Clinical implications of NSAID pharmacokinetics: Special populations, special considerations

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are the centerpiece of pharmacologic therapy for most rheumatic disorders and related conditions, and as such are used in great numbers. These drugs are relatively safe and effective, but the pharmacokinetics of NSAIDs can be substantially altered in certain groups of patients, including the elderly and patients with renal and hepatic disease. In these patients, the risk of NSAID toxicity is increased. An understanding of NSAID pharmacokinetics in these groups can help physicians to adjust therapeutic regimens in order to limit the potentially serious complications of long-term NSAID therapy. The author discusses the age-related physiologic changes that may affect the various areas of drug pharmacokinetics and ways in which NSAIDs may interact with other drugs. Risk assessment and monitoring methods are also discussed.

(Key words: NSAIDs, arthritis therapy, NSAID pharmacokinetics, drug therapy in elderly)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed to control the pain associated with osteoarthritis and other musculoskeletal disorders. According to the Arthritis Foundation,[1] approximately 17 million people with arthritis in the United States take NSAIDs, and this number will undoubtedly increase as the population ages.

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The popularity of NSAIDs derives, in part, from their record for safety and efficacy in the treatment of rheumatic pain and inflammation. But these drugs do cause occasional serious adverse effects. In the gastrointestinal (GI) tract, for example, side effects range from mild symptoms, such as dyspepsia and nausea, to the more serious complications of gastric erosions, ulceration, and bleeding.

Serious gastric complications have been attributed to NSAIDs' inhibition of prostaglandin synthesis. Prostaglandins are synthesized throughout the body and have localized effects, including cytoprotective functions in the GI tract. Renal dysfunction is another common result of long-term NSAID use; and NSAIDs can have hepatic, cardiovascular, hematologic, central nervous system, and dermatologic effects as well.

The prevalence of serious side effects in NSAID users is relatively small. The Food and Drug Administration estimates that serious GI complications occur in 2% to 4% of all patients receiving long-term NSAID therapy for 1 year or longer.[2] In some patient populations, however, the risk of side effects resulting from long-term NSAID use increases substantially. This is particularly the case for patients older than 60 years; these patients receive approximately half of all NSAID prescriptions.[3]

According to recent epidemiologic studies, patients 60 years of age and older have two and a half times the risk of hospitalization and three times the risk of death due to GI complications secondary to NSAID therapy as do those younger than age 60.[3] Other special populations—most notably, patients with renal or hepatic impairment—also are at increased risk for NSAID toxicity.

The precise reasons for increased NSAID toxicity in these groups is not entirely clear. Most likely, a combination of factors conspire to increase patients' vulnerability to long-term NSAID use. Elderly patients, for example, may not tolerate injury to the GI tract as well as younger patients, and may be less resilient when damage does occur.

Age-related changes in drug metabolism can affect the absorption, clearance, distribution, and excretion of drugs. These changes are thought to play a role in the increased toxicity of NSAIDs in the elderly and in patients with renal and hepatic dysfunction. In addition, polypharmacy—a situation common both to elderly patients and to those with other diseases—can cause drug interactions affecting the toxicity of NSAIDs and other drugs taken concomitantly. In this context, a familiarity with NSAID pharmacokinetics in patients at risk for complications helps the physician to adjust therapeutic regimens in order to prevent or limit serious adverse reactions.

Table 1
Physiologic Changes With Aging That May Affect Pharmacokinetics of Nonsteroidal Anti-inflammatory Drugs

Physiologic change	Possible effect
Absorption	Decreased gastric acid production Increased gastric pH Decreased gastrointestinal mucosal cell mass Reduced gastrointestinal motility
Distribution	Reduced total body water Decreased lean body mass Increased body fat Reduced serum albumin Reduced cardiac output Preservation of flow to heart, brain, and muscles
Metabolism	Decreased hepatic blood flow Decreased hepatic mass Reduced enzymatic activity
Excretion	Decreased renal plasma flow Decreased glomerular filtration rate Decreased tubular function

Source: Used with permission from Buchanan WW: Implications of NSAID therapy in elderly patients. *J Rheumatology* 1990;17(suppl 20):29-32.

