Nonsteroidal Anti-inflammatory Drugs: Making the Right Choices

Robert G. Berger, MD

Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most prescribed pharmacologic agents in medicine. The ability of these drugs to decrease inflammation is linked to their inhibitory effect on the synthesis of prostaglandins. This mechanism also results in toxicity that can cause gastrointestinal ulceration and bleeding, renal failure, and worsening of preexisting congestive heart failure. The superiority of one NSAID over another has not been clinically demonstrated in musculoskeletal conditions, nor has the efficacy of NSAIDs in noninflammatory rheumatic conditions been shown to be better than that of simple analgesics, such as acetaminophen. The use of these drugs, particularly in the elderly patient with osteoarthritis, should be carefully considered, and alternative, less toxic therapies should be sought whenever possible.

J Am Acad Orthop Surg 1994;2:255-260

Physicians in the United States have more than 15 nonsteroidal anti-inflammatory drugs (NSAIDs) in their arsenal of pharmacologic weapons against musculoskeletal ailments (Table 1). Which drug is the best for a given disease? Which has the fewest side effects? Should the latest agent be used simply because it is the newest? Why are so many on the market anyway? In this review, I will try to answer these questions and will suggest an approach to the reasonable use of these drugs in rheumatic conditions.

The following fictitious, but common, case-presentation scenarios will serve as a springboard for discussions of the efficacy, toxicity, and pharm a-cologic differences among the many NSAIDs. After reading the history for each scenario, take a minute and jot down the pharmacologic agent you currently might recommend as first therapy. Then, after reading the ens u-ing discussion, decide whether your initial choice still seems appropriate.

Scenario 1

History

A 35-year-old woman presents with a 6-month history of symmetrical hand swelling and pain involving the proximal interphalangeal joints and the metacarpophalangeal joints. She experiences stiffness for 2 hours every morning and has noticed small nodules over her olecranon processes. Her past history is benign, and she has received no therapy for these symptoms. She is a lawyer, and her husband is an orthopaedic surgeon. On physical examination, she is found to have symmetrical synovitis in the hands and small olecranon nodules. Laboratory studies disclose an erythrocyte sedimentation rate of 90 mm/hr and a latex rheumatoid factor test result that is positive at a level of 1:640.

Pharmacologic Considerations

The patient has rheumatoid arthritis, a disease that is both inflammatory and chronic. Use of NSAIDs is indicated as initial therapy to decrease the inflammatory component of the illness and to reduce the pain and stiffness.

Nonsteroidal anti-inflammatory agents are derived from various classes of chemical structures, and most of their actions are linked to the ability to decrease the synthesis of proinflammatory prostaglandins by inhibiting the cyclo-oxygenase pathway of arachidonic acid metabolism. Some NSAIDs (e.g., diclofenac and indomethacin) also can decrease the production of leukotriene inflammatory mediators by inhibition of the lipoxygenase side of the arachidonic pathway as well. This in vitro explanation for the clinical action of the NSAIDs has recently been called into question because of the observation that nonacetylated salicylates (e.g., salicylsalicylic acid), which do not inhibit prostaglandin synthesis, are as effective in rheumatoid arthritis as aspirin.[1] In addition, the clinically effective dosages of NSAIDs usually far exceed the in vitro drug concentrations required for prosta-

Dr. Berger is Associate Professor of Medicine, Division of Rheumatology and Immunology, University of North Carolina School of Medicine, Chapel Hill.

Reprint requests: Dr. Berger, Ambulatory Care Center, CB #7705, Chapel Hill, NC 27514.

