CME

Newer, safer nonsteroidal anti-inflammatory drugs

Rational NSAID selection for arthritis

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ABSTRACT

OBJECTIVE To summarize current evidence that three new additions to nonsteroidal anti-inflammatory drugs (NSAIDs) offer comparable efficacy with fewer adverse effects than established NSAIDs.

QUALITY OF EVIDENCE No large randomized controlled trials (RCTs) have compared all important NSAIDs. Several RCTs have shown that H_2 antagonists do not protect against NSAID side effects, but some RCTs compared the protective effect of misoprostol (Cytotec) used with other NSAIDs; others have compared etodolac (Ultradol) or nabumetone (Relafen) with placebo and naproxen (eg, Naprosyn). Postmarketing surveys have been used to support claims that the new NSAIDs have few gastric or renal side effects.

MAIN FINDINGS Using misoprostol in conjunction with traditional NSAIDs reduces gastric and renal adverse effects. Misoprostol can be taken at the same time as NSAIDs or in a combination tablet. Two new NSAIDS, etodolac and nabumetone, do not inhibit cyclooxygenase 1 prostaglandins, which occur in the stomach and kidneys, but more selectively block cyclooxygenase 2 prostaglandins, which cause arthritic inflammation. These two NSAIDs have efficacy profiles comparable to older NSAIDs but have markedly fewer side effects.

CONCLUSIONS Safer treatment for arthritis can be achieved by combining misoprostol with traditional NSAIDs or by using one of two new agents, nabumetone or etodolac.

RÉSUMÉ

OBJECTIF Passer en revue les preuves actuelles démontrant que trois nouveaux anti-inflammatoires non stéroïdiens (AINS) sont d'efficacité comparable aux AINS traditionnels mais qu'ils comportent moins d'effets indésirables.

QUALITÉ DES PREUVES À grande échelle, aucun essai randomisé et contrôlé (ERC) n'a comparé l'ensemble des AINS importants. Plusieurs ERC ont démontré que les antagonistes des récepteurs H_2 ne protègent pas contre les effets indésirables des AINS. Par ailleurs, certains ERC ont comparé l'effet protecteur du misoprostol (Cytotec) en association avec d'autres AINS; d'autres essais ont comparé l'étodolac (Ultradol) et la nabumétone (Relafen) au placebo et au naproxen (p. ex. Naprosyn). On a fait appel à des sondages post-commercialisation pour confirmer les prétentions voulant que les nouveaux AINS comportaient moins d'effets indésirables gastriques ou rénaux.

PRINCIPAUX RÉSULTATS L'utilisation concomitante du misoprostol et des AINS traditionnels réduit les effets indésirables gastriques et rénaux. Le misoprostol peut se prendre en même temps que les AINS ou combiné dans un même comprimé. Deux nouveaux AINS, l'étodolac et la nabumétone, n'inhibent pas les prostaglandines cyclo-oxygénase-1 (COX-1) que l'on retrouve dans l'estomac et les reins, mais inhibent de façon plus sélective les prostaglandines cyclo-oxygénase-2 (COX-2) responsables de l'inflammation arthritique. Ces deux nouveaux AINS montrent des profils d'efficacité comparables à ceux des anciens AINS mais leur profil d'innocuité comporte beaucoup moins d'effets indésirables.

CONCLUSION On peut réduire les risques du traitement de l'arthrite en combinant le misoprostol aux AINS traditionnels ou en prescrivant l'un des deux nouveaux agents, soit la nabumétone, soit l'étodolac.

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CME

Newer, safer nonsteroidal anti-inflammatory drugs

Arthritis is the sleeping giant of Canadian health care. Arthritic diseases are the leading cause of chronic disability, workers' compensation injuries, and time off work.[1]

More than 3 million Canadians are affected by osteoarthritis (OA), and 300 000 Canadians have rheumatoid arthritis (RA). As our population ages (the number of Canadians older than 65 is expected to double during the next 40 years), the prevalence of arthritic diseases, especially OA, is likely to increase dramatically.[2]

Both RA and OA, although caused by distinct disease processes, have the common pathway of inflammation characterized by pain, swelling, and stiffness. Nonsteroidal anti-inflammatory drugs (NSAIDs), which limit inflammation, form the backbone of current arthritis therapy.

Most patients with OA or RA require NSAIDs to control inflammation and relieve symptoms. Despite the recent preoccupation with NSAID safety and the recommended use of acetaminophen, most Canadian rheumatologists believe the NSAIDs remain baseline treatment for both OA and RA.[3] Only a few patients with "noninflammatory OA" get sufficient pain relief with acetaminophen alone.[4]

All NSAIDs are not equal. The more than 20 NSAIDs and 40 dosing options currently available in Canada cause confusion over which drugs are superior for managing arthritis. Despite the current lack of specific, comparative, double-blind trials, we have clear choices between NSAIDs based on their safety, efficacy, cost, and convenience.

