Recommendations for the appropriate use of anti-inflammatory drugs in the era of the coxibs: Defining the role of gastroprotective agents

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Treatment with anti-inflammatory drugs and the analgesic efficacy of conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are compromised by a two- to fourfold increased risk of gastrointestinal complications. This increased risk has resulted in an increasing use of the new selective cyclooxygenase-2 inhibitors or coxibs, which, in clinical trials and outcomes studies, reduced gastrointestinal adverse events by 50% to 65% compared with conventional NSAIDs. However, the coxibs are not available to all patients who need them, and NSAIDs are still widely used. Moreover, treatment with a coxib cannot heal preexisting gastrointestinal lesions, and cotherapy with an antisecretory drug or mucosal protective agent may be required.

This paper addresses the management of patients with risk factors for gastrointestinal complications who are taking NSAIDs and makes recommendations for the appropriate use of 'gastroprotec-

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tive' agents (GPAs) in patients who need to take an NSAID or a coxib. When economically possible, a coxib alone is preferable to a conventional NSAID plus a GPA to minimize exposure to potential gastrointestinal damage and avoid unnecessary dual therapy. Patients at high risk require a GPA in addition to a coxib.

Key Words: *Coxibs; Cyclooxygenase-2 inhibitors; Gastroprotective agents; Nonsteroidal anti-inflammatory drugs*

Recommandations concernant l'utilisation appropriée des anti-inflammatoires à l'ère des coxibs : définition du rôle des agents gastro-protecteurs

RÉSUMÉ : Le traitement aux anti-inflammatoires et l'efficacité analgésique des anti-inflammatoires non stéroïdiens (AINS) classiques voient leur portée réduite par l'augmentation, de deux à quatre fois, du risque de complications gastro-intestinales. Ce risque accru a entraîné une utilisation plus grande des nouveaux inhibiteurs sélectifs de la cyclo-oxygénase 2 (coxibs) qui, d'après les essais cliniques et les études sur les résultats, réduisent les effets gastro-intestinaux indésirables de 50 à 65 % par rapport aux AINS classiques. Toutefois, les coxibs ne sont pas accessibles à tous les patients et les AINS sont encore d'usage très courant. De plus, les coxibs ne permettent pas la cicatrisation des lésions gastro-intestinales pré-existantes et il peut être nécessaire de recourir à la bithérapie composée d'un médicament antisécrétoire ou d'un agent protecteur de la muqueuse. Le présent article porte sur la prise en charge des patients présentant des facteurs de risque de complications gastro-intestinales dues aux AINS et formule des recommandations quant à l'utilisation appropriée des agents gastro-protecteurs (AGP) chez les patients qui doivent prendre un AINS ou un coxib. Lorsque la chose est économiquement possible, un coxib seul est préférable à l'association AINS-AGP pour réduire le risque de troubles gastro-intestinaux et éviter le traitement à double modalité. Il faut quand même prescrire un AGP aux patients à risque élevé qui prennent un coxib.

Conventional nonsteroidal anti-inflammatory drugs (NSAIDs) are effective anti-inflammatory and analgesic drugs, but their use is accompanied by an enhanced risk of upper gastrointestinal complications. The management of these events, which range from mild to potentially life-threatening, is an important and practical clinical issue.

Cyclooxygenase (COX) exists in two isoforms – COX-1 and COX-2. COX-1 is important for the protection of the gastric and duodenal mucosa, and the gastrointestinal toxicity resulting from nonselective NSAIDs is mediated by inhibition of COX-1. COX-2 is highly expressed at sites of inflammation, which has led to the development of selective COX-2 inhibitors (coxibs) (1), which control pain and inflammation while sparing the protective effects of COX-1. Initial studies provided evidence of a reduced incidence of endoscopic ulcers and gastrointestinal bleeding with coxibs compared with conventional NSAIDs (2-5) – a finding that has been confirmed subsequently in clinical outcome studies (6-8).

Prescribing practices are currently shifting with respect to patients requiring anti-inflammatory therapy. On the strength of the present evidence, several therapeutic approaches are available: the prescription of conventional NSAIDs, with the addition of a gastroprotective agent (GPA) when it is considered necessary based on the patient's risk of having a gastrointestinal adverse event, or treatment with a coxib, with the addition of a GPA being an option in high-risk patients.

