 months of this therapy, his blood pressure begins to rise. This increase in blood pressure is most likely due to
(A) Inhibition of COX-2 by rofecoxib, which leads to decreased renal blood flow
(B) Increased metabolism of losartan due to induction of CYP2C9 by rofecoxib
(C) Increased excretion of hydrochlorothiazide due to increased renal blood flow caused by rofecoxib
(D) Arteriolar contraction in the peripheral circulation caused by inhibition of COX-1 by rofecoxib
(E) Weight gain caused by rofecoxib's ability to decrease basal metabolic rate.

2. The use of low-dose methotrexate in the treatment of rheumatoid arthritis is most frequently
(A) Reserved for cases in which NSAIDs no longer adequately control pain and stiffness
(B) Initiated only after significant joint destruction
(C) Contraindicated in individuals being treated with NSAIDs
(D) Used for pregnant women, since it is the DMARD with the least fetal toxicity
(E) Initiated early in the course of moderate to severe forms of the disease

3. A 52-year-old woman with a history of eczema and heavy alcohol use begins taking ibuprofen to control hip and knee pain due to osteoarthritis. Over the course of 6 months, as the pain worsens, she increases her dosage to a high level (600 mg four times daily). What toxicity is most likely to occur, and why?
(A) Abnormal heart rhythms; alcohol induces cytochrome P450 isozymes that convert ibuprofen to a cardiotoxic free radical metabolite
(B) Necrotizing fasciitis; eczema predisposes an individual to this toxicity of ibuprofen
(C) Gastric ulceration; heavy alcohol use increases the susceptibility of an individual to ibuprofen-induced GI toxicity
(D) Confusion and ataxia; these CNS toxicities of ibuprofen are additive with those of ethanol
(E) Eosinophilia; this rare complication of ibuprofen therapy is exacerbated by the immunosuppression frequently seen in alcoholics

4. Etanercept produces its antirheumatic effects by direct
(A) Inhibition of cAMP phosphodiesterase in monocytic lineage leukocytes
(B) Selective inhibition of COX-2
(C) Enhancement of leukotriene synthesis at the expense of prostaglandin synthesis
(D) Reduction of circulating active TNF-α levels
(E) Inhibition of the production of autoantibodies

5. An advantage of celecoxib over most other NSAIDs is
(A) Less inhibition of PGE_2 effects on the gastric mucosal
(B) Less risk of bronchospasm and hypersensitivity reactions

(C) Once-daily dosing allows the patient convenience
(D) Less risk of harm to the developing fetus in the third trimester
(E) Greater degree of efficacy in the treatment of rheumatoid arthritis

ANSWERS

1. **A.** By blocking renal prostaglandin synthesis, COX-2 inhibitors, such as rofecoxib, decrease the blood flow to the juxtaglomerular apparatus, thus stimulating the release of renin and subsequent Na^+ retention and blood pressure elevation. Rofecoxib is neither metabolized nor induced by CYP2C9. It decreases rather than increases renal blood flow and does not increase the excretion of hydrochlorothiazide. Item D is incorrect because rofecoxib has very little effect on COX-1 and prostaglandins are not a major controlling factor of peripheral vascular tone. Rofecoxib does not decrease basal metabolic rate.
2. **E.** Treatment guidelines suggest the use of DMARDs early in the course of rheumatoid arthritis to slow the joint deterioration associated with the disease. Methotrexate is the DMARD of choice for people with moderate to severe forms of rheumatoid arthritis. Although NSAIDs can decrease methotrexate clearance, NSAIDs can be safely used with the low doses of methotrexate used in the therapy of rheumatoid arthritis. Methotrexate is highly teratogenic and should not be used by women who are or may become pregnant.
3. **C.** The likelihood of gastric ulceration and GI bleeding is increased by heavy alcohol use, poor health, advanced age, long-term NSAID use, and use of drugs such as corticosteroids and anticoagulants. Ibuprofen is not converted to a cardiotoxic metabolite. Dermal toxicities, such as epidermal necrolysis, are rare complications of ibuprofen therapy, but necrotizing fasciitis is not one of them. Confusion and ataxia are not side effects associated with ibuprofen, nor is eosinophilia.
4. **D.** Etanercept is a recombinant fusion protein consisting of two TNF receptor domains linked to one IgG Fc molecule. It binds to soluble TNF-α and TNF-β and forms inactive complexes. It does not directly affect cAMP phosphodiesterase, leukotriene synthesis, or autoantibody production.
5. **A.** Celecoxib selectively inhibits COX-2, so it does not inhibit the constitutive activity of COX-1 in the regulation of gastric acid secretion. When prostaglandin synthesis by COX-1 or COX-2 is blocked, eicosanoids are shifted into the leukotriene pathway, so bronchospasm and hypersensitivity reactions are favored. The shorter half-life of celecoxib does not allow once-daily dosing. This drug is no less able than other NSAIDs to close the ductus arteriosus during the third trimester. None of the NSAIDs is empirically more efficacious than the others; a patient's own response and side effects determine the best drug for him or her.

SUPPLEMENTAL READING

Beehrle DM and Evans D. A review of NSAID complications: Gastrointestinal and more. Prim Care Pract 1999;3:305–315.

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Lee DM and Weinblatt ME. Rheumatoid arthritis. Lancet 2001;358:903–911.

McCarberg BH and Herr KA. Osteoarthritis: How to manage pain and improve patient function. Geriatrics 2001;56:14–17, 20–22, 24.

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CASE Study A Visit to University Student Health

A 21-year-old college student presented to her university's student health center with an acute exacerbation of asthma. Her respiratory rate was increased, and she was in obvious respiratory distress, with wheezes audible on both sides of the chest. The examination of the nasal passages revealed mucosal edema and a polyp on the right. There was marked swelling about the eyes, and her upper lip was swollen (angioedema). Her fingertips were slightly cyanotic. Her peak expiratory flow rate was 25% of the predicted normal value. Oxygen was given by face mask. She was given 1:1000 aqueous epinephrine 0.3 mL subcutaneously, diphenhydramine HCl 50 mg intramuscularly, and prednisone 40 mg by mouth. Subsequently she was given nebulized albuterol, and the peak flow rate improved to 75% of predicted. When questioned further, she said she had taken a friend's ibuprofen for menstrual cramps.

The case in context: Dysmenorrhea is a common condition caused by uterine contraction during menses. $PGF_{2\alpha}$ may be the uterine contractant. NSAIDs, such as ibuprofen, relieve dysmenorrhea by inhibiting the biosynthesis of $PGF_{2\alpha}$. This allows for enhanced production of the leukotrienes by a 5-lipoxygenase. The leukotrienes are potent bronchoconstrictors, and patients with asthma and nasal polyps are often much more sensitive to them than are other asthmatics and normal individuals. The logic of her therapy is as follows: Oxygen is needed in patients with peak flow rates less than 30% of their predicted value; epinephrine is a bronchodilator (β-adrenergic effect) and vasoconstrictor that prevents further angioedema (α-adrenergic effect); diphenhydramine is an H_1 antihistamine; albuterol is a β_2-adrenergic agonist; prednisone (a glucocorticoid) is the most effective drug for asthma. Although its onset of action is slow (about 4 hours), many patients with an acute attack of asthma have a late response several hours later due to the influx and activation of lymphocytes, eosinophils, and perhaps neutrophils, which release further mediators of inflammation, such as the leukotriene-5. The patient should be warned to avoid NSAIDs in the future.