Cyclooxygenase (COX-2) selective inhibitors

Any better than NSAIDs?

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Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study. A randomized controlled trial. Celecoxib long-term Arthritis Safety Study. JAMA **2000;284: 1247-55.**

Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med **2000;343: 1520-8.**

Research question

How do COX-2 selective inhibitors (C2SIs) compare with conventional nonsteroidal anti-inflammatory drugs (NSAIDs) with respect to gastrointestinal (GI) toxicity?

Type of article and design

Randomized, double-blind, placebo-controlled, multicentre trials.

Relevance to family physicians

Nonsteroidal anti-inflammatory drugs are one of the most easily accessible and commonly recommended and prescribed medications. Inhibition of prostaglandin synthesis by the cyclooxygenase (COX) enzyme explains the anti-inflammatory and toxicity profile of these drugs.[1] Two isoforms of COX have been identified: COX-1 and COX-2. Gastrointestinal toxicities from conventional NSAIDs are common and are due to their COX-1 inhibitory effect; COX-2 inhibition is the main mechanism for NSAIDs' anti-inflammatory benefit.

Gastroduodenal ulcers are seen on endoscopic evaluation of 10% to 20% of patients who take NSAIDs regularly; clinically important GI complications occur in 2% to 4% of patients[2] and are responsible for an estimated 1900 deaths yearly in Canada (personal communication from E. Lam of the Canadian Arthritis Society in British Columbia).

Recently, two trials investigated whether the incidence of clinically relevant end points (ie, perforation, ulceration, obstruction, and bleeding) were less frequent with C2SIs (ie, celecoxib and rofecoxib) than with conventional NSAIDs (eg, ibuprofen, diclofenac, naproxen).

Overview of study and outcomes

The Celecoxib Long-term Arthritis Safety Study (CLASS) randomized patients with osteoarthritis (OA) or rheumatoid arthritis (RA) into groups receiving 400 mg of celecoxib—two to four times the United States Federal Drug Administration's approved dose—(3987 patients) or 800 mg of ibuprofen (1985 patients) or 75 mg of diclofenac (1996 patients). The NSAIDs were analyzed as a group. All medications were taken twice daily for 6 months.

Except for stable doses of ≤ 325 mg/d of acetylsalicylic acid and antiulcer drugs, other NSAIDS were not permitted. Patients were excluded if they had had active GI, hepatic, or coagulation disorders or esophageal or gastroduodenal ulceration within the previous 30 days. All clinical events were documented and sent to a committee for blinded confirmation of GI complications.

Primary outcome for the CLASS trial was the annualized incidence of upper GI ulcer complications. Analysis was by intention to treat.

The Vioxx Gastrointestinal Outcomes Research (VIGOR) study randomized 8076 patients with RA to receive 50 mg of rofecoxib once daily (4047 patients) or 500 mg of naproxen twice daily (4029 patients) for a median duration of 9 months (range 0.5 to 13 months). Low daily doses of histamine H_2 receptor

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antagonists were permitted (150 mg of ranitidine, 20 mg of famotidine, 400 mg of cimetidine, or 150 mg of nizatidine). Other NSAIDs and ASA were not permitted. Patients were excluded if they had positive test results for occult blood at baseline. All clinical events were documented and sent to a committee for blinded confirmation of GI complications.

Primary outcome for the VIGOR trial was incidence of confirmed upper GI events (perforation, obstruction, bleeding, and symptomatic ulceration). Analysis was by intention to treat.

Results

In the CLASS study, baseline characteristics of the two groups were similar, and risk factors for NSAID–associated ulcers were well balanced. Most patients were female and white; average age was 60 years. More than 20% of patients in both groups were taking ASA therapy. More patients withdrew from the NSAID group than from the celecoxib group because of adverse drug effects (20.6% vs 18.4%, $P \leq .05$, number needed to harm [NNH] = 46) or lack of therapeutic efficacy (14.8% vs 12.6%, $P \leq .05$, NNH = 46).

Efficacy was not formally assessed, but patients in both groups continued to experience GI symptoms, such as dyspepsia, abdominal pain, diarrhea, nausea, and constipation (36.8% in the NSAID group vs 31.4% in the celecoxib group, $P \leq .05$, NNH = 19). *P* values were simplified to either > .05 or ≤ .05.

The annualized rate of upper GI ulcer complications (primary end point) was similar for both groups (celecoxib 0.76% vs NSAIDs 1.45%, $P > .05$). When the annualized rate of upper GI ulcer complications was combined with that of symptomatic ulcers, the rate reached significance (2.08% vs 3.54%, $P \leq .05$, number needed to treat [NNT] = 69). The rate of upper GI ulcer complications (whether or not symptomatic ulcers were included) was similar in both groups among patients taking ASA, but significantly different among patients not taking ASA (celecoxib 0.44% vs NSAIDs 1.27%, $P \leq .05$, NNT = 121).

In the VIGOR study, the two groups had similar baseline characteristics, but not all risk factors for NSAID-associated ulcers were listed. Most patients were female and white; average age was 58 years. Overall discontinuation rates were similar in both groups. Both drugs were similarly efficacious against RA. Patients in both groups continued to experience GI symptoms, such as dyspepsia, abdominal pain, epigastric discomfort, nausea, and heartburn (data not provided).