Data from outcome studies, plus evidence from current clinical practice, indicate that coxibs offer a clinical efficacy equivalent to that of conventional NSAIDs, with an improved gastrointestinal tolerability profile. Clear, evidence-based recommendations with respect to gastrointestinal safety issues are required to guide prescribing practices. This review presents therapeutic guidelines for physicians who prescribe anti-inflammatory agents, with a view to optimizing the cost effective use of currently available drugs.

SCOPE OF NSAID-ASSOCIATED GASTROINTESTINAL TOXICITY

Gastrointestinal complications of conventional NSAID therapy

The adverse effects of NSAIDs in the upper gastrointestinal tract include erosions, ulceration, bleeding and perforation, while in the small and large intestine, ulcers, strictures and fibrous diaphragms have been reported. In addition, diverticular bleeding and relapse of inflammatory bowel disease have been described (9).

Endoscopic studies of users of conventional NSAIDs indicate a prevalence of gastric or duodenal ulcers of 15% to 30% (10), with 15% to 20% of patients having gastric ulcers and 5% to 8% having duodenal ulcers. Studies conclude that NSAID use is associated with an approximate fourfold increase in the risk of gastrointestinal complications, which are reported to have an annual incidence of 1% to 4% (11-14).

There is an increasing awareness of the need to consider ulcers according to their site, with duodenal ulcer considered to be a *Helicobacter pylori*-related condition and gastric ulcer an NSAID-related condition. However, due to their effects on COX-1, conventional NSAIDs may cause the ulcer to either bleed or perforate.

Dyspepsia

Dyspepsia is common, with an estimated prevalence in Canada of 28.6% (15). It is unclear whether NSAID therapy causes dyspepsia or simply worsens a pre-existing condition. Studies indicate that 15% to 25% of patients taking NSAIDs experience dyspepsia and that, due to intolerance, treatment is discontinued or medication is changed in about 10% of patients (11-14). Clinical trials enroll highly selected patient populations and exclude patients with co-

morbidity and extensive use of comedication; therefore, estimates of NSAID-related dyspepsia rates may be biased. A recent telephone survey reported that 48% of patients with arthritis and 30% of patients suffering from hypertension who were taking NSAIDs experienced dyspepsia (16). These findings are consistent with those of a previous meta-analysis demonstrating a positive association between NSAID use and dyspepsia (17).

Mortality

Data on the excess gastrointestinal mortality associated with conventional NSAID use are limited (18). The ARAMIS database reported an annual mortality rate of 0.22% in patients suffering from rheumatoid arthritis who were taking conventional NSAIDs compared with 0.05% in those who were not taking NSAIDs (19). However, the background mortality rate in patients with rheumatoid arthritis is likely to be higher than that of the general population. A Canadian report estimated that 1900 deaths each year are attributable to NSAID consumption, which exceeds the number of deaths ascribed to motor vehicle accidents (20). This incidence is consistent with the estimated NSAID-related mortality rate in the United States of 16,500 deaths annually (21).

Most studies of risk factors of peptic ulcer disease associated with NSAID use have been case-control studies in which relative risk was calculated. In practice, absolute event rates are more relevant. The Vioxx Gastrointestinal Outcomes Research (VIGOR) study – a prospective, randomized study (vide infra) – allowed for the calculation of relative and absolute risk (7); age and previous gastrointestinal history were confirmed to be significant risk factors. In patients taking naproxen, the absolute annual risk of having a clinically important gastrointestinal event was 19% for those with a previous gastrointestinal complication and 14% for those older than 75 years of age (22).

Cost implications

Although less than 5% of patients taking NSAIDs experience gastrointestinal complications, such events are associated with substantial direct and indirect costs, which increase with patient age (23,24).

Significant excess costs are attributed to managing NSAID-associated gastrointestinal events. A recent analysis of the Quebec health insurance database (1993 to 1997) noted a higher incidence of gastrointestinal events among NSAID users than among acetaminophen users (odds ratio [OR] 2.4, 95% CI 2.1 to 3.0) (21). The average daily direct medical costs of managing gastrointestinal events was $0.84 per day of NSAID therapy, and for each $1 spent on NSAIDs, an additional $0.66 was spent managing NSAID-related gastrointestinal side effects. A similar review of the Régie de L'assurance-Maladie du Québec database (1993 to 1997) reported that the direct medical costs of gastrointestinal events was $1.34 per day for NSAID therapy, of which $0.94 was directly attributable to the NSAID treatment (25,26).

