An evidence-based approach to prescribing NSAIDs in musculoskeletal disease: a Canadian consensus

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Abstract • Résumé

Objective: To make recommendations for the long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) in primary care practice, particularly for patients at high risk for NSAID-induced complications.

Options: The use of misoprostol to prevent gastrointestinal ulceration and other unwanted NSAIDs effects was considered. The role of cyclooxygenase-2 (COX-2) versus COX-1 inhibiting agents was also examined.

Outcomes: Reduction of complications associated with long-term use of NSAIDs.

Evidence: Evidence was gathered in late 1995 from published research studies and reviews. Position papers were prepared by faculty and advisory board members and discussed at the Canadian NSAID Consensus Symposium in Cambridge, Ont., Jan. 26 and 27, 1996.

Values: Recommendations were based on randomized, placebo-controlled clinical trials (level I evidence) and case–control studies (level II evidence) involving NSAID use when such evidence was available. When the scientific literature was incomplete or inconsistent in a particular area, recommendations reflect the consensus of the participants at the symposium (level III evidence). Physicians were recruited from across Canada for their expertise in rheumatology, gastroenterology, epidemiology, gerontology, family practice, and clinical and basic scientific research.

Benefits, harms and costs: Although a reduction in complications due to inappropriate NSAID use should reduce costs of additional investigations, admissions to hospital and time lost from work, definitive cost analysis studies are not yet available.

Recommendations: Currently, no NSAID is available that lacks potential for serious toxicity; therefore, long-term use of NSAIDs should be avoided whenever possible, particularly in high-risk patients (e.g., those who are elderly, suffer from hypertension, congestive heart failure, renal or hepatic impairment or volume depletion, take certain concomitant medications or have a history of peptic ulcer disease) (level I evidence). If NSAIDs are to be used in patients with gastric or nephrotoxic risk factors, the lowest effective dose of NSAID should be used (level III evidence); NSAIDs that are weak COX-1 inhibitors may be preferred (level II evidence). In addition, concomitant administration of misoprostol is recommended in patients at increased risk for upper gastrointestinal complications (level I evidence). However, the clinical judgement of the practising clinician must always be part of any therapeutic decision.

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Validation: These recommendations are based on the consensus of Canadian experts in rheumatology, gastroenterology and epidemiology, and have been subjected to external peer review.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed medications.[1] They account for about 4.5% of all prescriptions[2] in addition to significant over-the-counter (OTC) sales. Wilcox and colleagues[3] examined the prevalence of prescribed and OTC NSAID use in patients admitted to an inner-city hospital in the United States for upper gastrointestinal (GI) hemorrhage. They found that, on admission, 35% of these patients were using OTC acetylsalicylic acid (ASA) and 9% were using non-ASA NSAIDs, but only 14% were using prescribed ASA and 6% prescribed NSAIDs.

Among NSAID users, 40% to 60% are over 60 years of age.[4] In this age group, the use of medications may cause a higher incidence of adverse effects because of changes in renal and liver function and an increased likelihood of concomitant medical conditions and polypharmacy.[5–8]

Concern about overuse of NSAIDs stems from the potential toxicity of these agents, particularly with respect to GI complications. A meta-analysis of 16 controlled studies[9] demonstrated that NSAID users had a higher risk of GI complications than nonusers, which led to increased use of anti-ulcer and gastroprotective agents. However, Canadian data from 1991[10] showed that only 3.5% of those prescribed an NSAID were concomitantly prescribed the cytoprotective agent, misoprostol. In patients treated with NSAIDs, the overall incidence of symptomatic or endoscopic GI toxicity is approximately 20%;[9,11] the incidence of life-threatening GI bleeding or perforation is 1% to 3%.[12,13]

Other effects include impairment of renal or liver function and hematologic abnormalities. Although these occur in fewer than 1% of NSAID users, they may also be life threatening. Less severe effects, including headache, rash, edema, pruritus, nausea and diarrhea, occur in 1% to 5% of people taking NSAIDs.[10]

NSAIDs are clearly more toxic in the elderly.[4,9,11,14,15] In addition to the increased risk of gastric and renal effects, NSAIDs may cause confusion in the elderly. The relative risk of central nervous system toxicity seems to vary among NSAID medications; the greatest risk is associated with indomethacin.[16]

Appropriate use of NSAIDs in the elderly has been the subject of many studies. The Alberta Blue Cross database[10] revealed that although people 65 years of age and over who were prescribed an NSAID were more likely to be prescribed anti-ulcer or gastroprotective agents, they were also more likely to be prescribed medications with the potential for adverse interactions with NSAIDs, such as warfarin, diuretics and oral corticosteroids.

A retrospective study using provincial databases in Quebec[17] estimated the prevalence of questionable prescribing of NSAIDs among the elderly. Of the 63 268 eligible patients studied, 56.2% had received a prescription for an NSAID during 1990. The most common questionable combination consisted of two NSAIDs (5.3% of patients). Other than the use of low-dose ASA as an antithrombotic agent along with an NSAID as an anti-inflammatory or analgesic, the rationale for prescribing more than one NSAID concurrently is unclear.