Incidence of confirmed upper GI events (primary end point) with use of rofecoxib was significantly lower than with naproxen (1.4% vs 3.0%, $P \leq .05$, NNT = 63). Incidence of myocardial infarction (MI) was higher in the rofecoxib group (0.4% vs 0.1%, $P \leq .05$, NNH = 334), but 38% of those with MIs had valid indications for, but were not receiving, ASA therapy. When the data were analyzed without patients who needed ASA, there was no difference in incidence of MI.

Analysis of methodology

Before publication of the CLASS and VIGOR studies, comparison of C2SIs and NSAIDs was based on endoscopic end points. Because not all ulcers seen on endoscopy were clinically relevant, the results of these trials answered some important questions about differences in toxicity between C2SIs and NSAIDs. The trials were well designed and included Canadian centres, which increases the generalizability of the findings to our practice settings. The C2SI doses were higher than those recommended in clinical practice, so we are assured of fair dose comparisons.

We should be aware, however, that these trials were sponsored by pharmaceutical companies. Also, we only have short-term data (<13 months), making it difficult to extrapolate for the long term. Moreover, use of ASA (or not) has caused much confusion. The CLASS trial is faulted for including ASA users; VIGOR is faulted for not including them. The VIGOR trial, however, supports the hypothesis that, in a clinical setting, C2SIs do not inhibit platelet function and do indeed exhibit a COX-1–sparing effect.

Application to clinical practice

Conventional NSAIDs are COX-2 inhibitors (in that they are anti-inflammatory) but they also inhibit COX-1, an enzyme with protective and homeostatic benefits. The C2SIs do not inhibit the beneficial COX-1 enzyme at therapeutic doses, but the COX-1–sparing effect is never complete. The C2SIs are not more effective anti-inflammatories than traditional NSAIDs are. Choosing to use C2SIs would be based on the benefits seen in the toxicity profile.

Because C2SIs are two to five times more expensive than ASA and traditional NSAIDs and because they reduce but do not eliminate GI complications, they should be reserved for patients with risk factors for NSAID–associated ulcers (eg, advanced age, history of ulcer, concomitant corticosteroids or anticoagulants, high doses of NSAIDs, serious systemic disorders, smoking, and alcohol consumption).[3] Because neither trial included enough patients at high risk for NSAID–associated ulcers, we must make decisions based on the available data and hope that unanswered questions will be addressed in future clinical trials.

The trials enrolled only older patients, so the clinical benefit of C2SIs for young, healthy people has not been rigorously assessed. Also, the fact that the VIGOR primary end point was positive does not make rofecoxib a better drug than celecoxib. Could the difference be due to the fact that all patients enrolled in VIGOR had RA and would tend to be sicker than most of the patients in CLASS who had OA? Could there have been an imbalance between the VIGOR groups as to risk factors for NSAID–associated ulcers?

The high overall drop-out rate in both trials (20% to 30%) was mainly due to adverse drug effects. It is a misconception that these drugs have no GI side effects. We should remember also that different end points are not equally clinically relevant. Careful scrutiny of the data reveals that most patients do not have perforation or obstruction; most of the C2SI benefit is in preventing ulceration and bleeding. In addition, patients who need ASA but do not take it could be at increased risk of MI if they use rofecoxib (or possibly any C2SI) alone. More data are needed to determine the interaction between C2SIs and ASA. Finally, comparisons between C2SIs and NSAIDs plus misoprostol or NSAIDs plus proton pump inhibitors need to be made to determine the safest and most cost-effective regimen for our patients.

Bottom line

- COX-2 selective inhibitors are not more effective than conventional NSAIDs and need not be used as first-line therapy for young, healthy people.
- The C2SIs can be considered for patients at higher risk of NSAID–induced ulcers.
- Patients can still experience GI side effects while using C2SIs.
- Concomitant use of ASA might attenuate any GI toxicity benefits that C2SIs have over conventional NSAIDs. It is likely safer to use ASA and C2SIs than ASA and conventional NSAIDs.

Points saillants

- Les inhibiteurs sélectifs de la COX-2 ne sont pas plus efficaces que les AINS conventionnels et ne doivent pas nécessairement constituer la thérapie privilégiée pour les personnes jeunes et en santé.
- Les inhibiteurs sélectifs de la cyclo-oxygénase 2 (ISCO2) peuvent être envisagés chez les patients à risque de souffrir d'ulcères causés par les AINS.
- L'usage des ISCO2 peut quand même produire des effets secondaires gastro-intestinaux chez les patients.
- Le recours concomitant d'AAS peut atténuer les avantages que présentent les ISCO2 de réduire la toxicité gastro-intestinale par rapport aux AINS. Il est probablement plus sûr d'utiliser l'AAS et les ISCO2 que l'AAS et les AINS conventionnels.

Addendum

Another C2SI, meloxicam, released 5 years ago in Europe, was recently introduced in Canada. Like celecoxib and rofecoxib, it is no more effective than conventional NSAIDs.[4,5] While no large clinical trials using serious upper GI events as the primary end point have been published, meloxicam has been strategically priced lower than celecoxib or rofecoxib.

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