NSAID pharmacokinetics in the elderly

It is difficult to generalize about the effects of age on the pharmacokinetics of any given NSAID or class of NSAIDs, in large part because not all patients age at the same rate or in the same way. In addition, there have been few reliable studies of NSAID pharmacokinetics in the elderly or in those with diseases that may predispose patients to NSAID toxicity. There are, however, age-related physiologic changes that may affect all four areas of drug pharmacokinetics: the absorption, distribution, metabolism, and excretion of these drugs (*Table 1*).

Absorption

Although age-related changes in the GI tract do occur, these are probably the pharmacokinetic variables least likely to affect NSAID metabolism. We know, however, that gastric acid production decreases with age, as do GI mucosal cell mass, motility, and blood flow, whereas gastric pH increases. Because NSAIDs inhibit prostaglandins, some of which play a "gastroprotective" role (prostaglandins, for example, may enhance mucosal blood flow and increase mucus secretion), NSAIDs may compound these changes, leading to a direct toxic effect on the GI tract.

Distribution

Age-related changes in body composition and protein binding have more meaningful implications for altered NSAID pharmacokinetics in the elderly. The volume of distribution for NSAIDs may be reduced with age by changes in body composition, including a decline in total body size; an increase in body fat stores; and declines in total body water and lean body mass.

As the volume of distribution decreases, NSAID half-life increases. Because steady-state concentrations are achieved over a period of approximately four times the drug's half-life, a longer half-life may result—at least theoretically—in accumulation of the drug for a longer time and at a higher, more toxic level. This drug accumula-

Table 2
Antihypertensive Drugs With Which Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Interact*

NSAIDs	Antihypertensive drug
Aspirin	β-blockers, spironolactone
Diclofenac sodium	Hydralazine hydrochloride
Flurbiprofen	β-blockers
Ibuprofen	Thiazide diuretics, β-blockers
Indomethacin	Thiazide diuretics, furosemide, β-blockers, angiotensin-converting enzyme inhibitors
Naproxen	Thiazide diuretics, β-blockers (timolol maleate)
Oxaprozin	β-blockers
Piroxicam	Thiazide diuretics, furosemide, β-blockers (propranolol hydrochloride)
Aspirin and most other NSAIDs reduce effects of	Thiazide and loop diuretics, spironolactone

*Current drug information based on limited studies.
Source: Houston MC: Interactions between NSAIDs and antihypertensive drugs. *J Musculoskel Med* 1991;8(8):31-46.

tion has not necessarily been found to be the case in clinical practice, however.

In addition, serum albumin levels fall in the elderly and in persons with hypoalbuminemia, such as those with active rheumatoid arthritis. Most NSAIDs are extensively bound to serum proteins, and even a small decrease in serum albumin can lead to higher concentrations of unbound, pharmacologically active and more toxic drug. Studies of drug disposition in the elderly comparing bound and unbound drug concentrations have suggested that dosages of some NSAIDs (for example, naproxen) may need to be reduced in elderly patients.[4]

Metabolism
Hepatic blood flow decreases with age, as does hepatic mass in relation to total body size. Hepatic enzyme activity, especially oxidation, may also be reduced in the elderly. Evidence indicating to what extent these factors actually affect NSAID metabolism is scant and somewhat conflicting. Because NSAIDs are predominantly metabolized by the liver, these age-related decreases in hepatic function might be expected to increase plasma half-life and drug accumulation in the elderly, and thus the potential for toxicity. However, other variables—including hepatic and renal disease, smoking, and alcohol use—may be more important than chronologic age in affecting hepatic drug metabolism.

Excretion
The excretion of NSAIDs and their metabolites may be substantially affected by notable age-related declines in renal function. Both glomerular filtration rate and creatinine clearance decline with age, as does renal tubular function. Decreased capacity to eliminate NSAIDs may result in prolongation of plasma half-life and plasma accumulation. In addition, renal insufficiency may cause diminished clearance of unstable acylglucuronide metabolites of certain propionic acid NSAIDs (for example, fenoprofen, naproxen, ketoprofen, and carprofen), which are then retained and create a "reservoir" for reformation of the parent NSAID, resulting in further accumulation of the drug.[5]

Other special populations
Patients may have a higher risk for NSAID toxicity if they have certain underlying illnesses, especially renal or hepatic disease, or if they take any of a number of drugs that interact with NSAIDs.

