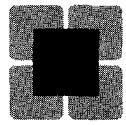

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Nonsteroidal anti-inflammatory drug therapy

Clinical use in a high-risk group — the elderly

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■ Nonsteroidal anti-inflammatory drugs (NSAIDs) play an important role in the management of many patients, including the elderly with both rheumatic and nonrheumatic disorders. Efficacy among the agents is similar and patient response is highly variable. Potential differences in toxicity may be more important than differences in efficacy when selecting an NSAID for a particular patient. Gastrointestinal toxicity is common and prevention and management differ from classic peptic ulcer disease. Recently, NSAID effects on the small bowel have been recognized to be clinically significant. Acute renal insufficiency related to NSAIDs may be avoided to some extent by careful patient selection. Current development of newer NSAIDs is focused on finding drugs offering significant advantages in terms of efficacy or toxicity, particularly the latter.

□ INDEX TERMS: ANTI-INFLAMMATORY AGENTS; RHEUMATISM, DRUG THERAPY □ CLEVE CLIN J MED 1988; 55:419–425

SINCE the introduction of phenylbutazone in the 1950s, the role of nonsteroidal anti-inflammatory drugs (NSAIDs) in clinical medicine has grown dramatically. Currently, at least 16 different NSAIDs are approved for use in the United States (*Table 1*). Many more are available in Europe and many of those are awaiting final FDA approval for use in this country. In 1983, 66.5 million prescriptions for non-salicylate NSAIDs were dispensed, representing 4% of the total prescription market, at a cost of over $1 billion to the consumer.[1]

As the number of available NSAIDs has increased, so have the indications for which they are prescribed. Presently these include a wide variety of rheumatic conditions, both articular and non-articular, as well as dysmenorrhea and, increasingly, analgesia. Since the prevalence of many arthritic conditions increases with increasing age, many patients taking NSAIDs are elderly.

As use of these drugs has expanded, their potential toxicity, particularly in the elderly, has been recognized increasingly. In such patients, polypharmacy (including over-the-counter medications), potential for medication error, and non-compliance magnify the risk of adverse effects.[2]

This article focuses on pharmacology of the NSAIDs as it relates to clinical practice, with an emphasis on use in the elderly.

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CLINICAL PHARMACOLOGY

Despite their apparent diversity, the NSAIDs share many similarities in the clinically important aspects of their pharmacology. In fact, for the clinician, it is useful to view this group of agents as a single class and focus on similarities rather than differences in metabolism. All currently available NSAIDs share analgesic, antipyretic,

TABLE 1
AVAILABLE NSAIDs

Fenamic acids
Meclofenamate (Meclomen)
Mefenamic acid (Ponstel)
Indole acetic acids
Indomethacin (Indocin)
Sulindac (Clinoril)
Tolmetin (Tolectin)
Oxicams
Piroxicam (Feldene)
Phenylalkanoic acids
Carprofen (Rimadyl)
Fenoprofen (Nalfon)
Ibuprofen (Motrin, Rufen)
Ketoprofen (Orudis)
Naproxen (Naprosyn)
Naproxen sodium (Anaprox)
Pyrazoles
Oxyphenbutazone (Oxalid, Tandearil)
Phenylbutazone
Salicylates
Aspirin
Choline magnesium trisalicylate (Trilisate)
Diflunisal (Dolobid)
Magnesium salicylate
Salsalate (Acrylate, Disalcid)

and anti-inflammatory properties comparable to full doses (3.5–5 g) of aspirin.[3] Most are weak organic acids (pKa, 3.5–5) and are well absorbed in the gastrointestinal tract.[4,5] Sulindac undergoes substantial enterohepatic cycling.[6]

Following absorption, most of the NSAIDs are highly protein bound, almost exclusively to albumin. With increased concentration of total drug, saturation of albumin binding sites occurs and free-drug concentration increases disproportionately. O'Brien[5] has suggested that this results in a "built-in safety mechanism" as more rapid renal excretion of free drug occurs, preventing accumulation. Because of the high degree of protein binding by NSAIDs, the potential exists for displacement of other highly protein-bound drugs, such as warfarin, with resultant increased free-drug and anticoagulant effect.[7]

Clearance of NSAIDs is principally via hepatic metabolism with renal excretion of inactive metabolites. For most NSAIDs, only a small percentage of free drug is excreted by the kidney. In the presence of liver disease, potential for accumulation of NSAID is of concern. For example, Juhl et al[8] demonstrated a fourfold increase in the plasma area under the concentration-time curve for sulindac in patients with severe liver disease.