Table 1
Dosage Data and Cost of Currently Available NSAIDs

Generic Name	Proprietary Name	Largest Unit Dose	Half-life, hr	Dosing Frequency*	Monthly Cost†
Aspirin	. . .	325 mg	0.25	2 q4h	NA / $10
Diclofenac	Voltaren	75 mg	2	bid	$84 / NA
Diflunisal	Dolobid	500 mg	10	bid	$90 / $81
Etodolac	Lodine	300 mg	6	qid	$134 / NA
Fenoprofen	Nalfon	600 mg	2–3	qid	$129 / $67
Flurbiprofen	Ansaid	100 mg	6	tid	$111 / NA
Ibuprofen	Motrin	800 mg	2	qid	$55 / $29
Indomethacin	Indocin	50 mg	4	tid	$101 / $32
Ketoprofen	Orudis	75 mg	3	tid	$118 / $118
Ketorolac	Toradol	10 mg	5	qid	$178 / NA
Meclofenamate	Meclomen	100 mg	2	tid	$126 / $25
Nabumetone	Relafen	500 mg	20–30	2 qd	$75 / NA
Naproxen	Naprosyn	500 mg	14	bid	$94 / NA
Oxaprozin	Daypro	600 mg	40–50	2 qd	$94 / NA
Piroxicam	Feldene	20 mg	30–86	qd	$96 / $86
Salicylsalicylic acid	Disalcid	750 mg	1	qid	$22 / $22
Sodium salicylate	. . .	650 mg	0.5	q4h	NA / $13
Sulindac	Clinoril	200 mg	8–14	bid	$71 / $71
Tolmetin	Tolectin	400 mg	1–2	tid	$115 / $88

* Dosage required for treatment of inflammation. Abbreviations: bid = twice a day; qd = each day; q4h = every 4 hours; qid = four times a day; tid = three times a day.

† Average wholesale price plus 40% pharmacy markup, expressed as price for proprietary drug / price for generic drug. (In some instances, the prices are the same because of the pricing strategies of the drug manufacturers.) NA = not applicable (because there is either no generic form or no proprietary form of the drug).

glandin inhibition in vitro. These findings suggest that there are alternative pharmacologic effects of the NSAIDs on the mechanism of inflammation. Selected NSAIDs have in vitro effects on neutrophil migration, transmembrane anion transport, and oxidative phosphorylation in mitochondria.

A wealth of animal and in vitro efficacy data exists on each NSAID. Often, NSAIDs are marketed on the basis of the assumption that they achieve high concentrations in synovium, have potent effects on a rat-ear model of inflammation, or inhibit T-cell proliferation. The real question, however, is whether the many controlled trials that have been performed have revealed any clinically significant differences in efficacy among the NSAIDs. Large trials of patients with rheumatoid arthritis (the most studied inflammatory musculoskeletal disease), using standard objective measures of rheumatic disease, such as joint inflammatory scores, grip strength, morning stiffness, and physician-assessment global scores, have not demonstrated the superiority of any one NSAID over another.[2] Some newer NSAIDs, such as nabumetone and etodolac, have not been as rigorously studied in comparison trials in rheumatoid arthritis as the older drugs; therefore, the available efficacy data must be taken with some skepticism. However, all of the NSAIDs on the market have shown superior clinical efficacy in rheumatoid arthritis when compared with placebo. Several reports have shown differences in patient preference among the NSAIDs studied, but no clinically significant objective differences in disease activity have been documented.[3]

Individual patient preferences in rheumatoid arthritis therapy may be influenced by the combination of the chronicity and severity of the disease coupled with patient knowledge that many NSAIDs are available for use in treatment. It would be unusual for an individual patient to have critically reviewed the literature comparing the efficacies of various NSAIDs, yet not surprisingly the patient looks to the newest agent with renewed hope. This becomes a self-perpetuating cycle for the patient, the physician, and the pharmaceutical industry, resulting in more NSAID development, more requests by patients for

the "latest breakthrough," and more prescriptions by physicians. Using simple mathematics, assuming 20 available NSAIDs and a 3-month trial of each, the patient in this scenario could be treated for 5 years with agents that have no real differences in efficacy. This hypothetical treatment could result in progression of joint destruction that might have been prevented by early treatment with other antirheumatic drugs, such as methotrexate. In addition, none of the NSAIDs has been shown to alter the progression of cartilage destruction in rheumatoid arthritis; in fact, NSAIDs may have an inhibitory effect on chondrocyte function, resulting in increased cartilage destruction.[4]

Treatment Recommendations

I would begin this relatively young, otherwise healthy patient with rheumatoid arthritis on a regimen of the highest permissible dose of any of the NSAIDs that have been subjected to well-controlled clinical efficacy trials in rheumatoid arthritis and that have potent prostaglandin inhibitory effects in vitro. This group includes aspirin, indomethacin, ibuprofen, naproxen, and diclofenac. If cost is a major issue, I would use high-dose aspirin or ibuprofen.