TABLE 1
Risk factors for nonsteroidal anti-inflammatory drug (NSAID)-associated serious gastrointestinal adverse events

Characteristic	Odds ratio (95% CI)
History of ulcer complications	13.5 (10.3-17.7)
Multiple NSAIDs	9.0 (5.7-14.2)
High-dose NSAIDs	7.0 (5.2-9.6)
Concomitant anticoagulant use	6.4 (2.8-14.6)
Age ≥ 70 years	5.6 (4.6-6.9)
Age ≥ 60 years	3.1 (2.5-3.7)
Concomitant corticosteroid use	2.2 (1.4-3.5)
History of cardiovascular disease	1.8 (1.1-3.2)

Data from references 12, 13, 27 and 28

PREDICTORS OF NSAID-ASSOCIATED GASTROINTESTINAL EVENTS

Risk factors for NSAID-associated gastrointestinal complications

A meta-analysis of controlled trials from 1975 to 1990 described the relative risk of serious gastrointestinal complications associated with conventional NSAID use (27). The overall risk of gastrointestinal events was almost three times higher for NSAID users than for nonusers (OR 2.7, 95% CI 2.5 to 3.0), with the risk of gastrointestinal surgery (OR 7.8, 95% CI 5.8 to 10.3) or fatal outcomes (OR 4.8, 95% CI 3.6 to 6.2) being two- to threefold higher than the risk of gastrointestinal bleeding (OR 2.4, 95% CI 2.1 to 2.7). Additional risk factors were age 60 years or older, prior or unspecified history of gastrointestinal events and concomitant corticosteroid treatment. A possible increased risk in the first three months of NSAID therapy was also noted, although these data may have been based on estimated treatment duration or may reflect a higher level of compliance early in clinical trials. Data from more recent studies suggest that the risk of gastrointestinal events begins with the first NSAID ingestion, with the relative risk remaining similar over time (6,28,29).

Subsequent studies have confirmed these findings and have suggested additional risk factors (Table 1) (12,13,27,28). Patients who had recently switched from one NSAID to another were also at increased risk. However, a history of ulcer with complications was the single most important predictor of a serious gastrointestinal event, irrespective of NSAID use (28).

Relative toxicity of NSAIDs

There may be differences in the relative risks associated with the use of different NSAIDs (12,19,27,28). Data from the ARAMIS database suggest that nabumetone and etodolac are associated with fewer gastrointestinal adverse

events, although the number of patient-years of drug exposure is comparatively low (19).

Although it has been suggested that meloxicam and the nonacidic prodrug nabumetone possess a gastrointestinal tolerability profile superior to that of conventional NSAIDs (19,30,31), data from long term outcome studies are lacking. Individual, short term, comparative studies have not demonstrated a statistically significant benefit for patients with serious gastrointestinal risk – defined as perforations, ulcers and/or bleeds (PUBs) – although a meta-analysis of trials of each drug suggested that there is a pooled benefit, albeit with reservations (30,31). Furthermore, the low dose of meloxicam used in many trials may have resulted in an artificially low incidence of gastrointestinal events in relation to comparator NSAIDs.

H pylori infection

NSAID use and *H pylori* infection are independent risk factors for the development of an ulcer, but there are conflicting data on whether *H pylori* causes mucosal damage in concert with NSAIDs or whether it may be protective to the gastrointestinal tract.

Eradication of *H pylori* infection in long term NSAID users with a current or previous peptic ulcer leads to impaired gastric ulcer healing, with no effect on the incidence of peptic ulcer over six months of follow-up (32). In contrast, two studies of NSAID-naive subjects with no evidence of past or present ulcer disease found a reduced incidence of NSAID-induced ulcers in patients cured of *H pylori* infection before NSAID therapy (33,34).

In *H pylori*-positive NSAID users with endoscopically confirmed upper gastrointestinal bleeding who were randomly assigned after *H pylori* eradication to omeprazole maintenance therapy or no treatment, recurrent bleeding at six months in those continuing to take NSAIDs was significantly lower in those taking omeprazole than in those who had received *H pylori* eradication therapy but no further treatment (35). In contrast, *H pylori* eradication therapy was as effective as omeprazole maintenance treatment in the subgroup taking low dose acetylsalicylic acid (ASA).

