

DRUG THERAPY

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**NONSTEROIDAL ANTIINFLAMMATORY
DRUGS — DIFFERENCES AND
SIMILARITIES**

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THE nonsteroidal antiinflammatory drugs (NSAIDs) are very commonly prescribed. This fact reflects the high prevalence of rheumatic diseases; approximately 8 percent of people have a rheumatic symptom at any one time. In 1984, it was estimated that nearly one in seven Americans was treated with an NSAID,¹ and in 1986 100 million prescriptions were written for these drugs.² During the past 30 years, there has been a substantial increase in the number of NSAIDs, but their availability varies markedly between countries.³ In the United States, at least until recently, salicylates were the most common treatment for rheumatologic diseases,⁴ and 14 NSAIDs are now available. In contrast, 7 NSAIDs are available in Sweden, and 17 in Italy. Few data are available on the number of NSAIDs that are needed for the optimal treatment of patients with rheumatologic disorders. In a recent study of prescribing patterns of rheumatologists in the United States, 8 NSAIDs were found to have been used in 70 percent of the patients, whereas 14 preparations were prescribed for 90 percent.⁵ These results are consistent with the data of Dukes and Lunde⁶ indicating that 10 to 15 NSAIDs are needed to provide a reasonable choice and that the variations in availability of these drugs in different countries reflect regulatory differences rather than differences in rheumatologic practice.

Patients, physicians, regulatory agencies, and drug companies all have considerable interest in the question, Do NSAIDs really differ? As a group, these drugs have antiinflammatory, analgesic, antipyretic, and platelet-inhibitory actions. Although NSAIDs certainly do differ chemically, pharmacokinetically, and at least to some extent pharmacodynamically, the real question is, Are these differences of any consequence? Put another way, is variability in responsiveness

to different NSAIDs important for an individual patient?

**PHYSICOCHEMICAL DIFFERENCES BETWEEN VARIOUS
NSAIDs**

NSAIDs currently available come from a variety of chemical classes (Table 1). Their physicochemical properties determine their distribution in the body, and thus differences in these properties may lead to variable therapeutic performance. The more lipid-soluble NSAIDs penetrate the central nervous system more effectively and may have greater central effects. The central side effects of NSAIDs include mild changes of mood, cognition, and perception and are more common in the more lipid-soluble NSAIDs.^{7,8}

The vast majority of these drugs are weakly acidic, with ionization constants (pKa) ranging from 3 to 5. The proportion of an NSAID that is not ionized at a particular pH is a matter of considerable importance, because it influences the distribution of these drugs in tissue⁹ (Fig. 1). Acidic NSAIDs become sequestered preferentially in the synovial tissue of inflamed joints,¹⁰ which may be of potential advantage during episodes of arthritis. Some NSAIDs, such as sulindac, are pro-drugs, with the active drug being produced in vivo. It has been suggested that because sulindac does not seem to affect the renal synthesis of prostaglandins as much as other NSAIDs, it should be preferred in patients with renal disease or threatened renal perfusion, such as those who are hypovolemic.^{11,12} Others, however, have failed to demonstrate an advantage for sulindac in these situations.¹³⁻¹⁵

**MECHANISM OF ACTION OF NSAIDs: DO THEY
DIFFER?****Inhibition of Cyclooxygenase**

The major mechanism of action of NSAIDs is the inhibition of cyclooxygenase activity and therefore the synthesis of prostaglandins.¹⁶ The rank order of potency of NSAIDs as inhibitors of prostaglandin synthesis in vitro tends to reflect their antiinflammatory potency in vivo.¹⁷ The mode of inhibition of the cyclooxygenase enzyme is complex and varies among NSAIDs.¹⁸

Careful studies relating the degree of NSAID-induced inhibition of prostaglandin synthesis to antiinflammatory efficacy in individual subjects are not available. The doses of NSAIDs, notably aspirin, that are required to suppress inflammation may well exceed the doses required to inhibit prostaglandin synthesis substantially, at least in plasma.¹⁹ These and other data have led to the suggestion that these drugs have other mechanisms of action, particularly for their antiinflammatory actions^{19,20} (Table 2). In support of this suggestion, salicylate, which is a weak inhibitor of cyclooxygenase activity, appears to be as effective as aspirin, a potent inhibitor of cyclooxygenase.

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Table 1. Chemical Classification of NSAIDs.