The effects of aging on the pharmacokinetics of NSAIDs are potentially significant. Serum albumin levels fall with increasing age.[9] Likewise, a significant decline in hepatic blood flow of nearly 40%–50% occurs with aging.[10] A similar decline in glomerular filtration rate (GFR) may occur by age 80.[11] As renal excretion of active drug is a relatively minor component of NSAID elimination, this change may not be clinically significant. However, the aggregate effect of these changes is to create the potential for drug accumulation and enhanced risk of toxicity in the elderly patient. McVerry et al[12] compared the pharmacokinetics of naproxen in 13 elderly patients (mean age, 84.2 years) and in nine younger patients (mean age, 53.9 years) and found a significantly higher concentration of free drug in the elderly patients compared to controls, with significant reduction in clearance of naproxen in the elderly group. No excess of side effects was seen in the elderly patients, however. Upton et al[13] noted similar findings in a study comparing healthy elderly men with younger men taking naproxen (375 mg) twice daily. Unbound naproxen was doubled and clearance was decreased approximately 50% in the elderly group. No attempt at assessing the clinical significance of these findings was made. Richardson et al[14] reported clearance of piroxicam following a single oral dose was 33% lower in elderly women than in young women. This difference was reflected in piroxicam half-lives of 61.7 and 449 hours in elderly and young subjects, respectively.

The critical and as yet unanswered question is whether the above findings translate into clinically significant increased risk of toxicity in an elderly population as a result of drug accumulation. In fact, the bulk of current clinical evidence suggests that use of long-half-lived agents such as piroxicam and naproxen in elderly patients in the short and long term is not associated with significant increased serious toxicity. Zizic et al[15] reported a series of 30 patients, all women, with a mean age of 72.7 years, treated with piroxicam for a mean of 8.5 years (range, 5.3 to 11 years). The incidence of adverse events was less than one event per patient per year of exposure, and no significant laboratory evidence of renal, hepatic, or hematologic toxicity was noted. Similarly, in a shorter-term trial, Husby et al[16] compared naproxen and piroxicam in older patients, many of whom had medical problems associated with increasing risk of toxicity. The incidence of serious adverse effects related to either drug was approximately 1%. Sitar et al[17] studied the effect on hemostasis of a single dose of 150 mg of sulindac in young healthy subjects and in older patients with arthritis, and found no justification for

lowering the recommended dose of sulindac for patients older than 65 years. These studies would suggest that although elderly patients may be at greater risk for drug accumulation, particularly of long-lived agents, clinically important serious toxicity is uncommon. Further studies are necessary and should incorporate both pharmacokinetic assessment as well as actual clinical toxicity observed in elderly subjects.

CLINICAL USE

As has been noted by Huskisson,[18] differences in efficacy among the currently available NSAIDs are not clinically significant. Clinical strategy in the use of these agents is based on the recognition that there is considerable individual variation in response to this class of drugs. Scott et al[19] divided 36 patients into four groups; each group received four different NSAIDs. The variation between patients and their response to the NSAIDs was large, but no discernible difference between the drugs themselves was found. The marked variability and unpredictability in patient responses casts doubt on the value of comparative trials of different NSAIDs. Because of the similar efficacy and significant patient variability in terms of response to a particular agent, it is reasonable to try a series of NSAIDs in a single patient, looking for the best response and least toxicity. There is simply no way to predict which NSAID will be most effective for an individual patient.

Since efficacy among the agents is similar and patient response highly variable, other factors become more important in the selection of a particular agent in a given clinical situation. For example, in chronic inflammatory disease necessitating long-term therapy, one might expect improved compliance with long-acting agents requiring once or twice daily administration. Some patients may prefer an agent that is available in liquid form, rather than tablet or capsule. More importantly, potential differences in toxicity should direct choice of an NSAID in certain patient groups. For example, nonacetylated salicylates as weak prostaglandin synthesis inhibitors may be preferable in certain subgroups of patients in whom prostaglandin-mediated renal and gastrointestinal toxicity is a major concern. Similarly, there is some evidence that sulindac is less likely than other NSAIDs to interfere with hypertension control in patients taking beta blockers and diuretics. A recent study compared the effects of sulindac, placebo, piroxicam, and naproxen on hypertension control in 20 patients taking a diuretic and a beta blocker.[20] Blood pressure control was significantly better with sulindac than with a placebo, piroxicam, or naproxen. Furthermore, there is evidence that indomethacin may attenuate the antihypertensive effects of hydralazine and perhaps thiazide diuretics.[21,22] These findings might influence the choice of NSAID in treating the hypertensive patient, rather than any perceived differences in drug efficacy.