Utilization rates for NSAIDs based on number of prescriptions may not reflect the volume of NSAIDs actually consumed. A New Zealand study[18] examined compliance with NSAIDs compared with "prophylactic" drugs in an elderly population (70 years of age and over). Prophylactic drugs were defined as those that provided no immediate relief of symptoms and that had to be taken regularly to be effective (e.g., cholesterol-lowering medications). Compliance with NSAIDs was 59%, as compared with 94% for prophylactic medications. Most patients taking NSAIDs regarded them as analgesics and, as a result, noncompliance was high. If pain relief alone is the intent, simple analgesics and local measures are safer than NSAIDs.

In summary, NSAIDs are commonly prescribed medications, particularly among the elderly. NSAIDs are most frequently prescribed for degenerative arthritis, for which they are often not the most appropriate agents. NSAIDs are often used as analgesics and in many circumstances could be replaced by a simple analgesic. Because of the frequency of NSAID use and the significant risk of GI and other side effects, recommendations for prescribing these medications were deemed necessary to decrease NSAID-induced complications and their impact on the health care system.

Process

On Jan. 26 and 27, 1996, a group of rheumatologists and related physicians met to discuss the use of NSAIDs at a consensus symposium in Cambridge, Ont. The objective was to develop recommendations surrounding long-term NSAID use to reduce inappropriate use and decrease or prevent NSAID-induced complications and their associated morbidity and mortality.

Before the symposium, physicians were selected for

their expertise in rheumatology, gastroenterology, epidemiology, gerontology, and clinical and basic science research to review the appropriate literature and write position papers on specific topics. The papers were reviewed in small group sessions, then presented to the entire faculty and participants at the symposium. The group provided input and voted on key recommendations. The applicability of recommendations to clinical practice was explored in case-based workshops. After the symposium, the position papers were revised by the individual experts and coalesced into a single document, which was extensively reviewed by all participants and external reviewers.

When possible, recommendations were based on randomized, placebo-controlled clinical trials (level I evidence)[19] and case–control studies (level II evidence) involving NSAID use. If published reports were incomplete or inconsistent in a particular area, the recommendations reflected the consensus of the participants at the symposium (level III evidence).

The recommendations may not be appropriate for use in all circumstances. The judgement of the practising clinician, the availability of resources and the circumstances of individual patients must always be incorporated into any therapeutic decision.

Minimizing the adverse effects of NSAIDs

Adverse effects and drug interactions associated with NSAID use may be limited, in part, by careful prescribing and monitoring of drugs, particularly in high-risk patients. There is clear evidence of increased toxicity due to NSAIDs in certain patient groups, especially the elderly (Table 1).[4,9,11,14,15] The most common indication for NSAID use in this age group is degenerative arthritis,[20] despite a lack of convincing evidence of superior benefit over simple analgesics for this condition.[21,22]

Differences among traditional NSAIDs

There has been considerable controversy over the relative toxicity of various NSAIDs. NSAIDs appear to share a mechanism of action involving prostaglandin synthetase inhibition (Fig. 1). Historically, there has been little compelling evidence to suggest that the various "traditional" NSAIDs (those available before 1993) have different risks for GI or other toxic effects.[23–26] Reported differences in toxicity must be interpreted in light of the possibility of different use patterns for different NSAIDs and inter-subject variability.

One study,[27] using the pharmacy records of health maintenance organizations, examined the frequency of, and reason for, switches in NSAID prescription to find patterns that might yield useful information about the relative benefits or risks of various NSAIDs. Switching occurred in about 8% of prescriptions; the primary reason for switching — inefficacy (32.7%) — was cited 2.5 times more often than adverse reactions. No specific NSAID could be identified with either greater inefficacy or side effects.

A retrospective cohort study[24] using Saskatchewan Health databases compared the rate of admission to hospital for GI problems of users of specific NSAIDs and nonusers between 1982 and 1986. Although variations were seen among the various NSAIDs, no rate was significantly different from the overall rate for NSAID users.

Several strategies have evolved to circumvent the adverse effects of inhibition of prostaglandin production. Attempts to reduce GI effects, including enteric coating, nonacidic formulations and pro-drugs, have not had a significant impact.[28]

Cyclooxygenase isoenzymes

All NSAIDs appear to inhibit prostaglandin synthesis by blocking cyclooxygenase (COX) activity (Fig. 1). However, there may be some important differences. In the 1990s, two isoforms of COX were identified.[29,30] COX-1 is present in the stomach and kidneys of healthy people, mediating the production of prostaglandin, which may protect the stomach and kidneys. The larger, cytokine-induced COX-2 enzyme is induced in the joints of people with inflammatory arthritis, mediating the production of prostaglandin that may cause or aggravate inflammation.[28,31] In theory, NSAIDs that "selectively" inhibit COX-2 without any inhibition of COX-1 should have anti-inflammatory activity without GI and renal toxic effects.[31]

