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At a time when recent events have created a lot of confusion among health professionals, the opportunity to share the latest evidence-based recommendations on the use of NSAIDs/coxibs with fellow pharmacists is important. This article should ensure that pharmacists play a significant role in the appropriate and safe use of NSAIDs/coxibs.

De récents événements ayant provoqué beaucoup de confusion dans l'esprit des professionnels de la santé, il apparaît important d'avoir l'occasion d'échanger avec nos collègues pharmaciens sur les plus récentes recommandations fondées sur des données probantes, au sujet de l'utilisation des AINS et des inhibiteurs de la COX-2 (coxib). Le présent article vise à s'assurer que ces derniers jouent un rôle important dans l'utilisation adéquate et sans danger des AINS et des coxibs.

A pharmacist's perspective: Proceedings from the Third Canadian Consensus Conference: An Evidence-Based Approach to Prescribing NSAIDs in the Treatment of Osteoarthritis and Rheumatoid Arthritis

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Abstract

Recent events such as the withdrawal of rofecoxib and valdecoxib from the marketplace have led to confusion among physicians and patients about the safety of coxibs. Eight evidence-based recommendations regarding the appropriate and safe use of NSAIDs/coxibs were made by the Third Canadian Consensus Conference Group on the following specific topics: patient-physician communication, indication for the use of

NSAIDs, gastrointestinal toxicity, renal considerations, hypertension, cardiovascular risk, geriatric considerations, and pharmacoeconomics. This article discusses how pharmacists are to interpret new observations regarding the safety and efficacy of coxibs/NSAIDs, and what role pharmacists should play in maximizing the appropriate and safe use of NSAIDs based on the evidence-based guidelines.

More than 15 million prescriptions of various nonsteroidal anti-inflammatory drugs (NSAIDs) were dispensed in Canadian retail pharmacies in 2004, making this class of drugs one of the most commonly used in Canada.¹ With the aging of the population, one might expect a significant growth in the prevalence of painful degenerative and inflammatory rheumatic conditions, leading to an increase in the use of NSAIDs and a related upsurge in the number of adverse events related to NSAID use. Prior to the introduction of selective cyclooxy-

genase-2 (COX-2) inhibitors, referred to as coxibs (e.g., rofecoxib, celecoxib, or lumiracoxib), it had been estimated that approximately 20% of chronic NSAID users would develop an endoscopically visible ulcer, and 1 in 150 will develop serious complications each year, such as bleeding or perforation, which are the cause of death in many patients.²

Unlike the nonselective NSAIDs, which inhibit both cyclooxygenase isoenzymes (COX-1 and COX-2), the coxibs selectively inhibit the COX-2 isoenzyme and appear to be associated with fewer

gastrointestinal (GI) adverse events. However, recent events such as the September 2004 voluntary withdrawal of rofecoxib,³ the December 2004 US Food and Drug Administration request to withhold direct-to-consumer advertising of celecoxib in the United States,⁴ and the April 2005 voluntary suspension of sales of valdecoxib by the manufacturer⁵ have led to confusion among physicians and patients about the safety of coxibs.

The Third Canadian Consensus Conference: An Evidence-Based Approach to Prescribing NSAIDs in the Treatment of Osteoarthritis and Rheumatoid Arthritis was held from January 21 to 23, 2005, in Cambridge, Ontario. The goal of the meeting was to make recommendations to Canadian physicians on the appropriate and safe use of NSAIDs, including coxibs, in the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA).

A literature search was conducted using Medline, Ovid, and PubMed in order to develop a database of articles relating to NSAIDs (including coxibs) published in English in peer-reviewed journals between January 2000 and December 2004 using the search terms osteoarthritis, rheumatoid arthritis, guidelines/consensus, acetaminophen, NSAIDs, celecoxib, rofecoxib, valdecoxib, etoricoxib, and lumiracoxib. All clinical conferences, clinical trials, evaluation studies, meta-analyses, multicentre studies, randomized controlled trials, and technical reports were searched. A total of 373 articles were obtained for consideration. Participants were also free to conduct additional literature searches on their preassigned topics.

