Rofecoxib and Risk for Myocardial Infarction

Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet 2005;365:475–81.

Study Overview

Objective. To determine if risk for a serious cardiac event was enhanced with rofecoxib at either high or standard doses compared with remote nonsteroidal anti-inflammatory drug (NSAID) or celecoxib use.

Design. Nested case-control study.

Setting and participants. The cohort consisted of Kaiser Permanente patients in California aged 18 to 84 years treated with an NSAID between 1 January 1999 and 31 December 2001. Cases of serious coronary heart disease (acute myocardial infarction [MI] and sudden cardiac death) were risk-set matched with 4 controls for age, sex, and health plan region. NSAID exposure was classified on the index date (date of cardiac event).

Main outcome measure. Incident serious coronary heart disease (acute MI requiring admission or sudden cardiac death).

Main results. 8143 cases of serious coronary heart disease, including 2210 (27%) fatal cases, occurred during 2,302,029 person-years of follow-up. Patients taking rofecoxib (all doses) were more likely to have a serious cardiac event (adjusted odds ratio [OR], 1.34 [95% confidence interval {CI}, 0.98–1.82]; $P = 0.066$) when compared with those taking other NSAIDs. Coronary heart disease was 1.47 times more likely among patients currently taking standard-dose rofecoxib (≤ 25 mg/day) compared with those currently taking celecoxib (95% CI, 0.99–2.17; $P = 0.054$) and was 3.58 times more likely among high-dose rofecoxib users (> 25 mg/day) (95% CI, 1.27–10.11; $P = 0.016$). For naproxen versus remote NSAID use, the adjusted OR was 1.14 (95% CI, 1.00–1.30; $P = 0.05$).

Conclusion. Use of rofecoxib increases the risk of serious coronary heart disease as compared with celecoxib use. Naproxen does not protect against serious coronary heart disease.

Commentary

The cyclooxygenase-2 (COX-2) selective inhibitors have been widely prescribed since their licensing in the United States. The original safety trial by Bombardier et al (VIGOR trial) showed a fivefold increased risk of MI associated with the 50-mg dose of rofecoxib compared with naproxen [1]. Because the VIGOR trial did not have a placebo group, these findings could be explained either by an excess risk attributable to 50-mg rofecoxib, excess risk attributable to COX-2 inhibitors, or a cardioprotective effect of naproxen.

Graham et al used a case-control study design in a large integrated managed care organization providing health care to more than 6 million residents in California. The investigators identified the primary outcome of serious cardiovascular events using ICD-9 codes; a principal diagnosis code for acute MI has been shown to have a positive predictive value between 92% and 95%. They also used laboratory values (creatine kinase and troponin I) to confirm the diagnosis**.** The authors also chose to study only those patients who were hospitalized for their cardiac event. This may have missed or misclassified those patients who had a cardiac event in a nursing home or those who may have had a cardiac death but were incorrectly classified as noncardiac cause of death.

While this study by Graham et al was being conducted, the safety of rofecoxib was again questioned. In the APPROVe study (Adenomatous Polyp Prevention on Vioxx), rofecoxib 25 mg showed a doubling of risk of MI and stroke after approximately 18 months of use [2], leading Merck to announce a worldwide voluntary withdrawal of rofecoxib in September 2004.

Applications for Clinical Practice

Rofecoxib has been withdrawn from the market; however, 2 other COX-2 inhibitors are available in the United States,

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and others are currently being developed [2]. Postmarketing surveillance often reveals problems with new medications that are magnified by their use at higher than recommended doses [3,4]. We need to seriously question the practice of using drugs outside their licensed indications in the absence of strong data that would support such use. A continued re-evaluation of prescribing practices and the opportunities that exist to improve evidence-based prescribing are needed.

–Review by Christianne L. Roumie, MD, MPH

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