Selecting Nonsteroidal Anti-Inflammatory Drugs: Pharmacologic And Clinical Considerations

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Abstract: An increasing number of nonsteroidal anti-inflammatory drugs (NSAIDs) are available to treat a variety of conditions. There exist little comparative data examining efficacy for all NSAIDs for a particular illness. The major factors governing selection of these agents relate to the patient's condition and the drug's characteristics. Once efficacy has been established, selection of an NSAID is then determined by side-effect profile, potential for drug interactions, dosing frequency, and cost. This review presents a listing of commercially available NSAIDs, cost comparisons for average daily doses of NSAIDs, and the conditions and drug characteristics that might influence the choice of an NSAID. (J Am Bd Fam Pract 1989; 2:257-71.)

Initially, nonsteroidal anti-inflammatory drugs (NSAIDs) were developed to provide aspirin alternatives that would have fewer side effects. Phenylbutazone was first released in 1949, followed by oxyphenbutazone,[1] but their use has been limited by associated blood dyscrasias. In 1963, indomethacin was introduced and represented an improvement in the side-effect profile of NSAIDs.[1]

Today there are more than a dozen non-aspirin NSAIDs available in the United States (Table 1), and approximately 70 million prescriptions are dispensed annually. Consumers spend nearly $1 billion annually for NSAIDs; hence, manufacturers continue to introduce new agents to the market.[2] Despite the increasing number of NSAIDs available, there are few data comparing the old and new agents for efficacy and safety, and there are few guidelines governing choices of NSAIDs for particular patients. For example, carprofen and diclofenac sodium have recently been approved in the United States, but no particular niche has yet evolved for them.

Despite claims of superiority, few NSAIDs consistently show greater efficacy than the others. When evaluating these claims, it is important to note the dosage used, because the "less effective" drug may have been prescribed only in analgesic doses, not in higher, anti-inflammatory amounts required for valid comparisons. Presently, the issue of potency is a minimal consideration when selecting therapy, as dosage recommendations accommodate this factor.

NSAIDs differ in potency, duration of action, side-effect profile, potential for drug interactions, and cost. There exists considerable variability in clinical response to the same agent by different patients. Although each NSAID must fulfill criteria of excellent potency, efficacy, and apparent safety during clinical trials, some agents, such as benoxaprofen, zomepirac, and suprofen, have been withdrawn from the market, because of the later discovery of side effects.

This review summarizes the distinguishing features of the various NSAIDs and offers guidelines for selecting them based on pharmacologic and clinical considerations.

Pharmacology
Mechanism of Action
The nonsteroidal agents have antipyretic and analgesic properties as well as anti-inflammatory effects. The mechanism of action in decreasing inflammation is not completely defined. Theories have focused on the ability of NSAIDs to inhibit free-oxygen radicals, immune responses, and prostaglandin synthesis.[3] Inhibition of prostaglandin synthetase causes a decrease in the formation of prostaglandins and, consequently, a decrease in prostaglandin-mediated pain and inflammation (Figure 1). Indomethacin is one of the most potent inhibitors, which contributes not only to its efficacy but its side-effect profile as well.

Differences in effectiveness may depend upon the patient's primary disorder, e.g., exces-

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Table 1. Commercially Available Nonsteroidal Anti-Inflammatory Drugs.

Class	Generic Name	Brand Name
Fenamates	Meclofenamate	Meclomen
	Mefenamic acid	Ponstel
Indoles	Indomethacin	Indocin
	Sulindac	Clinoril
	Tolmetin	Tolectin
Oxicams	Piroxicam	Feldene
Propionic acids	Fenoprofen	Nalfon
	Ibuprofen	Motrin, Rufen, etc.
	Ketoprofon	Orudis
	Naproxen	Naprosyn
	Naproxen sodium	Anaprox
	Carprofen	Rimadyl
Pyrazolone	Phenylbutazone	Butazolidin
Phenylacetic acid	Diclofenac	Voltaren

sive prostaglandin production in dysmenorrhea, or immune injury in systemic lupus erythematosis (SLE).[4,5] Not all NSAIDs are alike in their immunomodulating properties. Indomethacin is associated with a decrease in the production of rheumatoid factor[6]; ibuprofen inhibits monocyte chemotaxis; but indomethacin, naproxen, and salicylates do not.[6] The extent to which these observations may serve as a rationale for selecting one NSAID over another is not known.
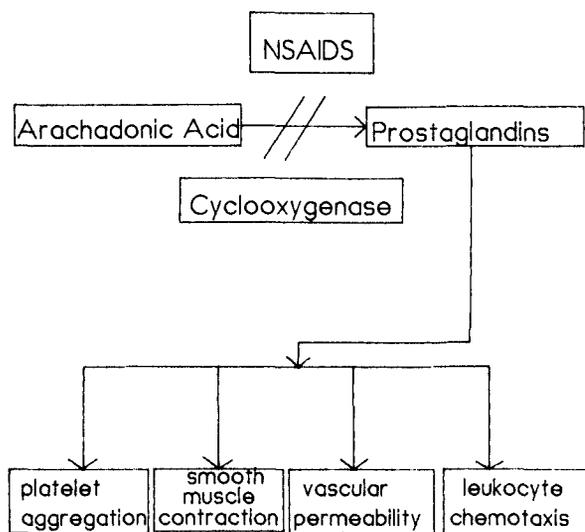

Figure 1. Proposed site of action of nonsteroidal anti-inflammatory drugs (NSAIDs).