Consensus participants included 28 recognized leaders from across Canada in the fields of rheumatology, internal medicine, family medicine, nephrology, cardiology, gastroenterology, geriatrics, pharmacology, pharmacy, orthopedics, and health economics. Two of the authors (BM, HT) attended the consensus meeting and present in this article a pharmacist's perspective on the use of NSAIDs. Newer information regarding the cardiovascular adverse events associated with acetaminophen, ibuprofen, and diclofenac, published since the consensus meeting, has also been included.^{6,7}

The Canadian Consensus Group made 8 evidence-based recommendations regarding the appropriate and safe use of NSAIDs/coxibs on the following specific topics: patient-physician communication, indication for the use of NSAIDs, gastrointestinal toxicity, renal considerations, hypertension, cardiovascular risk, geriatric considerations, and pharmacoeconomics (see Table 1). Each recommendation was graded according to level of evidence (see Tables 2 and 3).⁸

Recommendations

Patient-physician communication

Patients should be fully informed about the benefit-to-risk ratios of their treatment options, based on evidence where available. Evolving information should be discussed openly and frankly in order to enhance communication between the patient and the physician (Level 3, Grade C).

A survey carried out between December 13, 2004, and January 10, 2005, by a Canadian patient advocacy group yielded responses from 109 individuals and revealed that overall, 87% were very satisfied or satisfied with the information they had received about their NSAID. However, 20% reported that they had had no say in the choice of medication. Therefore, communication between the patient and the physician should include decision-making and education regarding the use of the medication.

Indications

NSAIDs, including coxibs, are generally more effective and preferred by patients over acetaminophen for pain control in OA and RA. The lowest effective oral dose should be used; topical therapy with an NSAID preparation may be appropriate. Depending on the individual patient, an initial clinical trial of acetaminophen may be warranted (Level 1, Grade A).

Both nonselective NSAIDs and coxibs have been found to be more effective than acetaminophen 4 g daily in patients with OA,⁹⁻¹³ and patient preference studies have found that over twice as many patients preferred NSAIDs or coxibs to acetaminophen.¹¹⁻¹³ However, given its safety profile, acetaminophen should still be considered the first-line drug for patients with OA.^{11,12}

Key points

- The goal of the Third Canadian Consensus Conference was to make recommendations to Canadian physicians on the appropriate and safe use of nonsteroidal anti-inflammatory drugs (NSAIDs), including selective COX-2 inhibitors, in the treatment of osteoarthritis and rheumatoid arthritis.
- The recommendations made by the Consensus Group could help pharmacists:
 - Properly inform patients of the potential benefits and risks that are associated with NSAID use
 - Identify patients at high risk for gastrointestinal events and recommend appropriate gastrointestinal protection
 - Recommend appropriate and safe ways of using NSAIDs in patients with renal insufficiency, hypertension, and cardiovascular disease