Carboxylic acids
Acetylated — aspirin
Nonacetylated — choline salicylate, diflunisal, magnesium salicylate, salicylamide, salicylate with magnesium salicylate, salsalate, and sodium salicylate
Acetic acids — diclofenac,* indomethacin,* tolmetin,* sulindac,* and etodolac
Propionic acids — ibuprofen,* naproxen,* fenoprofen,* pirofen, indoprofen, tiaprofenic acid, oxaprozin, ketoprofen,* fenbufen, flurbiprofen, carprofen, and suprofen
Fenamic acids — flufenamic acid, mefenamic acid,* meclofenamic acid,* and niflumic acid
Enolic acids — oxyphenbutazone, phenylbutazone,* piroxicam,* sudoxicam, tenoxicam, and isoxicam
Nonacidic compounds — nabumetone, proquazone, and bufexamac

*Available in the United States.

nase activity, in controlling inflammation in patients with rheumatoid arthritis.²¹

Inhibition of Lipoxygenase

Arachidonic acid can also be metabolized to an array of lipoxygenase products that have an important role in inflammatory responses.²² A number of NSAIDs inhibit various lipoxygenase enzymes in vitro or in animals.^{23,24} These include diclofenac and indomethacin, both of which decrease the production of leukotrienes and prostaglandins from leukocytes and synovial cells by stimulating the reincorporation of free arachidonic acid into triglycerides.^{25,26}

Cell-Membrane Processes

NSAIDs interfere with a variety of membrane-associated processes, including the activity of NADPH oxidase in neutrophils²⁷ and the activity of phospholipase C in macrophages.²⁸ A number of NSAIDs, including indomethacin, piroxicam, ibuprofen, and the salicylates, inhibit neutrophil function.^{29,30} Although all NSAIDs affect some neutrophil functions, such as cell-cell aggregation, other functions of these cells respond variably to different NSAIDs. Piroxicam but not ibuprofen inhibits the generation of hydrogen peroxide from neutrophils exposed to phorbol myristate acetate or concanavalin A in vitro.^{23,30} These data led Abramson and Weissman to postulate that some NSAIDs inhibit cellular processes by uncoupling protein-protein interactions within the lipid bilayer of the plasma membrane, including the processes regulated by G protein.¹⁹

Other Nonprostaglandin Processes

Although NSAIDs inhibit the biosynthesis of prostaglandins at low doses, high (antiinflammatory) doses interfere in addition with processes not dependent on prostaglandins, such as the activity of enzymes (i.e., phospholipase C), the synthesis of proteoglycan by chondrocytes,³¹ transmembrane ion fluxes, and cell-cell binding. Since these effects are concentration-dependent, the variations in dose and pharmaco-

kinetics of different NSAIDs may explain some of the variability in the response to NSAIDs. These "non-prostaglandin inhibitory actions" of NSAIDs have rarely been demonstrated in humans in vivo, nor have they been found to relate to a person's response to an NSAID or to explain the variability in responsiveness between subjects.

Lymphocyte Function

NSAIDs may also unmask T-cell-suppressor activity, thereby suppressing the production of rheumatoid factor.^{32,33} Such effects have previously been associated only with so-called disease-modifying antirheumatic drugs, such as gold or penicillamine.

PHARMACOKINETICS

There are both similarities and differences among the NSAIDs in their pharmacokinetic properties. In general, NSAIDs are absorbed almost completely, have low non-flow-dependent hepatic clearance and low to nonexistent first-pass metabolism, are highly albumin-bound, and have small volumes of distribution.

Dose-Response Effects

Naproxen,³⁴⁻³⁶ carprofen,³⁷ and ibuprofen³⁸ have apparently linear antiinflammatory actions that depend on the dose or plasma concentration in patients with rheumatoid arthritis. The relation between concentration and effect does not explain all the variation in responses to these drugs,^{34,39} indicating that some variability in response is pharmacokinetic in origin. It has been difficult to demonstrate relations between the plasma concentrations and toxicity of NSAIDs in humans, although linear relations between plasma con-

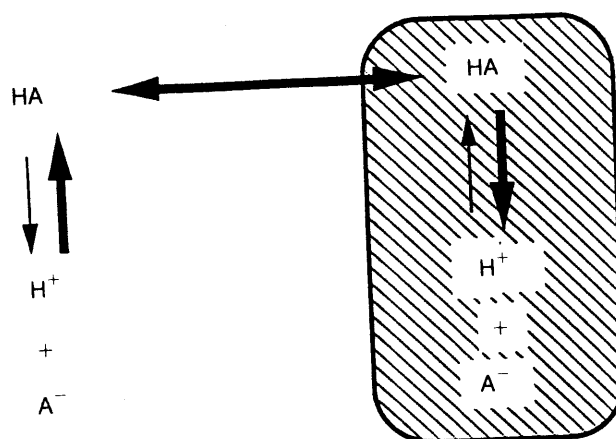


Figure 1. Ion Trapping of Weak Acids in an Acidic Milieu. The proportion of the nonionized form of a weak acid (HA) is higher in an acidic environment (left) than in a more neutral environment, such as that within cells (right). Because the nonionized form of the drug must be in equilibrium across the cell membrane (large arrow), the total intracellular drug concentration (HA + A⁻) must be higher than that outside the cell.