Side Effects
Gastrointestinal

All NSAIDs are organic acids, and they are caustic, resulting in gastrointestinal side effects in 15–25 percent of patients.[6] They produce gastrointestinal irritation by affecting the mucosal barrier and by prostaglandin inhibition.[7] Consequent to the latter, gastric mucus and bicarbonate production are inhibited, and a decrease in submucosal blood flow occurs.[7-9] Ulceration may result but, despite continued NSAID therapy, also may heal without having been recognized.[7]

Another potential consequence of NSAID-induced prostaglandin inhibition is reactivation of quiescent inflammatory bowel disease.[10-12] A decrease of prostaglandins in the colonic mucosa leads to relapse in some patients with ulcerative colitis[11]; therefore, the use of NSAIDs in patients with ulcerative colitis or Crohn disease should be undertaken with caution, if at all.

A comparative trial of *all* the NSAIDs for gastrointestinal tolerability is lacking; however, a recent report by Carson, et al. included the majority of NSAIDs commercially available.[13] They found sulindac to be associated with the highest rate of upper gastrointestinal tract bleeding. It was the only drug whose toxicity rate was significantly different from ibuprofen.[13] However, sulindac was administered in an average daily dose that was closest to the maximum recommended, in contrast to other NSAIDs, which were administered in lower relative doses. Because sulindac is a prodrug (not active until absorbed and metabolized by the liver to its active form, sulindac sulfide), it was believed at first to be of low ulcerogenic potential and was preferred in patients prone to, or unable to tolerate, gastrointestinal side effects. The study, however, by Carson, et al. suggests otherwise. Nonacetylated salicylates, such as choline magnesium trisalicylate (Trilisate™) or salsalate (Disalcid™) may be used as alternatives to other NSAIDs, because they are associated with a low rate of gastrointestinal upset.[14] Seventy-five percent of patients not able to tolerate indomethacin will be able to take tolmetin sodium.[15] An analgesic dose of enteric-coated aspirin (or ibuprofen 1200 mg/day) causes little or no mucosal damage.[16] Buffering, although it enhances the rate of dissolution, does not appreciably reduce mucosal damage.[9] Meclofenamate sodium causes diarrhea in 10–35 per-

cent of patients,[17] and its use should not extend beyond 1 week to minimize gastrointestinal irritation. Available studies suggest that when NSAIDs are used in comparable doses, there are minimal differences in gastrointestinal symptoms. Additional controlled studies are needed to determine whether significant differences exist among NSAIDs in producing gastrointestinal injury.

Concurrent therapy to minimize gastrointestinal effects associated with NSAIDs has been investigated. In patients who have gastric distress due to NSAID therapy, antacids may alleviate some symptoms, but because they do not alter the NSAID-induced effects on the gastric mucosal barrier, complete relief will not be afforded.

The use of histamine receptor type 2 (H_2) antagonists also has been studied as a means of decreasing NSAID-associated gastrointestinal upset,[18] but the results are variable. In a double-blind comparison, cimetidine (200 mg) protected the gastric mucosa from the hemorrhagic effects of a single 1300 mg dose of aspirin.[19] Ranitidine hydrochloride is also effective in protecting the gastric mucosa in studies of aspirin-induced injury of 3–30 days duration.[20] In a study of 24 patients, ranitidine (300 mg/day) reduced mucosal damage from aspirin (650 mg orally 4 times a day).[21] Additionally, ranitidine (300 mg) retained its anti-ulcer efficacy in 15 patients with gastric ulcer and 30 patients with duodenal ulcer who were taking carprofen (300 mg/day).[22] In other studies, however, cimetidine therapy did not improve the rate of healing of NSAID-induced gastric irritation better than the placebo.[7,13] In an endoscopic study of 104 patients who used NSAIDs, 56 percent (22/43) receiving cimetidine (300 mg 4 times a day) and 52 percent (22/42) receiving the placebo showed worsening of endoscopic lesions over an 8-week period.[23] In another study, no statistical difference between cimetidine and the placebo was found in the healing ratios in patients with gastroscopically proved peptic ulcers who were maintained on NSAID therapy.[7] Studies have yet to be published about the efficacy, if any, of famotidine and nizatidine when given concurrently with NSAIDs. Because H_2 antagonist therapy is not uniformly effective, alternative therapy should be sought.

Sucralfate, a polysaccharide, forms a barrier to acid by forming a complex with proteinaceous exudate within gastric mucosa.[24] When adminis-

tered orally (1 g 4 times a day), sucralfate was more effective than the placebo in relieving gastrointestinal symptoms and gastric lesions in patients receiving NSAIDs.[25] This effect occurred without impairing absorption or bioavailability of the drug.[26] Improvement was better in patients receiving long half-life NSAIDs, such as piroxicam, diflunisal, naproxen, and sulindac, than in those treated with short-acting agents. When administered for protective effects against aspirin-associated gastrointestinal injury, sucralfate's effects were negated by preadministration of indomethacin.[27] This suggests that, in order to be effective, sucralfate must be prescribed when NSAID therapy is begun. The effectiveness and cost of this approach need to be explored further.