These conflicting data with respect to the relationship between NSAIDs and *H pylori* infection have recently been partly clarified by a meta-analysis by Huang and colleagues (36). This study showed that *H pylori* infection is associated with a prevalence of peptic ulcers similar to that seen in NSAID users (25.0% and 26.0%, respectively) compared with non-NSAID-taking, non-*H pylori*-infected control subjects (5.5%) (36). In NSAID users who are also infected with *H pylori,* the prevalence of ulcer is additive (49.2%). The prevalence of 5.5% reported in the present article represents the background level of peptic ulcer disease in the general population of people not taking NSAIDs and not infected with *H pylori.* This is consistent with the prevalence of 7.3% at 12 weeks reported for osteoarthritis patients taking placebo in a recent endoscopic study of an NSAID and the COX-2 selective inhibitor rofecoxib (2), and of 4% at 12 weeks in a trial of patients with rheumatoid arthritis taking celecoxib (4).

Moreover, a prospective study (37) showed that the six-month probability of developing an ulcer was reduced significantly by *H pylori* eradication before treatment with nonselective NSAIDs – 12.1% (95% CI 3.1 to 21.1) in the eradication group and 34.4% (95% CI 21.1 to 47.7) in the placebo group (P=0.0085). The corresponding six-month probabilities of complicated ulcers were 4.2% (95% CI 1.3 to 9.7) and 27.1% (95% CI 14.7 to 39.5; P=0.0026). An editorial that accompanied that paper (37) and the meta-analysis (36) suggested that *H pylori*-infected patients requiring NSAID therapy should be cured of *H pylori* infection before starting their NSAID treatment (38).

NSAID THERAPY AND COPRESCRIPTION OF GPAs

Ulcer healing

Numerous endoscopic studies have examined the healing of ulcers in patients taking NSAIDs. Ranitidine promotes NSAID-associated ulcer healing following 12 weeks of therapy (39). Healing was more effective when the patients stopped taking NSAIDs, suggesting that NSAIDs delay healing even when gastric acid is suppressed by ranitidine. While ranitidine was effective in preventing duodenal ulcers in NSAID users, it was found to be relatively ineffective in preventing gastric ulcers (40,41). A study of an H_2-receptor antagonist (H_2RA), famotidine, in high doses, found a significant reduction in gastric ulcers (42), indicating that a greater degree of acid suppression over that of standard-dose H_2RAs is required to protect against NSAID-associated gastric damage. Two large, double-blind, randomized studies have investigated ulcer healing in patients requiring continued NSAID therapy (43,44). One study comparing omeprazole with ranitidine in standard doses reported significantly higher healing rates after four and eight weeks of treatment with omeprazole for duodenal ulcers (92% versus 81%, P=0.03) and gastric ulcers (84% versus 64%, P<0.001) (43). A further comparative study found significantly higher healing rates after eight weeks of treatment with omeprazole than with misoprostol in patients with duodenal ulcers (93.2% versus 76.6%, P=0.001) and gastric ulcers (87.2% versus 72.8%, P<0.004) (44). Moreover, omeprazole achieved a higher healing rate for duodenal ulcers than for gastric ulcers. The incidence of diarrhea was similar in patients who took omeprazole and those who took misoprostol in that trial (7.6% versus 8.4%). A subsequent study comparing lansoprazole with misoprostol reported a significantly higher incidence of diarrhea with misoprostol (45), which the authors attributed to the misoprostol treatment.

A similar study in patients with gastric ulcers who were still taking NSAIDs reported a significantly higher healing rate with lansoprazole 30 mg daily than with ranitidine 150 mg bid (46). The 20% therapeutic gain for lansoprazole compared with ranitidine in that study is comparable with that reported for omeprazole compared with ranitidine (43).

Prevention of ulcer recurrence

Maintenance studies of ulcer healing in patients taking NSAIDs have shown that significantly more patients remain in remission at six months when treated with omeprazole 20 mg or 40 mg daily than when treated with ranitidine 150 mg bid (72% versus 59%, P=0.004) or misoprostol 200 µg qid (61% versus 48%, P=0.001) (43,44). In the omeprazole- and ranitidine-treated groups, a higher relapse rate was seen for gastric ulcers (5.2% versus 16.3%) than for duodenal ulcers (0.5% versus 4.2%) and erosions (5.7% versus 7.0) (41). For those taking omeprazole, recurrence rates were higher for gastric ulcers than for duodenal ulcers (7.7% versus 2.6%), but for those taking misoprostol, recurrence rates were similar for both ulcer sites (7.8% versus 8.9%), emphasizing the added benefit of acid suppression in patients with duodenal ulcer (44).

