CHAPTER 41

Nonsteroidal Anti-Inflammatory Drugs

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- Nonsteriodal anti-inflammatory drugs (NSAIDs) relieve inflammation and pain by inhibiting the production of prostaglandins.
- Prostaglandin (PG) biosynthesis occurs via a three-enzyme cascade. Current NSAIDs inhibit the enzyme cyclooxygenase (COX), accounting for their efficacy and toxicity.
- Pharmacologic properties of the different NSAIDs, including specificity for COX-1 or -2 and drug half-life, influence the toxicity profile.
- The most important NSAID toxicities include gastrointestinal ulceration, asthma and allergic reactions, and effects on the kidneys, liver, and cardiovascular system.
- Safe use of NSAIDs requires consideration of individual comorbidities to choose the best agent, appropriate monitoring for toxicity, and use of appropriate gastroprotective agents.

Pain (dolor), swelling (tumor), erythema (rubor), and warmth (calor), the cardinal features of inflammation, are present in most patients with rheumatic diseases. Therapeutic strategies to reduce inflammation have been used for centuries, beginning with botanical treatments in both Western and Eastern medical traditions (1). The first isolated plant constituent to be tested as an anti-inflammatory drug was salicylic acid from willow bark, which was chemically altered to acetyl salicylic acid to improve its pharmacologic properties. Acetyl salicylic acid became "aspirin" in 1899, one of the first drugs to be widely marketed, and aspirin remains one of the most widely used drugs today. Other drugs that share the anti-inflammatory, analgesic, and antipyretic properties of aspirin are termed *nonsteroidal anti-inflammatory drugs* (NSAIDs), and are a chemically diverse group of compounds (Table 41-1). It was established in 1971 that salicylates and other NSAIDs act by blocking the synthesis of prostaglandins (PGs), products of the metabolism of the membrane-associated fatty acid arachidonic acid. This finding demonstrated conclusively that PGs play an important role in mediating symptoms and signs of inflammation. However, PGs play a role in normal physiology as well as in disease. As a consequence, all NSAIDs possess predictable therapeutic and adverse effects that must be understood in order to use these drugs safely.

Prostaglandins are synthesized by the action of at least three biosynthetic enzymes, one of which, cyclooxygenase (COX), is the target of all currently available NSAIDs. In recent years, important progress has been made towards understanding the action of NSAIDs by clarifying the biology of PG production. This advance came with the discovery of COX-2, the isoform whose expression is increased during inflammation. Specific inhibition of COX-2 blocks production of high levels of PGs at sites of inflammation while preserving PG production mediated by COX-1 in certain other tissues. Nonspecific NSAIDs, which inhibit both COX-1 and COX-2, have some differences when compared with COX-2–specific NSAIDs with regard to their adverse-event profiles. Comparative studies, however, find equal efficacy demonstrating that COX-2–derived PGs are responsible for the inflammation and pain of arthritis. Other important differences between these NSAIDs are related to their chemical class and pharmacologic properties other than the specificity for COX isoforms. All these factors are involved in the relative efficacy and safety of NSAIDs for patients with rheumatic diseases. It should be emphasized that advances in the understanding of PG biology may lead to other targets that would further advance anti-inflammatory therapy.

PROSTAGLANDIN BIOLOGY

The diversity of PG functions is achieved by cell- and tissue-specific generation of different stable PGs, multiple PG receptors linked to different intracellular

TABLE 41-1. NONSTERIODAL ANTI-INFLAMMATORY DRUGS AND SALICYLATES.

CHEMICAL CLASS	GENERIC NAME	BRAND NAME(S)
Carboxylic acids: salicylic acids and esters	Aspirin Diflunisal	Anacin,[a] Ascriptin,[a] Bayer,[a] Bufferin,[a] Easprin, Ecotrin,[a] Empirin,[a] Midol,[a] others Dolobid
Carboxylic acids: phenyl acetic acid	Diclofenac potassium Diclofenac sodium Diclofenac sodium + misoprostol	Cataflam Voltaren, Voltaren XR Arthrotec
Carboxylic acids: carbo- and heterocyclic acids	Etodolac Indomethacin Ketorolac Sulindac Tolmetin sodium	Lodine, Lodine XL Indocin, Indocin SR Toradol Clinoril Tolectin
Proprionic acids	Flurbiprofen Ketoprofen Oxaprozin Naproxen Naproxen sodium Ibuprofen	Ansaid Odudis, Oruvail, Actron,[a] Orudis KT[a] Daypro Naprosyn, Naprelan Anaprox, Aleve[a] Motrin, Dolgesic, Advil,[a] Motrin IB,[a] Excedrin IB, Genpril,[a] Nuprin,[a] others
Fenamic acids	Meclofenamate sodium	Meclomen
Enolic acids	Piroxicam Meloxicam	Feldene Mobic
Nonacidic	Nabumetone	Relafen
Sulfonamide	Celecoxib	Celebrex
Nonacetylated salicylates	Choline salicylate Magnesium salicylate Choline magnesium trisalicylate Salsalate Sodium salicylate	Arthrotec Bayer Select,[a] Doan's Pills[a] Trilisate, tricosal Amigesic, Disalcid, others

