

The Changing Landscape for COX-2 Inhibitors: A Summary of Recent Events

The announcement on September 30, 2004 of the withdrawal of Merck & Co.'s Vioxx® (rofecoxib) from the international market sent shock waves throughout the medical community and instigated a public outcry over the current regulatory approach to monitoring drug safety (Horton 2004). The events leading up to the largest drug withdrawal in history certainly warrant discussion.

Vioxx® belongs to a relatively new type of non-steroidal anti-inflammatory drugs (NSAIDs) known as cyclooxygenase (COX)-2 inhibitors. NSAIDs are commonly used to manage pain and inflammation associated with acute conditions, such as sports injuries, and chronic conditions, such as arthritis. Approximately one in four elderly people use these drugs. While COX-2 inhibitors offer similar levels of pain relief relative to older, traditional NSAIDs, they are marketed as possessing lower rates of adverse gastrointestinal effects.

The publication of a large randomized controlled trial in November 2000 convincingly demonstrated a favourable gastrointestinal adverse event profile associated with Vioxx® compared to a commonly used traditional NSAID, Naprosyn® (naproxen). A 50% relative risk reduction in serious gastrointestinal outcomes was observed among Vioxx® users relative to Naprosyn (Bombardier et al. 2000). However, in a secondary analysis of general safety, the same clinical trial also suggested a five fold increased risk of heart attack associated with Vioxx® relative to Naprosyn. Consequently, this prompted numerous systematic reviews and observational studies, the results of which further supported a possible adverse cardiovascular effect of Vioxx®, and were published long before Vioxx's® withdrawal from the market.

Despite this mounting evidence, Vioxx® was not withdrawn until the interim results of a second large randomized controlled trial demonstrated an associated increased cardiovascular risk with the drug; this withdrawal of Vioxx® occurred about four years after the first clinical trial suggested cardiovascular risk. Allegations that the cardiovascular risks associated with Vioxx® were suspected by Merck scientists well before the launch of Vioxx® – as early as 1996 (Lenzer 2004) – have cast serious doubts on the ethical conduct of the pharmaceutical industry and its relationship with the Food and Drug Administration (FDA) of the United States, the federal drug regulatory body.

The Vioxx® withdrawal created a common state of confusion about alternative treatments for frustrated patients and prescribing physicians. At this point, the evidence supporting the use of alternative treatments to Vioxx® varies significantly. Alternatives to Vioxx® include treatment with other drugs marketed as COX-2 inhibitors in Canada, such as Celebrex® (celecoxib), Bextra™ (valdecoxib) and Mobic® (meloxicam); traditional NSAIDs, such as Naprosyn® and Advil® (ibuprofen); topical NSAIDs, such as Pennsaid® (topical diclofenac) for limited joint pain; alternative

therapies, such as Lakota®; and non-drug therapies, such as weight-bearing exercise, knee taping and acupuncture. A first choice for many physicians was to switch patients to Celebrex®, as the overwhelming majority of evidence from large comparative studies suggested no excess cardiovascular risk with exposure to commonly used doses.

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In December 2004, however, three large randomized clinical trials examining Celebrex® were halted due to concerns from interim analyses that indicated cardiovascular risks associated not only with Celebrex®, but also with traditional NSAIDs. Two large clinical trials compared Celebrex® at varying doses to placebo for the prevention of pre-malignant colon tumours in more than 3,000 patients. The first of these trials was the Adenoma Prevention with Celebrex® (APC) trial, funded by the US National Institutes of Health (NIH). Among users of Celebrex® at doses of 400 mg daily, the trial found a greater than two-fold risk of cardiovascular events (though not statistically significant). Among those using 800 mg daily of Celebrex®, the trial found a statistically significant three-fold higher risk of such events (Topol 2005). The second of these clinical trials, the Prevention of Spontaneous Adenomatous Polyps (PreSAP), funded by the pharmaceutical company Pfizer, did not find any excess cardiovascular risk associated with Celebrex® at doses of 400 mg daily relative to placebo.

The third trial, the Alzheimer Disease Anti-inflammatory Prevention Trial (ADAPT), funded by the NIH, compared Naprosyn® at doses of 220 mg twice daily to Celebrex® at doses of 200 mg twice daily in roughly 2,400 patients. An approximately 50% greater risk of cardiovascular events among users of Naprosyn®, but not Celebrex®, was demonstrated. With all this confusing and conflicting information, in February 2005, the FDA convened an expert group to review available data and provide recommendations.

The recent events have cast considerable suspicion over the cardiovascular safety of not just COX-2 inhibitors as a drug class, but also the entire NSAID category. Further evaluation will determine the future role of COX-2 inhibitors in managing patients with pain and inflammation. Time will tell whether public confidence in the pharmaceutical industry and government regulatory bodies will be restored.

References

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Wide Variation in Use of Practices to Protect Patients from Harm

According to the latest survey of over 1000 US hospitals conducted by the Leapfrog Group:

- 80% have implemented procedures to prevent wrong-site surgeries
- 70% require a pharmacist to review all medication orders before they are administered

However:

- 70% do not have a formal protocol to assure adequate nursing staff.
- 70% do not have a policy to check with patients to see that they understand the risks of their procedures.
- 60% do not have procedures for preventing malnutrition in patients.
- 40% do not have policies requiring workers to wash hands with disinfectant before and after seeing a patient.

Source: The Leapfrog Group. Date published: 11-16-04

These speakers can change your mind:

Graham Scott, Anthony Fell, Maureen Quigley, Dr. John Frank, Tom Closson, Dr. Mary Ferguson-Paré, Tony Dagnone, Phil Hassen, Dr. Donald Low, Joseph Mapa, Dr. Robert Maunder, Fran McBride, Leslie Vincent, Dr. Matt Morgan, Dr. Ross Baker, Sheila Weatherill, Dr. Sue MacLean, Matthew Anderson, Tom Closson, Hugh MacLeod, Dr. Jim MacLean, Minister George Smitherman, Michael Decter, Dr. Alan Hudson, Dr. Michael Guerriere. They have been our special guests. Before summer we'll hear: Richard Alvarez, Hume Martin, Adalsteinn Brown, Mary Jo Haddad, Gail Paech.

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