Several studies have addressed the possibility of combining an NSAID with aspirin or other salicylates. Willkens and Segre[23] studied 36 patients with rheumatoid arthritis in a crossover trial comparing naproxen (250 mg twice daily) plus a placebo with the same dose of naproxen added to a prior stable salicylate dose (median, 3.25 g/day). Tolerance to the two regimens was comparable and combination therapy was demonstrated to be more effective than aspirin alone. Conversely, a recent study by Furst et al[24] compared groups taking full-dose choline magnesium trisalicylate, full-dose naproxen, full dose of both, and half dose of both, and found no clinically important additive or synergistic effect due to the full-dose combination. Furthermore, the full-dose combination was more toxic than the alternatives.

Unfortunately, the relevance of plasma concentration of NSAID to clinical effect has not been well studied. Brooks and Day[25] have recently reviewed the difficulties in discerning the relationship between plasma concentration and response in patients with arthritis. They concluded that the current practice of administering a series of NSAIDs in an individual patient to discover the preferred drug may be reasonable, and increasing the dose of an NSAID is rational if the response is unsatisfactory and no toxicity is evident.

ADVERSE EFFECTS

Inhibition of prostaglandin synthesis accounts for most adverse effects related to NSAID therapy (*Table 2*). This review focuses on gastrointestinal and renal toxicity, which are the major concerns in the elderly. Another group of potential adverse reactions to NSAIDs is not clearly prostaglandin-related and is more "drug specific" (*Table 3*). These problems are unique to one or a few agents and not the entire NSAID class. In general, the pathophysiology of adverse effects of this type is unclear.

Gastropathy

Gastrointestinal toxicity related to NSAID therapy represents the most common form of adverse effects seen with this class of agents, occurring in approximately 10%–35% of patients.[26] Roth and Bennett[27] have re-

TABLE 2
PROSTAGLANDIN-RELATED ADVERSE EFFECTS RELATED TO NSAID THERAPY

Hematologic	Impaired platelet aggregation
Gastrointestinal	Gastritis, erosions, ulcers
Pulmonary	Bronchospasm
Gynecologic	Delayed/prolonged labor
Renal	Sodium/water retention, hyperkalemia, renal failure

TABLE 3
DRUG-SPECIFIC ADVERSE EFFECTS

Ibuprofen	Toxic amblyopia Aseptic meningitis
Indomethacin	Headache Confusion
Meclofenamate	Diarrhea
Phenylbutazone	Agranulocytosis Aplastic anemia
Suprofen	Flank pain/renal insufficiency
Tolmetin	Pseudoproteinuria

cently introduced the term "NSAID gastropathy" to define the unique range of gastric lesions associated with NSAID therapy, including erythema, diffuse gastritis, erosive gastritis, and frank gastric ulcer crater disease with upper gastrointestinal bleeding. The scope of this problem is suggested in a study of the rate of upper GI tract bleeding in the 30 days following exposure to NSAID therapy, as recently reported by Carson et al[28] in a retrospective analysis of Medicaid patients in Michigan and Minnesota. The incidence of GI bleeding per 1,000 exposed patients ranged from as low as 0.5 with phenylbutazone to as high as 5.0 with sulindac. Significantly, the risk of upper GI tract bleeding was greater with increasing age and male sex. A similar association of increased risk of GI bleeding related to NSAID use with increasing age was noted by Bartle et al.[29] Somerville et al[30] have suggested that the relative risk of GI bleeding in NSAID users over 60 years of age is 2.7 times the risk in age-matched non-users. In a retrospective study, however, evaluating elderly patients hospitalized because of bleeding from the stomach or esophagus, Beard et al[31] noted no significant increase in frequency of hospitalization in NSAID-treated elderly patients compared with non-users of NSAIDs. Clearly, the use of NSAIDs increases the risk of upper GI tract bleeding, perhaps by as much as 50%. It is uncertain whether this increased risk is augmented in older patients.