All NSAIDs that are currently available in Canada block both COX-1 and COX-2, but there are differences in their relative selectivity for the two isoforms.[28,32] Some current evidence points toward etodolac and nabumetone as NSAIDs with the highest COX-2 to COX-1 inhibition ratios.[32–37] This relative selectivity is

Table 1: Conditions associated with risk for toxic effects from nonsteroidal anti-inflammatory drugs (NSAIDs)

Elderly
Hypertension
Congestive heart failure
Renal failure
Hepatic failure
Volume depletion (e.g., hemorrhage)
Prior peptic ulcer disease
Concomitant medications (e.g., diuretics, ACE* inhibitors)

*ACE = angiotensin converting enzyme.

mainly due to a significant decrease in COX-1 inhibition, coupled with a somewhat marginal increase in COX-2 inhibition.

Potential clinical relevance of COX-2 inhibition

Many studies[38–43] have shown that the newer NSAIDs are significantly better than traditional NSAIDs in terms of reduced microbleeding and endoscopically demonstrable GI lesions and ulcers.[37–42] Furthermore, postmarketing surveillance has shown that these NSAIDs (at current therapeutic doses) are safer and are associated with fewer side effects defined by multiple criteria including clinical ulceration.[44,45] Results of long-term controlled clinical trials to assess whether relatively selective COX-2 inhibitors can reduce clinically important upper GI complications are not yet available.

Further support for the relevance of COX selectivity can be seen in the experiences with the prostaglandin E_1 analog, misoprostol. When administered with an NSAID, this agent counteracts the inhibition of the protective gastric prostaglandin. In clinical trials it has been shown to reduce the frequency of NSAID-induced endoscopically demonstrable upper GI ulcers.[12,46] Silverstein and coworkers[12] recently confirmed that reduction of endoscopic ulcers translates into reduction of clinically important GI hemorrhage and perforations.

The nonacetylated salicylate, salsalate, may have a prostaglandin-independent mechanism of action. It appears to be a weak prostaglandin inhibitor, and reduced GI toxicity has been demonstrated.[47]

The future

More potent, truly selective COX-2 inhibitors, some with COX-2 inhibiting effect 300 times their COX-1 inhibiting effect, will be available soon. Incorporating the NSAID molecule into a nitric oxide generating moiety is also being studied. Other new NSAIDs with different mechanisms of action, such as cytokine inhibition and lipoxygenase inhibition, are also being developed and tested. Despite the theoretical importance of these agents, conclusions regarding their use must await the results of clinical trials demonstrating their effectiveness and safety.

Recommendations

- Avoid chronic use of NSAIDs if possible, particularly in high-risk patients (Table 1) (level I evidence).
- If pain relief alone is the intent, simple analgesics and local measures are safer than NSAIDs (level II evidence).
- For most patients with degenerative arthritis, simple analgesics are preferable to NSAIDs, unless an inflammatory component is clearly present (level II evidence).
- When NSAID therapy is indicated in high-risk pa-