TABLE 1 Summary of Recommendations

Category	Recommendation	Level of evidence*	Grade of recommendation**
Patient-physician communication	Patients should be fully informed about the benefit-to-risk ratios of their treatment options, based on evidence where available. Evolving information should be discussed openly and frankly in order to enhance communication between the patient and the physician.	3	C
Indications	NSAIDs, including coxibs, are generally more effective and preferred by patients over acetaminophen for pain control in OA and RA. The lowest effective oral dose should be used; topical therapy with an NSAID preparation may be appropriate. Depending on the individual patient, an initial clinical trial of acetaminophen may be warranted.	1	A
GI toxicity	In patients with risk factors for perforations, ulcers, and bleeds, a coxib is still the NSAID of choice, depending on the patient's cardiovascular risks. If NSAIDs must be used in high-risk patients (e.g., those with a history of GI bleeding), prescribe a PPI as well. NSAIDs can adversely affect the entire GI tract; however, the prevalence of clinically relevant NSAID-associated lower GI disease is unclear.	1	A
Renal considerations	Before starting a nonselective NSAID or coxib, determine creatinine clearance in patients over age 65 or in those with comorbid conditions that may affect renal function. Coxibs, like nonselective NSAIDs, should be used with caution in any patient with significant renal disease (proteinuria or glomerular filtration rate <60 mL/min).	3	C
	Volume depletion is a risk factor for NSAID-induced acute renal failure. Consider recommending that patients refrain from the use of their NSAID if they cannot eat or drink that day.	4	D
Hypertension	In patients receiving antihypertensive drugs, re-measure blood pressure within a few weeks after initiating NSAID or coxib therapy and monitor appropriately. If the introduction of the drug is associated with a rise in blood pressure, the dose of the NSAID/coxib and/or the antihypertensive drug must be modified.	1	A
Cardiovascular risk	Patients on rofecoxib have been shown to have an increased risk of cardiovascular events. Current data suggest that this increased cardiovascular risk is a class effect of the coxibs.	1	A
	Given that information on cardiovascular risk is evolving, physicians and patients should weigh the benefits and risks of NSAID/coxib therapy. This concern emphasizes the need to routinely assess patients' cardiovascular risks.	4	D
Geriatric considerations	The use of nonpharmacologic therapies should be maximized before considering the use of NSAIDs/coxibs. These drugs should be used with caution in elderly patients, who are at the greatest risk for serious GI, renal, and cardiovascular side effects. Risks associated with NSAID/coxib combinations are cumulative.	3	C
Pharmacoeconomics	Although the data from health economic studies are ambiguous, prescription of coxibs in patients at high risk for developing GI events may be a more cost-effective strategy than the use of nonselective NSAIDs plus a proprietary PPI.	3	C

* See Table 2 for categories of evidence; ** See Table 3 for grades of recommendation; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; PPI = proton pump inhibitor.

TABLE 2 Categories of evidence

Category	Level
Meta-analysis of RCTs	1A
At least one RCT	1B
At least one controlled study without randomization	2A
At least one quasi-experimental study	2B
Descriptive studies, such as comparative, correlation or case-control studies	3
Expert committee reports or opinions and/or clinical experience of respected authorities	4

RCT = randomized, controlled trial

TABLE 3 Grades of recommendation

Evidence	Grade
Category 1 evidence	A
Category 2 evidence or extrapolated recommendation from Category 1 evidence	B
Category 3 evidence or extrapolated recommendation from Category 1 or 2 evidence	C
Category 4 evidence or extrapolated recommendation from Category 2 or 3 evidence	D

TABLE 4 Risk factors for NSAID-associated ulcer complications

Risk factor	RR
History of complicated ulcer	13.5
Use of multiple NSAIDs (including ASA)	9.0
Use of high-dose NSAIDs	7.0
Use of anticoagulant	6.4
Age >70 years	5.6
Use of steroids	2.2

RR = relative risk; NSAID = nonsteroidal anti-inflammatory drug; ASA = acetylsalicylic acid.

At present, only one commercially prepared topical anti-inflammatory agent, diclofenac 1.5% in dimethylsulfoxide (Pennsaid), is available in Canada.¹⁶ Results from 3 randomized, controlled

trials suggest that this formulation of diclofenac is more effective than placebo and as effective as oral diclofenac for the treatment of OA of the knee, but with a lower rate of adverse events.¹⁷⁻²⁰ This treatment is a reasonable alternative or additional therapy for patients who prefer a topical treatment, are intolerant of oral medications, are insufficiently improved by acetaminophen, or fall into high-risk groups for the use of oral NSAIDs.

Gastrointestinal toxicity

In patients with risk factors for perforations, ulcers, and bleeds (PUBs), a coxib is still the NSAID of choice, depending on the patient's cardiovascular risks. If NSAIDs must be used in high-risk patients (e.g., those with a history of GI bleeding), prescribe a proton pump inhibitor as well (Level 1, Grade A). NSAIDs can adversely affect the entire GI tract; however, the prevalence of clinically relevant NSAID-associated lower GI disease is unclear.

