Prescribing NSAIDs In 2005

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Why was rofecoxib taken off the market?

Selective cyclooxygenase (COX)-2 inhibitors have been available in Canada since 1999. They were developed as anti-inflammatory analgesic agents with fewer gastrointestinal (GI) side-effects than traditional non-steroidal anti-inflammatory drugs (NSAIDs).[1-3]

Rofecoxib was withdrawn from the market on September 30, 2004, because of an increased risk of cardiovascular complications associated with its long-term use.[4-5] This was based on results of an unpublished trial that used a 25 mg/day dose of rofecoxib to prevent GI polyps. A four-fold increased incidence of serious thromboembolic adverse events became detectable after 18 months in the rofecoxib group compared to placebo. For this reason the study was halted in 2004.

Another trial in 2000, reported a 1.11% incidence of thrombotic cardiovascular events in patients taking 50 mg/day of rofecoxib compared to a 0.47% incidence in patients taking naproxen.[2]

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How safe are the other COX-2 inhibitors?

COX-1 blockade is anti-thrombotic, however, COX-2 blockade is prothrombotic. Selective COX-2 inhibition is associated with reduced prostaglandin I2 production by vascular endothelium with little inhibitory effect on production of the prothrombotic, platelet thromboxane A2.[6] Aspirin and traditional NSAIDs inhibit both thromboxane A2 and prostaglandin I2. The coxibs leave thromboxane A2 generation unaffected.

Rofecoxib is the most selective COX-2 agent, followed closely by valdecoxib. It appears that celecoxib and meloxicam are much less selective agents and have some COX-1

mediated effect on thromboxane. This COX-1 activity might help reduce their cardiovascular risk.[7]

In 2004, Pfizer released new information about cardiovascular risks associated with valdecoxib. In a study of 1,500 patients treated for acute pain after coronary artery bypass, an increased risk of cardiovascular events was observed in patients treated with valdecoxib.[8] The adverse events included myocardial infarction, cerebrovascular accident, deep vein thrombosis and pulmonary embolism. The risk of these adverse effects was observed to be greatest with the intravenous form of the drug (2% incidence) in comparison to the oral form of the drug (1% incidence). Patients taking placebo had about 0.5% incidence of adverse cardiovascular events.

Valdecoxib also caries a warning for serious skin reactions, including Stevens-Johnson Syndrome and toxic epidermal necrolysis. The risk is greatest in patients with sulfa allergy. For this reason, in April 2005, Health Canada asked Pfizer to voluntarily discontinue sales of valdecoxib until safety issues have been resolved.[9]

Health Canada has withdrawn market authorization for the use of celecoxib for prevention of recurrence of familial adenomatous polyposis and has recently restricted its use to treating the pain and inflammation of arthritis and certain types of acute pain. Patients who have had coronary artery disease or stroke should not use this medication.

What about the safety of first-generation NSAIDs?

The Medical Letter reported in August, 2004, that regular use of ibuprofen may interfere with the cardioprotective effect of low-dose acetylsalicylic acid (ASA).[10]

In December, 2004, A National Institute of Health-sponsored clinical trial comparing naproxen to placebo in patients at risk of developing Alzheimer's disease was prematurely aborted after preliminary information showed increased risk of cardiovascular events with naproxen compared to placebo.[11] Use of non-selective NSAIDs is associated with increased incidence of hypertension, edema and congestive heart failure. This has also been demonstrated to be the case with rofecoxib, but not with celecoxib.[12]

Ibuprofen, up to 1,800 mg/day (in divided doses), may be used on its own or in combination with acetaminophen. Sulindac

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is the most renoprotective NSAID; it causes less fluid and sodium retention and is less likely to increase blood pressure. The combination of diclofenac with misoprostel added for GI cytoprotection is available in a single tablet formulation. The addition of a proton pump inhibitor to a first generation NSAID also reduces the risk of serious GI adverse effects.

What alternatives to NSAIDs should patients consider?

Safer alternatives to NSAIDs include such topical agents as:

1. capsaicin, which has been shown to provide some relief for neuropathic and musculoskeletal pain;
2. topical diclofenac gel, which is applied over painful joints by gently rubbing into the overlying skin, has been shown to achieve comparable pain relief to that of oral diclofenac.

Glucosamine or chondroitin sulfate is safe and has demonstrated benefit for some patients with arthritic pain (the combination of the two together is not more likely to help relieve pain than either agent used on its own).[13] Acetaminaphen in dosages up to 3 g/day may be used.

Who is at relatively higher risk when taking NSAIDs?

Patients with a history of hypertension, congestive heart failure or coronary artery disease are at particular risk of adverse cardiovascular events on NSAIDs.

Patients with impaired renal function are at increased risk of fluid retention, hyperkalemia and high blood pressure.

Patients on long-term anticoagulation are at increased risk of bleeding complications. Patients with known coronary heart disease or cerebrovascular disease who require concomitant therapy with low-dose ASA and are also receiving a selective COX-2 inhibitor have a risk of gastroduodenal damage and ulcer complications similar to that of patients taking non-selective NSAIDs.

Currently, who is an appropriate candidate for a COX-2 inhibitor?

For patients who require NSAIDs due to the pain and inflammation of arthritis, but are at high risk for NSAID-related gastroduodenal toxicity, primary therapy with a COX-2 selective inhibitor is still a reasonable option if the following conditions are met: the patient is less 70 years with low cardiovascular risk

and reasonable kidney function. Once pain has come under control or stabilized, attempts should be made to reduce the dosage or discontinue the medication.

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