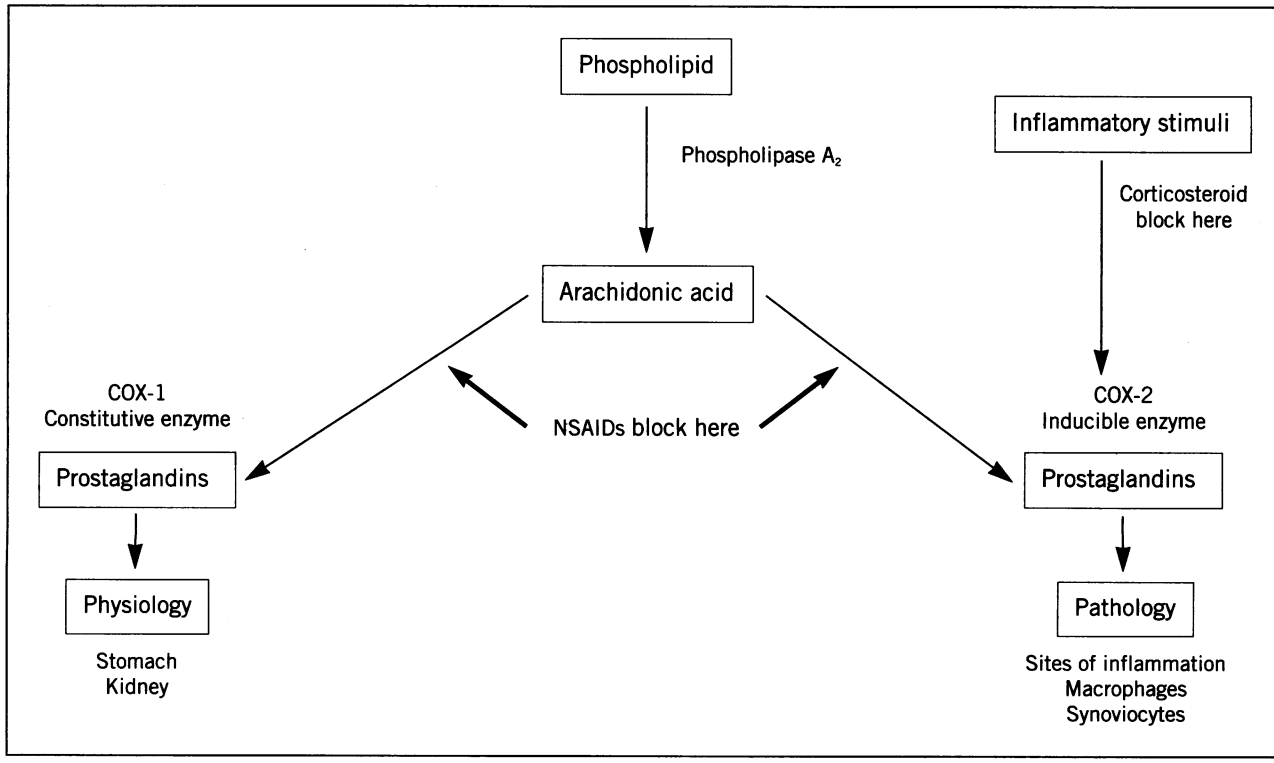

Fig. 1: New paradigm for prostaglandin biosynthesis. COX = cyclooxygenase, NSAIDs = nonsteroidal anti-inflammatory drugs.

tients, NSAIDs that are weak inhibitors of COX-1 may be safer (level II evidence).

NSAID-RELATED GASTROINTESTINAL EFFECTS

NSAIDs and *Helicobacter pylori* underlie almost all cases of peptic ulcer disease. Over 95% of duodenal ulcers have been associated with *H. pylori*. However, for gastric ulcers, where there is a significant association with NSAID use, the prevalence of *H. pylori* is only 60% to 80%.[48] Therefore, although eradication of *H. pylori* holds great promise, NSAIDs continue to be a major cause of clinically important peptic ulcer disease. In reviewing studies of NSAID toxicity, careful distinction must be made between reported endpoints of endoscopically observed acute erosions and clinically important disease (i.e., bleeding, perforation, ulcer or death).

INHIBITION OF GASTRIC PROSTAGLANDIN SYNTHESIS

Strategies to reduce NSAID toxicity in the GI tract have largely focused on two pathogenic mechanisms: topical irritation of the mucosa, and inhibition of gastric prostaglandin synthesis. Evidence strongly suggests that inhibition of gastric prostaglandin production is largely responsible for clinically important peptic ulcer disease.[28] Consequently, strategies to reduce topical irritation, such as enteric coating, nonacidic formulations or prodrugs whose active metabolites inhibit COX activity, have not had a major impact on reducing GI toxicity.[28]

Prostaglandin E_1 analog

A strategy to counteract the NSAID-induced inhibition of gastric prostaglandin synthesis has been the coadministration of a prostaglandin E_1 analog, misoprostol. This agent is known to reduce acute gastric damage significantly and, in a large placebo-controlled, double-blind study,[12] has been shown to reduce the incidence of complicated peptic ulcer disease by 40%. As in previous studies, this benefit is offset by dropout due to misoprostol-related diarrhea and cost–benefit issues. Misoprostol at 200 μg three times daily appears to be as effective as it is four times daily and has fewer side effects.[12,49]

An additional theoretical concern has been the potential for prostaglandin E_1 analogs to promote colonic polyp growth. Sulindac has been shown to reduce the size and numbers of polyps in familial polyposis syndromes, and case–control studies suggest that ASA and NSAIDs decrease the risk of polyps and cancer.[50] The mechanism by which this occurs is unknown and may not simply involve inhibition of prostaglandin synthesis. There is currently insufficient evidence to suggest that this factor provides a contraindication to the use of misoprostol.

Lower risk NSAIDs

In clinical studies, newer drugs such as etodolac and nabumetone, which have a higher degree of activity with COX-2 than with COX-1,[28,51] have been associated with a significant reduction in endoscopically identified ulcers compared with other NSAIDs whose actions with COX-1 predominate.[41,52,53] Small, short-term trials of these drugs have also shown a greater than 50% decrease in clinically important peptic ulcer disease compared with other NSAIDs.[41,53] Long-term, open-label studies provide similar promising data,[44,54] but well-designed, long-term studies are lacking. Preliminary results of a recent meta-analysis suggest that GI complication rates are similar among the currently available lower-risk NSAIDs.[55]

NSAID–nitric oxide compounds

The most recent strategy has been to incorporate the NSAID molecule into a nitric-oxide-generating moiety.[28] These NSAID–nitric oxide compounds exhibit similar anti-inflammatory properties to those of other NSAIDs but display markedly reduced ulcerogenic action in animal models.[56,57] These agents are thought to act by increasing gastric blood flow and inhibiting neutrophil adherence, presumably through the release and actions of nitric oxide.[28] Clinical trials with this agent have yet to be completed.

