COX-2 Inhibitors:
Are They All Dangerous?

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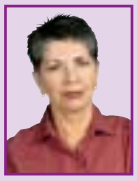
Mary's Case



- Mary, 57, has chronic osteoarthritis involving her fingers and knees.
- Her cardiovascular risk factors include abdominal obesity, borderline diabetes and prior cigarette smoking.
- She has previously tried a number of medications for her osteoarthritis, but only obtained relief with rofecoxib, which was recently removed from the market.
- She comes to seek an alternative drug for her arthritis.

How can you help Mary? Go to page 71 to find out.

Non-steroidal anti-inflammatory drugs (NSAIDs) have important analgesic and anti-inflammatory properties that are used in the treatment of musculoskeletal pain, although often at the expense of gastrotoxicity. NSAIDs exert beneficial effects through the non-selective inhibition of the cyclo-oxygenase (COX) enzyme.

The COX-1 enzyme is normally expressed in many tissues and regulates many important homeostatic processes, including gastro-protection. Thus, COX-1 inhibition may contribute to the gastrointestinal toxicity associated with NSAIDs. The COX-2 enzyme shows increased expression in inflammatory states, such as arthritis, and, importantly, does not appear to be involved in gastro-protection. Therefore, selective COX-2 inhibitors (coxibs) were developed in the late 1990s to provide anti-inflammatory drugs that were less likely to cause gastrotoxicity.

Following their introduction in 1999, celecoxib and rofecoxib had sales in excess of $3 billion in the US by October of 2000. However, on September 30, 2004, rofecoxib was withdrawn from the world market because of concerns regarding increased cardiovascular risk.

What's the link between coxibs and cardiovascular disease?

Initially, it was hypothesized that coxibs might cause increased ischemic cardiovascular events due to their inherent pro-thrombotic effects. By selectively inhibiting COX-2, coxibs reduce the availability of the anti-thrombotic substance prostacyclin, while platelets can continue to generate the pro-thrombotic substance thromboxane, through unopposed COX-1. This imbalance of prostacyclin and thromboxane may lead to an increased risk of thrombotic complications, such as myocardial infarction (MI).

The first indication that rofecoxib could lead to increased

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What about other coxibs?

cardiovascular complications came from the VIoxx Gastrointestinal Outcomes Research (VIGOR) trial, which compared the gastro-toxicity of rofecoxib (50 mg/day) vs. naproxen in 8,076 patients with rheumatoid arthritis.[1] A post-hoc analysis of the VIGOR study by Mukherjee *et al.* found that the rofecoxib group had a significant increase in MI, compared to the naproxen group (0.4% vs. 0.1%), although the rate was relatively small.[2]

Rofecoxib was ultimately withdrawn from the market in 2004 following the pre-release of data from the Adenomatous Polyp Prevention On Vioxx trial (APPROVe), which followed 2,586 patients with prior colorectal adenomas randomized to rofecoxib (25 mg/day) or placebo.[3] The rates of thrombotic events in patients taking rofecoxib (1.5 per 100 patient-years) were nearly twice as high as the placebo group (0.78) after 18 months (p=0.008). A subsequent meta-analysis of 18 clinical trials involving 20,472 patients confirmed rofecoxib to be associated with an increased risk of MI, especially at doses > 25 mg per day.[4]

Initially, celecoxib, unlike rofecoxib, did not appear to be associated with an increased risk of cardiovascular events. In the Celecoxib Long-term Arthritis Safety Study (CLASS), celecoxib (400 mg, twice daily [BID]) was compared to ibuprofen or diclofenac in terms of gastro-toxicity.[5] At six months, the rate of MI was similar in both groups (0.3%), irrespective of concomitant acetylsalicylic acid use. However, the more recent Adenomatous Prevention with Celecoxib (APC) trial suggested that celecoxib may be associated with adverse cardiovascular events when used at high doses for almost three years.[6] Among the 2,035 APC patients, there was a dose-related increase in cardiovascular events with celecoxib (relative risk: 3.4 for 400 mg, BID, and 2.5 for 200 mg, BID) compared to placebo. While the APC findings differ from the other celecoxib trials (PreSAP and ADAPT),[7] the Food and Drug Administration (FDA) and Health Canada have issued increased warnings regarding cardiovascular safety, especially in those patients with established cardiovascular disease.

Valdecoxib has been associated with an increased risk of cardiovascular events in patients following bypass surgery.[8] Valdecoxib was subsequently withdrawn from the market because of concerns about serious cutaneous reactions.

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Are there any other cardiovascular effects?

Non-selective NSAIDs and coxibs can worsen or precipitate congestive heart failure (CHF). In general, NSAIDs and coxibs should be avoided in patients with known CHF, especially since they may cause acute renal failure. In addition, NSAIDs and coxibs have also been shown to increase blood pressure and peripheral edema in some patients.

What are the cardiovascular risks of NSAID use?

Interestingly, the traditional NSAIDs have not been well-studied for cardiovascular safety. However, observational data reviewed by the FDA and Health Canada suggests that NSAIDs, including over-the-counter medications, may have similar cardiovascular risks as coxibs.

Take-home message

- Virtually all non-steroidal anti-inflamatory's and coxibs have been associated with an increased risk of cardiovascular events.
- The absolute risk for adverse events appears to be small.
- There is no evidence that concomitant low-dose acetylsalicylic acid reduces risks.
- Celecoxib at lower doses (200 mg per day) appears to be relatively safe when used for short durations.
- Other alternatives, including high-dose acetaminophen and NSAIDs with proton pump inhibitors, should be considered.

Treating Mary

- Mary was effectively treated with celecoxib, 200 mg, daily. Another option would be a traditional NSAID (*e.g.*, naproxen) with a proton pump inhibitor (*e.g.*, omeprazole).
- There is no utility to adding acetylsalicylic acid to mitigate her cardiovascular risk.

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