The ulcer disease associated with NSAID gastropathy appears to differ significantly from classic peptic ulcer disease. Patients with NSAID-induced ulcers are usually older, reflecting the population for whom these drugs are most often prescribed, and the disease is typically gastric (antral, prepyloric) rather than duodenal. Roth and Bennett[27] suggest that these differences stem from significant differences in pathogenesis of the primary lesion. While classic acid peptic disease is, as the name implies, acid mediated, NSAID gastropathy is probably the result of inhibition of prostaglandin E2 synthesis resulting in impaired gastric cytoprotection. PGE2 plays a significant role in repair of gastric mucosa following injury. As Roth and Bennett have pointed out, prostaglandins increase gastric mucus production and augment mucosal blood flow. This cytoprotective effect occurs at levels of prostaglandins that do not inhibit gastric acid secretion.[32]

Based on the above pathophysiologic consideration, prevention and treatment of serious NSAID gastropathy may differ from management of classic peptic ulcer disease. Studies of histamine (H2) blocking agents such as cimetidine and ranitidine in the prevention or treatment of NSAID gastropathy have yielded conflicting results. Davies et al[33] studied 27 patients with ulcer disease, mainly gastric, and found no difference in ulcer healing rate between a placebo and cimetidine. Similarly, Roth et al[34] noted progression of endoscopically defined NSAID gastropathy despite cimetidine treatment. As NSAID gastropathy is likely a result of prostaglandin synthesis inhibition, the use of sucralfate, which has been shown to increase gastric luminal release of prostaglandins, might offer an alternative strategy for prevention.[35] A recent randomized double-blind trial comparing sucralfate therapy with a placebo in 143 symptomatic patients taking NSAIDs and studied endoscopically showed significant reduction in lesion scores in the sucralfate-treated group.[36] At present, appropriate prevention and management of NSAID gastropathy should include a reassessment of the patient's need for a prostaglandin synthesis inhibitor. Nonacetylated salicylates, which are relatively weak inhibitors of prostaglandin synthesis, may be less toxic to the gastrointestinal tract. Co-therapy with sucralfate, as described above, provides some degree of protection. Co-therapy with prostaglandin analogs conceivably might offer even more significant protection, but these agents are as yet unavailable in the United States.

An effect of NSAIDs on the small bowel has only recently been recognized and studied. Cases of acute enterocolitis thought to be related to NSAID therapy have been reported recently.[37,38] Symptoms typically included bloody diarrhea and malaise. Histologic studies, when available, have revealed superficial ulceration and non-specific inflammatory infiltrate. Discontinuation of NSAID therapy resulted in prompt resolution of symptoms. In patients with pre-existing but quiescent inflammatory bowel disease, NSAID ingestion may result in exacerbation of the underlying colitis.[39] Intestinal permeability in patients with rheumatoid arthritis who are taking NSAIDs has been found to be significantly increased.[40] A recent study using labelled leukocytes and red blood cells identified significant intestinal inflammation and corresponding blood loss in patients on NSAID therapy.[41] The same study suggested significant intestinal protein loss as well. In a rheumatoid arthritis patient undergoing chronic NSAID therapy, this "enteropathy" might contribute significantly to the general ill health and anemia often found in such patients. The mechanism may be related to inhibition of prostaglandin synthesis with subsequent impairment of intestinal defense mechanisms.[42]

Nephrotoxicity

The spectrum of renal adverse effects ranges from sodium retention, the most common, to acute renal failure (*Table 4*). This review focuses on acute renal failure, a particular concern in the elderly, a group with frequent coexisting medical problems and medical treatment that may increase the risk of this adverse effect.

Acute renal insufficiency related to NSAIDs is suggested by increasing BUN, creatinine, and serum potassium levels with decreasing urine output and body weight gain within days of beginning therapy. If recognized, the problem is completely reversible, but continued therapy despite deteriorating renal function may lead to irreversible renal failure.[43] The frequency of this particular renal complication of NSAID therapy is unknown and controversial. In view of the millions of people exposed to these agents daily, it has been considered relatively rare in otherwise healthy individuals.[44] However, a recent study reported that in 11 patients who were hospitalized in a rheumatology ward and in whom long-term NSAID therapy was discontinued, improvement in creatinine clearance after three to 28 days occurred in all 11.[45] Furthermore, six of the patients did not have any risk factors other than age for NSAID-induced renal insufficiency. Whatever the incidence, an understanding of the pathophysiology of this complication may allow an attempt at avoidance by careful patient selection.