centrations of salicylate and ototoxicity were recently demonstrated,⁴⁰ and a large record-linkage study revealed a relation between the NSAID dosage and upper gastrointestinal bleeding.⁴¹

The suggestion that the pharmacokinetics of NSAIDs in patients who respond to therapy and in those who do not respond may differ has not been supported by the results of studies involving indomethacin and flurbiprofen.^{42,43} It has been hypothesized that a relation between plasma concentration and response is discernible among patients who respond to a particular NSAID, whereas failure to respond can be explained pharmacodynamically.⁴⁴

Timing of Dose

Circadian rhythms have been demonstrated for both pain and inflammation.⁴⁵ Thus, there may be preferable times for the administration even of sustained-release preparations.⁴⁶

Plasma Half-Lives

NSAIDs tend to divide into two groups on the basis of their plasma elimination half-lives — those with a short half-life (less than 6 hours) and those with a long one (more than 10 hours)⁴⁷ (Table 3). Because steady-state plasma concentrations are achieved after a period of dosing extending for three to five half-lives, NSAIDs with long half-lives do not achieve plateau concentrations in plasma and maximal clinical effects as fast as NSAIDs with short half-lives unless a loading-dose regimen is used.

Synovial Drug Concentrations

The concentrations of NSAIDs in synovial fluid are important, because this compartment is close to the most likely site of action of the drugs. Because of the relatively slow transfer rate of NSAIDs into and out of the synovial compartment, there is a discrepancy between plasma and synovial fluid in the time course of the drug concentrations in the case of NSAIDs with short half-lives (Fig. 2).⁴⁷ The mean total drug concentration (bound plus unbound) in synovial fluid within a dosing interval is approximately 60 percent of the mean concentration in plasma over that period, re-

Table 3. Mean ($\pm$ SD) Plasma Half-Lives of Different NSAIDs.*

DRUG	HALF-LIFE (HR)
Short half-life	
Aspirin	0.25 $\pm$ 0.03
Diclofenac	1.1 $\pm$ 0.2
Etodolac	3.0; 6.5 $\pm$ 0.3†
Fenoprofen	2.5 $\pm$ 0.5
Flufenamic acid	1.4; 9.0†
Flurbiprofen	3.8 $\pm$ 1.2
Ibuprofen	2.1 $\pm$ 0.3
Indomethacin	4.6 $\pm$ 0.7
Ketoprofen	1.8 $\pm$ 0.4
Pirprofen	3.8; 6.8†
Tiaprofenic acid	3.0 $\pm$ 0.2
Tolmetin	1.0 $\pm$ 0.3; 6.8 $\pm$ 1.5†
Long half-life	
Apazone	15 $\pm$ 4
Diffunisal	13 $\pm$ 2
Fenbufen	11.0
Nabumetone	26 $\pm$ 5
Naproxen	14 $\pm$ 2
Oxaprozin	58 $\pm$ 10
Phenylbutazone	68 $\pm$ 25
Piroxicam	57 $\pm$ 22
Salicylate	2–15‡
Sulindac (sulfide)	14 $\pm$ 8
Tenoxicam	60 $\pm$ 11

*Adapted from Day et al.⁴⁷ with the permission of the publisher.

†Elimination of this drug occurs in two phases (indicated by semicolon), of which the first is generally the most important.⁴⁸

‡Elimination of this drug is dose-dependent.

gardless of the elimination half-life,⁴⁷ and the concentration varies little between patients.⁴⁷ The lower concentration of NSAID in the synovial fluid is a result of the lower albumin concentration in synovial fluid as compared with plasma.

Because of reported problems with compliance, sustained-release preparations of NSAIDs with short half-lives, such as ketoprofen and indomethacin, have been developed. These, theoretically, should provide sustained plasma concentrations throughout a 24-hour period, but this is not always the case.⁴⁹ For short-half-life NSAIDs such as ketoprofen, however, profiles of the concentration in synovial fluid should not be altered much as the result of the drug's formulation as a slow-release preparation.

Protein Binding

Most NSAIDs are bound extensively (more than 95 percent) to albumin, and the free fraction of drug is usually increased in patients with hypoalbuminemia, as may occur in patients with active rheumatoid arthritis.⁵⁰ Protein binding is saturable in the usual dose range for some NSAIDs, including naproxen, phenylbutazone, and ibuprofen, so that an increasing daily dose leads to less than proportional increases in trough steady-state concentrations⁴⁷; unbound drug concentrations increase proportionally with the dose. Unbound concentrations of naproxen are higher in elderly patients⁵¹ and those with active rheuma-

Table 2. Processes Influenced by NSAIDs.