ROLE OF *H. PYLORI* IN NSAID-INDUCED ULCEROGENESIS

The cellular pathways underlying NSAID- and *H. pylori*-induced ulcers have been shown to be independent; *H. pylori* does not confer a greater risk of NSAID-induced toxicity.[58] However, patients with previous peptic ulcers secondary to *H. pylori* are at high risk of relapse,[59] and NSAIDs may well complicate these lesions. In addition, in patients presenting with a symptomatic peptic ulcer who are *H. pylori* positive and are taking NSAIDs, it is not always clear which is the precipitating agent. Therefore, although this has not been studied in clinical trials, *H. pylori* should be eradicated in patients taking NSAIDs.

NSAID TOXICITY IN SMALL AND LARGE INTESTINES

NSAIDs are now recognized as also causing significant toxicity in the small and large intestines.[60] In the small intestine, an enteropathy characterized by occult blood, protein loss or both has been demonstrated in as many as 70% of cases, although this is usually subclini-

cal.[60] None the less, this may well account for a number of previously undiagnosed cases of iron-deficiency anemia caused by NSAIDs. Intestinal perforations and strictures have also been reported, and, although the colon is rarely affected, NSAIDs may cause acute colitis.[60]

Case–control studies and anecdotal reports have implicated NSAIDs in complicated diverticular disease. Small case series have also suggested that NSAIDs can reactivate inflammatory bowel disease, but direct proof of this association is lacking.[61,62] Thus, there are insufficient data to suggest that NSAIDs are contraindicated in this group, but clinicians must be aware of this association. The mechanism underlying intestinal damage is unclear but appears to involve interaction with bile salts.[28,51] Sulfasalazine, misoprostol and metronidazole have been shown in small studies to decrease the degree of small-intestine damage caused by NSAIDs,[60,63,64] but in patients with clinically important small-intestine damage, there is no evidence indicating that they confer sufficient protection to prevent ongoing NSAID damage.

Recommendations

- Currently, no NSAID lacks the potential for serious toxicity in the GI tract; therefore, long-term use of these agents should be avoided whenever possible (level I evidence).
- When NSAID therapy is indicated for high-risk patients (elderly patients, those with previous peptic ulcer or cardiovascular disease, concomitant with corticosteroid use), NSAIDs should be used at low doses and a prostaglandin E_1 analog (misoprostol) should be co-administered (level I evidence); a weak COX-1 inhibitor may be preferred (level II evidence).
- *H. pylori* should be eradicated in patients with prior duodenal or gastric ulcer (level I evidence).
- NSAIDs should be avoided in patients who have previously developed clinically important peptic ulcer disease while receiving misoprostol (level III evidence).

Renal effects of NSAIDs

NSAID blockage of COX activity with a resultant decrease in production of prostaglandins leads to decreased renal blood flow and glomerular filtration rate (GFR), decreased chloride and sodium excretion, lower renin production with a decrease in aldosterone and a rise in antidiuretic hormone levels to prevent volume contraction (Fig. 2).[65–69] The adverse effects may include acute renal failure, reduced efficacy of antihypertensives and diuretics, and interstitial nephritis. In most people, the risk of NSAID nephropathy is low. Mild fluid retention occurs in fewer than 5% of NSAID users and other renal function abnormalities in fewer than 1%.[65,67,70] However, certain at-risk patients can be readily identified. Other than interstitial nephritis, the risk of NSAID renal toxicity is greatest in patients with pre-existing renal disease, renal hypoperfusion or concomitant drug therapy (Table 2).[65,71–73]

Inhibition of prostaglandins

Prostaglandins play an important role in the regulation of renal blood flow and of sodium and water resorption, particularly in the presence of reduced renal blood perfusion or chronic renal failure. Interstitial nephritis