Regardless of which agent is chosen, it should be given a full month's trial. If no efficacy is demonstrated, a switch to another NSAID can then be made. In general, however, I have found no clinical benefit in switching from one NSAID to another. I would switch only once for efficacy failure and would add an antirheumatic agent, such as gold or methotrexate, as the next line of therapy.

If gastrointestinal symptoms or other evidence of toxicity develops, I would switch once to another prostaglandin-inhibiting NSAID. If the new agent is not tolerated, I would consider using an enteric-coated (for gastrointestinal tolerability) or nonacetylated salicylate, realizing that anti-inflammatory efficacy would decrease.

Scenario 2

History

A 75-year-old woman presents with a 10-year history of gradually worsening right knee pain that is worse with use and is relieved somewhat by rest. Her past history is remarkable for mild congestive heart failure, which has been controlled with diuretics, and a duodenal ulcer, which was documented endoscopically 10 years ago and successfully treated with histamine H_2-receptor blockers without recurrence. She tried aspirin, which helped relieve the symptoms, but experienced mild dyspepsia and stopped therapy. She is a retired schoolteacher. Physical examination discloses a slight decrease in range of motion of the knee with tenderness in the medial joint line. Plain radiographs of the knee reveal medial compartment narrowing and mild osteophytosis. The erythrocyte sedimentation rate is normal, and the rheumatoid factor test is negative.

Pharmacologic Considerations

This scenario is typical of the elderly patient with moderate symptoms of osteoarthritis. Her functional state has not deteriorated enough and her pain level is not severe enough to warrant joint replacement. Should she receive an NSAID? If so, which one? What are the risks of treatment in this patient?

The data on the efficacy of NSAID therapy in osteoarthritis are almost identical to those in rheumatoid arthritis, although clinical outcome measures in osteoarthritis are even more subjective than those used in rheumatoid arthritis. All NSAIDs studied to date have proved superior to placebo as measured by outcomes that include range of motion, pain scores, walking time, and patient and physician preference. However, these same studies show no major objective differences in efficacy between NSAIDs. Recently, an anti-inflammatory dosage of ibuprofen showed no statistically significant superiority over acetaminophen in the treatment of knee osteoarthritis.[5] This result is not unexpected, since very few patients with osteoarthritis have clinical signs or pathologic evidence of joint inflammation, except for the small subset with inflammatory osteoarthritis.

Although there are no clinical studies comparing a pure analgesic with an NSAID for tendinitis or bursitis, the same result might be expected in treatment of these regional soft-tissue complaints. Other than the rare occurrence of true inflammatory tenosynovitis or bursitis (usually associated with an underlying rheumatic disease), the muscle-tendon unit pain associated with overuse or a direct stretch injury has little or no tissue inflammatory response.

When prescribing for the elderly osteoarthritic patient, one should recall that there has never been a reported death from osteoarthritis. However, significant morbidity and even mortality can result from use of NSAIDs; these complications are often not brought to the attention of the prescribing orthopaedist because the patient ends up in the care of a gastroenterologist, nephrologist, or other specialist. A not uncommon course for the patient in this scenario might be as follows:

History (continued)

The patient's knee pain is much improved after 1 week's administration of an NSAID. However, 2 weeks after beginning the drug she complains of increased ankle swelling, dyspnea, orthopnea, and nausea. Shortly thereafter she presents to the emergency room with hematemesis.

She has clinical evidence of pulmonary edema and laboratory evidence of acute renal failure.

