Review of the selective COX-2 inhibitors celecoxib and rofecoxib: focus on clinical aspects

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ABSTRACT

The selective cyclooxygenase-2 (COX-2) inhibitors celecoxib and rofecoxib were designed to have similar efficacy but less gastrointestinal toxicity than traditional nonsteroidal anti-inflammatory drugs (NSAIDs). Their efficacy has been demonstrated in the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, postoperative dental pain and dysmenorrhea. These agents produce fewer endoscopic ulcers, symptomatic ulcers and gastrointestinal bleeds than traditional NSAIDs; although the absolute benefit is small and the gastropreserving effect is negated by concurrent use of low-dose aspirin for cardiovascular risk reduction. Nephrotoxicity and hyptertension remain concerns with COX-2 inhibitors, as they are with traditional NSAIDs. COX-2 inhibitors may be safe alternatives to traditional NSAIDs for patients with aspirin-sensitive asthma.

Key words: celecoxib, rofecoxib, osteoarthritis, rheumatoid arthritis, gastrointestinal bleeding, hypertension, nephrotoxicity, cyclooxygenase, nonsteroidal anti-inflammatory

RÉSUMÉ

Les inhibiteurs sélectifs de la cyclo-oxygénase-2 (COX-2) célécoxib et rofécoxib ont été conçus pour agir de manière aussi efficace que les anti-inflammatoires non stéroïdiens (AINS) traditionnels, mais avec moins de toxicité gastro-intestinale. Ils se sont révélés efficaces dans le traitement de l'arthrose, de l'arthrite rhumatoïde, de la spondylarthrite ankylosante, de la dentalgie post-chirurgicale et de la dysménorrhée. Ces agents provoquent moins d'ulcères endoscopiques, d'ulcères symptomatiques et de saignements gastro-intestinaux que les AINS traditionnels; cependant, le bienfait absolu est faible et l'effet de gastro-préservation est annulé par le recours concomitant à de l'aspirine à faible dose pour la réduction du risque cardiovasculaire. La néphrotoxicité et l'hypertension demeurent une préoccupation avec les inhibiteurs de la COX-2, tout comme avec les AINS traditionnels. Les inhibiteurs de la COX-2 peuvent se révéler une solution de rechange sécuritaire aux AINS traditionnels chez les patients atteints d'asthme hypersensible à l'aspirine.

Introduction

Cyclooxygenase (COX) enzymes mediate prostaglandin generation. COX-1 is expressed in all cells, producing prostaglandins that maintain cellular homeostasis, and COX-2 is an inducible enzyme that generates inflammatory prostaglandins at sites of inflammation and healing. In the stomach, COX-1 enhances mucosal perfusion, bicarbonate production and mucus production — key gastric defense mechanisms. Nonsteroidal anti-inflammatory drugs (NSAIDs) that nonselectively inhibit COX-1 and COX-2 therefore predispose to ulcer formation and upper gastroin-

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testinal bleeding. Selective cyclooxygenase-2 (COX-2) inhibitors were designed around the hypothesis that selective inhibition of the COX-2 isoform should reduce pain and inflammation without compromising gastric mucosal integrity. This hypothesis has been tested in numerous clinical trials.[1–3]

Two COX-2 inhibitors are currently marketed in Canada: celecoxib (Celebrex, Pharmacia Corp., Peapack, NJ) and rofecoxib (Vioxx, Merck & Co., Inc., Whitehouse Station, NJ). Other agents, including valdecoxib, parecoxib and etoricoxib, may be available in the near future. These agents have differing degrees of COX-2 selectivity, but different methods of quantifying COX-2 selectivity provide different results[4] and the lack of a common method leads to confusion about the relative COX-2 selectivity (i.e., specificity) of competing agents. Meloxicam is marketed in Canada and is more COX-2 selective than traditional NSAIDs, however it is generally not regarded as a COX-2 selective inhibitor[4,5] and will not be discussed in this review.

This article reviews the efficacy and safety data available for celecoxib and rofecoxib, emphasizing comparisons between COX-2 inhibitors and traditional NSAIDs rather than comparisons between these two COX-2 inhibitors. The objective is to provide emergency physicians with relevant clinical information to guide their prescribing of these new agents.