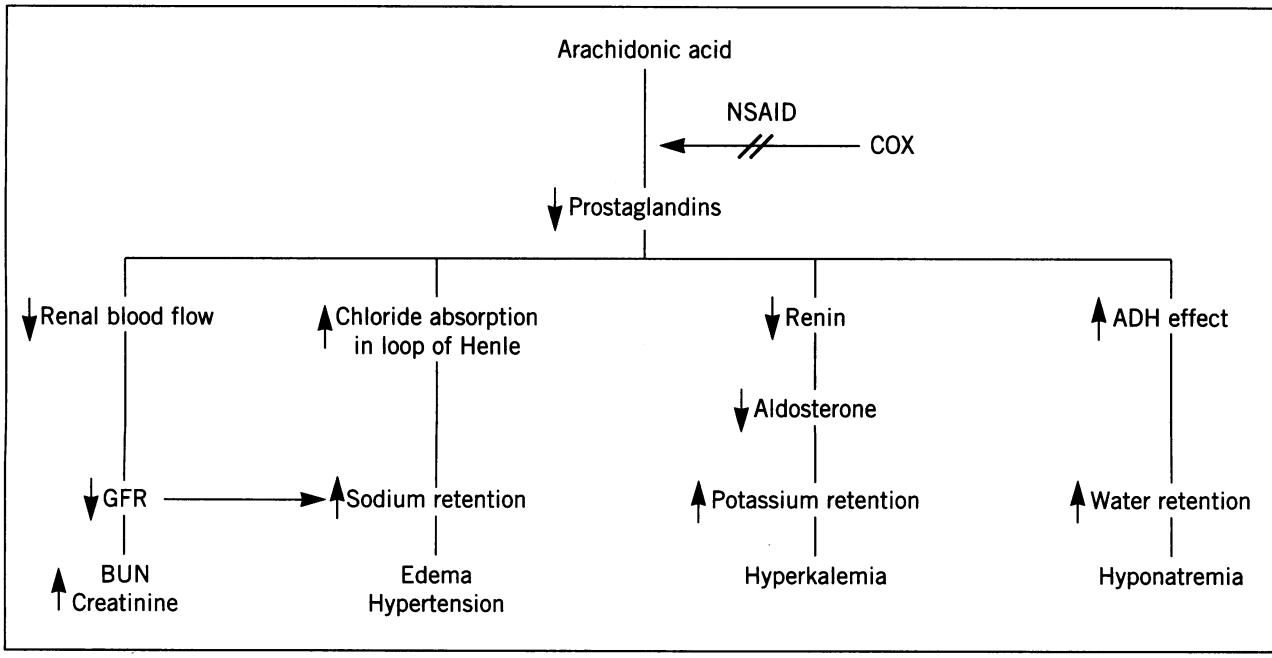

Fig. 2: Renal effects of NSAIDs. ADH = antidiuretic hormone, GFR = glomerular filtration rate, BUN = blood urea nitrogen.

appears to be an idiosyncratic allergic reaction. All other renal adverse effects of NSAIDs are thought to be due to their inhibition of prostaglandin production.[65,67,74–76] Of the two isoforms of COX, COX-1 is thought to be involved in autoregulation of renal perfusion.[77]

COX-2 selective NSAIDs

Although all currently available NSAIDs are capable of inducing NSAID nephropathy, NSAIDs that block COX-2 predominantly, while sparing COX-1, would be expected to cause less nephrotoxicity than nonselective NSAIDs. Confirmation of this hypothesis and its clinical importance require further study.

Other NSAIDs

The nonacetylated salicylate, salsalate, is a weak prostaglandin inhibitor and appears to cause less renal insufficiency than traditional NSAIDs.[47,78] Similarly, the pro-drug, sulindac, has been reported to cause less renal insufficiency in patients with very mild pre-existing renal disease, but this remains controversial.[79,80]

Prostaglandin E_1 analog

Studies using supplemental misoprostol for the prevention of NSAID nephropathy have yielded promising but conflicting results. Supplemental misoprostol appeared to be helpful in both elderly[81] and hypertensive[82] patients and in patients with diabetes.[83] It does not appear to protect renal function in patients with rheumatoid arthritis treated with cyclosporin A,[84] but if misoprostol is commenced at the same time as cyclosporin A in patients receiving a renal transplant, there is enhanced preservation of renal function and prolonged renal graft survival.[85]

Table 2: Risk factors for increased NSAID renal toxicity

Pre-existing renal disease
Nephrosclerosis (e.g., hypertension, diabetes)
Glomerulonephritis (e.g., autoimmune disease)
Nephron drop out (e.g., high age, previous renal disease)
Renal hypoperfusion
Low-output cardiac disease
Liver disease
Hypovolemia
Sodium depletion
Hypoalbuminemia
Hypertension
Diuretic therapy
Extreme exercise
Concomitant drug therapy
Diuretics
Antihypertensives (e.g., ACE inhibitors)
Cyclosporin A

Recommendations

- Alternative therapy should be considered in patients with nephrotoxic risk factors (level II evidence).
- If nephrotoxic risk factors are present and therapy with NSAIDs is felt to be warranted, the lowest effective dose of NSAID should be used (level III evidence); concomitant therapy with other potentially nephrotoxic medications should be avoided (level II evidence); blood pressure and serum creatinine and electrolyte levels should be checked 1 to 2 weeks after starting NSAID therapy and as clinically warranted thereafter (level III evidence).
- Treatment of NSAID nephropathy is currently limited to withdrawal of the NSAID and correction of any blood volume, blood pressure and electrolyte abnormalities (level II evidence).