Pharmacologic Considerations (continued)

This elderly patient with preexisting heart disease has suffered acute renal failure, worsening congestive heart failure, and bleeding in the upper gastrointestinal tract. The physiologic explanation for this clinical picture is the inhibition by NSAIDs of the beneficial effects of prostaglandin on renal blood flow, sodium balance, platelet function, and gastric mucosal protection. These deleterious effects, along with specific additional idiosyncratic toxicities, are summarized for the various NSAIDs in Table 2.

In the kidney, prostaglandin I_2 (prostacyclin) and prostaglandin E_2 are potent vasodilators of the efferent and afferent arterioles. These agents, which are synthesized locally in the kidney, mitigate the renal vasoconstrictive effects of angiotensin, vasopressin, and norepinephrine.[6] This intrinsic mechanism of preservation of renal blood flow is responsible for maintaining renal function in the face of hypovolemia. In patients with heart disease, liver disease, or intrinsic renal disease, the kidney may sense a relatively hypovolemic state; the intrinsic prostaglandin mechanism then becomes essential for maintenance of glomerular filtration and renal blood flow. When this mechanism is inhibited by an NSAID, acute renal failure may ensue.

Renal prostaglandin inhibition also causes sodium retention through a renal tubular mechanism; this, along with the decrease in glomerular filtration, results in worsening of existing total body volume overload, which, in this scenario of a patient with compensated congestive heart failure, results in acute pulmonary edema. Nonacetylated salicylates, because of their weak to nonexistent effects on prostaglandin synthesis, do not have deleterious effects on renal blood flow. Sulindac, in doses used in inflammatory arthritis, appears to exhibit preferential sparing of renal prostaglandin effects and may be unique among the currently available NSAIDs,[7] although the renal effects of the newer agents are still being investigated.

The bleeding in the upper gastrointestinal tract in this patient is due to the effects of the NSAID on the gastrointestinal mucosa combined with decreased platelet function resulting from inhibition of thromboxane A (a cyclo-oxygenase–dependent metabolite of arachidonic acid) and the qualitative functional platelet effects of azotemia. The recovery of normal hemostasis is dependent on the reversibility of thromboxane inhibition, which varies with different NSAIDs. The adverse effects of NSAIDs on platelet function must be considered not only in the clinical situation of acute bleeding, but also in planned elective surgical procedures.

The site of bleeding due to NSAID administration is almost always gastrointestinal (usually the stomach or duodenum, but occasionally the small or large intestine). Prostaglandin E_2, beyond its beneficial renal effects, is "gastroprotective"; it blocks parietal cell activation by histamine and also exerts poorly understood direct effects on gastric mucosa to prevent peptic damage.[8] The inhibition of this gastroprotective prostaglandin, along with decreased platelet function, is the proposed mechanism for the increased relative risk of death due to gastrointestinal hemorrhage, which in the elderly population has been estimated at four to five times that in a matched group not taking NSAIDs.[9] Those NSAIDs with weak or no prostaglandin inhibitory effects have little gastrointestinal toxicity (Table 2). Enteric-coated NSAIDs reduce gastric and duodenal ulceration, but this occurs at the expense of an increased risk of small-bowel ulceration.[10] It has been proposed that the newer NSAIDs nabumetone and etodolac are safer because of selective sparing of inhibition of gastric prostaglandin. However, studies comparing the gastric effects of these drugs with those of other NSAIDs in doses producing clinical efficacy in inflammatory rheumatic diseases have yet to be performed.

It has been shown that concomitant administration of misoprostol (a prostaglandin E_1 analogue) decreases the number of small erosive (but usually asymptomatic) lesions seen at endoscopy, but it has yet to be proved that misoprostol is efficacious in preventing death or serious morbidity due to NSAID-induced gastrointestinal bleeding.[11] Misoprostol produces diarrhea in many patients, and this side effect limits compliance. The jury appears still to be out on misoprostol, and I currently do not routinely use it as prophylaxis against NSAID-induced gastrointestinal bleeding.

A less frequent toxicity of NSAIDs that are potent prostaglandin inhibitors is angioedema, urticaria, or asthma in "aspirin-sensitive" patients. These patients commonly will have a past medical history of urticaria due to aspirin and may also have nasal polyps and asthma. This is of particular concern to the surgeon and anesthesiologist because intramuscular ketorolac (Toradol) has become popular as a postoperative nonnarcotic analgesic.