The use of exogenous prostaglandins to protect the gastrointestinal mucosa from NSAID-mediated injury holds promise. Misoprostol, a synthetic analogue of prostaglandin E^1 protected against injurious effects of naproxen and aspirin.[28-30] In an endoscopic study of 140 men, misoprostol (200 µg) protected 50–70 percent of those exposed to 1300 mg aspirin as a single dose versus 20 percent in the placebo group.[29] Misoprostol also significantly decreased fecal blood loss in 41 patients enrolled in a placebo-controlled study who received aspirin (975 mg 4 times a day) for at least 2 weeks.[31] Nearly 60 percent (11/19) of the patients treated with misoprostol had at least a 50 percent reduction in blood loss, whereas only 1 of 22 patients receiving the placebo experienced such a reduction ($P = 0.003$).[30] In 32 patients treated with naproxen (500 mg twice daily) concurrently with either misoprostol (200 µg) or the placebo, the endoscopic score was 1.24 ± 0.09 with the placebo and 0.2 ± 0.07 with misoprostol ($P < 0.001$).[31] Enthusiasm for the use of misoprostol, however, needs to be tempered, given the recent finding that misoprostol reduced the steady-state plasma levels of indomethacin 20 to 60 percent by days 2 to 6 when administered concurrently.[32] Thus, misoprostol holds considerable promise for protecting the gastrointestinal mucosa from NSAID effects, but more study is needed.

Hematologic
NSAIDs inhibit platelet aggregation in varying degrees and prolong the bleeding time. This is important both to patients planning elective surgery and those who develop gastric ulceration

and bleeding. Two factors determine the time required for bleeding to become normal following cessation of NSAID use: (1) half-life of the NSAID, and (2) the nature of the binding to cyclo-oxygenase. Aspirin *irreversibly* binds to cyclo-oxygenase; thus, new platelet production, which requires 7–12 days, will be required before the bleeding time returns to normal. For NSAIDs *reversibly* binding to cyclo-oxygenase, the half-life of the agent is the main determinant, because antiplatelet effects last only as long as there is an effective drug concentration.[32,33] For example, piroxicam has a half-life of approximately 50 hours, and five half-lives are required for it to decline to negligible levels after discontinuation. Approximately 250 hours would be required before platelet effects are reversed.

Sulindac and ibuprofen have only transient effects on platelet function. In some patients, however, up to 24 hours is required for the bleeding time to return to normal following exposure to ibuprofen.[33] Nonacetylated salicylates, which have a negligible effect on platelet function, are an alternative to NSAIDs for patients in whom platelet dysfunction must be avoided. Table 2 lists the time required for platelet function to become normal following use of various NSAIDs.

Renal

NSAIDs can affect the kidney adversely, producing either nephrotic syndrome, acute interstitial nephritis, or tubular necrosis. Acute interstitial nephritis can occur with or without proteinuria. Fenoprofen is reportedly the NSAID with the greatest nephrotoxicity, accounting for 50 percent of the reports of nephrotic syndrome, 30 percent with acute tubular necrosis, and 28 percent with acute interstitial nephritis.[34]

Episodes of renal insufficiency are estimated at 1 per 1000 or more patient days of therapy for each of the NSAIDs used.[35] The mean duration of NSAID therapy before development of renal insufficiency has been estimated at 4.2 days, while the time to return to baseline renal function after NSAID discontinuation is 5.3 days.[35] The rapidity of onset and resolution of renal insufficiency reflects alterations in renal hemodynamics during NSAID therapy.

NSAIDs, when used by healthy patients, will not produce a significant change in renal function.[36,37] However, healthy persons treated with diuretics or placed on low-sodium diets come to rely upon prostaglandin-mediated vasodilatation of the renal vasculature to maintain a normal glomerular filtration rate (GFR).[38] This phenomenon may occur in any condition that compromises renal perfusion, such as volume depletion (diuretic use, blood loss), heart failure, cirrhosis, or atherosclerotic vascular disease. Prostaglandin inhibition induced by NSAID therapy reverses this compensatory mechanism, resulting in renal vasoconstriction with consequent diminution in GFR. Serum creatinine and urea nitrogen increase and oliguria may result. Serum potassium increases and is often out of proportion to the increase in serum creatinine because of NSAID inhibition of the renin angiotensin system.[39] Patients with systemic lupus erythematosus also depend on the prostaglandins for renal vasodilatation, because they have increased synthesis of the vasoconstrictor, thromboxane A_2.[39,40] This vasoconstricting effect is attenuated, however, by chronic glomerular disease of lupus nephritis.[40] Intrinsic vascular disease, such as long-standing hypertension, diabetes mellitus, or atherosclerosis, may also predispose the patient to dependence upon prostaglandin-mediated renal vasodilatation.[41]

All NSAIDs that inhibit renal cyclo-oxygenase will suppress prostaglandin-mediated vasodilatation and result in adverse renal hemodynamics. When used at full anti-inflammatory doses, NSAIDs reduce urinary prostaglandin excretion

Table 2. Time Required for Return of Normal Platelet Function Following Cessation of NSAIDs.