Some of the risk factors for NSAID-associated ulcer complications are summarized in Table 4.²¹⁻²³ Infection with *Helicobacter pylori* is a predisposing factor for ulcers even without the use of NSAIDs; however, NSAIDs appear to increase *H. pylori*-associated risks. In a meta-analysis of 5 controlled studies involving 661 patients, the endoscopically proven ulcer rate was 25% among *H. pylori*-negative and 49.2% among *H. pylori*-positive patients who were using NSAIDs.²⁴ *H. pylori* eradication and the concomitant use of a PPI decrease the incidence of ulcers among NSAID users.^{25,26}

Nonselective NSAIDs are appropriate for patients at low risk for GI complications (i.e., under age 65, with no other risk factors for upper GI complications). Patients over age 65 — or with a suspected history of ulcer — should be tested for *H. pylori* and undergo eradication therapy if they are *H. pylori*-positive before embarking on a long-term course of NSAID therapy.

In patients over age 65, unless cardiovascular risk factors are present, coxibs are preferred to nonselective NSAIDs because they are less frequently associated with either upper or lower GI bleeding or interactions with anticoagulants, selective serotonin reuptake inhibitors (SSRIs), clopidogrel, or corticosteroids.^{21-23,27,28}

Patients at risk who are taking low-dose ASA and who require an NSAID should also receive a PPI for gastroprotection.²⁹ Recent data have revealed that ASA plus a coxib is superior to ASA plus a nonselective NSAID with respect to GI complications.^{30,31} In addition, it should be noted that

TABLE 5 Guidelines for the use of NSAIDs/coxibs

	No elevated GI risk	Elevated GI risk
Not on ASA	Nonselective NSAID alone*	Coxib OR Nonselective NSAID + PPI
On ASA	Nonselective NSAID + PPI** OR coxib + PPI	nonselective NSAID + PPI** OR coxib + PPI

ASA = acetylsalicylic acid; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.

*An individual aged 65 or over would be considered to have an elevated GI risk.

**Generic nonselective NSAID + generic PPI preferred on pharmaco-economic grounds.

the combination of ASA plus a coxib carries a risk of GI complications that is similar to that of a nonselective NSAID alone.^{32,33} Guidelines for the use of NSAIDs/coxibs in patients with GI risk factors are summarized in Table 5.

Renal considerations

Before starting a nonselective NSAID or coxib, determine creatinine clearance in patients over age 65 or in those with comorbid conditions that may affect renal function (Level 3, Grade C). Coxibs, like nonselective NSAIDs, should be used with caution in any patient with significant renal disease (proteinuria or glomerular filtration rate <60 mL/min) (Level 4, Grade D).

Volume depletion is a risk factor for NSAID-induced acute renal failure. Consider recommending that patients refrain from the use of their NSAID if they cannot eat or drink that day (Level 4, Grade D).

It is important to check creatinine clearance both before and after initiating chronic NSAID/coxib therapy, especially in individuals at high risk of renal failure, such as the elderly. Creatinine clearance should be estimated using the Cockcroft-Gault formula, which takes into consideration patient's age, weight, and sex^{34†}:

$$\text{Creatinine clearance} = \frac{140 - \text{age [y]} \times \text{weight (kg)}}{\text{Serum creatinine } (\mu\text{mol/L})}$$

(Multiply by 1.2 for male patients)

The risk of NSAID-associated renal dysfunction is low in most people and is usually reversible upon the discontinuation of the NSAID.³⁵ However, in the presence of pre-existing renal disease or renal hypoperfusion, the risks of NSAID-induced renal toxicity may be much higher.³⁶ This is also true in cases of concomitant therapy with other drugs, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, other antihypertensive agents, aminoglycosides, or cyclosporine A.³⁶ It is important to recognize that coxibs do not offer greater renal safety than nonselective NSAIDs.^{37,38}

Hypertension

In patients receiving antihypertensive drugs, re-measure blood pressure within a few weeks after initiating NSAID or coxib therapy and monitor appropriately (Level 1, Grade A). If the introduction of the drug is associated with a rise in blood pressure, the dose of the NSAID/coxib and/or the antihypertensive drug must be modified (Level 1, Grade A).