Efficacy in selected conditions

Osteoarthritis

Most of the relevant efficacy data comes from trials comparing celecoxib or rofecoxib to various NSAIDs (e.g., naproxen, ibuprofen, diclofenac, piroxicam) in patients with osteoarthritis (OA). In general, these trials were rigorously conducted, used the accepted WOMAC osteoarthritis evaluation system (Western Ontario and McMaster Universities Osteoarthritis Index) and were of sufficient duration to confidently conclude that there are no clinically relevant efficacy differences between COX-2 agents and traditional NSAIDs for OA.[6,7]

Recently, the first head-to-head trial of celecoxib and rofecoxib, sponsored by Merck & Co., Inc., the manufacturer of rofecoxib, concluded that rofecoxib (25 mg/d) was superior to celecoxib (200 mg/d) and acetaminophen 4000 mg/d in reducing pain at rest, stiffness, and in patients' global assessment of response to therapy over a 6-week period in patients with OA of the knee.[8]

Rheumatoid arthritis and ankylosing spondylitis

Published trials comparing celecoxib or rofecoxib to traditional NSAIDs suggest no significant efficacy differences in patients with rheumatoid arthritis (RA) or ankylosing spondylitis.[9] Recommendations from a 1999 consensus conference (sponsored by the manufacturer of celecoxib), upgraded NSAIDs, including COX-2 inhibitors in selected patients, to first-line therapy for moderate or severe OA and RA.[6] Notably, this group downgraded acetaminophen to an "alternative agent" to be used in patients with mild OA. These recommendations, which conflict with a previous guideline favouring acetaminophen as first-line therapy, were based on unpublished studies indicating that patients prefer NSAIDs to acetaminophen.[10] The American College of Rheumatology's current recommendations also include COX-2 inhibitors as first-line agents for OA of the hip and knee.[11]

Acute pain syndromes

A randomized, double-blind crossover study comparing 3 days of treatment with rofecoxib or naproxen for primary dysmenorrhea showed no significant efficacy differences between the 2 agents.[12] Several trials suggest that rofecoxib (50 mg/d) and ibuprofen have similar efficacy in patients with acute postoperative dental pain and other types of postoperative pain.[13–16] As yet there are no published studies evaluating COX-2 inhibitors in renal colic, acute gout, headache syndromes, sickle cell crisis or soft tissue injury — important conditions in the emergency department (ED) setting.

Other indications

COX-2 inhibitors are effective for treating fever. This appears to be a COX-2–mediated phenomenon,[17] and COX-2 inhibitors may have a future role in cancer prevention, particularly colon cancer in patients with familial adenomatous polyposis. Colonic polyps avidly express COX-2, and traditional NSAIDs (e.g., ASA) have been shown to reduce the risk of colon cancer.[18–20] A clinical trial established celecoxib's ability to reduce polyp burden in such patients.[21] The US National Cancer Institute is sponsoring several trials involving celecoxib and rofecoxib for prevention of colorectal and other cancers in precancerous conditions such as Barrett's esophagus, bladder dysplasia and actinic keratoses.[22]

Summary

There is no evidence of a clinically meaningful efficacy difference between COX-2 inhibitors and traditional NSAIDs. Efficacy differences between COX-2 inhibitors may exist, and further research is required to characterize these.

Toxicity of COX-2 inhibitors

Effects on gastric mucosa

Short-term endoscopic studies support the hypothesis that

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COX-2 selective agents cause fewer gastric mucosal ulcers than traditional NSAIDs.[1] In one study, 1149 patients with RA were treated with placebo, celecoxib (100, 200 or 400 mg/d) or naproxen (500 mg/d). Endoscopy done after 12 weeks of treatment showed that 25% of naproxen-treated patients had detectable lesions >3 mm in diameter, compared to 3%–6% of placebo- or celecoxib-treated patients. There was no evidence of a dose-response relationship for celecoxib, and only 1 of the ulcers was symptomatic.[2] In another study, 742 patients with OA were treated with placebo, rofecoxib (25 or 50 mg/d) or ibuprofen (2400 mg/d). Endoscopy after 12 weeks of treatment showed that the incidence of lesions greater than 3 mm was 28%, 9.9%, 7.3% and 4.1% in the ibuprofen, placebo, rofecoxib (50 mg/d) and rofecoxib (25 mg/d) groups respectively. Two gastrointestinal (GI) bleeds occurred in the ibuprofen group and 1 in the rofecoxib group (although, in the latter group the patient was taking only ASA at the time of the bleed).[3]

Endoscopic ulceration is a common trial outcome measure, but the clinical relevance of endoscopic ulcers has been debated. These ulcers are typically asymptomatic, transient and benign; they are rarely associated with clinically important events. In addition, ulcer detection is subject to interobserver variability, and it is important to point out that the durations of therapy used in these trials is much longer than typical treatment courses prescribed by emergency physicians.