Drug	Time Required for Return to Normal Platelet Function
Piroxicam	2 weeks
Aspirin	7–12 days
Tolmetin	3 days
Ibuprofen	24 hours
Indomethacin (150 mg)	18–32 hours
Indomethacin (35.5 mg)	10–12 hours
Sulindac	No appreciable effect
Nonacetylated salicylates	No appreciable effect

by at least 50 percent, with a maximal reduction of 60–80 percent.[40] The exception to this NSAID effect is sulindac. Renal oxidative enzymes apparently metabolize sulindac sulfide to the inactive prodrug sulindac sulfoxide as well as to the inactive metabolite sulindac sulfone. The renal cortical sites of cyclo-oxygenase activity are thereby protected.[42] Indomethacin reduces renal synthesis of prostaglandins, as measured by urinary prostaglandin excretion, by more than 50 percent, whereas sulindac spares renal prostaglandin synthesis.[43-45] Consequently, indomethacin causes a tenfold greater frequency of renal insufficiency than does sulindac.[41]

In view of other reports of compromised renal function associated with sulindac, its renal-sparing effect is questioned. In patients with chronic renal failure, sulindac decreased urinary prostaglandin E_2 excretion by 47 percent.[46] Moreover, sulindac is not exempt from inducing immune-mediated renal diseases.[35] While sulindac appears to be the least offensive NSAID in patients with potential or established renal insufficiency, close monitoring is required regardless of which NSAID is prescribed.

Monitoring should focus on patients at increased risk. Risk factors include age greater than 60 years, diuretic use, gout, and atherosclerotic cardiovascular disease.[41] Other conditions, cited above, that compromise renal hemodynamics would also predispose the patient to NSAID-induced renal insufficiency. A rapid rise in blood urea nitrogen (BUN), serum creatinine, and a transient increase in serum potassium or gain in body weight despite diuretic therapy may indicate evolving NSAID-associated nephropathy, and NSAID therapy should be discontinued.[41] Renal recovery may occur as early as 8–24 hours.[41]

All NSAIDs are excreted by the kidneys. Indomethacin and sulindac also undergo enterohepatic recirculation.[47] The extent to which the NSAIDs accumulate once renal insufficiency occurs or to what extent there is additional compromise of renal function has not been determined. It has been shown that end-stage renal failure impairs the reduction of sulindac to the active sulfide, while oxidation to the inactive sulfone remains intact.[48]

Hepatic

Before assigning adverse hepatic effects to NSAIDs, it is important to exclude other causes. The conditions for which the NSAID is prescribed may themselves be associated with liver involvement. Twenty-five to 50 percent of patients with rheumatoid arthritis not receiving drug therapy have elevated serum alkaline phosphatase.[49-51] Of patients with SLE, 25 percent may have jaundice, and 21 percent have twofold elevations of liver function tests at some time in the course of their illness.[52] These effects may occur independently of NSAID exposure.

Although liver toxicity is rare, it occurs to some extent with nearly all NSAIDs.[53] Benoxaprofen, a member of the propionic acid family was withdrawn from the market worldwide in 1982 after 60 fatalities were reported, many of which involved hepatotoxicity.[54] NSAIDs from the pyrazolone, indole, and propionic acid classes (Table 1) are associated with the greatest number of reports of adverse hepatic reactions.[53] Generally, fewer than 5 percent of the adverse drug reactions associated with currently available propionic acids are hepatic in nature.[53]

Hepatotoxicity, well recognized from phenylbutazone and oxyphenbutazone, is evenly distributed between men and women.[1,53] An exact frequency of hepatotoxicity has not been ascribed to sulindac, and fewer than 5 percent of all adverse reactions associated with indomethacin are hepatic in nature.[53,55] No hepatotoxicity is ascribed to tolmetin to date.[53]

Liver function tests (LFTs) may allow early detection of evolving hepatic injury due to NSAID therapy. It has been suggested that testing of alanine aminotransferase (ALT, SGPT) should be conducted every 6 weeks for patients taking sulindac or phenylbutazone,[53] but this recommendation is difficult to defend because prospective toxicity data are lacking. For agents with a lesser risk of hepatotoxicity (i.e., tolmetin, naproxen, ibuprofen, and the fenamates), testing should be conducted every 6 weeks during the first 3 months of therapy.[53] Thereafter, testing every 2–3 months, in the absence of elevated values, is recommended.[53] If an abnormality is detected but subsides or does not progress, therapy can be continued, although monthly evaluation is then recommended. If a test value exceeds 3 times the upper limit of normal, or if symptoms of liver disease develop, the NSAID should be discontinued.[53] For patients with preexisting

liver disease and elevated LFTs, therapy with an NSAID may be initiated if the LFT elevation is less than twice the upper limit of normal. Frequent monitoring (weekly or biweekly during the first month) should be initiated. If the abnormalities remain stable or resolve, therapy may be continued using the standard monitoring schedule. If the LFTs worsen, NSAID therapy should be discontinued. If the LFTs return to baseline, initiating NSAID therapy again with a drug from another class may be considered. Piroxicam is a member of the oxicam family that appears to be the least offensive to the liver and may be the preferred agent for patients who are predisposed to hepatotoxicity. Fenamates are also associated with a low frequency of liver toxicity. Members of the pyrazolone, indole, and propionic classes should be avoided if possible. Large-scale retrospective or prospective studies evaluating relative hepatotoxicities of the NSAIDs are needed.