Meta-analyses, randomized, controlled trials, and case control studies have shown that NSAIDs/coxibs can raise blood pressure in both normotensive and hypertensive individuals.³⁹⁻⁴⁴ Increases in blood pressure were seen more frequently with rofecoxib than celecoxib.^{40,41,45} Blood pressure monitoring should be done on a regular basis in all patients receiving NSAIDs/coxibs.

*In order to facilitate the estimation of the creatinine clearance, participants at the Second Canadian Consensus Conference on NSAIDs developed a creatinine clearance slide rule based on the Cockcroft-Gault formula. The physician simply aligns the patient's serum creatinine level against weight and reads the calculated creatinine clearance according to the patient's age and sex. Individuals may obtain a ruler upon request from creatinineclear@aol.com.

†This tool was created and developed by the Consensus Committee. Its distribution gratis for physicians via an e-mail request was possible through sponsorship by all the contributors to the Consensus Meeting.

Moreover, coxibs and other NSAIDs antagonize the antihypertensive effects of agents blocking the renin-angiotensin-aldosterone system, such as ACE inhibitors or angiotensin II receptor blockers, and (to a lesser degree) beta-adrenergic blockers.

To avoid destabilizing blood pressure, the lowest feasible dose of NSAID/coxib should be used for the shortest time necessary to achieve the desired therapeutic effect.

Cardiovascular risk

Patients on rofecoxib have been shown to have an increased risk of cardiovascular events (Level 1A, Grade A). Current data suggest that this increased cardiovascular risk is a class effect of the coxibs (Level 1A, Grade A).

Given that information on cardiovascular risk is evolving, physicians and patients should weigh the benefits and risks of NSAID/coxib therapy (Level 4, Grade D). This concern emphasizes the need to routinely assess patients' cardiovascular risks (Level 4, Grade D).

The proposed mechanism explaining the increased incidence of cardiovascular events associated with the use of selective COX-2 inhibitors is that selective inhibition of prostacyclin (an inhibitor of platelet aggregation) without concomitant inhibition of thromboxane (a potent promoter of platelet aggregation and vasoconstriction) could create an imbalance in favour of thrombosis and thus increase the risk of a cardiovascular event.

The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial was the first study to show an increase in overall cardiovascular events with a coxib: rofecoxib 50 mg daily was associated with a significantly greater event rate than naproxen 500 mg twice daily.^{46,47} This difference was driven by a significant 5-fold increase in the incidence of myocardial infarctions. Subsequent meta-analyses of cardiovascular events in all rofecoxib trials showed that rofecoxib was associated with more cardiovascular events than naproxen, but not with other nonselective NSAIDs or placebo.^{48,49}

The Adenomatous Polyp Prevention on Vioxx (APPROVe) trial provided clear evidence for an increased risk of cardiovascular events with rofecoxib over placebo.⁵⁰ This trial was terminated early when the data showed a significant 2-fold increase in the incidence of thromboembolic adverse events in the rofecoxib 25 mg daily group over the placebo group. These results led to the withdrawal of rofecoxib from the market on September 30, 2004.³

Is the increased risk of cardiovascular events a class effect of the coxibs?

In the Celecoxib Long-term Arthritis Safety Study (CLASS), there was no evidence for increased risk of cardiothrombotic events with celecoxib compared to nonselective NSAIDs.³² However, in the Adenoma Prevention with Celecoxib (APC) study, there was a significant increase in cardiovascular events among patients receiving celecoxib 400 mg twice daily and 200 mg twice daily.⁵¹ In contrast, preliminary analysis of data from the Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial showed no increase in cardiovascular risk with celecoxib 400 mg once daily,⁵² nor did an early analysis of data from the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), which evaluated celecoxib 200 mg twice daily.⁵³

In the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) study, lumiracoxib, approved in November 2006 by Health Canada, was associated with a nonsignificant increase in the risk of cardiovascular events compared with naproxen, but not with ibuprofen, and only among patients in the non-ASA group.³³ Etoricoxib, which has been approved by the European regulatory authority, has been associated with rates of thrombotic cardiovascular events similar to diclofenac.⁵⁴