Renal disease
The prostaglandin-inhibition properties of NSAIDs can exacerbate existing disease in patients with underlying pathologic renal conditions. Prostaglandins help to maintain glomerular filtration rate and renal blood flow, and also influence the tubular transport of ions and water. Their role in maintaining homeostasis is especially important for patients in whom renal function is compromised.

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Complications that increase patient vulnerability to renal prostaglandin suppression include congestive heart failure, cirrhosis with ascites, nephrosis and nephritis, sodium depletion, and diuretic therapy; all cause hypovolemic states that may lead to higher NSAID plasma concentrations. Prostaglandins also help to modulate vascular tone and, in patients with an underlying renal pathologic lesion, NSAIDs can accentuate renal vasoconstriction and induce reversible hemodynamic renal failure. Renal disease can also decrease serum albumin levels, leading to higher concentrations of unbound, pharmacologically active NSAIDs.

Hepatic disease
Depending on the extent of liver disease, hepatic clearance may be markedly reduced, leading to toxic accumulations of NSAIDs. Liver disease can also affect serum protein concentrations, which, as aforesaid, can lead to potentially toxic increases in free, pharmacologically active drugs.[6]

Drug interactions
The frequency with which NSAIDs are prescribed for a multitude of complaints with other medications (and possibly even other NSAIDs, in either prescription or over-the-counter formulations), allows for potentially serious drug interactions to occur. One form of drug interaction takes place when some NSAIDs (that is, phenylbutazone and salicylates) compete with other highly protein-bound drugs (for example, oral anticoagulants, sulfonylurea hypoglycemics, sulfonamides, and phenytoin) and displace them or are displaced by them, temporarily increasing their pharmacologic activity.[5,7] Nonsteroidal anti-inflammatory drugs may also impair renal elimination of certain drugs, including methotrexate and lithium, by competing at the proximal tubules for active renal tubular secretion.[5,7]

In addition, NSAIDs may reduce the hypotensive effects of some antihypertensive agents (*Table 2*). This effect is a potential problem for a great many patients as it is estimated that some 20 million people in the United States take both NSAIDs and antihypertensives.[8] The mechanisms of action for a number of antihypertensives (for example, diuretics, β-blockers, and angiotensin-converting enzymes [ACE] inhibitors) depend on the release of renal prostaglandins; their effects are the ones most likely to be attenuated by the prostaglandin-inhibition action of most NSAIDs. The effects of other antihypertensives (for example, calcium channel blockers or central α-agonists) are thought to be achieved independently of renal prostaglandins, and NSAID interactions with these drugs have not been reported.[8]

Clinical implications
In view of the heightened risk of NSAID toxicity in specific patient populations, a few key principles should guide the physician when initiating NSAID therapy.

Assess risk
In general, NSAIDs should be prescribed cautiously in those patients at greatest risk for toxicity (*Table 3*). Risk factors for GI complications include advanced age, history of previous gastric ulcer, prednisone use, cigarette smoking, and possibly rheumatoid arthritis.

To aid in evaluating the potential for renal or hepatic NSAID toxicity, baseline renal and hepatic profiles (complete blood cell [CBC] count, and measurements of serum creatinine and serum aspartate aminotransferase [AST] or serum alanine aminotransferase [ALT] levels) should be conducted to detect underlying disease. A thorough medical history should elicit information about other medications being taken, with special attention to antihypertensives and other drugs that may require use with caution when taken together with NSAIDs.

Assess need
Before a therapeutic regimen is determined, the need for NSAIDs should be carefully evaluated. Are there nonmedical approaches—behavior modification, mechanical interventions, or exercises—that might mitigate discomfort without the need for medication? If drug therapy is necessary, analgesics such as acetaminophen, which has fewer gastric side effects, and intermittent dosing might be effective for some patients who have mild to moderate pain. If NSAIDs are prescribed, it is best to begin with the lowest effective dose and encourage the patient to give the drug time to work and reach steady state concentrations (1 to 2 weeks, if possible) before the dosage or choice of drug is reevaluated.