Prostaglandin production
Leukotriene synthesis
Superoxide generation
Lysosomal enzyme release
Neutrophil aggregation and adhesion
Cell-membrane functions
Enzyme activity (NADPH oxidase, phospholipase C)
Transmembrane anion transport
Oxidative phosphorylation
Uptake of arachidonate
Lymphocyte function
Rheumatoid factor production
Cartilage metabolism

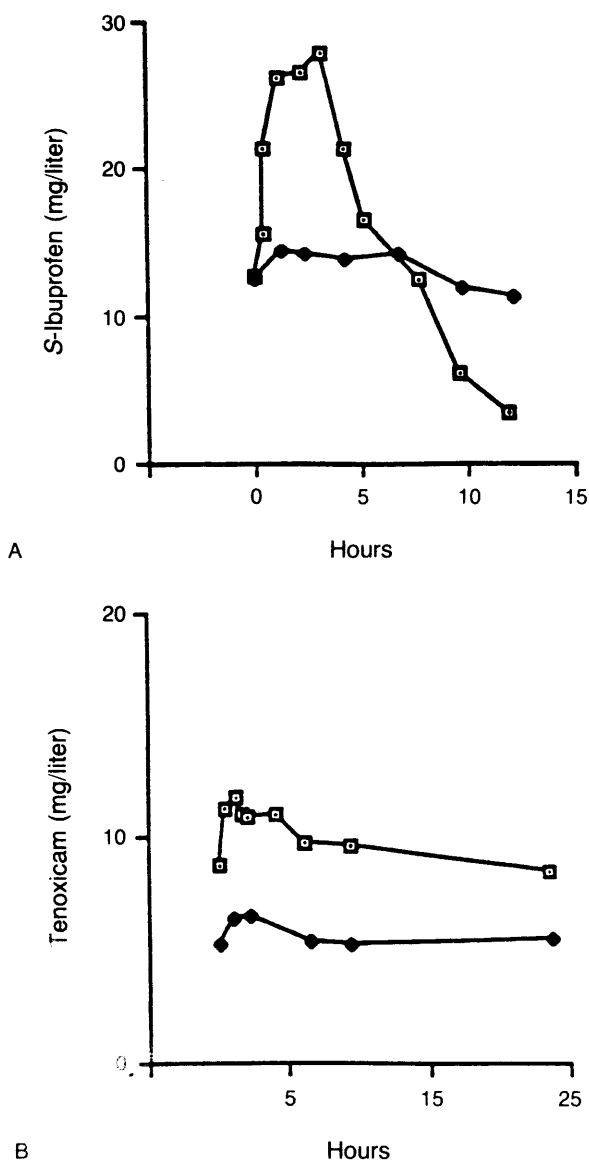


Figure 2. Drug Concentrations in Plasma (□) and Synovial Fluid (●) after the Administration of NSAIDs with Short Half-Lives (Panel A) and Long Half-Lives (Panel B).

Peak and trough drug concentrations in synovial fluid vary little over a dosage interval at steady state, but plasma concentrations vary markedly for NSAIDs with short half-lives, such as S-ibuprofen (Panel A), and those with long half-lives, such as tenoxicam (Panel B).

toed arthritis⁵⁰ than in other patients with similar total concentrations.

Enantiomeric NSAIDs

The disposition of some NSAIDs is complicated by the fact that they exist as two optical isomers or enantiomers. Naproxen is marketed as the *S* enantiomer, which inhibits cyclooxygenase, but the other arylpropionic acids, such as ibuprofen, ketoprofen, and flurbiprofen, are available as equal mixtures of inactive

R and active *S* enantiomers (racemic mixtures). A unique unidirectional conversion of the arylpropionic acid NSAIDs from the *R* to the *S* form occurs to a variable degree in vivo,⁵² depending on the drug and the individual subject.⁵³ Thus, the *R* enantiomer of fenopropfen is converted almost totally to the *S* form, whereas little if any *R*-ketoprofen or *R*-flurbiprofen is converted to the *S* form.

Enterohepatic Recycling

Studies of the enterohepatic circulation of NSAIDs are limited, but the available results suggest that there is substantial biliary excretion of indomethacin and sulindac.⁵⁴

Urinary Excretion

Although a small proportion of most NSAIDs are excreted unchanged in the urine, the clearance of ketoprofen, fenopropfen, naproxen, and carprofen is decreased to a variable degree in patients with renal failure or those taking probenecid, because the acylglucuronide metabolites of these drugs are retained and hydrolyzed to reform the parent compound.⁵⁵ This recycling is one reason NSAIDs should be used cautiously in patients with renal impairment.⁵⁶