Therapeutic choice

Despite studies comparing safety, efficacy, and tolerability of NSAIDs, there has never been (and likely never will be) a head-to-head comparative study of the relative merits of the most widely used NSAIDs. Most physicians rely on their own clinical experience and on lessons learned from multiple therapeutic trials between one or two NSAIDs.

To manage arthritis it is important to use the "best" NSAIDs currently available. New evidence-based guidelines for caring for arthritic patients also stress this point.[3] Choosing the best NSAIDs would profoundly affect patients' control of arthritis inflammation.

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Gastrointestinal complications

Nonsteroidal anti-inflammatory drugs exert their anti-inflammatory effects by inhibiting prostaglandins (PGE_2, PGI_2). Because prostaglandins protect the gastric mucosa, NSAID inhibition predisposes patients to gastric (and to a lesser extent duodenal) ulcers, GI hemorrhage, and perforation. Nonsteroidal anti-inflammatory drugs with the most potent inhibitory properties (a dose-related effect) have been shown to produce the most GI injury.[5]

Studies suggest that 15% to 20% of arthritic patients treated with NSAIDs develop gastric or duodenal ulcers.[6] Of these patients, an estimated 1% to 3% develop life-threatening complications, including upper GI bleeding and perforation.[7,8] An estimated 1900 deaths each year in Canada are caused by NSAID-related complications—more deaths than are attributed to either violence or AIDS.[9]

Unfortunately, GI complications caused by NSAIDs usually develop without warning or symptoms. Gastrointestinal safety, therefore, must be ensured by identifying patients at higher risk for NSAID-induced gastropathy. Currently, risk factors include:

- being older than 60 and especially older than 70,
- a history of peptic ulcer disease or GI bleeding,
- a history of cardiovascular disease, and
- using other drugs (steroids) or having severe concomitant diseases.

These risk factors are helpful in identifying the patients most likely to develop GI bleeding or perforation when they use NSAIDs.[10-13]

Renal effects

Prostaglandins are key to maintaining renal function and to regulating renal blood flow and perfusion. They are also involved in sodium and water excretion and in glomerular filtration. Inhibition of renal prostaglandins (PGE_2, PGI_2) thus could lead to hemodynamic renal failure and retention of salt and water, especially among elderly patients.[14]

Patient fear

Many patients fear NSAIDs because they have heard of or experienced NSAID toxicity. Fearful patients are unlikely to comply with NSAID regimens, leading to suboptimal efficacy, an important barrier to overcome in NSAID use.

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Issues and controversies

Cytoprotective strategies. Concomitant administration of misoprostol (a prostaglandin E_1 analog) with NSAIDs reverses the inhibition of protective gastroprostaglandins and decreases the incidence of ulceration and serious complications, including GI hemorrhage, by 40% in patients with RA. Other GI agents, such as cimetidine (eg, Tagamet) or ranitidine (eg, Zantac), often relieve symptoms but have little effect on ulceration.[15-17] The combination of diclofenac and misoprostol, marketed under the trade name Arthrotec, has been shown to prevent NSAID-induced GI damage to a similar degree as diclofenac (eg, Voltaren) and misoprostol separately.[7,18]

Thus, when patients' risk factors make them more likely to develop GI complications, concomitant use of misoprostol and an NSAID, or the combination formulation of misoprostol and diclofenac, are both appropriate gastroprotective strategies. Unfortunately, dosing with misoprostol and an NSAID does not protect all patients completely. Studies indicate that up to 6% of patients receiving misoprostol alone or in combination with diclofenac develop GI ulcers. Some patients do not tolerate misoprostol well. Side effects, including diarrhea, abdominal pain, cramping, and flatulence, occur with misoprostol, especially during the first week of therapy.[7,19] Although many patients can overcome these adverse reactions, in some they are intolerable and misoprostol alone or combined with diclofenac must be withdrawn. Clinicians and patients require other, potentially safer, NSAIDs.

Cyclooxygenase selectivity. Until 1993 we believed that all NSAIDs caused potential GI and renal toxicity.[20-22] However, two distinct cyclooxygenase (COX) enzymes have now been identified: COX-1, which facilitates production of gastric and renal prostaglandins (the housekeeping enzyme), and COX-2, which is responsible for production of prostaglandins in inflammatory tissues. In Canada two new agents, etodolac (Ultradol) and nabumetone (Relafen), have become available as alternative NSAIDs during the past 3 years. These two drugs selectively inhibit COX-2 more than COX-1 enzymes.[23,24]

In vitro human cellular assays used to evaluate COX-1 versus COX-2 selectivity have shown that etodolac produced a seven- to 10-fold selectivity for COX-2 inhibition relative to COX-1.[23] Other NSAIDs have demonstrated either COX-1 selectivity or nearly equal inhibition of COX-1 and COX-2.[23] Laine and colleagues[25] have demonstrated that gastromucosal prostaglandin production decreases significantly with naproxen (eg, Naprosyn) but is unchanged after treatment with placebo or etodolac.