Choose NSAIDs carefully
Most studies show little substantive difference in efficacy between NSAIDs. There is little doubt, however, that safety issues may vary considerably among individual NSAIDs, especially when considering individual organ systems (*Table 4*). Unfor-

Table 3

Risk Factors for Nonsteroidal Anti-inflammatory Drug (NSAID) Toxicity by Organ System

Gastrointestinal	Renal	Hepatic
Age (>60 years)	Age	Age
History	Congestive heart failure	Liver disease (cirrhosis, hepatitis)
Corticosteroid therapy	Cirrhosis with ascites	Decreased renal function
Cigarette smoking	Nephrosis/nephritis	High NSAID dose
Rheumatoid arthritis?	Hypotension	Alcohol use
	Hypovolemia	Polypharmacy
	Sodium depletion	
	Diuretic therapy	

Table 4

Nonsteroidal Anti-inflammatory Drug (NSAID) Safety Profile by Organ System

Risk	Gastrointestinal	Renal	Hepatic
Highest	Aspirin Phenylbutazone* Indomethacin (Indocin)	Indomethacin Phenylbutazone* Aspirin Fenoprofen (Nalfon)	Sulindac (Clinoril) Diclofenac (Voltaren) Phenylbutazone* Aspirin
Lowest	Nonacetylated salicylates (eg, Disalcid or Trilisate) Etodolac (Lodine) Nabumetaone (Relafen) Diclofenac sodium (Voltaren) Oxaprozin (Daypro)	Nonacetylated salicylates (eg, Disalcid, Trilisate) Sulindac (Clinoril) Etodolac (Lodine) Piroxicam (Feldene)	Fenamates Meclofenamate sodium (Meclomen) Mefenamic acid (Ponstel) Some propionic acids Ibuprofen (Motrin, Rufen) Naproxen (Naprosyn) Fenoprofen calcium (Nalfon) Piroxicam (Feldene)

*No longer available.
Sources: Derived with permission from Clive DM, Stoff JS: Renal syndromes associated with nonsteroidal anti-inflammatory drugs.

tunately, few studies have attempted to evaluate NSAID toxicity in patient populations most at risk for complications of long-term NSAID therapy. Furthermore, individual patient preferences and responses to any given NSAID vary greatly.

In general, patients at risk for GI complications should have prescribed NSAIDs that have been found to have fewer GI side effects. In a recent review of comparative data, ibuprofen and salsalate (a nonacetylated salicylate) were noted for receiving consistently good GI toxicity rankings.[9] Endoscopic and microbleeding studies with etodolac, the first member in a new class of NSAIDs called the pyranocarboxylic acids, indicate that etodolac may be better tolerated by the stomach than aspirin or other commonly used NSAIDs,[10] perhaps as the result of selective sparing of gastric and duodenal prostaglandins.[11]

Some reports have suggested that sulindac may have less of an inhibitory effect on renal prostaglandins and therefore may be preferred in patients with hypertensive renal disease.[8] Not all studies with sulindac have been conclusive, however. Etodolac has been studied in patients with renal impairment and renal failure, and in patients with stable liver cirrhosis.[6] The drug was not found to accumulate in these patients, indicating that dosing adjustments may not be necessary in patients with underlying renal or stable liver disease.

Regular monitoring

Despite the favorable safety profiles of certain NSAIDs, it is advisable to prescribe all NSAIDs with care in patients at high risk for toxicity and to monitor therapy with any NSAID conscientiously. After obtaining baseline measurements, the CBC count, serum creatinine levels, and liver function (AST or ALT) should be checked in elderly patients within the first 3 months of initiation of NSAID therapy (I prefer checking at 1 month) and every 3 to 6 months thereafter. The serum creatinine level should be checked within 2 weeks for patients with known liver or renal dysfunction.

