

Motion – Cyclo-oxygenase-2 selective nonsteroidal anti-inflammatory drugs are as safe as placebo for the stomach: Arguments against the motion

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Cyclo-oxygenase (COX) exists in two isoforms, COX-1 and COX-2, that direct the synthesis of prostaglandins, prostacyclin and thromboxane. Traditional nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both isoenzymes, resulting in damage to the mucosa of the stomach and duodenum, but also in cardioprotection. Selective COX-2 inhibitors are less likely to damage the upper gastrointestinal tract, as has been shown by large, randomized, controlled trials. Specifically, the newer agents are superior to ibuprofen and naproxen in this regard, but celecoxib and diclofenac were not significantly different in patients who were not also taking low-dose acetylsalicylic acid. These studies did not include a placebo arm, however, and controlled comparisons of COX-2 inhibitors with placebo have not enlisted enough subjects to demonstrate conclusively that they are equally safe. Selectivity for the COX-2 isoform affords protection against upper gastrointestinal toxicity possibly at the expense of the cardioprotective effect of traditional NSAIDs. This might explain the higher rate of nonfatal myocardial infarction in patients who are given rofecoxib compared with naproxen. A traditional NSAID, combined with either misoprostol or a proton pump inhibitor, is still a suitable alternative to selective COX-2 inhibitors for the treatment of arthritis.

Key Words: *Cyclo-oxygenase-2 inhibitors; Nonsteroidal anti-inflammatory drugs*

Nonsteroidal anti-inflammatory drugs (NSAIDs) are essential to the management of inflammatory musculoskeletal conditions, and are valuable therapeutic alternatives for patients with osteoarthritis (OA) who fail to respond to non-pharmacological interventions and acetaminophen. At the molecular level, NSAIDs are believed to inhibit the activity of two isoforms of the enzyme cyclo-oxygenase (COX) (1).

COX-1 is constitutively expressed in most cells and is responsible for the production of prostaglandins that protect the gastrointestinal (GI) mucosa and regulate renal blood flow. In platelets, COX-1 mediates the production of thromboxane A₂, which causes vasoconstriction and platelet activation and aggregation. The inhibition of this enzyme leads to inhibition of platelet aggregation and intestinal prostaglandin production and, therefore, to the disruption of the defence mechanisms in

Motion : Les anti-inflammatoires non stéroïdiens sélectifs de la cyclo-oxygénase 2 sont aussi sûrs pour l'estomac que les placebos : Arguments contre la proposition

La cyclo-oxygénase (COX) existe sous deux isoformes : la COX-1 et la COX-2, qui dirigent la synthèse des prostaglandines, de la prostacycline et du thromboxane. Les anti-inflammatoires non stéroïdiens (AINS) classiques inhibent les deux isoenzymes, ce qui porte atteinte à la muqueuse de l'estomac et du duodénum mais produit un effet cardioprotecteur. Les inhibiteurs sélectifs de la COX-2 sont moins susceptibles de léser les voies digestives hautes, comme le démontrent plusieurs essais comparatifs, de grande taille, sur échantillon aléatoire. Plus précisément, les nouveaux médicaments s'avèrent supérieurs à l'ibuprofène et au naproxène à cet égard, mais le célécoxib et le diclofénac n'ont pas produit de différences significatives chez les patients ne prenant pas d'acide acétylsalicylique à faible dose. Toutefois, ces études ne comportaient pas de groupe placebo et celles où les inhibiteurs de la COX-2 sont comparés à un placebo ne comptent pas suffisamment de sujets pour montrer hors de tout doute leur degré égal d'innocuité. En fait, la protection des voies digestives hautes par les inhibiteurs sélectifs de la COX-2 se fait aux dépens de l'effet cardioprotecteur des AINS classiques. Cela expliquerait peut-être le taux plus élevé d'infarctus du myocarde non mortels chez les patients prenant du rofécoxib plutôt que du naproxène. L'administration d'un AINS classique, associée à la prise de misoprostol ou d'un inhibiteur de la pompe à protons, pourrait s'avérer une solution de rechange valable aux inhibiteurs sélectifs de la COX-2 pour le traitement de l'arthrite.

the gastric mucosa. This results in the development of GI lesions.

COX-2, an inducible enzyme, is active in the kidney, brain and sites of inflammation, where it produces prostaglandins and prostacyclin, a vasodilator and inhibitor of platelet aggregation. The inhibition of COX-2 produces therapeutic analgesic, anti-inflammatory and antipyretic effects, but also inhibits prostacyclin, which could lead to thrombotic cardiovascular events.

