What's the Deal with NSAIDs?

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Arthritis is one of the most common chronic conditions that affects Canadians. Nearly one in seven Canadians suffer from one form of arthritis or another. With changing demographics, it is expected that one million Canadians in each of the next three decades will develop arthritis.

Osteoarthritis is the most common form of arthritis and accordingly is responsible for most patient visits to family physicians. However, inflammatory arthritides, especially rheumatoid arthritis (RA), affects a significant proportion of people (nearly 1% of the Canadian population), and causes rapid onset of joint damage and significant disability.

In 1991, an estimated 495,000 Canadians (2.3% of the population) had disability due to arthritis. By 2031, this number is expected to grow to 3.3%.

Pharmacologic therapy remains the mainstay of management of both inflammatory and non-inflammatory arthritis. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to relieve pain and reduce inflammation. In 1996, more than eight million prescriptions for NSAIDs were written in Canada. Acetylsalicylic acid (ASA) became commercially available in the late 19th century. Since that time, balancing efficacy versus safety has been an issue for physicians. With the onset of cycloxygenase-2 (COX-2) selective inhibitors in the '90s and better understanding of the mode of action of NSAIDs, the balancing act between efficacy and toxicity has become one of the major debates in the field of rheumatology.

Mrs. Jenkins' aches

Mrs. Jenkins, 75, has long-standing osteoarthritis of the knees. In the last year, she has had increasing pain, especially in the right knee, and difficulty with climbing stairs. She tried acetaminophen 1 g three times daily with no significant improvement of her symptoms.

She has hypertension that is well-controlled with hydrochlorothiazide, and had a duodenal ulcer 12 years ago (confirmed by endoscopy). She currently complains of intermittent heartburn, for which she occasionally takes antacids.

On examination, Mrs. Jenkins' blood pressure was 136/86 mmHg. She had crepitus in both knees. Her range of motion in the right joint was slightly limited. Flexion of both knees was painful, and a small effusion was detected in the right knee. Radiographs of the knees confirmed the presence of moderate osteoarthritic changes.

What can help control Mrs. Jenkins' symptoms?

See page 60 for answers.

NSAIDs may potentially cause a number of side-effects. Gastrointestinal (GI) toxicity, including peptic ulcer and ulcer complications, is the most common side-effect. However, cardiovascular hematopoietic, hepatic, and central nervous system toxicities were also reported. Other less common side-effects reported with NSAIDs

include hypersensitivity reactions.[1] GI toxicity is the most common, however, cardiovascular and renal toxicity (including hypertension) have received much attention in the last few years.[2,3]

GI ulceration secondary to classic NSAIDs ranges from two to 10 times compared to patients who are not taking NSAIDs. Risk factors for serious GI side-effects (perforation, ulceration and bleeds) secondary to NSAIDs are well-identified (Table 1).[4,5]

Serious GI toxicity can occur with or without dyspepsia or other warning symptoms. However, dyspepsia is a prevalent side-effect of NSAIDs and can affect up to 30% of patients taking these medications. Dyspepsia is the main reason why patients discontinue their NSAIDs. Most of these patients do not, and will not, develop serious GI side-effects.

The introduction of selective COX-2 inhibitors in 1999 was heralded as a breakthrough in the management of patients with arthritis. It carried the promise of reducing the serious GI side-effects of NSAIDs without impacting the efficacy of these medications. This is attained by blocking the newly discovered COX-2 enzyme, which was felt to be responsible for most of the deleterious side-effects of NSAIDs, while sparing the COX-1 enzyme. The latter enzyme is necessary for GI defense against ulceration.

The Phase 2 and Phase 3 studies, reported prior to the launch of the two commonly used selective COX-2 inhibitors (rofecoxib and celecoxib), seemed to confirm their GI safety. However, in two large studies published in 2000, new issues regarding the safety of these drugs came to light. In CLASS (Celecoxib Long-term Arthritis Safety Study), celecoxib (800 mg daily) was studied against ibuprofen and diclofenac. No statistically significant difference between the primary outcomes of serious GI side-effects was found between the groups. However, the secondary outcome of symptomatic complicated ulcers was lower in patients with celecoxib than those taking NSAID competitors. Many reasons were forwarded to explain this result. One explanation was that concomitant ASA use in many patients receiving celecoxib in the study led to the increased GI side-effects.[6]

The VIGOR[7] (Vioxx GI Clinical Outcomes Research) study investigated a high dose rofecoxib in RA patients versus naproxen (no ASA was

Answers for Mrs. Jenkins

Mrs. Jenkins has multiple risk factors for developing serious gastrointestinal complications with NSAIDs (*e.g.*, age and history of peptic ulcer disease).
Her hypertension is reasonably controlled now. The therapeutic options may include:

- intra-articular steroid injection of the right knee
- a course of physiotherapy for quads strengthening exercises
- pain relief modalities.