Treatment Recommendations

I believe NSAIDs are contraindicated for this patient and should not be considered as first-line therapy even in otherwise healthy patients with noninflammatory osteoarthritis. I would begin treatment of this patient with 1 gm of acetaminophen every 6 hours. If necessary, I would judiciously substitute acetaminophen with codeine as needed for severe physical activity-related or nocturnal pain. A nonacetylated salicylate could

Table 2
Toxicity Profiles of Currently Available NSAIDs

Generic Name	Proprietary Name	Gastrointestinal Toxicity	Renal Toxicity	Platelet Effects, days*	Other Toxicity†
Aspirin	...	High	Moderate	10	Tinnitus
Diclofenac	Voltaren	Moderate	Moderate	1	Hepatitis
Diflunisal‡	Dolobid	Low	Low	None	...
Etodolac	Lodine	Low§	Moderate	NA	...
Fenoprofen	Nalfon	Moderate	Moderate	1	...
Flurbiprofen	Ansaid	Moderate	Moderate	1	...
Ibuprofen	Motrin	Moderate	Moderate	1	...
Indomethacin	Indocin	High	Moderate	1	Headache
Ketoprofen	Orudis	Moderate	Moderate	2	...
Ketorolac	Toradol	High	Moderate	1	...
Meclofenamate	Meclomen	Moderate	Moderate	1	Diarrhea
Nabumetone	Relafen	Low§	Moderate	NA	Hepatitis
Naproxen	Naprosyn	Moderate	Moderate	4	...
Oxaprozin	Daypro	Moderate	Moderate	NA	...
Piroxicam	Feldene	Moderate	Moderate	14	...
Salicylsalicylic acid#	Disalcid	None	None	None	...
Sodium salicylate#	...	None	None	None	...
Sulindac	Clinoril	Moderate	Low	1	Dermatitis
Tolmetin	Tolectin	Moderate	Moderate	2	...

* Average time to normal platelet function after discontinuation of drug. NA = data not available.
† Other NSAIDs may have similar toxicity, but the effects are more prevalent with these agents.
‡ Weak prostaglandin inhibitor.
§ Simultaneous efficacy comparisons in inflammatory disease not available.
# No prostaglandin inhibition.

be used if acetaminophen is not tolerated or is ineffective in pain control. Sulindac would be an option but should be used with caution.

On occasion, a patient with severe osteoarthritis is not a surgical candidate. In these instances, a long-term narcotic analgesia program can be considered. The analgesia provided must be balanced against the side effects of obstipation and central nervous system depression, but if the patient's case is carefully managed, the toxicity of a narcotic analgesic can be less than that of an NSAID.

Scenario 3

History

A 40-year-old man presents with a 2-day history of severe pain and swelling of the metatarsophalangeal joint in the left great toe. He has had several identical episodes during the past 3 years and has a past medical history of kidney stones. He is unemployed and lacks medical insurance coverage. Physical examination reveals an exquisitely tender, red metatarsophalangeal joint in the great toe. Arthrocentesis shows inflammatory fluid with negatively birefringent, needle-shaped intracellular crystals.

Pharmacologic Considerations

The patient has acute gout, probably the most inflammatory of all rheumatic conditions. Additional factors of importance are that the patient has no job and no medical insurance. This combination of factors dictates the use of an inexpensive, quick-acting NSAID, given for a short period. This choice highlights the importance of considering the differences in onset of action, half-life, and cost of the various NSAIDs. The nonacetylated salicylate NSAIDs would not be appropriate treatment because they lack potent in vitro anti-inflammatory pharmacologic effects.

It is clear from Table 1 that the most inexpensive NSAID with a rapid onset of effect is aspirin. This is an appropriate, cost-effective choice in most inflammatory conditions, but is contraindicated in acute gout because aspirin causes an initial increase in serum uric acid and can worsen the acute attack. Drugs such as piroxicam and nabumetone, which have long half-lives and longer intervals until attainment of

peak levels, are not appropriate for acute self-limited inflammatory musculoskeletal diseases.