Most NSAIDs that were introduced subsequent to the discovery of acetylsalicylic acid (ASA) inhibit both enzymes and, therefore, incur both desirable and harmful effects. More recently developed NSAIDs, such as nabumetone and meloxicam, are said to cause fewer adverse effects than do traditional NSAIDs, such as naproxen and indomethacin. The newer

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agents have less activity against COX-1, and are thus expected to be less toxic to the gastric mucosa (2).

Clinically relevant toxicities to the gastric mucosa include gastric and duodenal ulcers. Although endoscopic studies have demonstrated the presence of ulcers in approximately 21% of users of standard NSAIDs (3), only 15% of these are associated with symptomatic upper gastrointestinal (UGI) events (4). The other 85% of ulcers are subclinical. Roughly half of the symptomatic ulcers are regarded as complicated UGI events, in that they exhibit active bleeding, perforation or gastric outlet obstruction. Complicated UGI events and other symptomatic ulcers that require clinical evaluation are defined as clinical UGI events. NSAID users are at an almost four-fold greater risk than are nonusers of experiencing a clinical UGI event (5).

Rofecoxib and celecoxib are two COX-2-selective NSAIDs, whose effects on clinical and complicated UGI events have been compared to less selective NSAIDs in randomized controlled trials enlisting roughly 8000 patients each (6,7). In addition, two meta-analyses that summarized the phase II and III experiences with these agents have been published (8,9). Although selective COX-2 inhibitors are less likely than regular NSAIDs to exhibit GI toxicity, it is not entirely clear that they are as safe as placebo.

WHY ARE SELECTIVE COX-2 INHIBITORS NOT AS SAFE AS PLACEBO?

The following arguments are supported by evidence that will be presented in detail:

- There are no studies that compare COX-2 inhibitors to placebo with clinical or complicated UGI events as outcomes;
- The absence of a proof of efficacy does not constitute proof of an absence of efficacy;
- The superiority of selective COX-2 inhibitors over traditional NSAIDs is not clearly established; and

- The lack of cardiovascular protection with selective COX-2 inhibitors requires the coprescription of low-dose ASA, which brings UGI toxicity to the level of traditional NSAIDs.

Argument 1: There are no studies that compare COX-2 inhibitors to placebo with clinical or complicated UGI events as outcomes

The incidence of clinical or complicated UGI events with selective COX-2 inhibitors has been evaluated in two large, randomized, controlled trials: the Celecoxib Long-Term Arthritis Safety Study (CLASS) (6) and the Vioxx Gastrointestinal Outcomes Research Study (VIGOR) (7). The results are given in Table 1.

In CLASS, celecoxib 400 mg bid (two to four times the maximum recommended dose) was compared with diclofenac 75 mg bid or ibuprofen 800 mg tid in 7982 patients over 12 months. In the study population, 28% had rheumatoid arthritis, 72% had OA, 22% received ASA, 30% received corticosteroids, the average age was 60 years and 70% were female (6,10).

In VIGOR, rofecoxib 50 mg daily (two times the maximum recommended dose) was compared with naproxen 500 mg bid in 8076 patients over 12 months. All of the patients in that study suffered from rheumatoid arthritis, none received low dose ASA, 56% were taking corticosteroids and 80% were female (7,11).

Evaluation of the final UGI outcomes was required to obtain approval from the Federal Drug Administration (FDA) to loosen the safety warnings that were included in the product monographs for celecoxib and rofecoxib. While those two studies provided insight into the GI safety profiles of selective COX-2 inhibitors compared with traditional NSAIDs, no comparison was made with placebo. It is, therefore, difficult to know whether there is any clinically relevant difference in terms of the safety between the new NSAIDs and placebo.

TABLE 1
Incidences of complications of nonsteroidal anti-inflammatory drugs (NSAIDs) in the Vioxx Gastrointestinal Outcomes Research Study (VIGOR) and Celecoxib Long-Term Arthritis Safety Study (CLASS) studies

	VIGOR		Celecoxib	CLASS†	
	Rofecoxib	Naproxen		Diclofenac	Ibuprofen
Total patient years	2697	2694	1804	841	874
Clinical UGI events					
Number	56	121	22	10	29
Rate per 100 patient-years	2.08	4.49	1.16	1.19	3.20
RRR COX-2-selective versus traditional NSAIDs		53.7%*		2.5%*	63.8%*
Complicated UGI events					
Number	16	37	9	4	11
Rate per 100 patient-years	0.59	1.37	0.44	0.48	1.14
RRR COX-2-selective versus traditional NSAIDs		56.9%*		8.3%*	61.4%*
Myocardial infarction					
Number	20	4	6	2	2
Rate per 100 patient-years	0.74	0.15	0.33	0.24	0.23
RR COX-2-selective versus traditional NSAIDs		4.93*		1.39*	1.44*

* $P < 0.05$; †CLASS study patients represent a subgroup of patients who were not taking acetylsalicylic acid. COX Cyclo-oxygenase; RR Relative risk; RRR Relative risk reduction; UGI Upper gastrointestinal. Data from references 6 and 7

Argument 2: The absence of a proof of efficacy does not constitute proof of an absence of efficacy

Even if clinically relevant differences in the incidence of clinical or complicated UGI events were not observed between selective COX-2 inhibitors and placebo, this would not be sufficient evidence that such a difference actually existed (12). Data on the final GI outcomes from studies that compared selective COX-2 inhibitors with placebo were compiled in two meta-analyses that summarized all phase II and phase III studies of rofecoxib (8) and celecoxib (9).