NSAID-related drug interactions

Adverse drug reactions involving NSAIDs account for over 25% of all observed drug reactions.[86] In the United States, about 50 million people consume an NSAID-related product daily; this means that one in every five US citizens is at daily risk of an NSAID-related adverse event.[87] Many of these people are elderly and are taking additional medications that may interact with NSAIDs. Studies have shown that the average number of prescriptions increases with age, 75% of ambulatory community-dwelling elderly people take at least one prescription medication, and the average number of drugs consumed per day is 12 to 15 including OTC drugs.[88,89]

The prevalence and incidence of adverse drug interactions involving NSAIDs remains unknown but, in general, if a patient is taking two medications, drug interactions occur in 6% of cases. The rate of interactions increases to 50% of cases among people taking five prescribed drugs, and 100% if eight prescribed drugs are taken.[85]

Over-the-counter medications

Prescriber and consumer ignorance are likely to be major determinants in many observed adverse events. Lamy[88] found that the extent of nonprescription drug use is often inadequately determined by the physician, thus increasing the risk of drug interactions. In fact, 40% to 60% of drugs consumed are OTC medications, most often analgesics (particularly ASA), laxatives and vitamins.[90] OTC analgesics can interact with other medications or with herbal treatments.[91] In the United States,

ASA, ibuprofen, naproxen and ketoprofen are available OTC, but only ASA and ibuprofen are available in Canada. The potential for patients consuming both OTC and prescribed NSAIDs can be expected to result in a greater frequency of NSAID-related adverse events.

Significant adverse drug interactions

Adverse drug interactions involving NSAIDs may be limited by careful prescribing and monitoring of drugs, particularly in patients who are at risk for NSAID-induced adverse effects (Table 1). NSAID use should be restricted in patients who are taking oral anticoagulants, as the combination increases risk of hemorrhage 13-fold.[92] Patients receiving corticosteroids and NSAIDs are at 15 times greater risk for peptic ulcer disease than are people receiving neither drug[93] (Table 3).

NSAIDs inhibit the renal clearance of lithium, digoxin and aminoglycosides, particularly in elderly patients.[86] Serum levels of these substances should be measured in all patients using these medications in combination with NSAIDs. Triamterene and NSAIDs, particularly indomethacin, can lead to an increased risk of renal failure. Ibuprofen may displace phenytoin from albumin, but unbound levels rise only if phenytoin metabolism is saturated or if folate depletion occurs. This may necessitate measuring phenytoin levels and reducing the dosage if necessary.[86] Cholestyramine binds to acidic drugs including NSAIDs and may reduce their absorption rate. Cholestyramine also enhances the elimination of piroxicam and tenoxicam by interrupting the enterohepatic cycle.[86]

Antihypertensive agents

NSAIDs interfere with the actions of thiazide and loop diuretics, diminishing their effectiveness as antihypertensive agents.[94,95] Under normal physiological circumstances, the inhibiting effects of NSAIDs on renal prostaglandin synthesis have little effect on GFR. In patients with preexisting volume contraction (renal, hepatic or congestive heart failure), introduction of an NSAID causes reduced production of vasodilating prostaglandins, which results in exaggerated renal vasoconstriction and a decreased GFR.

Patients with hypertension are frequently prescribed diuretics or drugs that inhibit angiotensin-converting-enzyme (ACE) inhibitors. ACE inhibitors counteract the vasoconstrictive properties of angiotensin, and in the presence of a concomitantly administered NSAID they place patients at markedly increased risk for acute renal impairment.[94,95] Physicians should be wary when prescribing an NSAID for a muscle strain or arthritis if patients are taking antihypertensive medications. Consideration should be given to using a calcium-channel blocker or a ß-blocker rather than an ACE inhibitor if NSAIDs will be used for extended periods. Blood tests for renal function should be obtained 1 to 2 weeks after an NSAID is prescribed in patients who are at risk for NSAID toxicity (Table 2).

Table 3: NSAID–drug interactions

Drug	Adverse event
OTC* NSAIDs	Increased NSAID toxicity
Anticoagulants	Hemorrhage
Corticosteroids	Peptic ulcer
Diuretics	Decreased blood pressure control
Antihypertensives	Decreased blood pressure control
ACE inhibitors	Acute renal failure
High-dose methotrexate (> 15 mg/wk)	Increased toxicity
Lithium	Decreased renal clearance
Digoxin	Decreased renal clearance
Aminoglycosides	Decreased renal clearance
Phenytoin	Decreased albumin binding
Antacids	Decreased NSAID levels

*OTC = over the counter.

Methotrexate

NSAIDs may interfere with methotrexate pharmacokinetics. Low doses of methotrexate (in the range of 7.5 mg per week) cause no problems when co-administered with NSAIDs. In patients receiving more than 15 mg methotrexate per week, NSAID use may result in decreased creatinine clearance and decreased renal clearance of methotrexate.[96] However, in clinical practice, there have been no reported problems associated with the chronic use of NSAIDs in patients receiving doses of methotrexate of up to 15 mg per week. Physicians may receive cautionary advice from local pharmacists regarding important drug interactions with methotrexate and NSAIDs (especially salicylates); however, this combination is used frequently, and generally the benefits outweigh the risks.