Central Nervous System

All NSAIDs have the potential to produce adverse effects on the central nervous system. Commonly encountered are somnolence, dizziness, tremor, confusion, depression, disorientation, insomnia, and headache.[1] Headaches are the result of NSAID-induced cerebral vasoconstriction; they occur in greatest frequency with indomethacin and are dose related. When the total dose exceeds 100 mg/day, 50 percent of patients will experience headache.[56] Although sulindac is structurally similar to indomethacin, it has far fewer central nervous system side effects.[15] Tolmetin, a member of the indole class as well, also has fewer CNS side effects.[57] Ibuprofen and naproxen are rarely associated with headache.

Aseptic meningitis, an uncommon complication, is associated with tolmetin, sulindac, and ibuprofen.[58-60] Most cases of ibuprofen-associated aseptic meningitis are in patients with SLE.[58] Progression from onset of headache to meningitis-like symptoms may occur within 48 hours.[58] A hypersensitivity mechanism has been proposed as the causative factor.

Pseudotumor cerebri may develop with NSAID-use in patients with the Bartter syndrome.[61,62] Bilateral abducens palsy and papilledema were observed in a 10-year-old girl who received indomethacin, 75 mg/day.[61] A 7-year-old patient, also with the Bartter syndrome, re-

Indomethicin>Aspirin>Ketoprofen

Naproxen   Ibuprofen

Diclofenac

Figure 2. Patient ranking of analgesic properties of NSAIDs.

ceived ketoprofen 20 mg/kg/day and developed headache, vomiting, bilateral abducens palsy, and papilledema.[62] In both cases, pseudotumor cerebri was attributed to water and sodium retention caused by the NSAID. Both cases resolved 3-4 weeks after discontinuation of the drug.

Uses of NSAIDs

NSAIDs have found greater use for specific conditions. It is doubtful, however, that this reflects a true difference in efficacy. In certain conditions, a nonsteroidal agent is avoided because of interplay between adverse drug effects and the condition itself. The potential for interactions with the NSAID and drugs used to treat a particular disease precludes the use of certain agents. The following discussion presents the rationale for these choices.

Rheumatoid Arthritis

Few objective comparisons have been reported to help select NSAIDs for patients with rheumatoid arthritis. When interpreting available studies, close attention should be paid to study design and assessment. Finding the right drug for a particular patient is often a matter of trial and error, balancing efficacy with side effects. Each drug should be given a trial for a minimum of 2 weeks, preferably 6 weeks, before selecting another NSAID.[63]

In the United States, no study exists that compares objectively all NSAIDs used to treat rheumatoid arthritis. One study, conducted in Finland in 1984, of patients with rheumatoid arthritis ranked various NSAIDs in terms of subjective pain relief, as opposed to anti-inflammatory effects, which usually require higher doses. Figure 2 lists the results of that ranking.[64] The study had a small number of patients, used subjective analysis, and must be viewed cautiously. The results cannot be extrapolated to other conditions such as osteoarthritis.

In a second study, aspirin, indomethacin, naproxen, fenoprofen, ibuprofen, and tolmetin were

equally effective in the treatment of rheumatoid arthritis.[65] Efficacy was also comparable between naproxen (250 mg twice daily), naproxen (500 mg at bedtime), and indomethacin (25 mg 4 times a day).[66] Naproxen was, however, better tolerated than indomethacin.

Ketoprofen, 200 mg/day, was compared in a third study with ibuprofen, 1200 mg/day, in patients with rheumatoid arthritis.[67] The authors concluded that ketoprofen is significantly better than ibuprofen for pain on pressure and movement, night pain, pain at walking, and the inflammation index. While the dose used for ibuprofen had analgesic effects, it was not optimal for countering inflammation. Thus, these results must also be interpreted with caution.

Osteoarthritis

Indomethacin is purported to provide the greatest relief for osteoarthritis of the hip,[68] with other osteoarthritic joints treated with indomethacin not as responsive.[68] Studies comparing indomethacin with naproxen (250 mg twice daily), isoxicam (200 mg/day*), and ketoprofen (25 mg 4 times a day), however, found these medications to be equal in efficacy, but the latter three had fewer side effects than indomethacin.[69-71] Again, selection should be based on what is effective for the individual patient and the side-effect profile of the NSAID.

Ankylosing Spondylitis

Indomethacin is the standard reference drug in NSAID trials for ankylosing spondylitis and is associated with 90 percent efficacy.[72] Diclofenac and tolmetin are equally efficacious with fewer side effects.[72-75] The slow release formulation of indomethacin, however, maintains effectiveness while decreasing side effects.[76]

To date, only one trial has compared a group of NSAIDs for the treatment of ankylosing spondylitis. Indomethacin, naproxen, and fenoprofen are superior to aspirin, ibuprofen, and tolmetin.[65] The determinants of these differences are unknown, but the results may be helpful when selecting a drug.