CLINICAL EVIDENCE OF VARIABILITY IN ANTIINFLAMMATORY RESPONSES TO NSAIDS

The many comparative trials of NSAIDs have rarely revealed clinically important differences between these agents. The absence of difference may be due in part to inadequate trial designs, insensitive measurements, or suboptimal methods of data analysis.⁵⁷ Indeed, there is evidence of overt or hidden bias in a large number of the reported studies, to such an extent that a reliable meta-analysis may be impossible.⁵⁸ It seems most likely, however, that there are no substantive differences in the responses to average doses of NSAIDs among patients with rheumatoid arthritis or osteoarthritis. The first suggestion that there might be individual differences in responses to NSAIDs was made by Huskisson et al.,⁵⁹ who compared fixed doses of ibuprofen, fenopropfen, ketoprofen, and naproxen in 105 patients with rheumatoid arthritis. Although only minor differences in the mean values for variables of disease activity were demonstrated between the drugs, there was marked variation in individual responses and preferences for these NSAIDs. The patients at either end of the response spectrum were termed "nonresponders" or "responders" to particular NSAIDs.⁶⁰ Gall et al.⁶¹ and Scott et al.,⁶² in trials using flexible doses, encountered similar difficulties in distinguishing between a panel of NSAIDs on the basis of group data, but again noted marked differences in response between patients. Wasner et al.⁶³ compared several NSAIDs in patients with rheumatoid arthritis and ankylosing spondylitis; they also found notable individual preferences for various NSAIDs and a

slightly different order of overall preference, depending on which disease the patients had.

If patients with rheumatoid arthritis are aware that a variety of NSAIDs are available to them, they are less likely to comply with a regimen involving one drug and will wish to try another NSAID in an attempt to gain greater relief from pain.⁶⁴ Thus, patients' responses, or at least their persistence with a drug regimen, are influenced by factors other than symptom relief. In fact, the duration of treatment with an individual NSAID has been used to measure the efficacy and tolerability of that NSAID,⁶⁵ but the results of such studies should be interpreted very cautiously.

What is the origin of the variability between patients in responsiveness and preference for different NSAIDs? Could the variable responses be due to the well-known fluctuations in the intensity of inflammatory and noninflammatory rheumatologic diseases that might coincide with the exposure to a particular NSAID? Although a balanced, randomized comparison of NSAIDs should compensate for such fluctuations with respect to mean results, considerable variability among individuals would generally be expected. Hence, the importance of studies that incorporate a blinded rechallenge with apparently more efficacious or preferred NSAIDs to test whether efficacy and preferences are sustained.^{66,67}

CLINICAL DIFFERENCES BETWEEN NSAIDS

Differences between NSAIDs in their physicochemical properties, mechanisms of action, pharmacokinetics, and pharmacodynamics may explain the differences in clinical responses to different drugs. Even so, selecting an NSAID for an individual patient remains more an art than a science.⁶⁸

Inflammatory Arthropathies

There has been a substantial trend toward the early use of disease-modifying agents in patients with rheumatoid arthritis that may reduce the requirements for NSAIDs.⁶⁹ Also, with respect to dose, Seidman and Melander⁷⁰ found that low doses of indomethacin and acetaminophen were as effective as high doses of indomethacin in patients with rheumatoid arthritis. Even though aspirin is still used extensively to treat rheumatologic conditions, it is tolerated less well than other NSAIDs, as is borne out by an analysis of 103 controlled trials comparing the efficacy and tolerance of NSAIDs with those of aspirin.⁷¹ There is some evidence that indomethacin is the most preferred NSAID for treating ankylosing spondylitis.

Osteoarthritis

The use of NSAIDs in osteoarthritis is more contentious, although over half of NSAID prescriptions are for this indication, which explains the heavy use of these drugs by the elderly. Osteoarthritis commonly has an inflammatory component, and NSAIDs have

been shown to be better than simple analgesics in relieving pain⁷² and providing a better quality of life⁷³ in this disorder. Although NSAIDs have proved efficacy in short-term studies in patients with osteoarthritis and musculoskeletal disorders such as back pain, their value over long periods is uncertain. Their continuous use may not be necessary, education, programs of physical therapy, and the intermittent administration of simple analgesics being very effective in a substantial proportion of patients. In addition, *in vitro* studies and studies in animals, although they are usually done with very large concentrations of NSAIDs, suggest that some of these drugs have a deleterious effect on chondrocyte function.⁷⁴ Whether this is an important action in humans is uncertain, but if it is, the result could be accelerated joint failure.^{75,76} A recent study⁷⁷ suggested that the deterioration of joints was faster in patients taking a potent inhibitor of prostaglandin synthetase (diclofenac) than in those taking a relatively mild prostaglandin inhibitor (apazone, or azapropazone). These data should be interpreted with caution, however, since pain scores differed significantly between the treatment groups at the end of the study, suggesting that the groups were not comparable. It has been suggested that effective pain relief for prolonged periods may lead to the excessive use of an already stressed joint.