Serious GI events (symptomatic ulcer, GI bleed, perforation, gastric outlet obstruction)

Two large randomized, double-blind trials assessed the safety of celecoxib and rofecoxib, relative to traditional NSAIDs in patients with OA and RA.

The CLASS trial

The Celecoxib Long-term Arthritis Safety Study (CLASS)[23] randomized 8059 patients with OA or RA to celecoxib, 400 mg bid (double the recommended maximum dose for RA and 4 times the recommended maximum dose for OA), diclofenac 150 mg/d, or ibuprofen 2400 mg/d. Low-dose ASA for cardiovascular or cerebrovascular prophylaxis was permitted and was used by 20% of patients in both groups. The reported treatment duration was 6 months, but only 57% remained in the study for that long. The primary outcome was clinically significant upper GI event: gastric outlet obstruction, upper GI bleeding or perforation. Many patients had risk factors for these events, including RA (27%), prior GI bleed or ulcer (1.5% and 8.3%), tobacco use (15.4%), *Helicobacter pylori* positivity (38.3%), alcohol use (30%) and age >75 (11.8%).

After a mean treatment duration of 4.25 months (2825 patient-years of follow-up), the investigators found a statistically insignificant reduction in upper GI events in the celecoxib group (0.76% vs. 1.45% per patient-year, $p = 0.09$). The rate of symptomatic gastroduodenal ulcers (a secondary outcome) was significantly reduced in the celecoxib group (2.08% vs. 3.54%, $p = 0.02$; number needed to treat [NNT] = 69 patients for 1 year). Outcome differences were driven entirely by GI bleeds ($n = 10$ vs. 20) and symptomatic ulcers ($n = 19$ vs. 29), since virtually no perforations or obstructions occurred. Among ASA users, there were no significant differences in symptomatic ulcers (4.7% vs. 6.0%; $p = 0.49$), or clinically significant upper GI events (2.01% vs. 2.12%; $p = 0.92$).

Emergency physicians are likely to prescribe shorter courses of therapy; therefore, it is worth noting that the incidence of clinically significant upper GI events for celecoxib vs. NSAIDs was 0% vs. 0.1% and 0.03% vs. 0.23%, at 7 and 28 days respectively ($p > 0.05$ for all comparisons). These data are difficult to interpret given the extremely low event rates.[24] The trial, its authors and the *Journal of the American Medical Association* (*JAMA*) were criticized for presenting misleading data when the US Food and Drug Administration (FDA) revealed that CLASS data actually came from 2 separate clinical trials: a 12-month celecoxib vs. diclofenac trial and a 16-month celecoxib vs. ibuprofen trial.[25–27] Between 6 and 16 months, outcome differences favouring celecoxib became insignificant. For various reasons, including a disproportionate dropout rate of NSAID recipients between 6 and 16 months, the *JAMA* article presented only 6-month data.[28] A review of all the CLASS data led FDA experts to declare: "For upper GI safety and also for global safety, there does not appear to be any meaningful advantage for Celebrex [celecoxib]."[29] The full CLASS study data set is publicly available on the FDA Web site.[30]

The VIGOR study

In the Vioxx Gastrointestinal Outcomes Research (VIGOR) study,[9] 8076 patients with RA were randomized to receive rofecoxib (Vioxx) 50 mg/d or naproxen 500 mg bid. Median duration of follow-up was 9 months, and ASA use was not permitted. The primary endpoint was a composite of symptomatic gastric ulcers, upper GI bleeds, ulcer perforations or gastric outlet obstructions. Many patients had GI risk factors, including prior GI events (7.8%) and systemic steroid use (56%).