It is also apparent from Table 1 that generally the older the agent, the lower the price and the more frequent the availability of a generic equivalent. Aspirin has been available for centuries either as willow bark or in its present tablet form. Indomethacin and ibuprofen are not as inexpensive as aspirin but have been available for close to 30 years. As discussed earlier, the phenomenon of the higher cost and greater popularity of a new NSAID is fueled by the patient's expectation that the most recently publicized NSAID is a breakthrough in the treatment of his or her rheumatic condition. Moreover, the physician faced with such a patient expectation often has to expend a great deal of time and effort to convince the patient that the older, less expensive drug, sometimes available without a prescription, is as effective as the newer agent.

Treatment Recommendations

Indomethacin at a dose of 75 mg three times a day or ibuprofen at a dose of 1,200 mg four times a day is a good choice for this patient with acute gout. Both drugs are rapid-acting anti-inflammatory NSAIDs and are inexpensive. The high doses of NSAID required for gout need be used only for the first 5 days. The dosage can then be tapered over the next 7 days. I reserve oral colchicine for patients with gout and cardiac, renal, or gastrointestinal disease for whom NSAIDs are contraindicated.

Summary

The NSAIDs are potent pharmacologic agents that should not be prescribed indiscriminately for musculoskeletal disease. They are efficacious in inflammatory rheumatic conditions but most likely act principally as analgesics in noninflammatory conditions. The toxicity associated with these drugs should be considered before using them for noninflammatory conditions, such as osteoarthritis. The elderly population, who are most likely to have musculoskeletal complaints, are also at the most risk for NSAID toxicity because of their associated medical conditions. The market for these drugs is perpetuated by patient expectations of pain relief in chronic musculoskeletal disease and resulting physician prescribing behavior. The morbidity and mortality from NSAIDs can be decreased if education of both physicians and patients leads to a change in their attitudes regarding the use of these drugs.

References

1. Multicenter Salsalate / Aspirin Comparison Study Group: Does the acetyl group of aspirin contribute to the antiinflammatory efficacy of salicylic acid in the treatment of rheumatoid arthritis? *J Rheumatol* 1989;16:321-327.
2. Brooks PM, Day RO: Nonsteroidal antiinflammatory drugs: Differences and similarities. *N Engl J Med* 1991;324: 1716-1725.
3. Huskisson EC, Woolf DL, Balme HW, et al: Four new anti-inflammatory drugs: Responses and variations. *BMJ* 1976;1: 1048-1049.
4. Pelletier JP, Martel-Pelletier J: The therapeutic effects of NSAID and corticosteroids in osteoarthritis: To be or not to be. *J Rheumatol* 1989;16:266-269.
5. Bradley JD, Brandt KD, Katz BP, et al: Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. *N Engl J Med* 1991;325: 87-91.
6. Clive DM, Stoff JS: Renal syndromes associated with nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1984; 310:563-572.
7. Ciabattoni G, Cinotti GA, Pierucci A, et al: Effects of sulindac and ibuprofen in patients with chronic glomerular disease: Evidence for the dependence of renal function on prostacyclin. *N Engl J Med* 1984;310:279-283.
8. Soll AH, Weinstein WM, Kurata J, et al: Nonsteroidal anti-inflammatory drugs and peptic ulcer disease. *Ann Intern Med* 1991;114:307-319.
9. Griffin MR, Ray WA, Schaffner W: Nonsteroidal anti-inflammatory drug use and death from peptic ulcer in elderly persons. *Ann Intern Med* 1988;109: 359-363.
10. Lanza FL, Royer GL Jr, Nelson RS: Endoscopic evaluation of the effects of aspirin, buffered aspirin, and enteric-coated aspirin on gastric and duodenal mucosa. *N Engl J Med* 1980;303:136-138.
11. Walt RP: Misoprostol for the treatment of peptic ulcer and antiinflammatory-drug–induced gastroduodenal ulceration. *N Engl J Med* 1992;327:1575-1580.