Toxic side effects will frequently manifest themselves soon after initiation of NSAID therapy. Also, physicians should advise patients to report any warning signs of trouble, such as edema, weight gain, changes in bowel habits, and vision or hearing abnormalities.

Gastrointestinal complications, on the contrary, are often asymptomatic, especially in elderly patients, confounding attempts to detect such problems before serious GI bleeding and ulceration occur.[12] Endoscopy cannot be recommended routinely in most patients. Stool studies for occult blood may be done periodically, although I check for occult blood only if a follow-up CBC count shows a drop in the hemoglobin value.

Misoprostol, a prostaglandin analogue that acts as a gastroprotective agent is of use in patients clearly at high risk for serious GI complications (for example, the elderly, patients with previous peptic ulcers, patients on steroid therapy, cigarette smokers, and patients with multiple debilitating illnesses). Persistent GI symptoms of blood loss, especially after rechallenge with another NSAID, merits endoscopy to rule out gastric erosions and ulcerations. However, it must be noted that not all GI bleeding in patients treated with NSAIDs is caused by upper GI lesions.

Comment

By virtue of their generally excellent safety and efficacy profile, NSAIDs occupy a large and increasing role in the management of rheumatic diseases and other painful conditions. However, the stage is set for potentially serious NSAID-induced toxicity when the pharmacokinetics of NSAIDs are substantially altered in elderly patients and in those with renal or hepatic impairment. Interactions with other commonly prescribed drugs are also of major concern in the elderly and in those with multiple illnesses.

Information about the complexities of NSAID pharmacokinetics in special patient populations is useful for guiding prescribing decisions. Recent research has refined our understanding in this area relative to certain high-risk conditions and a few specific NSAID preparations. It is my opinion that NSAIDs can be used in a safe and judicious manner if the physician is somewhat knowledgeable about these drugs, and is especially knowledgeable about the populations at high risk for a toxic reaction. However, future inquiry must further elucidate the differences between NSAIDs in terms of their mechanisms of action and toxic potential if NSAID prescribing is to become more science than art.

References

1. Arthritis Foundation: *Arthritis Foundation Survey on NSAID Ulcer Prevention.* Westport, Conn, Yakelovich, Skelley, White/Clancy, Shulman, 1989.

2. Paulus HE: FDA Arthritis Advisory Committee meeting. *Arth Rheum* 1988;31:1450-1451.

3. Fries JF, Miller SR, Spitz PW, et al: Toward an epidemiology of gastropathy associated with nonsteroidal anti-inflammatory drug use. *Gastroenterology* 1989;96:647-655.

4. Upton RA, Williams RL, Kelly J, et al: Naproxen pharmacokinetics in the elderly. *Br J Clin Pharmacol* 1984;18:207-214.

5. Brater DC: Clinical pharmacology of NSAIDs. *J Clin Pharmacol* 1988;28:518-523.

6. Brater DC, Lasseter KC: Profile of etodolac: Pharmacokinetic evaluation in special populations. *Clin Rheumatol* 1989;8(suppl 1):25-35.

7. Furst DE: Clinically important interactions of nonsteroidal anti-inflammatory drugs with other medications. *J Rheumatol* 1988;15(suppl 17):58-62.

8. Houston MC: Interactions between NSAIDs and antihypertensive drugs. *J Musculoskel Med* 1991;8(8):31-46.

9. Fries JF: Choosing an appropriate NSAID. *Drug Ther* 1991;21(10)19-29.

10. Lanza FL, Arnold JD: Etodolac, a new nonsteroidal anti-inflammatory drug: Gastrointestinal microbleeding and endoscopic studies. *Clin Rheumatol* 1989;8(suppl 1):5-15.

11. Taha AS, McLaughlin S, Holland PJ, et al: Effect on gastric and duodenal mucosal prostaglandins of repeated intake of therapeutic doses of naproxen and etodolac in rheumatoid arthritis. *Ann Rheum Dis* 1990;49:354-358.

12. Sager DS, Bennett RM: Individualizing the risk/benefit ratio of NSAIDs in older patients. *Geriatrics* 1992;47:24-31.