Practical Prescribing

From a practical point of view, it is important to consider whether an NSAID is indicated for a particular musculoskeletal problem and then to select a suitable drug, taking into account the diagnosis and the previous experiences of the physician and the patient.⁷⁸ The dose can be increased to the recommended maximum over a period of one to two weeks, if needed. If the results are disappointing, an alternative NSAID can be tried. In patients with osteoarthritis or noninflammatory musculoskeletal syndromes, such as back pain, physical therapy and analgesic agents such as acetaminophen should be prescribed initially. The use and dose of NSAIDs should be titrated against symptoms; doing so gives patients an obvious way of managing their own therapy.

DIFFERENCES IN ADVERSE REACTIONS

One quarter of all adverse drug reactions reported to the Committee on Safety of Medicines in the United Kingdom several years ago were due to NSAIDs,⁷⁹ and the spectrum of reactions was broad.^{80,81} The most frequent problems are gastrointestinal, the most common being dyspepsia. Peptic ulceration and its complications are much less common. Renal adverse effects are the next most common, and in addition they are probably often overlooked. Skin reactions are also relatively frequent, followed by central nervous system reactions. There are a number of rare adverse reactions, including blood dyscrasias; skin reactions, such as erythema multiforme, urticaria, and fixed drug

eruptions; hepatic syndromes; pneumonitis; and neurologic problems, such as headaches, aseptic meningitis, dizziness, and nausea.⁸⁰ Some of the rarer side effects, such as aseptic meningitis, have been reported only with a few NSAIDs, such as ibuprofen, sulindac, and tolmetin.⁸⁰ On the other hand, other rare effects, such as aplastic anemia, have been reported with most NSAIDs. Hepatic reactions are more commonly reported with the pyrazolone, indole, and propionic acid classes of NSAIDs,⁸⁰ and diclofenac is now being recognized as a rare cause of acute hepatocellular damage.⁸¹

Gastrointestinal Effects

Since prostaglandins have a major role in the maintenance of normal gastrointestinal physiology, it is not surprising that drugs that inhibit the formation of prostaglandins interfere with normal gastrointestinal function. All NSAIDs cause dyspepsia, but its occurrence does not predict any particular gastric pathologic effect. The gastrointestinal effects of NSAIDs include gastric erosion, peptic-ulcer formation and perforation,⁸² major upper gastrointestinal hemorrhage, and inflammation and change in the permeability of the intestine and lower bowel.⁸³ It has been hard to estimate the true relation between NSAID use and peptic ulceration. Estimates of the absolute risk vary from approximately two cases of NSAID-induced serious upper gastrointestinal adverse effects per 10,000 person-months of prescriptions⁸⁴ to a sevenfold increase in the risk of hospitalization in patients with rheumatoid arthritis.⁸⁵ Prospective, controlled studies have suggested relative risks of around 1.5 for the perforation or hemorrhage of a peptic ulcer as a result of NSAID therapy,^{86,87} whereas prospective case-control studies have demonstrated a relative risk for these serious upper gastrointestinal adverse effects that is between three and four times higher.^{82,88}

In a univariate analysis of 2400 patients with rheumatoid arthritis who were followed prospectively for an average period of 3½ years, Fries et al.⁸⁵ demonstrated a hazard ratio (an approximation of the relative risk) for hospitalization due to gastrointestinal adverse effects seven times that of patients not treated with NSAIDs. These results led these investigators to suggest that in the United States the syndrome of NSAID-associated gastropathy accounts for at least 2600 deaths and 20,000 hospitalizations each year in patients with rheumatoid arthritis alone. The results of this study and others suggest that the patients at particular risk for the development of NSAID-associated peptic ulceration or substantial upper gastrointestinal complications, including death, are the elderly and those with a history of peptic ulceration.^{85,89}

To date, there is no striking evidence that clearly differentiates roughly equipotent antiinflammatory doses of one NSAID from another with respect to the risk of serious upper gastrointestinal side effects.⁴¹ Although the relative and absolute risks of these par-

ticular side effects are not high, in communities in which NSAID use is high (and likely to increase with our aging population), this level of risk would mean that NSAIDs were the direct cause of 20 to 30 percent of all cases of complications of peptic ulcer disease.⁸²

The question of prophylaxis for NSAID-associated peptic ulceration is a difficult one and has recently been reviewed extensively.^{90,91} Histamine-H₂-antagonist drugs reduce the incidence of gastroscopically diagnosed NSAID-induced duodenal ulcers.⁹² Omeprazole reduces the formation of gastric ulcers, and the prostaglandin analogue misoprostol inhibits both gastric and duodenal ulceration.^{94,95} Whether the reduction in ulcer formation in patients taking NSAIDs is reflected in a decrease in rates of perforation, bleeding, or other serious complications is not yet known. If misoprostol is effective in preventing bleeding, it might be cost effective in patients with a history of gastrointestinal bleeding.⁹⁶ Just how long antiulcer preparations should be prescribed together with NSAIDs is also not clear, but some studies suggest that adaptation to the antiulcer drug may occur, thus negating any benefits of long-term use.^{86,90}