The rates of clinical UGI events in the patient populations on traditional NSAIDs, rofecoxib and placebo were 7.2, 2.5 and 2.7 per 100 patient-years of observation, respectively (8). While rofecoxib had slightly lower event rates than placebo, with a relative risk of 0.9, the 95% CI around this figure ranged from 0.25 to 3.6. This implied the possibility of an up to 3.6-fold higher rate of clinical UGI events in the population taking rofecoxib.

Similarly, the pooled analysis of phase II and phase III studies of celecoxib found 4.9, 1.2 and zero clinical UGI events per 100 patient-years of observation among users of traditional NSAIDs, celecoxib and placebo, respectively (9). Assuming one event in the placebo population, calculation of relative risks lead to estimates of 10.1- and 2.5-fold increased rates of clinical UGI events among users of traditional NSAIDs and celecoxib users, respectively, compared with placebo. The 95% CI for the celecoxib group included an up to 50-times higher rate of clinical UGI events. This value is so large because of the small number of patient-years of observation in the phase II and III trials.

Therefore, calculation of CIs, which place bounds on the possible size of the difference between treatments, shows that they include values of clinical importance. Equivalence between selective COX-2 inhibitors and placebo is thus not proven, and will require further studies with appropriate methodology and adequate sample sizes. This recommendation applies only to patients with OA, because it would be unethical to conduct placebo-controlled trials in rheumatoid arthritis.

Argument 3: The superiority of selective COX-2 inhibitors over traditional NSAIDs is not clearly established

Although it is difficult to prove conclusively that the GI safety of selective COX-2 inhibitors is equivalent to that of placebo, it may be almost as difficult to demonstrate the improved safety profile of these agents over traditional NSAIDs. For example, reanalysis of the CLASS data by the FDA showed that, among the 78% of patients who did not take low-dose ASA, the rate of clinical UGI events among celecoxib users was almost identical to the rate observed in patients taking diclofenac, whereas there was a suggestion of

superiority of celecoxib over ibuprofen. The FDA consultant's report concluded:

"No statistically significant differences were shown for the entire population for the primary endpoint of complicated ulcer between Celebrex and the NSAID comparators – combined or individually. Relevant endpoints of the composite of symptomatic/complicated ulcers suggested a difference between Celebrex and ibuprofen in favor of Celebrex. No difference was seen between Celebrex and diclofenac" (11).

Argument 4: The lack of cardiovascular protection with selective COX-2 inhibitors requires the coprescription of low-dose ASA, which brings UGI toxicity to the level of traditional NSAIDs

While a clear superiority in GI toxicity may be demonstrated for rofecoxib compared with naproxen, this result comes with a caveat. As shown in Table 1, there was a significantly higher rate of nonfatal myocardial infarction in the rofecoxib group in the VIGOR study (7). This significant difference might not imply a higher cardiovascular risk for the selective COX-2 inhibitor, but rather a cardioprotective effect of the traditional agent. Traditional NSAIDs exert this effect through the inhibition of the COX-1 isoenzyme. It appears that cardiovascular protection is inversely related to GI safety: high COX-2 selectivity implies high UGI safety but low cardiovascular protection (13).

Celecoxib, whose COX-2 selectivity is reported to be close to that of diclofenac, may be more suitable from a cardiovascular risk perspective, but is less advantageous with respect to UGI safety. These subtle differences need to be considered when prescribing selective COX-2 inhibitors to patients, particularly older patients with rheumatoid arthritis who are at increased cardiovascular risk. The relative lack of a cardioprotective effect with these agents means that there is a need for low-dose ASA, which can lead to clinical UGI events. The use of misoprostol or proton pump inhibitors, in combination with traditional NSAIDs, may well be an adequate therapeutic alternative in such patients.

SUMMARY

It is not clear that selective inhibitors of the COX-2 isoenzyme are as safe for the UGI tract as placebo. Selective COX-2 inhibitors have been shown to cause fewer clinical UGI events than do traditional NSAIDs, but the data comparing the effects of these drugs with placebo are less convincing. Moreover, the newer agents do not share the cardioprotective effects of ASA or traditional NSAIDs. Further studies with adequate sample sizes are required to establish the GI safety of COX-2 inhibitors.

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