The preferential selectivity of the newer NSAIDs for COX-2 rather than COX-1 would be expected to lead to fewer adverse effects on the gastric mucosa and kidneys.[26] Research supports this hypothesis. Endoscopic evaluation of normal healthy volunteers showed that the area of gastric ulcers after 4 weeks of therapy was greater with naproxen (58.3 mm^2) than with either etodolac (13.9 mm^2) or placebo (29.0 mm^2).[25] Both etodolac and nabumetone cause less gastric ulceration than older NSAIDs.[25,27,28]

Large-scale postmarketing studies involving almost 5000 patients with RA, OA, or ankylosing spondylitis identified only three adverse reactions related to etodolac, for an adverse reaction rate of 0.1%.[29,30] A larger survey of more than 50 000 patients identified only 21 severe adverse reactions with etodolac use, for an adverse reaction rate of 0.0005%.[30] A final evaluation of the data from both double-blind studies as well as open-label trials with etodolac found no evidence of hemorrhage or perforation and a gastroduodenal ulcer incidence of 0.3%.[29,30]

Large-scale postmarketing surveys have similarly associated nabumetone with a very low risk of serious adverse events. In a US-based study of close to 2000 patients, ulcers were detected in 13 patients, but there were no reports of either GI bleeding or perforation.[29] In a second study of 8865 patients receiving nabumetone, only two patients experienced GI bleeding; in a third trial of more than 10 000 patients, there were only 11 serious events, seven of them GI bleeding.[31]

A large meta-analysis has also indicated that rates of NSAID-associated GI complications are lower for newer, low-risk NSAIDs.[32] Thomas Schnitzer, Director of Clinical Research at Northwestern University, reported at the international conference on immunopharmacology in March 1997 a study comparing etodolac and ibuprofen (eg, Advil) for GI toxicity in RA patients. Serious GI events occurred in 0.43% of patients with low-dose etodolac, 0.67 patients with high-dose etodolac, and 4.7% of patients with high-dose ibuprofen. Both etodolac groups showed more clinical improvement than the ibuprofen group.[33]

Both in vitro and postmarketing studies show that two newer NSAIDs, nabumetone, and etodolac, which are selective for COX-2, are clearly safer than traditional NSAIDs. Thus the doclofenac-misoprostol

Table 1. Approximate costs of nonsteroidal anti-inflammatory drugs

DRUG NAME	DOSE	NUMBER OF PILLS	PRICE PER MONTH ($9.95 DISPENSING FEE INCLUDED)
Tiaprofenic acid (eg, Surgam SR)	300 mg	60	$53.81
Tiaprofenic acid (generic)	300 mg	60	$36.60
Piroxicam (eg, Feldene)	20 mg	30	$34.56
Diclofenac (eg, Voltaren)	50 mg	90	$49.87
Diclofenac and misoprostol (Arthrotec)	50 mg and 200 µg	90	$79.61
Etodolac (Ultradol)	300 mg	60	$65.15
Nabumetone (Relafen)	500 mg	90	$79.61
Misoprostol (Cytotec)	200 µg	60	$39.84

combination, nabumetone, or etodolac represent the safest alternatives for patients who cannot tolerate misoprostol or who require higher NSAID doses than usual.

Efficacy. All forms of arthritis are not the same. Clinical experience suggests patients respond differently to different NSAIDs. After a period of initial success, patients frequently report that an NSAID loses its efficacy and an alternative drug must be found. Having alternative NSAIDs is, therefore, critical to appropriate management of most arthritic diseases.

Newer, safer NSAID alternatives include the combination of diclofenac and misoprostol, nabumetone, and etodolac. Because these drugs have equivalent efficacy to the older drugs and a notable advantage in terms of gastric and renal toxicity, they have become preferred for most patients with OA and RA. Although etodolac is not indicated specifically for ankylosing spondylitis, our experience suggests that it is particularly useful for the morning stiffness and pain of this condition.

Cost. Often patients must consider cost when filling prescriptions, which affects compliance. Newer NSAIDs are similar in cost to older NSAIDs combined with misoprostol **(Table 1)**.

Key point
Newer NSAIDs with COX-2 selectivity, such as nabumetone and etodolac, offer clear advantages over older medications by reducing gastrointestinal toxicity.

Conclusion

Although 20 NSAIDs are available in Canada, they are not equal. Newer NSAIDs with COX-2 selectivity, such as nabumetone and etodolac, offer clear advantages over older medications in terms of GI toxicity. Another choice is to add cytoprotection as misoprostol to a more toxic NSAID or to take the NSAID in combination with diclofenac as Arthrotec. These three NSAIDs remain the NSAIDs of choice for managing arthritic diseases because the evidence currently available indicates they offer the best balance of efficacy and safety.

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