[a] Available over-the-counter.
Not intended to be an exhaustive list.

signaling pathways, and PG production pathways involving enzymes that are induced to dramatically increase local PG production. Biosynthesis of PGs involves a three-step sequence including (i) hydrolysis of the 20 carbon-containing polyunsaturated fatty acid, arachidonic acid, from cell membranes; (ii) oxygenation to the endoperoxide PGH_2 by COX; and (iii) conversion to the biologically active end products via specific PG synthases (Figure 41-1). The first step in PG synthesis is mediated by a phospholipase A_2 (PLA_2). Although the synthesis of PGs is regulated acutely by activation of phospholipases and release of arachidonate, the net level of prostanoid production is determined by the level of COX expression (2).

Cyclooxygenase-1 and COX-2 are homodimers that insert into one half of the lipid bilayer of the nuclear envelope and endoplasmic reticulum. They are bifunctional enzymes that catalyze both cyclooxygenation and peroxidation reactions. Although structurally similar, there are important differences in a small number of amino acids that lead to important biologic differences. For example, COX-2 is more easily "primed" by intracellular hydroperoxides and is active at lower concentrations of arachidonic acid. In addition, amino acid changes in the hydrophobic core of the enzymes lead to differences in "shape" of the COX active site that has been exploited to develop drugs that specifically inhibit COX-2 (2).

The most striking difference between the COX isoforms, however, is at the level of expression and regulation of mRNA and protein levels. These differences lead directly to the differing biological roles of COX-1 and COX-2. COX-1 is expressed in most tissues and levels do not vary greatly. COX-1–derived PGs mediate important physiologic processes in many tissues and COX-1 is available to increase PG production acutely when an abrupt increase in levels of arachidonic acid occurs following cell stimulation. However, COX-1

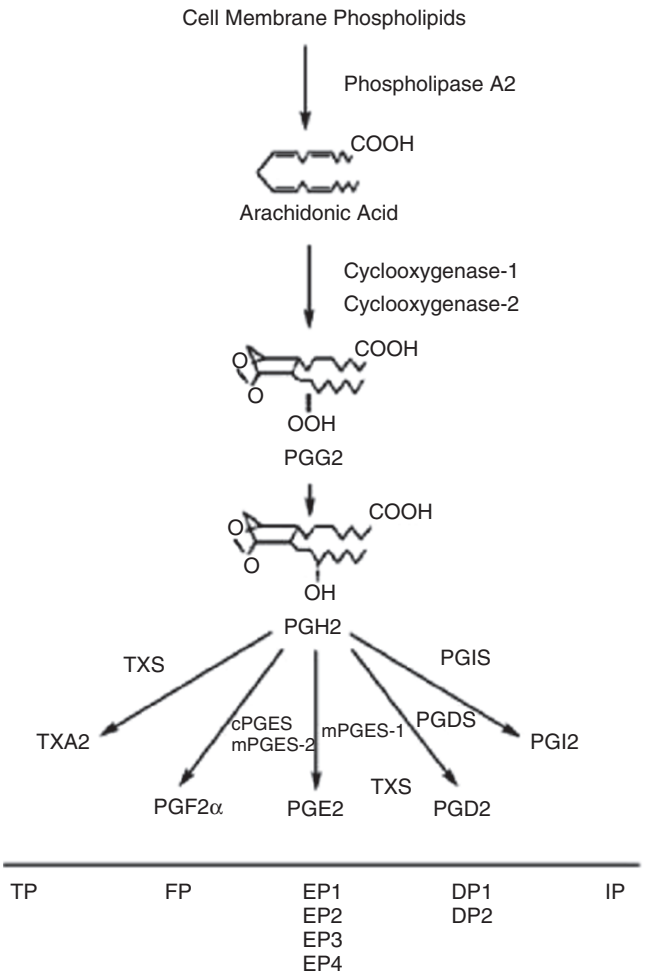

FIGURE 41-1

Prostaglandin biosynthetic pathway. The first step in prostaglandin (PG) biosynthesis is the release of arachidonic acid from cell membrane phospholipids by phospholipase A2. Cyclooxygenase (COX)-1 and COX-2 then adds two molecules of oxygen followed by a hydroperoxidase reaction to create first PGG_2 and then PGH_2. PGH_2 is an unstable intermediate rapidly converted to stable PGs by the respective PG synthases in a cell- and tissue-specific manner. PGE_2 has three different synthase enzymes, one of which (mPGES-1) is inducible by proinflammatory signals similar to COX-2. Stable PGs act in an autocrine or paracrine manner on cell surface receptors.

does not contribute substantially to the large increases in PG production that occur during inflammation. COX-1 is the only isoform expressed in mature platelets and is the dominant isoform in normal gastric mucosa (3).