After 9 months of follow-up, annualized event rates were 2.1% and 4.5% in the rofecoxib and naproxen arms ($p < 0.001$; NNT = 42 patients for 1 year). When only seri-

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ous events (GI bleeds, perforations or obstructions) were included, the event rates were 0.6 vs. 1.4% per year (p = 0.005; NNT = 125 patients for 1 year). As with the CLASS study, these benefits were entirely due to reductions in GI bleeds (n = 14 vs. 35) and symptomatic ulcers (n = 28 vs. 81). There were no significant differences in perforations, obstructions or duodenal ulcers. Short term (7- or 28-day) data are not available for this trial; however, inspection of the Kaplan–Meier plots for complicated GI events during these time periods reveal no visible divergence of the distributions.[31]

This evidence confirms that rofecoxib and celecoxib are less likely to induce upper GI bleeds and symptomatic ulcers than traditional NSAIDs. The absolute risk reduction is small due to the low baseline event rates, and any benefit appears to be negated by the use of even low-doses of ASA. The ability of low-dose ASA to produce upper GI bleeding has been recently confirmed.[32] Epidemiological data indicate that upper GI bleeds are associated with a cost of Can$2690 per hospitalization and carry a 5%–15% mortality rate.[33,34] Of note, no mortality differences were seen in the CLASS or VIGOR studies.

Although COX-2 inhibitors may have less potential to induce new lesions, COX-2 is important in the healing of gastric erosions. Thus, COX-2 inhibitors may prolong or delay ulcer healing,[35,36] precluding their use in patients recovering from NSAID-induced GI events until it is shown that healing occurs during COX-2 inhibitor therapy. Other case reports of serious GI events while on COX-2 inhibitor therapy have been published,[37–39] although many of these involved patients with other risk factors.

Several approaches are available for patients at risk of upper GI events. These include a COX-2 inhibitor alone, a traditional NSAID plus gastroprotective agent (e.g., misoprostol or proton-pump inhibitor), or a COX-2 inhibitor plus gastroprotective agent. It is not known which is the superior strategy. Neither rofecoxib nor celecoxib have been systematically studied in patients with recent or previous GI bleeds, the group for whom these drugs are most appealing.

Serious non-gastrointestinal adverse effects

Like traditional NSAIDs, COX-2 agents may cause cardiovascular events, renal effects, hypertension and congestive heart failure exacerbations. In the CLASS trial, the overall rate of serious adverse events was slightly higher in the celecoxib groups (6.8% vs. 5.8%, p = NS). In the VIGOR trial, the rate of serious adverse events was significantly higher among rofecoxib than naproxen recipients (9.3% vs. 7.8%; absolute risk increase = 1.5%, number needed to harm = 67 patients for 9 months). Neither trial showed mortality differences.

Cardiovascular effects

COX-2 inhibitors reduce prostacyclin synthesis, which may predispose to adverse cardiovascular effects.[40] Such effects were not apparent in early trials, but data from the VIGOR trial, which prohibited ASA use, showed that significantly fewer myocardial infarctions occurred among naproxen than rofecoxib recipients (0.1% vs. 0.4%; relative risk [RR] = 0.2; 95% CI, 0.1–0.7).[9] The debate was fuelled further by a meta-analysis, based mainly on the VIGOR and CLASS data, which reported a higher overall cardiovascular event rate (including myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden death, ischemic stroke or transient ischemic attack) with rofecoxib (RR = 2.38, 95% CI, 1.39–4.0) but not with celecoxib versus the comparator NSAIDs.[41] This analysis resulted in a whirlwind of criticism identifying significant methodological flaws.[42–48]

A subsequent meta-analysis of 23 trials involving over 28 000 patients addressed the overall safety of rofecoxib compared to placebo, naproxen, ibuprofen, diclofenac or nabumetone.[49] The authors, among them 5 Merck & Co., Inc. employees, concluded that there was no difference between rofecoxib and the studied NSAIDs with respect to a composite endpoint of cardiovascular, hemorrhagic or unknown death plus nonfatal myocardial infarction or stroke (1.09% vs. 1.42%; absolute risk reduction [ARR] = 0.33%; p = NS). For rofecoxib compared to placebo, event rates were 1.51 vs. 1.91 respectively (ARR = 0.4%; p = NS). However, event rates were significantly different with rofecoxib vs. naproxen (1.23% vs. 0.72%; absolute risk increase = 0.51%; NNT = 196).

