



THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

Rofecoxib (Vioxx[®]) withdrawal generates uncertainty about "COX-2s"

Do product monographs adequately inform?

Product Monographs are legal documents that in effect transfer responsibility to the prescribing physician. At issue in this letter is whether the Product Monographs for rofecoxib and the other non-steroidal anti-inflammatory drugs marketed as COX-2 selective NSAID's adequately inform clinicians about the benefits and harms of these drugs.

Health Canada provided us with the following statement about how monographs are prepared: "Draft product monographs are developed by the drug manufacturer according to Health Canada guidelines that provide direction on the content and format. Health Canada reviews the product monograph, makes changes as appropriate, and signs-off on the product monograph before the product is authorized for sale in Canada. **The product monograph serves as a standard against which all professional literature, promotional material, or advertising distributed by the sponsor about the drug can be compared.** Package inserts developed for health professionals, patient package inserts developed for consumers and other forms of drug information are based on information contained in the product monograph. Each year the Canadian Pharmacists Association surveys drug manufacturers for publication of the product monograph in the *Compendium of Pharmaceuticals and Specialties (CPS)*. The Canadian Pharmacists Association formats and publishes the drug monograph as provided by the drug manufacturer."¹

Consider the following case:

A 75 year-old woman with a history of peptic ulcer disease presents to her physician for renewal of her rofecoxib (Vioxx[®]) 25 mg tablets. For 3 years she has taken them daily for osteoarthritis. She initially felt rofecoxib was effective in reducing her symptoms, but is less sure now. She heard that the drug has been withdrawn world-wide and is upset and anxious.

This patient confronts her physician with two relevant questions:

- Was rofecoxib a good choice to treat her osteoarthritis in the first place?
- Should she now be switched to another COX-2 selective NSAID?



For a trustworthy answer, we must restrict the search to evidence from randomized controlled trials (RCTs) that report on validated outcomes that matter to this or similar patients:

- symptoms of arthritis,
- complicated ulcers (major upper gastrointestinal (GI) bleeding, perforation, or obstruction),
- myocardial infarction,
- serious cardiovascular thrombotic events (sudden death, myocardial infarction, unstable angina, ischemic stroke, transient ischemic attack, and peripheral venous and arterial thromboses).

We searched for data regarding these outcomes in the 2004 CPS monographs of rofecoxib², celecoxib³, meloxicam⁴, and valdecoxib⁵.

Do COX-2 selective NSAIDs improve arthritis symptoms more than non-selective NSAIDs?

None of the 4 monographs claims greater symptomatic improvement for the COX-2 selective NSAIDs, compared with older NSAIDs, based on head-to-head RCTs designed to answer this question.

Do COX-2 selective NSAIDs cause fewer complicated ulcers than non-selective NSAIDs?

For rofecoxib the answer is YES, based on data from the VIGOR trial: rofecoxib 0.4%, naproxen 0.9% (RR 0.4 (0.2, 0.8), ARR 0.5%, NNT 200 for 9 months)². For celecoxib the answer is NO, based on the CLASS trials designed to answer this question: celecoxib (0.43%), ibuprofen (0.55%) and diclofenac (0.50%).³ The meloxicam and valdecoxib monographs do not report on RCTs designed to measure this outcome.^{4,5}



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Importantly for this patient all 4 monographs state under **Warnings**: “NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease, ... Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. For high risk patients alternate therapies that do not involve NSAIDs should be considered. Studies have shown that patients with a prior history of peptic ulcer disease and/or GI bleeding and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors.”

Do COX-2 selective NSAIDs cause more cardiovascular thrombotic events than non-selective NSAIDs?

For rofecoxib the answer is YES, based on data from the VIGOR trial: myocardial infarction: rofecoxib, 0.6%, as compared to naproxen, 0.2% (RR 2.9 (1.3, 6.4)*, ARI 0.4%, NNH 250 for 9 months) and serious cardiovascular thrombotic events: rofecoxib, 1.1%, as compared to naproxen, 0.5% (RR 2.4 (1.4, 4.0)*, ARI 0.6%, NNH 167 for 9 months).²

The celecoxib monograph provides data from the CLASS trials for myocardial infarction: celecoxib, 0.5%, diclofenac, 0.2%, and ibuprofen, 0.5%; and for total serious adverse events: celecoxib, 6.8%, diclofenac, 5.6%, and ibuprofen, 6.0%; but states that none of the differences are statistically different. It does not provide serious cardiovascular thrombotic event data.³

The meloxicam monograph presents no data but demonstrates awareness of the potential problem: **Pharmacology**: “Inhibition of COX-2 also inhibits the production of systemic prostacyclin. Inhibition of prostacyclin may have a prothrombotic effect.”⁴

The valdecoxib monograph has a section on **Cardiovascular safety**: It provides a table on the incidence of investigator-reported serious thromboembolic cardiovascular adverse events in controlled trials. These were: placebo, 1.2%, pooled valdecoxib 10-80 mg daily, 1.6% and naproxen 1000 mg, 1.0%.⁵

This Letter contains an assessment and synthesis of publications up to November 5, 2004. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 40 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

Case discussion

After reading the 2001 CPS rofecoxib monograph, the physician would have learned that rofecoxib was not superior to other NSAIDs for relief of arthritis symptoms, been warned against prescribing rofecoxib to this patient with prior peptic ulcer disease, and should have been aware that rofecoxib had not been proven to reduce complicated ulcers (including GI bleeds). In 2003, the rofecoxib monograph was revised to include the evidence from VIGOR that rofecoxib did reduce complicated ulcers and did increase myocardial infarctions and cardiovascular thrombotic events as compared with naproxen. The 2003 and 2004 monographs do **not** mention that the VIGOR trial applies to patients **without** a history of peptic ulcer disease.⁶

In 2004, an astute physician who reads the monographs for celecoxib, meloxicam, and valdecoxib would again be warned against prescribing them to a patient with a history of peptic ulcer disease, and would be left with uncertainty about the benefit of reducing complicated ulcers and the harm of increasing cardiovascular thrombotic events in this patient.

Conclusions:

Product monographs

- Sometimes provide data about drug harms including serious adverse events that is not published elsewhere.
- Represent a challenge in finding, extracting and interpreting the relevant information.
- **Do not adequately inform clinicians** (e.g. the rofecoxib monograph does not provide a complete picture of the relative risk of myocardial infarction and total serious adverse events for rofecoxib versus comparators in all RCTs⁷).

Celecoxib, meloxicam and valdecoxib 2004 monographs

- Do not claim to improve arthritis symptoms better than non-selective NSAIDs.
- Warn against prescribing to patients with a history of peptic ulcer disease.
- Do not claim to reduce complicated ulcers as compared with non-selective NSAIDs.
- **Provide insufficient information as to whether or not these drugs increase myocardial infarction or total cardiovascular thrombotic events.**

* calculated using Cochrane Review Manager software.

References

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For more information see previous Therapeutics Letters on COX-2 selective NSAIDs: #31, #39, and #43.