Renal Effects

The other major, potentially serious side effects of NSAIDs are those affecting the kidney.¹ Prostaglandins participate in the autoregulation of renal blood flow and glomerular filtration^{97,98} and also influence the tubular transport of ions and water.^{99,100} NSAIDs can cause reversible impairment of glomerular filtration, acute renal failure, edema, interstitial nephritis, papillary necrosis, chronic renal failure, and hyperkalemia. They are particularly likely to decrease glomerular filtration in patients with hypovolemic states due to salt depletion or hypoalbuminemia and in those with preexisting renal impairment due to age, atherosclerosis, hypertensive renal disease, or other intrinsic renal disease. A recent study suggesting that these effects are more likely to occur in patients treated with ibuprofen than in those treated with piroxicam or sulindac¹⁰¹ has been criticized for flaws in experimental design.¹⁰² There is general agreement that no NSAID can be prescribed with absolute safety with respect to renal adverse effects. Although acute interstitial nephritis and acute tubular necrosis are much rarer than renal dysfunction due to the inhibition of renal prostaglandin synthesis, the first two effects have been reported occasionally with most NSAIDs, most often fenoprofen.¹⁰³

Hypertensive Effects

Prostaglandins have a role in modulating vascular tone, and some antihypertensive and diuretic agents may stimulate the release of prostaglandins.¹⁰⁴ For example, thiazide diuretics, in addition to inhibiting renal tubular resorption of sodium and chloride, may stimulate the production of prostacyclin,¹⁰⁵ and the

Table 4. Interactions of NSAIDs with Other Drugs.

DRUG AFFECTED	NSAID IMPLICATED	EFFECT	APPROACH TO MANAGEMENT
Pharmacokinetic interactions			
<i>NSAID affecting other drug</i>			
Oral anticoagulants	Phenylbutazone Oxyphenbutazone Apazone	Inhibition of metabolism of <i>S</i> -warfarin, increasing anticoagulant effect	Avoid NSAID if possible, or use careful monitoring.
Lithium	Probably all (except possibly sulindac and aspirin)	Inhibition of renal excretion of lithium, increasing plasma lithium concentrations and risk of toxicity	Use sulindac or aspirin if NSAID must be used. Monitor lithium concentration carefully and make appropriate dose reduction.
Oral hypoglycemic agents	Phenylbutazone Oxyphenbutazone Apazone	Inhibition of metabolism of sulfonylurea drugs, prolonging their half-life and increasing the risk of hypoglycemia	Avoid these NSAIDs if possible; if not, monitor blood glucose level closely.
Phenytoin	Phenylbutazone Oxyphenbutazone	Inhibition of metabolism of phenytoin, increasing plasma phenytoin concentration and risk of toxicity	Avoid these NSAIDs if possible; if not, intensify therapeutic-drug monitoring.
	Others	Displacement of phenytoin from plasma protein, reducing total concentration for the same unbound (active) concentration	Interpret total plasma concentration of phenytoin carefully; measuring the unbound concentration may be helpful.
Methotrexate (high, nonrheumatologic dose)	Probably all	Reduced clearance of methotrexate (by unknown mechanism), increasing plasma methotrexate concentration and risk of toxicity	Simultaneous dosing is contraindicated. Use of NSAIDs between cycles of chemotherapy is probably safe. Interaction not seen with rheumatologic doses of methotrexate.
Sodium valproate	Aspirin	Inhibition of valproate metabolism, increasing plasma valproate concentration	Avoid aspirin; monitor plasma valproate concentration closely if another NSAID is used.
Digoxin	All	Potential reduction in renal function (particularly in very young and very old patients), reducing digoxin clearance and increasing plasma digoxin concentration and risk of toxicity (no interaction if renal function normal)	Avoid NSAIDs if possible; if not, measure plasma digoxin and creatinine concentrations frequently.
Aminoglycosides	All	Reduction in renal function in susceptible persons, lowering aminoglycoside clearance and increasing plasma aminoglycoside concentration	Monitor plasma aminoglycoside concentration closely and adjust the dose accordingly.
<i>Other drug affecting NSAID</i>			
Antacids	Indomethacin Others	Variable effects of different preparations: rate and extent of absorption of indomethacin reduced by aluminum-containing antacids, but increased by sodium bicarbonate	No action required unless markedly reduced absorption results in a poor response to the NSAID; dose may need to be increased. Rate of absorption of other NSAIDs can be slowed by antacids.
Probenecid	Probably all	Reduction in metabolism and renal clearance of NSAIDs and acyl glucuronide metabolites, which are hydrolyzed back to parent drug	Increased metabolic clearance of NSAID
Barbiturates	Phenylbutazone, possibly others	Increased rate of absorption of aspirin	May require higher doses of phenylbutazone.
Caffeine	Aspirin	Anion-exchange resin binding of NSAIDs in gut, reducing rate (and possibly extent) of absorption	No action required.
Cholestyramine	Naproxen and probably others	Increased rate and extent of absorption of aspirin in patients with migraine	Separate dosing times by 4 hr; may need larger-than-expected doses of NSAID.
Metoclopramide	Aspirin and others		
Pharmacodynamic interactions			
<i>NSAID affecting other drug</i>			
Antihypertensive agents			
Beta-blockers	Indomethacin	Reduction in hypotensive effect, probably related to inhibition of prostaglandin synthesis in kidneys (producing retention of salt and water) and blood vessels (producing increased vasoconstriction)	Avoid all NSAID use in patients receiving treatment for hypertension if possible; if not, use sulindac preferentially. Check blood pressure measurements repeatedly after starting NSAID. Additional antihypertensive therapy may be needed.
Diuretics	Others (possibly except sulindac)		
Angiotensin-converting-enzyme inhibitors			
Diuretics	Indomethacin Others (possibly except sulindac)	Reduction in natriuretic and diuretic effects; may exacerbate congestive cardiac failure	Avoid NSAID use in patients with cardiac failure, if possible; use sulindac and monitor clinical signs of fluid retention.
Anticoagulants	All	Damage to mucosa of gastrointestinal tract and inhibition of platelet aggregation, both increasing risk of gastrointestinal bleeding in patients taking anticoagulants	Avoid all NSAIDs, if possible.
Hypoglycemic agents	Salicylate (high dose)	Potential of hypoglycemic effects (by unknown mechanism)	Monitor blood glucose level.
<i>Combination with increased risk of toxicity</i>			
Diuretics			
General	All	Combination associated with increased risk of hemodynamic renal failure	Avoid combination if possible.
Triamterene	Indomethacin	Potential of nephrotoxicity, even in subjects with normal renal function	Combination contraindicated.
Potassium-sparing	All	Potassium retention and hyperkalemia	Avoid combination; monitor plasma potassium level.