Cyclooxygenase-2 expression is restricted to a few tissues, notably the kidney and brain, under basal conditions. COX-2 also plays an important role in normal reproductive, cardiovascular, and skeletal physiology. Most important for rheumatic diseases is the fact that COX-2 expression is highly induced and accounts for the large increase in PG levels produced locally during inflammation. COX-2 expression is increased by a number of cytokines, including interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF-alpha), and other mediators associated with inflammation (3). COX-2 expression is inhibited by glucocorticoids, accounting for some of their anti-inflammatory properties (see Chapter 42).

The product of the COX enzymes, PGH_2, is an unstable intermediate that is rapidly converted to one of several possible prostanoids by terminal synthases. In general, this process is cell-specific with differentiated cells producing only one or two PGs in abundance (2). The most important stable prostanoids include PGD_2, PGE_2, $PGF_{2\alpha}$, prostacyclin (PGI_2), and thromboxane A_2 (TXA_2). All have different biological roles that are important to the understanding of NSAID efficacy and safety.

PGE_2 is thought to be the most important mediator of inflammation (4). There are several forms of PGE synthase enzymes, including the microsomal PGE synthase-1 (mPGES-1) which, like COX-2, is highly induced during inflammation. mPGES-1 expression is increased by proinflammatory cytokines and inhibited by glucocorticoids. mPGES-1 acts in concert with COX-2 to generate locally high levels of PGE_2 during inflammation. There are four receptors for PGE_2 (EP receptors) with different signaling pathways. Molecular evolution studies demonstrate several receptor clusters, all containing receptors for PGE_2 (5). The earliest divergence is between clusters associated with either an increase of cAMP (EP2, EP4, IP–prostacyclin receptor, and DP–PGD_2 receptor) or decrease of cAMP (one isoform of EP3, TP–thromboxane receptor). The ancestral EP1 receptor diverged from the EP3 receptors and functions to increase intracellular Ca^{2+} along with the FP ($PGF_{2\alpha}$) and TP receptors.

There is considerable interest in potential nuclear actions of PGs. This may occur by interaction with nuclear receptors or by interaction with intracellular proteins. In biological fluids, PGD_2 is slowly dehydrated to yield the cyclopentanone PGs, PGJ_2 (6). PGJ_2 and other cyclopentanone PGs contain a highly reactive alpha beta-unsaturated ketone moiety that allows aduct formation with other proteins. It is thought that the cyclopentanone PGs play a role in the resolution of inflammation by acting as ligands for peroxisome proliferator-activated receptors (PPARs). It has also been suggested that covalent modification of certain transcription factors may lead to modulation of immune and inflammatory responses (7).

MECHANISM OF ACTION

The most important mechanism of NSAID action is to inhibit production of PGs by competing with arachidonic acid for binding in the COX catalytic site. NSAIDs

have little effect on peroxidase activity (2). It should be noted here that acetaminophen, while not classified as an NSAID, inhibits COX activity in vitro. It is thought that acetaminophen acts by inhibiting the peroxidase activity of the COX enzymes. Failure of acetaminophen to act as an anti-inflammatory agent may be related to its lack of effect under conditions of high hydroperoxide tone such as is found in inflammatory sites (8). NSAIDs may exhibit different kinetic modes of inhibition including (i) rapid, reversible binding (e.g., ibuprofen); (ii) rapid, lower affinity reversible binding followed by time-dependent, higher affinity, slowly reversible binding (e.g., naproxen, celecoxib); or (iii) rapid, reversible binding followed by covalent modification (e.g., aspirin) (2). From a clinical perspective, it is important to characterize NSAIDs according to specificity for inhibition of COX-1 or COX-2 (9). All NSAIDs currently in clinical use that inhibit COX-1 also inhibit COX-2 at therapeutic concentrations. However, at low doses (81 mg) aspirin acts as a specific inhibitor of COX-1. The specificity for COX-2 is based on the structural difference between the hydrophobic channels resulting in an NSAID binding site about 20% larger than COX-1 and including a side pocket.