A study comparing lansoprazole 15 mg or 30 mg daily with misoprostol 200 µg qid in patients with a history of gastric ulcer but no active ulcer found no significant difference among the treatment groups at four, eight and 12 weeks, although all treatment groups had a significantly higher healing rate than the placebo groups (45).

Outcome studies

NSAID users receiving cotherapy with misoprostol have a reduced incidence of endoscopically visible erosions and ulcers (47,48). A randomized outcome study of patients with rheumatoid arthritis and no peptic ulcer disease but who were taking NSAIDs found that cotherapy with misoprostol reduced the incidence of serious upper gastrointestinal complications by 40% compared with placebo (14). While the absolute magnitude of this reduction (0.57% versus 0.95%) was small, the 51% reduction in serious ulcer complications recorded in this study was similar to the reductions in ulcer rates reported in endoscopic studies (49), suggesting that endoscopic findings may be predictive of the results in NSAIDs outcome studies. However, despite the reduced incidence of NSAID-associated upper gastrointestinal events, the use of misoprostol was complicated by diarrhea, abdominal pain and flatulence, which led to significantly more treatment withdrawals than placebo.

CLINICAL EXPERIENCE WITH COXIBS

Endoscopic studies

Two randomized, placebo controlled trials have demonstrated a significantly lower incidence of ulcers with rofecoxib treatment than with ibuprofen treatment (2,50). In one study, the rate of gastric and/or duodenal ulcers at 12 weeks was significantly lower in patients treated with rofecoxib 25 mg or placebo (4.1% versus 9.9%) than in those treated with ibuprofen 800 mg tid (27.7%, P<0.001) (2). Similarly low ulcer rates were reported in a second study comparing rofecoxib 25 mg with ibuprofen 800 mg tid (5.3% versus 29.2%, P<0.001) (50). In both studies, this reduced incidence of ulcers with the use of rofecoxib compared with ibuprofen was maintained at six months.

The use of celecoxib 200 mg to 800 mg daily is also associated with a low rate of endoscopically defined ulcers, which is similar to that of placebo (6% versus 4%) and significantly lower than that of naproxen (26%, P<0.01) (4).

Outcome studies

Outcome studies have been conducted to investigate whether the favourable endoscopic findings reported with the coxibs translate into a similar decrease in the incidence of clinically significant gastrointestinal events.

The VIGOR study investigated, over one year, the upper gastrointestinal toxicity of rofecoxib 50 mg daily compared with naproxen 1000 mg daily in more than 8000 patients with rheumatoid arthritis (7). The incidence of confirmed upper gastrointestinal events, over the study period of treatment, was significantly lower with rofecoxib 50 mg daily than with naproxen 1000 mg daily (1.4% versus 3.0%, relative risk 0.5; P<0.001). A significantly lower incidence of confirmed complicated upper gastrointestinal events was reported with rofecoxib than with naproxen (0.4% versus 0.9%, relative risk 0.4; P=0.005). This incidence of confirmed complicated upper gastrointestinal events translates into an annualized rate of 0.6%, and 1% to 4% per 100 patient-years, respectively.

The Celecoxib Long-term Arthritis Safety Study (CLASS), reported in *The Journal of the American Medical Association* (6), compared the gastrointestinal toxicities of celecoxib 800 mg daily, ibuprofen 2400 mg daily and diclofenac 150 mg daily over six months in more than 8000 patients with osteoarthritis and rheumatoid arthritis (6). Overall, this study did not reach its primary end point, and the authors reported a numerical, but not statistically significant, difference between the annualized incidences of ulcer complications in patients taking celecoxib and those taking NSAIDs (0.8% versus 1.4%) at six months, but no significant difference was observed at one year (51).

Among subjects not using ASA, the difference in the incidence of ulcer complications between the celecoxib and NSAID groups was significant (0.4% versus 1.3%, P=0.04). The incidence of symptomatic ulcer and ulcer complications was significantly lower with celecoxib use than with use of the comparator NSAIDs in all patients (2.1% versus 3.5%, P=0.02) and in non-ASA users (1.4% versus 2.9%, P=0.02).