One logical explanation for these findings is that naproxen has a protective antiplatelet effect,[50] but rofecoxib, diclofenac, nabumetone and ibuprofen do not (in fact, recent data suggest that ibuprofen may inhibit the cardioprotective effects of ASA).[51] The apparent lack of cardiovascular risk seen with celecoxib may be because in the CLASS trial, patients with cardiovascular risk factors were allowed to take low-dose ASA, because celecoxib has only one-fifth the COX-2 selectivity of rofecoxib,[52] because of less vigilant tracking of cardiovascular events, or due to some other as yet unidentified property of the drug.

In summary, there is a theoretical concern regarding the cardiovascular safety of selective COX-2 inhibitors, and there are some data supporting this theory. Until definitive data are available, clinicians should be aware when treating

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patients with cardiovascular risk factors that COX-2 inhibitors lack protective antiplatelet effects,[53] and that the addition of ASA appears to negate COX-2 gastroprotective benefits.

Renal adverse effects

Traditional NSAIDs are thought to cause nephrotoxicity via 3 mechanisms: 1) COX-1 dependant impairment of renal blood flow that can decrease glomerular filtration rate (GFR) and increase creatinine levels in susceptible individuals; 2) sodium and water retention leading to edema and hypertension, and; 3) rarely, papillary necrosis.[4] Initial hopes were that COX-2 did not have an important role in renal homeostasis; however, it is clear that COX-2 is expressed in the kidney[54] and is up-regulated in animal models of salt depletion and experimental heart failure.[55] Therefore, COX-2 inhibitors may have nephrotoxic potential.

Studies in healthy elderly volunteers show that rofecoxib and celecoxib cause a similar degree of sodium and water retention as do traditional NSAIDs,[56,57] and similar or lesser reductions in GFR.[56–59] In otherwise healthy patients with OA or RA, celecoxib and rofecoxib appear to cause a low rate of renal adverse effects similar to traditional NSAIDs (~1% per year).[9] In elderly hypertensive patients, celecoxib and rofecoxib exhibited similar negative effects on serum creatinine, serum potassium and blood urea nitrogen in ~1.5% of patients.[60]

Case reports have documented episodes of acute renal failure, hyperkalemia, metabolic acidosis, hyponatremia, heart failure and tubulo-interstitial nephritis in patients taking celecoxib or rofecoxib,[61–64] although these events occurred mostly in patients with risk factors for nephrotoxicity. In patients with chronic renal insufficiency or renal allografts, celecoxib and rofecoxib have been reported to cause acute renal failure with accompanying congestive heart failure (CHF) and hyperkalemia.[65,66]

It appears that COX-2 inhibitors do not have significant advantages over traditional NSAIDs with respect to nephrotoxicity. These agents, like other NSAIDs, must be used cautiously or not at all in patients with renal disease and those at risk of renal disease (e.g., diabetes, peripheral vascular disease, hypertension, concurrent angiotensin-converting enzyme [ACE]-inhibitor or nephrotoxic drug therapy, congestive heart failure and volume or sodium depletion).

Hypertension

In the CLASS trial, celecoxib produced a lower incidence of hypertension than diclofenac/ibuprofen (1.7% vs. 2.3% per year, NNT = 167).[3] Data from a rofecoxib vs. nabumetone study involving 341 normotensive octegenarians with OA showed no significant effects on blood pressure with either drug.[67]

In a randomized, controlled trial by the SUCCESS VI Study Group, 810 elderly hypertensives with osteoarthritis were randomized to 6 weeks of therapy with rofecoxib or celecoxib.[60] During the study period, 17% of rofecoxib patients and 11% of celecoxib patients ($p = 0.032$) had significant (>20 mm Hg) increases in systolic blood pressure. No significant difference in diastolic blood pressure were noted.

These data suggest that, like traditional NSAIDs, celecoxib and rofecoxib can increase blood pressure in normotensive and hypertensive patients, and that these agents should be used cautiously with frequent blood pressure monitoring in hypertensive patients.