The general practitioner may maximize the dose of acetaminophen to 4 g daily (this will require monitoring liver functions). COX-2 inhibitors (with close monitoring of the blood pressure) are an option in Mrs. Jenkins' case. Alternatively, the physician may prescribe one of the classic NSAIDs with a proton pump inhibitor (blood pressure monitoring is advised here also).

allowed). Statistically significant reduction of the serious GI side-effects was found in the group taking the rofecoxib. However, there was an increase in the incidence of non-fatal myocardial infarctions (MIs) in the patients receiving rofecoxib. Many explanations were forwarded to account for this result, including the lack of ASA use as an antiplatelet agent in these patients.

With these results on hand, debate of the toxicity versus safety of NSAIDs (including COX-2 selective inhibitors) return to face physicians prescribing NSAIDs.[2] As a rheumatologist, I encounter daily situations in which I have to decide whether to prescribe NSAIDs or not, and which ones to prescribe.

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Table 1
Risk factors for serious GI side-effects

- Previous peptic ulcer disease
- Advanced age
- Comorbid illness, such as hypertension and congestive heart failure
- Concomitant use of steroids or warfarin
- Concomitant multiple NSAID use

NSAID: Nonsteroidal anti-inflammatory drug

What's best for a patient with a high risk of developing serious upper GI side-effects?

The first decision point will be whether this particular patient needs NSAIDs or if the problem can be treated with other modalities, such as acetaminophen, local steroid injections, hyaluronate intra-articular injections, or physiotherapy. For example, patients who have osteoarthritis of the knee alone may be candidates for such alternative interventions. The presence of active peptic ulcer disease will effectively rule out the use of NSAIDs, and alternative therapeutic options should be considered.

The data on rofecoxib and celecoxib to date, in spite of the controversy, have shown that these medications are probably safer than classic NSAIDs when it comes to serious GI side-effects. The safety profile also seems to be true for the more recent commercially available COX-2 selective inhibitor (valdecoxib). However, there are no published studies yet available that look specifically at the serious GI side-effects (perforations, ulcers, bleeds) with this agent.[8]

The use of classic NSAIDs with proton pump inhibitors (PPIs) was shown to provide protection against peptic ulcer disease in patients with arthritis as compared to those receiving classic NSAIDs alone.[9]

Are there safe NSAIDs for patients with renal impairment?

Both COX-1 and COX-2 enzymes are pivotal in maintaining the function of the kidneys. Blockade of either or both cyclo-oxygenase enzymes in the kidneys may result in side-effects, such as water and salt retention, hypertension, oedema, and renal impairment.

As both hypertension and osteoarthritis are very common diseases, it is not unusual for hypertensive patients to require NSAID therapy for arthritis. Good control of the blood pressure, and close monitoring of hypertension and renal function are advised if you feel NSAID therapy is necessary. However, patients with uncontrolled hypertension, significant renal impairment, or congestive heart failure should not receive NSAIDs (including COX-2 selective inhibitors). Alternative therapeutics, such as those mentioned earlier, should be considered in managing patients with arthritis who cannot take NSAIDs. Hypertension control should be optimized and, accordingly, may allow patients to use NSAIDs at a later stage.

What if ASA is required to reduce MI and stroke risks?

With the exception of ASA, NSAIDs cause reversible inhibition of platelet aggregation. The selective COX-2 inhibitors cause only minimal inhibition of the platelet functions. Although there were initial reports that naproxen can be an important platelet aggregation inhibitor in vitro, there are no convincing clinical trials to suggest it is useful in preventing MIs and strokes in vivo. ASA is the only available NSAID that can be used as a prophylaxis in such conditions. Accordingly, prophylaxis with ASA should continue, if indicated, while taking other NSAIDs (including COX-2 selective inhibitors).

It has been shown, however, that the combination of COX-2 selective inhibitors and ASA increases the risk of GI side-effects (as shown in CLASS). A recent study also showed such increased risk with the use of rofecoxib. This fact should be taken into consideration when treating patients with high risk of developing GI side-effects with NSAIDs and ASA prophylaxis concomitantly.

Can I use NSAIDs in patients receiving anticoagulators?

Anticoagulation is a relative contraindication for the use of NSAIDs. The risk of a GI bleed increases with the combination of NSAIDs and warfarin. COX-2 selective

inhibitors (rofecoxib and celecoxib) have little antiplatelet function. However, post-marketing reports suggest there might be an increased risk of bleeding with these agents when combined with warfarin, especially in the elderly. If the use of these agents is deemed necessary, then close clinical monitoring and frequent international normalized ratio measurement would be necessary, especially at the initiation of the therapy or upon increasing the dosage. CME

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Take-home message

- The introduction of the new COX-2 selective inhibitors allows physicians to use this medication in many patients who would not normally be considered candidates for NSAIDs.
- Continuing vigilance, the time-honoured balance between safety and efficacy, will carry on being our best guide in protecting our patients while treating their pain and inflammation.

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