In terms of drug-to-drug interactions, coxibs may be preferred over nonselective NSAIDs for patients who are also taking anticoagulants, SSRIs, or clopidogrel, because these drugs are themselves associated with GI bleeds.^{21-23,27,28} Both coxibs and nonselective NSAIDs should be used with caution in patients receiving diuretics, antihypertensives, or cyclosporin A.^{35,36}

Geriatric considerations

The use of nonpharmacologic therapies should be maximized before considering the use of NSAIDs/coxibs. These drugs should be used with caution in elderly patients, who are at the greatest risk for serious GI, renal, and cardiovascular side effects (Level 3, Grade C). Risks associated with NSAID/coxib combinations are cumulative.

Patients over age 65 are especially vulnerable to drug toxicity for many reasons, including difficulties with treatment compliance, nutritional insufficiency, altered pharmacokinetics, and the potential for drug-drug interactions arising from polypharmacy.⁵⁵ Moreover, most clinical drug trials exclude the elderly (with or without comor-

Points clés

- Le but de la troisième Conférence consensuelle canadienne était de formuler des recommandations à l'intention des médecins canadiens, sur l'usage adéquat et sécuritaire des anti-inflammatoires non stéroïdiens (AINS), y compris des inhibiteurs sélectifs de la COX-2, pour le traitement de l'arthrose et de la polyarthrite rhumatoïde.
- Or les recommandations formulées lors de la Conférence pourraient également être utiles aux pharmaciens :
 - Bien renseigner les patients sur les avantages et les risques pouvant être associés à l'usage des AINS.
 - Déterminer les patients à hauts risques d'événements gastro-intestinaux et leur recommander une protection gastro-intestinale appropriée.
 - Recommander des façons appropriées et sécuritaires d'administrer des AINS pour les patients qui souffrent d'insuffisance rénale, d'hypertension et de maladies cardiovasculaires.

bid disease), and results obtained with younger patients cannot necessarily be extrapolated to the geriatric setting.

Cost-effectiveness

Although the data from health economic studies are ambiguous, prescription of coxibs in patients at high risk for developing GI events may be a more cost-effective strategy than the use of nonselective NSAIDs plus a proprietary PPI (Level 3, Grade C).

NSAID-induced GI adverse events have considerable economic consequences for health care budgets. A study using the Régie de l'assurance maladie du Québec (RAMQ) database in Quebec found that for each dollar spent on nonselective NSAIDs, an additional \$0.66 was spent on their side effects.⁵⁷

One of the most comprehensive economic analyses⁵⁸ compared the costs of celecoxib and rofecoxib to nonselective NSAIDs among patients in Canada with RA or OA whose average age was 58 years. The model analyzed decreases in quality-adjusted life years (QALY) associated with GI and cardiovascular events. Among high-risk patients, celecoxib and rofecoxib were both less costly and more effective than nonselective NSAIDs plus PPIs. Assuming a threshold of \$50,000 per QALY gained, analysis by age group showed that rofecoxib and celecoxib would be cost-effective in patients aged over 76 and 81 years, respectively, who had no additional risk factors. Doubling the GI risk reduced the age thresholds to 56 and 67 years, respectively. However, the estimated cost for PPIs used in this model was higher than the current cost of generic

PPIs available in Canada, a change that might affect the results.