Very high doses of NSAIDs have been shown to have COX-independent activities on cellular processes that could contribute to some of their actions. The practical importance of these mechanisms is unknown. Sodium salicylate and aspirin were shown to inhibit activation of the transcription factor NF-κB, leading some to suggest that this could be an important anti-inflammatory mechanism. Similar to some PGs, certain NSAIDs bind to and activate members of the PPAR family and other intracellular receptors. Another potential mechanism is induction of endogenous anti-inflammatory mechanisms. It was shown that the anti-inflammatory effect of salicylate can be inhibited by an adenosine A2 receptor antagonist in a murine model of inflammation, suggesting that salicylate may stimulate adenosine release. Specific COX-2 inhibitors may have unique structural features that promote COX-independent apoptosis of some cancer cells and angiogenesis (10).

CLINICAL PHARMACOLOGY

The chemical class and pharmacologic properties of various salicylates and other NSAIDs is listed in Table 41-1. Most NSAIDs are weak organic acids completely absorbed from the gastrointestinal (GI) tract. Once absorbed, NSAIDs are highly (> 95%) bound to plasma proteins, and the amount of free drug is relatively small. However, clinically significant reductions in albumin, such as occur in patients with active rheumatoid arthritis (RA), the elderly, and those with other chronic illnesses, can lead to an increase in free drug and an increased risk for toxicity. Due to increased vascular permeability in local sites of inflammation, the high degree of protein binding may result in delivery of higher levels of NSAIDs.

Nonsteriodal anti-inflammatory drugs with a longer half-life take a longer time to reach steady state concentrations. This can have consequences for the time to reach full therapeutic effect. The clearance of NSAIDs is usually by hepatic metabolism with production of inactive metabolites that are excreted in the bile and urine. Most NSAIDs are metabolized through the microsomal cytochrome P450-containing mixed-function oxidase system. Drugs metabolized through this pathway are expected to have drug interactions. Furthermore, there is genetic variation in enzyme activity such that some groups may metabolize drugs more slowly. The pharmacokinetics of some NSAIDs can be affected by liver disease, renal disease, or old age (11).

Salicylates are acetylated (e.g., aspirin) or nonacetylated (e.g., sodium salicylate, choline salicylate, choline magnesium trisalicylate, salicysalicylic acid). Aspirin and salicylates are readily absorbed in the acidic or neutralized stomach and intestine. The formulation of these agents affects the absorption properties, but not bioavailability. Buffered aspirin tablets contain antacids that increase the pH of the microenvironment, while enteric coating slows absorption. The bioavailability of rectal aspirin suppositories increases with retention time. Aspirin is rapidly deacetylated to salicylate either spontaneously or enzymatically. Albumin is the dominant protein to which salicylates bind, and in conditions where albumin concentrations are low, including active RA, the pharmacologic and toxic effects of an increment in dose are more pronounced. Salicylate is metabolized principally by the liver and excreted primarily by the kidney. The serum levels of salicylate bear only a modest relationship to the dose ingested and a small increment in dose may lead to a profound increment in serum level.

THERAPEUTIC ACTIONS

Nonsteriodal anti-inflammatory drugs have antipyretic, analgesic, and anti-inflammatory properties. The majority of evidence suggests that most of these properties are mediated by inhibition of COX-2 (3). Fever occurs in response to inflammation and induction of cytokines that function as endogenous pyrogens. PGs have long been known to mediate the fever response. COX-2 expression is induced in the brain vasculature with temporal correlation to the development of fever. In the absence of COX-2, fever fails to develop. PGs produced locally at the site of inflammation sensitize

peripheral nociceptors. PGs also prolong proinflammatory actions of bradykinin, histamine, nitric oxide, and other pain mediators. Recent studies have also demonstrated a role for PGs in central sensitization at the spinal level, resulting in hyperalgesia (increased pain to a normally painful stimulus) and allodynia (pain to a normally innocuous stimulus). There is constitutive expression of COX-2 in the dorsal horn of the spinal cord that is increased during inflammation, and inhibition of COX-2, but not COX-1, reduces spinal PG production (12).

Nonsteriodal anti-inflammatory drugs are used in virtually all rheumatic diseases associated with pain and inflammation. Their efficacy is best studied in osteoarthritis (OA), RA, gout, and acute pain. The question of whether an individual NSAID provides improved efficacy for a particular indication has been difficult to discern in randomized, controlled trials. However, historical preference for some agents in some conditions (e.g., indomethacin for gout or ankylosing spondylitis) continues, and a mechanistic basis for this preference may yet be identified. The utility of NSAIDs is limited chiefly by their adverse-effect profile and, in general, NSAIDs should be used for the shortest time possible and at the lowest dose that controls symptoms.