Gout

Most NSAIDs have the same degree of effectiveness in treating symptoms of gout with good-to-

*Investigational in the United States.

excellent responses encountered in 75 to 90 percent of patients.[77] High doses are usually given for the first 48 hours of therapy, followed by reduction to a maintenance level of approximately half the initial dose.[77] For acute gout, naproxen is usually given in a loading dose (750 mg) followed by 250 mg every 8 hours until the attack subsides. Sloan[78] reported that phenylbutazone and indomethacin are the superior NSAIDs for acute gout and for the management of chronic gouty arthropathy. Phenylbutazone is given initially (400–600 mg/day) and then tapered over the following 7 days.[78] Its use is limited by its associated blood dyscrasias. Indomethacin is prescribed for gout (100–200 mg/day) using doses in the upper end of the range during the first 24 hours.[78] A trial comparing all of the NSAIDs for use in acute gout and gouty arthritis is lacking.

Analgesia

NSAIDs are frequently prescribed for nonarthritic musculoskeletal pain syndromes, dental pain, or following mild trauma. In these instances, agents such as naproxen or ibuprofen should be considered because of their perceived greater analgesic properties (Figure 2) and short half-life.

Dysmenorrhea

Not all NSAIDs are marketed for dysmenorrhea, but by virtue of their ability to inhibit prostaglandin synthesis, all possess a pharmacologic basis for efficacy. NSAIDs are associated with a response rate of 84 percent in patients with dysmenorrhea.[79] Comparative studies do not show one agent to be superior to another.[5] Selection should be based on the side-effect profile and number of doses per day. Naproxen and naproxen sodium are widely accepted due to their efficacy and enhanced compliance because of twice daily doses.[5,80-83] Therapy may be started 1–2 days before onset and continued through menses,[5] or alternatively, one may wait until the first symptom of dysmenorrhea to begin NSAID therapy.[81]

Headache Syndromes

Naproxen and aspirin are preferred for the treatment of muscle contraction headache, whereas indomethacin should be avoided.[84,85] Indometha-

cin, which is chemically similar to serotonin, can produce severe headache by virtue of its ability to act as a direct vasoconstrictor.[84] Aspirin and naproxen are completely devoid of such actions on cerebral vasculature.[84]

In contrast, indomethacin is the drug of choice for chronic paroxysmal hemicrania and hemicrania continua.[86-90] Chronic paroxysmal hemicrania, characterized by daily headaches with an attack frequency of greater than 15 episodes per 24 hours, is aborted by indomethacin.[90] A response to 25 mg of oral indomethacin may occur within 2 hours after the first dose.[86] Continuous therapy is usually required, because remissions have been reported.[87] Hemicrania continua, which differs from chronic paroxysmal hemicrania in its pain pattern, absence of pupil changes, and other accompanying symptoms, also responds dramatically to indomethacin.[88-90] Comparative trials with other NSAIDs for these rare syndromes have not been performed; hence, indomethacin should be considered the first line of therapy.

Nonsteroidal agents are effective in the prophylaxis of migraine. Naproxen has, thus far, been the most extensively evaluated and decreases both frequency and severity of migraine headaches in controlled prospective trials.[91-94] In two double-blind, placebo-controlled studies enrolling 68 patients, naproxen is superior for reducing duration and intensity of pain, photophobia, lightheadedness, and disability.[92-93] When compared with a placebo–propranolol study in 109 patients, naproxen again is effective for migraines, but due to its gastrointestinal side effects, propranolol is the preferred agent.[91] Thus, naproxen is not the drug of choice for migraine treatment.

Diabetic Neuropathy

The discovery of aldose reductase inhibiting properties of NSAIDs has led to interest in their use to treat peripheral neuropathy associated with diabetes mellitus.[95-97] It has been proposed that inhibition of aldose reductase may facilitate nerve conduction and decrease neuropathic pain. In one study enrolling 18 men outpatients, sulindac (200 mg twice daily) was more effective than ibuprofen (600 mg 4 times a day) for moderate pain.[97] Combined use with investigational aldose reductase inhibitors, sorbinil or tolrenstat, would be of interest for treatment of severe diabetic neuropathy where NSAID therapy alone is ineffective.

Until more comparative data are available regarding NSAID use in diabetic neuropathy, it is not possible to determine which NSAID is most effective for this indication. Sulindac, with its favorable results in diabetic neuropathy, combined with its renal-sparing effects, should be the first NSAID considered. However, the first approach to therapy should be directed at optimizing control of hyperglycemia. Initial treatment with tricyclic antidepressants (e.g., amitriptyline) or phenytoin may be considered because there is greater experience with these agents.