Heart failure exacerbations

Available evidence confirms that NSAIDs may cause CHF exacerbations.[68] Animal models show that rofecoxib interferes with diuretic efficacy,[69] and published case reports suggest that this is also true of celecoxib.[64]

In a study of elderly hypertensives, 9.5% of rofecoxib-recipients vs. 4.9% of celecoxib-recipients developed edema,[60] but the significance of this difference is unclear since more celecoxib patients were on concurrent ACE-inhibitor therapy, which may have been protective. In summary, the limited data available to date suggest that COX-2 inhibitors are as likely as traditional NSAIDs to cause CHF.

Hypersensitivity

In the CLASS trial, the annualized rate of cutaneous reactions (rash, pruritis, urticaria) was 7.5% in the celecoxib group and 4.1% in NSAID controls (number needed to harm = 30 patients for 1 year). Celecoxib has a sulfonamide moiety, and the product monograph states that it is contraindicated in patients with sulfonamide allergy (US prescribing information available at www.celebrex.com). In 1999, there were 74 reports of allergic-type reactions to celecoxib in Canada.[70] Despite this, a meta-analysis involving 11 008 patients enrolled in celecoxib arthritis trials documented only 1 bronchospastic episode and 7 cutaneous reactions in 135 patients who received celecoxib despite documented sulfa allergies.[71] In addition, the rate of allergic-type reactions was the same in patients who received celecoxib, placebo or another active comparator. Celecoxib appears safe in the majority of patients with sulfonamide allergy and may be no more likely than other agents to produce allergic reactions, but close monitoring is prudent.

Patients with ASA-sensitive asthma tend to develop respiratory reactions with all nonselective NSAIDs. Conversely, neither rofecoxib nor celecoxib produce hypersen-

sitivity reactions in ASA-sensitive patients with asthma,[72–74] and rofecoxib has been used safely in non-asthmatics with NSAID-induced angioedema and urticaria.[75] Nonetheless, the monographs for both celecoxib and rofecoxib state that they are contraindicated in patients who have had allergic-type reactions to ASA or other NSAIDs. Time will tell whether COX-2 agents cause serious hypersensitivity reactions in patients with NSAID allergy.

Tolerability

The VIGOR trial does not adequately describe non-GI adverse effects; therefore, the most useful tolerability data comes from the CLASS study and from 2 rofecoxib combined analyses.[76,77] For both celecoxib and rofecoxib, discontinuation rates due to GI adverse effects are lower than for other NSAIDs; however, the clinical importance of these differences is questionable since COX-2 inhibitors still appear to cause a significant amount of dyspepsia and abdominal pain, and the absolute magnitude of any COX-2 benefit is small (NNT to prevent 1 case of dyspepsia = 50–60 patients for 6 months).

In a head-to-head comparison between celecoxib and rofecoxib,[60] the overall rates of noncardiac, nonrenal adverse effects were similar between the drugs (61% vs. 58%), as were withdrawal rates (9% in both groups).

Summary

The selective COX-2 inhibitors rofecoxib and celecoxib have similar efficacy to traditional NSAIDs in a wide spectrum of acute and chronic pain syndromes. They cause fewer endoscopic ulcers than traditional NSAIDs, although the clinical relevance of this is uncertain. With prolonged therapy over several months, rofecoxib and celecoxib cause fewer GI bleeds and symptomatic ulcers. Their relative benefit in preventing upper GI events is significant, but the absolute benefit is extremely small — and benefits are annulled by the concurrent use of even low doses of ASA, which limits the utility of these drugs in elderly patients with cardiovascular disease. Furthermore, selective COX-2 inhibitors may increase the risk of cardiovascular adverse events, and the overall rate of serious adverse events is similar to or higher than the rate with traditional NSAIDs.

COX-2 inhibitors have not been sufficiently studied in patients at risk of serious GI events to conclude that they offer an important safety advantage over traditional NSAIDs combined with gastroprotective agents. They do not have clinically meaningful advantages over traditional NSAIDs with respect to dyspepsia, nephrotoxicity, hypertension or salt and water retention; however, they may be safe alternatives in patients with NSAID hypersensitivity — especially those with ASA-sensitive asthma.

Competing interests: Dr. Loewen received speaker honoraria from Merck–Frosst Canada (manufacturer of Vioxx®) in 2000 for Canadian Council for Continuing Education in Pharmacy (CCCEP)-approved education events.

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