action of loop diuretics such as furosemide is prostaglandin-dependent.¹⁰⁶ It is not surprising, therefore, that interactions between these agents and NSAIDs are common. All NSAIDs, and indomethacin in particular, can interfere with the pharmacologic control of hypertension and cardiac failure in patients receiving beta-adrenergic antagonists, diuretics, or angiotensin-converting-enzyme inhibitors, although as noted in a recent review, many of these studies were poorly designed.¹⁰⁷ It is also apparent that the average effects of NSAIDs on blood-pressure control, for example, may be quite small, but that variability between subjects is substantial.

DIFFERENCES IN INTERACTIONS OF NSAIDS

Since elderly people are the most likely to have multiple organ dysfunction and NSAIDs are most commonly used in this group, there is an enormous potential for interactions between NSAIDs and other drugs. These interactions were reviewed recently,¹⁰⁸ and the common ones are summarized in Table 4. Some interactions occur with specific NSAIDs (e.g., that between phenylbutazone and oral anticoagulants),¹⁰⁹ but most can occur with any NSAID. Although certain NSAIDs are mentioned in Table 4, often this is because they are the ones for which the interaction has been studied.

CONCLUSIONS

There does seem to be variability in the response of patients to NSAIDs, in terms of both relief from symptoms and the occurrence of adverse drug reactions. Furthermore, different NSAIDs do have subtle differences in their physicochemical properties, pharmacokinetics, and mechanisms of action, in addition to their common property of interfering with the production of prostaglandins, but there is little evidence of substantial differences in their effects in patients, and the side effects and interactions of these drugs are generally not unique to any one of them.

The indications for NSAIDs are increasing rapidly, so that they now include postoperative analgesia, cancer-associated pain, the treatment of proteinuria and dysmenorrhea, and the prevention of thrombosis. With the broadening range of use, differences may emerge between the different NSAIDs. Unresolved issues include the role of prostaglandin-independent mechanisms in the action of individual NSAIDs, the proof of the assertion that some patients respond to particular NSAIDs whereas others do not, the documentation of potential deleterious effects on cartilage in vivo, and the determination of the optimal number and types of NSAIDs required for the effective management of acute pain and inflammation in patients with musculoskeletal disorders. Finally, we need more knowledge of the risk of serious adverse effects in various categories of users of NSAIDs, along with better appreciation of what constitutes the rational use of these valuable drugs in the various indications for which they are prescribed.

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