Porphyria

Reports of acute porphyria are associated with ketoprofen, phenylbutazone, and diclofenac.[98] NSAIDs considered safe for use in patients at risk for porphyria include indomethacin, mefenamic acid, ibuprofen, sulindac, fenoprofen, and naproxen.[98] Pseudoporphyria, where the patient presents with skin manifestations of photosensitivity, erythema, and blistering but no biochemical evidence of porphyria, has been reported with naproxen.[99,100]

Drug Interactions

NSAIDs may adversely interact with lithium. Eighty percent of lithium is reabsorbed from glomerular filtrate and is heavily dependent on renal function.[101] With diminished glomerular filtrate rate (GFR), which could be induced by NSAIDs, lithium excretion may be impaired with subsequent increase in blood levels. Additionally, NSAIDs may cause sodium retention with concomitant retention of lithium, which would also result in elevated lithium levels.[102] Both indomethacin and diclofenac are associated with a decrease in lithium clearance.[101-103] Indomethacin decreased lithium excretion by 23 percent with a 40 percent increase in blood levels.[101] Diclofenac increased in blood levels by 20 percent, while ibuprofen was associated with 50 percent increase.[104,105] The effect of ibuprofen, however, on lithium concentration is inconsistent.[103,104] This is in contrast to aspirin, which increased lithium excretion only 6 percent and had no effect on blood levels.[102] Sulindac also had a lithium-sparing effect, causing a transient decrease in blood levels, which returned to baseline without dosage adjustments.[106] If NSAID therapy must be initiated in a patient receiving lithium therapy, sulindac or aspirin should be considered.

NSAIDs may antagonize blood pressure and lower the effects of antihypertensive medications.[107] Antihypertensive effects of propranolol and pindolol were decreased or abolished during a 10-day period by indomethacin.[108] The pressor effect of NSAIDs is primarily related to renal cyclo-oxygenase inhibition and renal retention of sodium.[107-109] Indomethacin, which caused a 78 percent reduction in PGE^2 excretion, was associated with increased blood pressure (11 mmHg systolic and 4 mmHg diastolic) by the end of the first week of therapy. In contrast, sulindac, which did not cause reduction in PGE^2 excretion, produced a fall in blood pressure similar to that seen with patients treated with a placebo.[107] Ibuprofen, in doses as high as 2400 mg/day for up to 7 days in healthy persons had no effect on blood pressure.[110] In a dose of 100 mg/day in hypertensive patients, however, ibuprofen significantly increased blood pressure.[111] It was suggested that a threshold of prostaglandin inhibition must be achieved before the pressor effect is seen. Thus, the pressor effect of the potent PG inhibitor, indomethacin, is readily noted clinically, while sulindac in normal doses exerts minimal, if any, pressor effect. Blood pressure elevation with indomethacin was maximum at day 7 but approached baseline by day 28 despite continued therapy.[107] Apparently, compensatory mechanisms attentuate sustained elevations of blood pressure. Consequently, of the NSAIDs studied, sulindac appears to be the least offensive to the hypertensive patient, but close monitoring of blood pressure is still warranted. If, however, other NSAIDs are used, it is possible that, with continued therapy, the pressor effects will diminish. Additional long-term studies concerning the pressor effects of NSAIDs, and interactions with antihypertensive agents, are needed.

There are reports of increased toxicity when methotrexate is coadministered with NSAIDs.[112] Phenylbutazone, oxyphenbutazone, indomethacin, ketoprofen and naproxen are all implicated. Methotrexate clearance decreased by two-thirds as a result of combination therapy with NSAIDs.[112] Considering the increased use of methotrexate for refractory rheumatoid arthritis, there is greater opportunity for this interaction. Coadministration of NSAIDs with methotrexate warrants extreme caution and close monitoring because the interactions may be fatal.[113]

Cost and Adherence

Once the issues of efficacy, toxicity, and drug interactions are considered, cost and adherence to a regimen should be reviewed. Table 3 lists the average minimum anti-inflammatory dosage and the cost of therapy per month for brand-name NSAIDs. Where available, the cost of the generic medication is also tabulated. There are no data to

Table 3. Monthly Cost Comparisons for Average Daily NSAID Doses.

Generic Name	Brand Name	Average Minimum Anti-Inflammatory Daily Dosage	Cost of Brand-Name Product Per Month*	Cost of Generic Product Per Month*
Ibuprofen	Motrin	400 mg qid	$22.60	$8.25
Naproxen sodium	Anaprox	275 mg bid	$31.02	NA
Tolmetin	Tolectin	200 mg tid	$31.39	NA
Meclofenamate	Meclomen	100 mg bid	$31.81	$26.40
Naproxen	Naprosyn	250 mg bid	$32.03	NA
Ketoprofen	Orudis	75 mg bid	$32.67	NA
Fenoprofen	Nalfon	300 mg tid	$32.85	NA
Indomethacin	Indocin	25 mg tid	$35.67	$6.30
Phenylbutazone	Butzolidin	100 mg tid	$37.48	$6.08
Sulindac	Clinoril	150 mg bid	$41.65	NA
Piroxicam	Feldene	20 mg d	$42.30	NA
Indomethicin; sustained release	Indocin SR	75 mg bid	$57.34	$43.13

*AWP = Average wholesale price based on Redbook Drug Topics 1988. This is the cost to the pharmacy; prices charged to the patient will vary markedly.
NA = Drug not available in generic formulation.

indicate that FDA-approved generic formulations are inferior to brand-name products.

Determinants of adherence to a therapeutic regimen include cost and dosing frequency. Once-daily administration, as with piroxicam, may be more acceptable than ibuprofen, which is administered 4 times daily. Products administered twice daily are well accepted and should be considered for patients who require a simpler regimen.

