CLIN-IQ PROJECT

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Question: Do Cox-2 inhibitors relieve pain more effectively than nonselective NSAIDs?

Answer: No

Date the answer was determined: December 29, 2005

Level of Evidence: A

A summary of the issues

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often the first line treatment for osteoarthritis and other musculoskeletal painful conditions. Non-selective NSAIDs are thought to act by blocking the production of prostaglandins through the inhibition of both cyclooxygenase (COX-1 and COX-2) enzymes. Inhibition of the COX-1 enzyme is primarily responsible for the adverse GI effects (i.e. gastritis and PUD) of traditional NSAIDs, while COX-2 inhibition is thought to be responsible for most of the therapeutic effect of NSAIDs. The first generation of COX-2 selective inhibitors was introduced in 1999 with the goal of providing potent anti-inflammatory and analgesic effects while diminishing the dangerous GI effects of non-selective NSAIDs. Since 2004, several COX-2 inhibitors have been withdrawn from the market due to an increased risk of serious cardiovascular complications, such as heart attack and stroke. However, two are still available.

Although the COX-2 inhibitors were only FDA approved for the treatment of osteoarthritis and adult rheumatoid arthritis, many physicians prescribe these drugs off-label for the treatment of various acute pain conditions. Though their manufacturers never claimed that the COX-2 inhibitors were more effective, perhaps because of massive advertising campaigns, many patients and perhaps some physicians may assume that they are.

Summary of the Evidence:

In a 12-week study of 1003 patients with symptomatic osteoarthritis of the knee by Bensen et al,[2] there was no significant difference in analgesic efficacy between celecoxib (50 mg, 100 mg or 200 mg BID) and naproxen (500 mg BID). This was measured by WOMAC indices (pain, stiffness, physical function, and composite) and the patient assessment of arthritis pain visual analog scale (VAS) ($p<0.05$).

In a 12-week RCT study of 1016 patients, Kivitz et al[3] concluded that valdecoxib (10 mg and 20 mg once daily) demonstrated similar efficacy to naproxen (500 mg BID) in relieving moderate to severe osteoarthritis of the knee. While both are better than placebo, there is no significant difference between them ($p< 0.05$). This was measured by the WOMAC indices (pain, stiffness, physical function, and composite) and the pain-visual analog scale (PVAS).

A 397-patient RCT by Petrella et al[4] compared the analgesic efficacy of that celecoxib (200 mg BID) and naproxen (500 mg BID) in the management of acute first- or second-degree ankle sprain. Using patient's global assessment, there was no significant difference in pain response at day 4 between celecoxib (71%) and naproxen (72%) [OR, 0.89; 95% CI, 0.53 – 1.49; $p = 0.7$]. Furthermore the pain response rate at day 8 was similarly 89% for celecoxib and 90% for naproxen [OR, 0.78; CI, 0.38 – 1.62; $p = 0.5$].

A meta-analysis including 26 RCT's conducted by Garner et al[1] concluded that rofecoxib was more effective than placebo (patient global response RR 1.75 95% CI: 1.35, 2.26) for relieving osteoarthritis pain. There were no differences in the efficacy between rofecoxib and diclofenac (RR: 1.11 CI: 0.80, 1.54); rofecoxib and ibuprofen (RR: 0.96 95% CI: 0.81, 1.13); rofecoxib and naproxen (RR 1.05 CI: 0.93, 1.18); rofecoxib and nimesulide (RR: 0.83 CI: 0.67, 1.03), rofecoxib and nabumetone (RR: 1.17 CI: 1.05, 1.29); rofecoxib and celecoxib (RR: 0.76 CI: 0.47, 1.24).

Search terms: Osteoarthritis, Pain control, NSAIDs, COX-2 inhibitors

Inclusion/Exclusion criteria: We included RCTs that compared the analgesic efficacy of various COX-2 inhibitors to naproxen compared as well as meta-analysis of several of RCTs that pitted Vioxx® against multiple NSAIDs agents. We excluded studies involving adolescents and children.

Comments: There were no consistent differences in efficacy between rofecoxib and any of the comparators, including celecoxib. However, patients experienced fewer side effects with the COX-2 inhibitors and on average tolerated their treatment better than non-selective NSAIDs. All of the comparative studies were short term (less than 6 months duration).

List of articles reviewed:

1. Garner SE, Fidan DD, Franksih R, Maxwell L, et al. Meta-analysis of rofecoxib for osteoarthritis. *Cochrane Database Syst Rev.* 2005; 4: CD003685.
2. Bensen WG, Fiechtner JJ, McMillen JI, Zhao WW, et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: A randomized controlled trial. *Mayo Clin Proc.* 1999; 74(11):1095-105.
3. Kivitz A, Eisen G, Zhao WW, Bevirt T, Recker DP. Randomized placebo-controlled trial comparing efficacy and safety of valdecoxib with naproxen in patients with osteoarthritis. *J Fam Pract* 2002; 51(6):530-7.
4. Petrella R, Ekman EF, Schuller R, Fort JG. Efficacy of celecoxib, a COX-2 inhibitor, and naproxen in the management of acute ankle sprain: Results of a double-blind, randomized controlled trial. *Clin J Sport Med.* 2004; 14(4):225-31.
5. Noble SL, King DS, Olutade JI. Cyclooxygenase-2 enzyme inhibitors: place in therapy. *Am Fam Physician* 2000; 61(12):3669-76.

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