Relationship between endoscopic and clinical findings

Endoscopy studies demonstrate that treatment with a coxib decreases the risk of endoscopic ulcer by 70% to 75% at six months compared with conventional NSAIDs (number needed to treat is three to nine), and that coxibs are associated with an incidence of ulcer similar to that seen with placebo (2,4). Outcome studies reflect these findings, with a risk reduction of around 50% in all clinical upper gastrointestinal events at one year (number needed to treat is 41 to 100) (6,7). The risk reduction of complicated upper gastrointestinal events was significant with rofecoxib (60% at one year, number needed to treat is 125) (7).

TABLE 2
Stratification of risk for upper gastrointestinal events

Risk factor	Subgroup
Age	<60 years
	≥75 years
Ulcer	Endoscopically proven
	Time elapsed since diagnosis
	Complications
Cotherapy	Anticoagulants
	Steroids
	Multiple high dose NSAIDs and/or over-the-counter medications

NSAIDs Nonsteroidal anti-inflammatory drugs

ASSOCIATED BENEFITS OF COXIB THERAPY

Incidence of cotherapy

Before the listing of coxibs on the Ontario Drug Benefit Formulary in 2000, 21.6% of patients receiving conventional NSAIDs were coprescribed a GPA (proton pump inhibitor [PPI], or H_2RA, with a small proportion receiving misoprostol) (52). Following the introduction of the coxibs, the rate of coprescription of a GPA with traditional NSAIDs remained unchanged (22.0%), while only 6.8% of patients receiving rofecoxib were coprescribed a GPA. This change in practice was confirmed by a survey of 360 Canadian family physicians, which reported that 37% of patients receiving NSAIDs were coprescribed a GPA compared with only 6% of patients prescribed a coxib. In Ontario, the coprescription rate was 47% for NSAID- and 5% for coxib-takers, respectively (53).

Health resources analysis

An analysis of health care resource use by subjects enrolled in the VIGOR study showed a potential cost savings among coxib users (54). Subjects in the rofecoxib arm required less gastroprotective therapy (23%), fewer upper gastrointestinal procedures (25%) and fewer hospitalizations (50%). A 12-week trial comprising 13,274 patients with osteoarthritis showed that hospitalization rates for upper gastrointestinal diagnoses were two to four times lower and fewer upper gastrointestinal-related health care resources were used by celecoxib-treated patients than by NSAID-treated patients (55).

Risk reduction

An analysis of various risk factors in the VIGOR trial indicated a risk reduction of 88% in the low-risk subgroup, 51% in the high-risk subgroup and 54% in the intermediate-risk subgroup. The risk factors that were significantly associated with gastrointestinal events included age, prior history of clinical gastrointestinal events (complicated or uncomplicated), disease severity, duration of disease, prior history of gastrointestinal symptoms, and prior use of low dose H_2RAs, steroids or NSAIDs (7,22).

USE OF ASA

ASA is widely used for cardiovascular prophylaxis but is a clearly identified risk factor for gastrointestinal hemorrhage (56-59). A meta-analysis of 24 randomized, controlled trials that recruited 66,000 patients reported that 2.5% of patients receiving ASA experienced gastrointestinal hemorrhage, compared with 1.4% taking placebo (59). In subjects who were receiving lower doses of ASA (less than 163 mg/day), the incidence of bleeding fell slightly to 2.3%, compared with 1.5% in the placebo group. However, a meta-regression suggested that there was no relationship between gastrointestinal hemorrhage and ASA dose, and no benefit of modified release formulations.

Although an increased incidence of upper gastrointestinal bleeding has been reported in patients coprescribed low dose ASA and NSAIDs (58), only the CLASS and Successive Celecoxib Efficacy and Safety Study (SUCCESS-I) have attempted to look at this issue prospectively (6,60). The CLASS study reported a lower risk of PUBs in patients receiving a coxib plus ASA than in those receiving an NSAID plus ASA, although this study was not powered to detect these differences (6). Moreover, the difference in the rate of complicated ulcers was very small. Although no statistical analysis was presented in the abstract of the SUCCESS-I study, in this patient subgroup, a reduction was seen in the coxib-treated group for all outcomes studied (60). Compared with conventional NSAIDs, coxib use resulted in a risk reduction of 30% to 88% in serious upper gastrointestinal events in non-ASA users compared with 43% to 63% in ASA users (60). It remains to be determined from appropriately designed, prospective studies whether there is a true difference between these two treatment groups.