Aspirin is indicated for secondary prevention of cardiovascular disease. The use of aspirin to prevent cardiovascular disease events in patients without a prior history of cardiovascular disease is controversial. However, recent recommendations from the US Preventive Services Task Force suggest that those patients with an increased (3%–5%) risk for coronary heart disease events over 5 years may receive greater benefit than harm from aspirin chemoprophylaxis (13). There is no data to suggest that NSAIDs other than aspirin are effective agents for prophylaxis of cardiovascular thrombotic events, therefore NSAIDs are commonly used in combination with low-dose aspirin. Care should be taken to illicit the history of aspirin use and to consider drug interactions. There is recent data to suggest that some NSAIDs may reduce the ability of aspirin to exert its antithrombotic effect (14,15).

ADVERSE EFFECTS

Nonsteriodal anti-inflammatory drugs produce toxic effects in many organ systems (Table 41-2). Most of these adverse effects are related to inhibition of PGs mediating important physiologic functions. Because the therapeutic and adverse effects are related to the same mechanism of action, the therapeutic window for these medications is relatively narrow. Of course, there are adverse effects related to specific drugs and unrelated to inhibition of PGs.

TABLE 41-2. ADVERSE EFFECTS OF NONSPECIFIC AND COX-2–SPECIFIC NONSTERIODAL ANTI-INFLAMMATORY DRUGS.

ORGAN SYSTEM	NONSPECIFIC NSAIDS	DIFFERENCES WITH COX-2–SPECIFIC NSAIDs
Gastrointestinal	Dyspepsia Gastroduodenal ulceration Bleeding (all levels) Colitis	Decreased UGI ulceration Decreased bleeding
Renal	Hypertension Edema Acute renal failure Interstitial nephritis Papillary necrosis	
Hepatic	Elevated transaminases Rare severe hepatic reactions	
Asthma	Exacerbation of AERD	No cross-reactivity in AERD
Allergic reactions	Hypersensitivity reactions	Celecoxib contraindicated in patients with sulfonamide allergies
Cardiovascular	Platelet dysfunction	Arterial thrombosis in high-risk patients with high-dose, long-acting, highly specific inhibitors (rofecoxib)
Central nervous system	Dizziness Somnolence Cognitive dysfunction Aseptic meningitis	

ABBREVIATIONS: AERD, aspirin-exacerbated respiratory disease; NSAIDs, nonsteriodal anti-inflammatory drugs; UGI, upper gastrointestinal tract.

Gastrointestinal

Injury to the upper gastrointestinal tract in the form of ulcers and their complications are the most important toxicity associated with aspirin and nonspecific NSAIDs. Millions of individuals regularly use aspirin and NSAIDs, magnifying the overall importance of NSAID gastroenteropathy from a public health standpoint. It was the expectation of reduced gastroduodenal injury that drove development of specific COX-2 inhibitors. The risk profile for gastric injury is reduced for those agents with the lowest potential for COX-1 inhibition.

Prospective data derived from Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) showed that 13 of every 1000 patients with RA that take nonspecific NSAIDs for 1 year have a serious gastrointestinal complication (16). Although the rate of NSAID-related serious gastrointestinal complications has decreased, in part due to use of protective strategies and COX-2–specific NSAIDs, no protective strategy has eliminated the risk of NSAID use. Unfortunately, despite a number of strategies available for risk reduction, there is a high level of failure to adequately protect patients using NSAIDs. The mortality rate among patients who are hospitalized for NSAID-induced upper gastrointestinal bleeding is 5% to 10%. Bleeding is by far the most common ulcer complication, but obstruction and perforation may also occur (17).

Epidemiological studies have shown that the use of nonspecific NSAIDs increases the risk of ulcer complications by a factor of 4 compared with nonusers, and even low-dose aspirin ($\leq$325 mg) doubles the risk of bleeding ulcers (18). The absolute risk of serious GI complications (bleeding, perforation, or obstruction) in a patient with no other risk factors is about 0.5% per year and the risk in RA patients is about 2% to 4% per year (16).