Allergy

Once a patient shows an allergy to an agent, further use of that drug or other NSAIDs is contraindicated. Methods of oral challenge are available to confirm hypersensitivity.[114]

There is a high degree of "cross-sensitivity" between aspirin and NSAIDs in patients who have symptoms of rhinitis or asthma.[114,115] The degree of sensitivity correlates with the prostaglandin inhibition potency and appears to be a pharmacologic effect rather than an immunologic response.[114] In one study, asthmatic patients who were aspirin sensitive were sensitive to indomethacin, fenoprofen, naproxen, and tolmetin.[114] A single case report showed a similar cross-sensi-

tivity between sulindac and aspirin. Sodium or choline salicylate may be tried in these patients with caution and close monitoring. It is believed that among the salicylates, the reaction is specific for acetylsalicylic acid and not the metabolite (sodium salicylate).[114]

For patients who develop urticaria upon exposure to aspirin, an immunological mechanism is probably involved,[116,117] and all salicylates should be avoided. It is thought that the salicylate radical or its metabolite is responsible for the immunological response.[116] There is no cross-reactivity with the structurally dissimilar NSAIDs, but it is prudent to avoid their use until more definite data are available.

Summary

The NSAIDs, though similar in pharmacology, differ in their side effects, indications for use, potential for drug interactions, and effects upon associated illnesses. The physician should become familiar with the use of a few, selected NSAIDs. Members of the pyrazolone (e.g., phenylbutazone) and fenamate families (e.g., meclofenamate) (Table 1) should rarely be used because of side effects. Selection from the remain-

Table 4. Conditions and Drug Characteristics that Might Influence the Choice of an NSAID.

Considerations	Comments
Gastrointestinal intolerance	Select ibuprofen or perhaps sulindac; when used in comparable doses, NSAIDs differ minimally in GI symptoms
Platelet function	Select sulindac, ibuprofen or nonacetylated salicylates; avoid aspirin
Renal function	Sulindac is the preferred agent but monitor closely in patients with chronic renal insufficiency; avoid indomethacin
Hepatotoxicity	Piroxicam or a fenamate is preferred; avoid members of pyrazolone, indole, or propionic classes
Headache, muscle contraction	Ibuprofen, aspirin, or naproxen are preferred; avoid indomethacin
Headache, chronic paroxysmal or hemicrania continia	Indomethacin is the drug of choice
Rheumatoid arthritis	NSAIDs appear to be equally efficacious; base selection on side-effect profile and patient considerations
Osteoarthritis	NSAIDs appear to be equally efficacious; base selection on side-effect profile and patient considerations
Ankylosing spondylitis	Indomethacin, naproxen, and fenoprofen are the preferred agents
Gout	Comparative data are lacking; indomethacin, phenylbutazone, and naproxen have been used successfully
Analgesia	Naproxen or ibuprofen is preferred
Dysmenorrhea	All NSAIDs possess the pharmacologic basis for efficacy; naproxen is widely used
Diabetic neuropathy	Sulindac may be the preferred NSAID; more study in this area is needed
Porphyria	Preferred agents are ibuprofen, sulindac, naproxen, fenoprofen, indomethacin, and mefanamic acid; avoid ketoprofen, phenylbutazone, and diclofenac
Lithium	Aspirin or sulindac is preferred; avoid indomethacin or diclofenac
Antihypertensives	Effectiveness of antihypertensives attenuated by concomittant NSAID therapy during the first month; compensatory mechanisms may alleviate untoward interactions
Methotrexate	Avoid NSAIDs if possible; co-administration may result in methotrexate toxicity

ing classes should be based on adverse effects, potential for drug interactions, cost, and dosing frequency. Efficacy is rarely at issue, as individual variability, rather than pharmacology, is usually the basis for the variance. If one drug does not prove efficacious after 1–3 weeks at the maximally tolerated dose, another agent should be substituted.[1] A favorable response from a member of the same NSAID class is not precluded.[118] There is no proved advantage to using more than one NSAID at a time unless a rapid onset of action is needed.[1] Table 4 presents a synopsis of pertinent conditions and characteristics for choosing NSAIDs.

For patients with gastric intolerance to one NSAID, alternative therapy from another class should be considered. If unsuccessful, therapy with choline magnesium trisalicylate (Trilisate™), salsalate (Discalcid™), or enteric-coated aspirin may prove useful. The addition of sucralfate to the regimen may prove helpful, but cost and efficacy issues have yet to be completely resolved. When adverse effects of NSAIDs on platelets are of concern, sulindac or ibuprofen should be considered, with nonacetylated salicylates as alternatives. If renal function is compromised, avoid NSAIDs, especially fenoprofen if possible; sulindac is perhaps the least offensive agent, but close monitoring should be instituted. Piroxicam is presently the NSAID of choice where potential for hepatotoxicity exists. Fenamates may be considered as alternatives. When central nervous system side effects such as headache occur, aspirin or naproxen may be used. For patients taking lithium, sulindac is preferred, and indomethacin should be avoided. In hypertensive patients, blood pressure control may be diminished, or lost, during the first week of NSAID therapy. Pressor effects may be minimized by prescribing sulindac and avoiding indomethacin. It would be prudent to avoid all NSAIDs in patients taking methotrexate until a particular NSAID has been proved consistently safe. For patients thought to be allergic to NSAIDs, further questioning as to the nature of the reaction (rhinitis and asthma versus urticaria) must be pursued before determining if therapy with another NSAID would be appropriate.

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