OPTIMIZING THE USE OF ANTI-INFLAMMATORY TREATMENTS

Determination of patients at risk

To optimize the use of anti-inflammatory drug treatment, clear guidelines are needed to identify patients at increased risk of adverse upper gastrointestinal events. Evidence from numerous studies indicates that several factors can be used to stratify patients according to risk (Table 2).

Treatment recommendations

Based on a critical review of the current clinical evidence and the opinion of the expert panel, recommendations can be made for the optimal use of conventional NSAIDs and coxibs according to individual patient risk profiles (Table 3).

When considering a GPA, more predictable and prolonged acid suppression with a PPI is effective for ulcer healing and prevention (43,44), while misoprostol is effective for the prevention of gastric ulcer but is not widely prescribed because of side effects (44).

Patients can be stratified by risk. For de novo patients with none of the specified risk factors for gastrointestinal injury, both conventional NSAIDs and coxibs given alone can be considered, following a discussion with the patient

TABLE 3
Treatment recommendations for patients requiring anti-inflammatory therapy

Patient profile	Treatment recommendations
De novo patient	
High-risk patient	Coxib plus GPA
Previous upper gastrointestinal bleeding; age 75 years or older; concomitant treatment with steroids or anticoagulants; or two or more other risk factors (Table 1)	
Intermediate-risk patient	Coxib alone
One risk factor plus no upper gastrointestinal bleeding plus aged 60 to 75 years	
Low-risk patient	NSAID or coxib alone
No risk factors	Discuss features of both drugs with patient
Previously treated patient	
Previous ulcer disease (*Helicobacter pylori*-positive or -negative)	Coxib, eradication of *H pylori* if present
Prior complicated ulcer at any site	Coxib plus GPA
	Eradication of *H pylori* if present
Dyspepsia	
Mild or intermittent	H_2RA or PPI
Moderate or nonresponding	PPI
Current therapy with NSAID plus GPA	Re-evaluate as for de novo patients Risk factors: treat as for de novo patients

GPA Gastroprotective agent; H_2RA H_2-receptor antagonist; NSAID Nonsteroidal anti-inflammatory drug; PPI Proton pump inhibitor

about the relative effectiveness, adverse effects and cost. For high-risk patients with a history of previous upper gastrointestinal bleeding, aged 75 years or older, on cotherapy with corticosteroids or anticoagulants, or having at least two other risk factors (see Table 1), it is wise to combine a coxib with a GPA. In the remaining patients at intermediate risk, defined as the presence of one risk factor in patients younger than 75 years of age but older than 60 years of age and no history of bleeding, a coxib is recommended as the treatment of choice.

Intermediate- and low-risk patients with previous ulcer disease should be considered for treatment with a coxib, irrespective of *H pylori* status, with eradication therapy being prescribed when appropriate and in keeping with current Canadian guidelines (61). In patients with previous complicated ulcer disease (ie, bleeding or perforation), the addition of a GPA should be considered. Patients who require an NSAID for the first time and who have a history of an *H pylori*-positive duodenal ulcer disease with confirmed *H pylori* eradication, can probably be considered to have returned to a baseline risk of gastrointestinal injury.

Although GPA coprescription is frequently driven by the presence of abdominal pain and dyspeptic symptoms, these are not predictive of endoscopic findings or the potential for a serious outcome in patients receiving NSAIDs. In the absence of other risk factors, dyspepsia in NSAID users can be managed initially with an H_2RA, although it is important to emphasize that there is no evidence that this strategy protects against other serious gastrointestinal events. There are no primary studies of symptomatic relief with the use of PPIs in patients with NSAID-associated dyspepsia, but due to their superior antisecretory effect, PPIs are likely to be more effective than H_2RAs in this situation. Moreover, PPIs may provide the additional benefit of a reduction in ulcer incidence and gastrointestinal complications. Outcome studies have reported a similar and significant reduction in dyspepsia with the use of coxibs that was maintained across the duration of the studies; however, some dyspeptic symptoms were still present (6,7,62).