In addition to injury of the gastroduodenal mucosa, NSAID use is associated with symptoms of dyspepsia and damage to other regions of the gastrointestinal tract. At least 10% to 20% of patients taking NSAIDs experience dyspepsia (17). Symptoms or the lack thereof are not good predictors of NSAID-related GI complications because only a minority of patients with serious GI events report antecedent dyspepsia (16). Other adverse GI events include pill esophagitis, small bowel ulceration, small bowel strictures, colonic strictures, diverticular disease, and exacerbation of inflammatory bowel disease (17). Patients admitted to the hospital with large or small bowel perforations or bleeding are twice as likely to be taking NSAIDs. In an autopsy series of over 700 patients, 8% of patients taking NSAIDs or low-dose aspirin compared with 0.6% of those not taking NSAIDs revealed small intestinal ulceration, while 24% of NSAID users had gastroduodenal ulcers (19). COX-2 expression is higher in the colon than in more proximal portions of the GI tract under basal conditions and increases markedly if colonic inflammation is present. COX-2 inhibition or genetic deficiency markedly exacerbates experimental colitis, suggesting that COX-2–derived PGs may be a protective mechanism for mucosal defense (20).

Mucosal damage associated with inhibiting PG synthesis is associated with a decrease in epithelial mucus, secretion of bicarbonate, mucosal blood flow, epithelial proliferation, and mucosal resistance to injury. Impaired mucosal resistance permits injury by endogenous factors (e.g., acid, pepsin, and bile salts) and exogenous factors (e.g., NSAIDs), thereby amplifying bleeding risk by causing new mucosal lesions. Topical mucosal injury is initiated by the acidic properties of aspirin and many other NSAIDs. In addition, topical injury may occur as a result of indirect mechanisms, mediated through the biliary excretion and subsequent duodenogastric reflux of active NSAID metabolites (e.g., sulindac). Inhibition of prostaglandins, however, is the principal mechanism underlying development of gastroduodenal ulceration. This is most graphically illustrated by the fact that enteric coating and parenteral or rectal administration fails to reduce ulcer risk. In addition, platelet dysfunction can increase the risk of bleeding associated with damaged gastrointestinal mucosa (17).

In the normal gastroduodenal mucosa and in platelets, COX-1 is the isoform responsible for PG production. However, inhibition of COX-2 may contribute to risk in situations where damage is present. During injury of the GI tract, as in other tissues, COX-2 is induced. PGs derived from COX-2 would normally exert suppressive effects on inflammatory cells, notably neutrophils, that contribute to damage. These findings are perhaps relevant to the high risk of recurrence (~ 25%) in patients with previous ulcers even when protective strategies are used (21).

Not all patients are at similar risk for NSAID-related GI bleeding. Factors consistently associated with increased risk for developing NSAID-associated gastroduodenal ulcers are shown in Table 41-3 (17). These risk factors can be identified in prospective clinical trials of gastroprotective strategies and risk reduction is higher in those at greatest risk (22). The only way to completely prevent NSAID-associated GI injury is not to use them; however, using the lowest effective dose of an NSAID for the shortest time required may reduce risk. There are several other strategies available to reduce the risks of upper GI complications due to aspirin and NSAID use (Table 41-3).

Several large randomized, controlled clinical trails have been performed to evaluated the occurrence of clinical significant ulcers and ulcer complications in patients treated with specific COX-2 inhibitors compared to nonspecific NSAIDs (23–25). Data from these randomized controlled trials and other studies suggest that drugs that are more specific towards the COX-2

TABLE 41-3. NONSTERIODAL ANTI-INFLAMMATORY DRUG–INDUCED UPPER GASTROINTESTINAL ULCERS.

Established risk factors
Advanced age (linear increase in risk, substantial risk after age 65)
History of complicated or uncomplicated ulcer
Concomitant use of anticoagulants
Concomitant use of glucocorticoids
Serious systemic disorder
Higher dose or multiple NSAIDs (including low-dose aspirin)
Possible risk factors
Cigarette smoking
Alcohol consumption
Concomitant infection with *Helicobacter pylori*
Protective strategies
Proton pump inhibitor
Misoprostol (200 mcg four times daily)
Specific COX-2 inhibitor (unless concomitant aspirin)

ABBREVIATION: NSAIDs, nonsteriodal anti-inflammatory drugs.

isoform are associated with a lower risk of adverse GI events, reducing the risk of ulcers and ulcer complications by about 50%. However, use of concomitant aspirin may reduce the benefit and there is little data that use of COX-2 inhibitors is superior to other gastroprotective strategies (24).