Another study comparing an NSAID, an NSAID plus a PPI, or a coxib revealed that for patients at low risk for adverse events, generic NSAIDs were the most cost-effective. However, an NSAID plus a PPI appeared to be the better choice for higher-risk patients (e.g., those taking ASA and especially those with more than one risk factor for a gastrointestinal complication).²⁹

Emerging new data

Since this meeting was held, new evidence has been emerging rapidly, including the withdrawal of valdecoxib from the marketplace⁵ and data showing that traditional NSAIDs and even acetaminophen are associated with cardiovascular risk.⁶ Acetaminophen users consuming greater than 15 tablets per week had an increased risk (RR 1.68) for cardiovascular events compared with an RR of 1.86 for users of traditional NSAIDs.⁶

A recent meta-analysis examined 121 placebo-controlled trials comparing a selective COX-2 inhibitor versus placebo, and a 42% proportional increase of a first vascular event (RR 1.42) was noted in the users of COX-2 inhibitors.⁷ About two-thirds of the vascular events occurred in long-term users (greater than 1 year) of coxibs, and this appeared to be dose-related. When selective COX-2 inhibitors were compared with naproxen (500 mg twice daily), a highly significant increase (RR 1.57) in the incidence of a cardiovascular event was noted, driven mainly by a 2-fold increased risk of myocardial infarction. Compared with ibuprofen or diclofenac, there was no difference in cardiovascular risk with COX-2 inhibitors. However, both ibuprofen (800 mg 3 times daily) and diclofenac (75 mg twice daily) compared with placebo had an increased relative risk of a serious cardiovascular event of 1.51 and 1.63, respectively. These observations may be explained by the prolonged half-life of 14 hours for naproxen, which, when given at 500 mg twice daily, results in sustained inhibition of COX-1-dependent thromboxane synthesis, whereas ibuprofen and diclofenac have much shorter half-lives (1 to 2 hours), and standard 2 or 3 times daily dosing have only transient effects. The absolute risk of using a selective COX-2 inhibitor is associated with approximately 3 extra people having a vascular event per 1000 per year, with most of this excess attributable to myocardial infarction.⁷

Conclusion

The mandate of the Third Canadian Consensus Conference was to update previous evidence-based

recommendations on the appropriate use of traditional NSAIDs and selective COX-2 inhibitors.⁵⁶

How are pharmacists to interpret these new observations, and what advice are we to give to consumers? Coxibs were developed to fulfill an unmet need by reducing the gastrointestinal complications seen with traditional NSAIDs. In this regard, they are on average twice as safe as the traditional NSAID in decreasing the incidence of serious gastrointestinal ulcers. However, incidental to a large gastrointestinal outcome trial (VIGOR),³⁸ it was noted that rofecoxib was associated with a 5-fold increase in myocardial infarctions. At that time, it was unclear if this increased risk was due to a detrimental effect of rofecoxib or a beneficial effect of the comparator drug, notably naproxen. Subsequently, both rofecoxib and (high-dose) celecoxib have been shown to be associated with adverse cardiovascular events, suggesting that it is a class effect of the COX-2 inhibitors. However, recent studies have now demonstrated that ibuprofen and diclofenac and even acetaminophen (at high doses) carry cardiovascular risk.^{3,4,55}

Considering that anti-inflammatory drugs constitute one of the most commonly used medications in Canada, pharmacists should play a significant part in maximizing the appropriate and safe use of NSAIDs by doing the following:

- Helping inform patients of the potential benefits and risks associated with NSAID use

- Educating patients about the appropriate use of NSAIDs — dosage, dose intervals, stability, precautions, etc. (e.g., suggesting that patients use the lowest effective dose of the medication for the shortest duration, as well as emphasizing the importance of nonpharmacologic therapies)

- Identifying patients at high risk for GI events (perforations, ulcers, and bleeds) and recommending institution of gastroprotection

- Asking patients if their kidney function was evaluated by their physician (e.g., estimating patient's creatinine clearance) before embarking upon chronic NSAID therapy

- Monitoring blood pressure for all patients (hypertensive and normotensive) who are initiating NSAIDs

- Re-evaluating the use of NSAIDs in high-risk patients for cardiovascular events (e.g., recommending the use of a traditional NSAID such as naproxen plus a PPI instead of a COX-2 inhibitor).

In addition, many patients receive various prescriptions from specialized practitioners who may not be aware of their complete pharmacological profile, creating room for medication duplication, drug interactions, and medication errors. Pharmacists have a complete picture of patients' medications, and can determine whether an NSAID is being used safely and appropriately according to evidence-based guidelines. ■

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