Patients who are already receiving established therapy with an NSAID plus a GPA should be reviewed according to these recommendations. Patients moving from the high-risk to the intermediate-risk group by virtue of a change in their risk factors, such as cotherapy (multiple NSAIDs, corticosteroids or anticoagulant therapy), should be reassessed with a view to stopping the GPA when appropriate or switching to a coxib alone.

The use of multiple NSAIDs carries a high risk of adverse upper gastrointestinal events, and physicians who prescribe conventional NSAIDs or coxibs should warn their patients against taking concomitant over-the-counter NSAIDs. The use of conventional NSAIDs, even at over-the-counter doses, in combination with a coxib, reduces the benefits of the coxib and increases the patient's risk of having an adverse gastrointestinal event.

Management of ASA users

Patients at risk of gastrointestinal complications and taking ASA for cardiovascular protection are also at risk and,

therefore, should receive a GPA according to current recommendations (63).

The VIGOR study suggested that patients receiving NSAIDs are not screened sufficiently for cardiovascular risk nor adequately considered for treatment with a cardioprotective agent (7). It is recommended that patients requiring treatment with either a conventional NSAID or a coxib should be screened for cardiovascular risk factors because low-dose ASA can provide the benefit of cardioprotection at the expense of a small risk of gastrointestinal complications (64). A recent abstract suggested that rofecoxib is unlikely to interfere with the cardioprotective effects of ASA (65).

H pylori testing

While there are studies supporting *H pylori* eradication treatment before the prescription of an NSAID (33,34), there are no Canadian data to support this practice. The prevalence of *H pylori* infection is relatively low in Canada, at 29% (66,67), and office-based serological testing is an inappropriate diagnostic method in primary care (66,61). Canadian recommendations do not advocate the routine testing of individuals before prescribing NSAIDs or coxibs, but do recommend eradication of *H pylori* infection in patients who are known to be *H pylori*-positive (61).

Ulcer location

The issue of ulcer location is confusing because of the lack of data in the majority of studies specifying a gastric or duodenal site. Thus, current data do not permit evidence-based recommendations for treatment according to prior ulcer location. However, because duodenal ulcer is essentially an *H pylori*-related disease, coxibs are expected to have less effect, other than delaying healing. Conventional NSAIDs have a greater causal role in gastric ulceration; therefore, coxib treatment is expected to reduce the incidence of these lesions. This hypothesis is supported by results of the VIGOR study, which showed a 50% reduction in gastric ulcers and a 15% reduction in duodenal ulcers in patients receiving rofecoxib (7). The COX-1-sparing effect of the coxibs decreases the incidence of bleeding in both cases. Because antisecretory therapy is more effective against NSAID-associated duodenal ulcers than against NSAID-associated gastric ulcers, a coxib would be a useful therapeutic option in this situation. However, the incremental benefit in this situation has not yet been studied.

GPA dose implications

Despite the tolerability and improved protective effect reported in the high-dose famotidine study (42), these are the only data available to support the use of high-dose H_2RAs. Standard-dose PPIs given once daily provide acid suppression that is superior to that of both standard-dose and high-dose H_2RAs. When used as gastroprotective agents for NSAID users, no advantage of higher PPI doses has been demonstrated in clinical trials (43,44,46). The best evidence for misoprostol supports its use at a dose of 200 mg qid, although this dose is not well tolerated.

DISCUSSION

Data from well designed and conducted outcome studies confirm that coxibs have a gastrointestinal tolerability profile that is safer than that of conventional NSAIDs (2,4-7,50). This improved tolerability and gastrointestinal safety are seen in both high-risk and low-risk patients. The reduced incidence of upper gastrointestinal events in patients receiving coxibs (6,7), coupled with the decreased requirement for GPA treatment, suggest that coxib therapy may be cost effective or even cost saving. However, further economic analysis is needed to evaluate this issue fully.

The availability of new anti-inflammatory agents necessitates an update of recommendations for the optimal use of current therapies and the role of gastroprotective agents. When economically possible, the use of a coxib alone is preferred to the use of conventional NSAIDs plus a gastroprotective agent to minimize risk by limiting exposure to potential gastrointestinal damage and avoiding unnecessary dual therapy.

The recommendations presented represent those of an expert panel, following careful consideration of the available evidence. However, guidelines cannot address all clinical scenarios and practice settings, and each case should be managed individually with appropriate clinical judgment.

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