Another strategy proven effective is replacement of PGs with misoprostol, a stable analogue of PGE_1. Misoprostol at a dose of 200 µcg four times daily was shown to reduce serious gastrointestinal complications by 40% [odds ratio (OR) 0.598; 95% confidence interval (CI), 0.36–0.98] in RA patients taking nonspecific NSAIDs. Misoprostol is often poorly tolerated at high doses with the most important side effect being diarrhea. There are endoscopic studies that suggest proton pump inhibitors (PPIs) may be effective in healing of gastroduodenal ulcers and reducing recurrence of gastroduodenal ulcers in patients taking NSAIDs. An epidemiologic study also suggested a 40% risk reduction for NSAID-associated GI bleeding associated with use of antisecretory agents. In patients continuing to use aspirin or NSAIDs after ulcers due to *Helicobacter pylori*, the PPI omeprazole was superior to the eradication of *H. pylori* in preventing recurrent bleeding in patients on NSAIDs (26). In patients taking NSAIDs and with a recent history of ulcer bleeding, the risk of recurrent ulcer bleeding was similar in patients receiving celecoxib (4.9%; 95% CI, 3.1–6.7) and diclofenac plus omeprazole (6.4%; 95% CI, 4.3–8.4). There is no data that use of H_2-blockers or antacids prevents serious GI complications (27).

Renal

Renal PGs are important for salt and water homeostasis and maintaining renal blood flow. Potential adverse effects of NSAIDs on renal function include fluid and electrolyte disturbances, acute deterioration of renal function, interstitial nephritis, and papillary necrosis. The most common effects are hypertension and edema associated with altered solute homeostasis. Acute renal failure is more likely in those patients with decreased effective circulating volume and, in particular, those with congestive heart failure, cirrhosis, and renal insufficiency (Table 41-4). An increased risk for worsening chronic renal failure is seen in patients with preexisting renal disease who regularly use aspirin (28).

Both COX-1 and COX-2 are constitutively expressed in the kidney; however, their distribution is somewhat different (28). Both COX-1 and COX-2 are expressed in the renal vasculature and glomerulus. COX-2 is expressed in the macula densa and is critical for basal and upregulated secretion of renin. In the medulla, COX-1 is expressed primarily in the medullary collecting ducts and COX-2 in the interstitial cells. In knockout mice and mice treated with specific inhibitors, COX-1 and COX-2 exert opposite effects on systemic blood pressure and renal function (29). COX-2 inhibitors reduce renal medullary blood flow, decrease urine flow, and enhance the pressor effect of angiotensin II. In contrast, the pressor effect of angiotensin II is blunted by COX-1 inhibition.

Studies of renal physiology demonstrate that specific COX-2 inhibitors have similar effects on renal function as nonspecific inhibitors. In patients with moderate-to-severe renal insufficiency or other risk factors for acute renal failure, both nonspecific and COX-2–specific NSAIDs should be avoided or used with great caution (28).

Hepatic

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of alanine aminotransferase (ALT) or asparte aminotransferase (AST; approximately three or more times the upper limit of normal) have been

TABLE 41-4. RISK FACTORS FOR RENAL TOXICITY.

High risk
Volume depletion (e.g., dehydration, hemodynamically significant bleed, septic shock)
Severe congestive heart failure
Hepatic cirrhosis
Low-to-moderate risk
Intrinsic renal disease (e.g., diabetic or hypertensive nephropathy, nephritic syndrome)
Induction of anesthesia
Possible risk
Advanced age

reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis, and hepatic failure (some with fatal outcome) have been reported with NSAIDs. Those NSAIDs that appear most likely to be associated with hepatic adverse events are diclofenac and sulindac. Transaminase elevations, which can occur with most NSAIDs, are particularly common with diclofenac. Sulindac is the drug most often associated with cholestasis. In children with viral illnesses, hepatocellular failure and fatty degeneration (Reye's syndrome) is associated with aspirin ingestion (30). After initiating treatment with an NSAID, patients should be evaluated within 8 to 12 weeks for changes in liver function tests.

Asthma and Allergic Reactions

Up to 10% to 20% of the general asthmatic population has hypersensitivity to aspirin and nonspecific NSAIDs, leading to severe exacerbation of asthma and naso-ocular reactions. Formerly termed *aspirin-sensitive asthma*, these patients are now characterized as having *aspirin-exacerbated respiratory disease* (AERD) because they have chronic upper and lower respiratory mucosal inflammation, sinusitis, nasal polyposis, and asthma independent of their hypersensitivity reactions. A number of studies have now been reported that demonstrate the safety of the specific COX-2 inhibitors in patients with AERD. Although these studies were performed as challenge tests rather than long-term placebo-controlled trials, they are convincing (31).

Aspirin and all NSAIDs can cause hypersensitivity reactions, including skin rash (including toxic epidermal necrolysis and Stevens–Johnson syndrome), urticaria/angioedema, cutaneous vascultis, and anaphylactoid or anaphylactic reaction. Celecoxib contains a sulfonamide group and should not be given to patients that report allergy to sulfa-containing drugs (31).