Antacids

Antacids and NSAIDs interact in a variety of ways; adverse effects can be avoided if these medications are taken at different times. Aluminum hydroxide antacids reduce the absorption of naproxen, and increased doses of naproxen may be required for therapeutic effect. Antacids in large doses can reduce serum salicylate levels by 25%, by increasing urinary pH and renal elimination of salicylates.

Recommendations

- NSAIDs should be avoided, if possible, in elderly patients with congestive heart failure or hepatic or renal impairment who are taking other medications (level II evidence).
- NSAIDs should be avoided, if possible, in patients taking oral anticoagulants or corticosteroids (level II evidence).
- Doses of lithium, digoxin, aminoglycosides and phenytoin may require adjustments if NSAIDs are added (level II evidence).
- Concomitant use of NSAIDs and triamterene should be avoided, if possible (level II evidence).
- NSAIDs can be used safely by patients receiving low doses of methotrexate (less than 15 mg per week) (level II evidence).
- If NSAIDs are used by patients receiving antihypertensive agents, blood pressure and creatinine and electrolyte levels should be monitored in high-risk patients (level III evidence), and a calcium-channel blocker or ß-blocker should be considered rather than an ACE inhibitor (level II evidence).
- Antacids and NSAIDs should be taken at different times (level II evidence).
- More than one NSAID should not be prescribed concurrently, except for low-dose ASA as an antithrombotic agent with an NSAID as an anti-inflammatory or analgesic agent (level II evidence).
- Patients should be cautioned to avoid concomitant OTC NSAID use when using prescription NSAIDs.
- Physicians should ask patients, particularly elderly patients, about the use of concomitant medications, especially OTC NSAIDs, at every visit.

NSAIDs and blood coagulation

Platelets

Thromboxane is the chief product of the action of platelet COX on arachidonic acid. Thromboxane causes secondary platelet aggregation and is pivotal in coagulation. ASA causes irreversible acetylation of COX. The platelet has no way of regenerating this enzyme, and thus the effect of ASA lasts for the life of the platelet (7 to 10 days).[97] All other NSAIDs cause reversible inhibition of platelet COX, which disappears when the NSAID is removed from the system. The preferential inhibition of COX-2, rather than COX-1, by nabumetone and etodolac may result in a minimal effect on platelets by these agents and is one way of testing for COX inhibition.[32,36]

For most patients, the antiplatelet activity of traditional NSAIDs is of no clinical significance, but occasionally adverse effects are seen (Table 4).

Clotting factors

Although most NSAIDs can result in transient elevation of liver transaminase levels, they rarely compromise hepatic function significantly and, with the exception of high-dose ASA, have no influence on the production of vitamin-K-dependent clotting factors. Through this mechanism, high-dose ASA can lead to a bleeding diathesis.[98]

Warfarin

Warfarin exists as two enantiomers, R and S, which occur in equal proportions in commercial preparations. The S enantiomer is the more potent form. Its metabolism can be altered by phenylbutazone, which decreases its clearance and results in a net increase in anticoagulant effect.[99] So far, no other NSAID has demonstrated significant effects on warfarin metabolism.

About 99% of warfarin is protein bound. NSAIDs are weak organic acids that are also bound to albumin to a high degree. NSAIDs can displace warfarin from albumin, thereby increasing the concentration of free warfarin and enhancing the drug's anticoagulant effect. However, although the concentration of free warfarin is increased, more of the drug is available for elimination, and a new steady-state is soon reached.

Recommendations

- Concomitant use of ASA in anti-inflammatory doses and warfarin should be avoided at all costs (level II evidence).
- Concomitant use of NSAIDs and warfarin should be avoided if possible (level II evidence).
- If NSAIDs are deemed necessary in patients receiving warfarin, the international normalized ratio (INR) should be monitored, as the dose of warfarin may require adjustment (level II evidence).
- If NSAIDs are introduced in patients receiving warfarin, physicians should consider one with weak COX-1 activity to minimize the effect on platelets (level III evidence), a nonacetylated salicylate that has little effect on either COX-1 or COX-2 (level III evidence), or the concomitant use of misoprostol to protect the gastric mucosa (level III evidence).

Table 4: Potential antiplatelet effects of NSAIDs

Spontaneous epistaxis
Easy bruising
Bleeding peptic ulcer
Maternal and neonatal bleeding at delivery
Excessive bleeding at surgery

SUMMARY

NSAIDs alone can have multiple deleterious effects, particularly on GI and renal systems. These effects are more common in patients who are at risk because of age, congestive heart failure or renal or hepatic impairment. The risks are further compounded by interactions of NSAIDs with a variety of other drugs. The increased availability of OTC NSAIDs will likely result in an increased frequency of NSAID-related adverse events. Safer NSAIDs are needed. Perhaps future NSAIDs with selective COX-2 inhibition activity will diminish the frequency of NSAID-related adverse events and drug interactions.

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