TABLE 4
RENAL SYNDROMES RELATED TO NSAIDs

Acute renal failure
Papillary necrosis
Interstitial nephritis
Hyperkalemia
Sodium/water retention

Numerous reviews[46–48] have emphasized the importance of intrarenal prostaglandin synthesis in the maintenance of renal blood flow and GFR in individuals with diminished effective intravascular volume and increased vasoconstrictive influences (adrenergic nervous system and renin angiotensin system). Intrarenal prostaglandin synthesis, predominantly of PGE2, modulates these vasoconstrictive influences and maintains adequate glomerular flow. In congestive heart failure, for example, the urinary prostaglandin excretion rate is four to five times higher than normal.[49] This compensatory mechanism probably plays little role in healthy normal individuals. Disruption of intrarenal prostaglandin synthesis by administration of prostaglandin-synthesis-inhibiting NSAIDs can allow nonbalanced renal vasoconstriction, subsequent decrease in GFR, and consequently, development of renal insufficiency. A similar prostaglandin-mediated compensatory mechanism probably operates in individuals with loss of renal mass (i,e., chronic glomerulonephritis).[50]

Identification of individuals dependent on renal prostaglandin synthesis for maintenance of renal function may allow reconsideration of the need for anti-inflammatory therapy with a prostaglandin-synthesis inhibitor and perhaps avoidance of toxicity. Patients with congestive heart failure, chronic renal disease, nephrotic syndrome, and cirrhosis with ascites are at greater risk for depression of renal function by NSAID therapy.[51] Furthermore, additional risk factors may include advanced age, use of diuretics, and evidence of renal vascular disease as inferred from the presence of longstanding hypertension, diabetes, or atherosclerotic cardiovascular disease. Therapy with NSAIDs in such patients needs to be carefully considered and, if initiated, carefully monitored. For example, an elderly patient with several of the above risk factors suffering from subdeltoid bursitis of the shoulder might be better treated by periarticular corticosteroid injection than by exposure to a prostaglandin inhibitor.

In high-risk patients for whom anti-inflammatory therapy is necessary, preferential consideration might be given to the use of a non-acetylated salicylate. As rela-

tively weak inhibitors of prostaglandin synthesis, this class of agents theoretically poses less risk for this adverse effect. However, large clinical studies to support this assumption are not available. The concept that sulindac, a prostaglandin-synthesis-inhibiting NSAID, might differ from other similar agents in effect on renal prostaglandin metabolism was suggested by Ciabattoni et al,[52] who noted no effect by sulindac (400 mg daily) on urinary prostaglandins, renin, or GFR in 10 patients with intrinsic renal disease. However, more recent studies[53,54] comparing the effects of sulindac with indomethacin on renal prostaglandin excretion in sodium-restricted normals, as well as in patients with existing renal disease, have revealed qualitatively similar effects (i.e., reduction in urinary prostaglandin excretion with both agents). Clearly, sulindac has some impact on renal prostaglandin synthesis and thereby potential for reduction in GFR and impairment of renal function.

FUTURE DIRECTIONS

In view of the large number of agents currently available and their striking similarity in terms of efficacy and potential for adverse effects, current development of newer NSAIDs is focused on finding drugs offering significant advantages in terms of efficacy or toxicity, particularly the latter. A sampling of the large number of such agents currently being studied follows.

Carprofen is a propionic acid derivative that has been studied extensively in the United States. The two most obvious clinical advantages of carprofen identified in studies to date include the convenience of a twice-a-day dosage and, more importantly, a relatively low risk of gastrointestinal adverse reactions.[55] This may be related to a lesser effect on gastric mucosal prostaglandin E2 synthesis, at least compared with aspirin or indomethacin.[56] Carprofen may be better tolerated by patients with asthma who are sensitive to other NSAIDs.[57]

Etodolac is an acetic acid derivative distinct from currently available agents. Its effects on radiographic progression of disease has been compared with aspirin in a one-year study of rheumatoid arthritis patients.[58] Of great interest, the progression of radiographic change was significantly less in the etodolac-treated patients. Obviously, further studies are required to confirm this finding, which would be of major significance in anti-inflammatory therapy.

Nabumetone is a prodrug, that is, the liver converts it to active metabolites, which accounts for its anti-inflammatory activity.[59] Nabumetone itself is non-acidic and a poor inhibitor of prostaglandin synthesis. This may account for the lesser endoscopic incidence of gastropathy noted by Roth.[60] Whether there is lesser impact on renal function in high-risk patients requires further study.

CONCLUSION

Future investigation and development of NSAIDs should focus on identifying which mechanisms for a particular agent account for the variability in patient response. A better understanding of important mechanisms of action may allow a rational selection of a particular drug in a given clinical situation, so as to optimize efficacy and reduce risk of toxicity. This is particularly important in the group of patients for whom these agents are most prescribed—the elderly.

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