Cardiovascular

Consideration of the cardiovascular effects of COX inhibition accompanied the development and widespread use of specific COX-2 inhibitors. The role of PGs in normal cardiovascular physiology and during cardiovascular injury is quite complex, making delineation of NSAID effects problematic. It is known that vascular PGI_2 production is mediated predominantly by COX-2 (32). PGI_2 is functionally antagonistic to TXA_2 in the vasculature, inhibiting platelet activation and acting as an important mediation of vasodilation. An increased risk for cardiovascular events caused withdrawal of a highly specific, long-acting COX-2–specific NSAID, rofecoxib. Beyond the clearly increased risk of rofecoxib, it remains controversial as to the magnitude of overall risk for nonspecific and COX-2–specific NSAIDs; however, the overall risk is likely to be low (33).

An increased risk of heart failure can be seen in patients taking NSAIDs, particularly in elderly patients with preexisting cardiorenal disease. This is likely related chiefly to renal effects of these agents, but it is important to recognize this relationship and discontinue NSAIDs in patients with congestive heart failure. There is some evidence that celecoxib may be safer than other NSAIDs in this group of patients (34).

Other Adverse Effects

Due to antiplatelet effects, nonselective NSAIDs increase risk of bleeding, particularly in patients on systemic anticoagulation. Non-aspirin salicylates and COX-2–specific NSAIDs are preferred in this situation. Other hematologic effects are uncommon, but neutropenia can be seen, particularly with indomethacin and phenylbutazone which are no longer available for human use.

Neurologic side effects include aseptic meningitis, particularly with ibuprofen and other proprionic acid derivatives and seen most commonly in patients with systemic lupus erythematosus (SLE) for unknown reasons. Psychosis and cognitive dysfunction is most common in elderly patients.

Effects on reproductive function include the possibility of increased infertility because COX-2–derived PGs are required for ovulation and implantation. Although this is likely uncommon, discontinuing NSAIDs in women with infertility problems seems reasonable. NSAIDs result in premature closure of the ductus arteriosis and they should not be used during the third trimester of pregnancy.

DRUG INTERACTIONS

Because NSAIDs are metabolized by hepatic microsomal cytochrome P450-containing mixed-function oxidase system, drug interactions are expected. When starting NSAIDs for chronic use, evaluation of potential drug interactions is essential.

Salicylate and Nonsteriodal Anti-Inflammatory Drug Interactions

Salicylates and NSAIDs compete with one another for protein binding sites and there may be metabolic interactions as well. This competition can result in either increased (e.g., with indomethacin) or decreased (e.g., with ibuprofen, naproxen) NSAID concentrations. It

has also been shown that chronic dosing of certain NSAIDs (e.g., ibuprofen, but not diclofenac or celecoxib) can prevent aspirin from blocking platelet COX-1 and inhibiting the antiplatelet effect of aspirin (14).

Antihypertensives

Nonsteriodal anti-inflammatory drugs reduce the response to diuretics, particularly loop diuretics. This effect is due to inhibition of PG synthesis as opposed to a pharmacokinetic interaction. NSAIDs also inhibit the effectiveness of angiotensin-converting enzyme inhibitors, perhaps due to increased sodium retention (28).

Anticoagulants

Clinically significant increases in prothrombin times can be seen in patients taking virtually any NSAID with warfarin. This can occur either due to protein binding displacement or due to altered metabolism of warfarin and prothrombin. Coagulation time should be monitored more closely than usual in patients starting NSAIDs.

Methotrexate

Aspirin reduces clearance of methotrexate and this effect is shared by some other NSAIDs (35). Celecoxib did not alter methotrexate pharmacokinetics in patients with rheumatoid arthritis (36).

SUMMARY AND CONCLUSIONS

Nonsteriodal anti-inflammatory drugs are an important part of the therapeutic armamentarium in patients with rheumatic diseases, but as with all drugs their benefit/risk ratio should be evaluated carefully. NSAIDs are effective anti-inflammatory and analgesic agents that allow many patients to achieve improved health-related quality of life. These very important beneficial effects should be weighted against the potential for adverse effects in an individual patient. It is of particular importance to evaluate risk in the elderly, those with multiple concomitant illnesses, and patients with multiple coprescriptions. In general, caution should be used in these patients and careful attention should be paid to using the lowest dose, shortest acting NSAIDs with care; to discontinuing these medications when not needed (e.g., use on an as-needed basis); using appropriate protective strategies for those with risk factors for GI toxicity is essential. In those at particular risk, acetaminophen and non-aspirin salicylates may provide viable alternatives. Although not currently available, strategies for reducing proinflammatory PGs by inhibiting other biosynthetic enzymes or PG receptors may prove fruitful.

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