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COX-2 INHIBITORS AND CARDIOVASCULAR RISK

The data are inconclusive, and these drugs are needed

DR. MUKHERJEE AND COLLEAGUES, in a retrospective analysis, raise the important question of whether COX-2 inhibitors increase the risk of cardiovascular events.¹

Unfortunately, their methods had problems that render their analysis inconclusive. Moreover, they ignore the need that these drugs fill in the care of patients with inflammatory diseases.

Therefore, unless a clear cause-and-effect relationship can be proved between the use of COX-2 inhibitors and cardiovascular events, we should go on using these drugs.

■ PROBLEMS WITH THE STUDY DESIGN

Before we accept the conclusions of Mukherjee et al at face value, we should consider various confounding variables, as well as the realities of clinical trial design.

The studies were not designed to assess cardiovascular risk

The Mukherjee report was a retrospective analysis of trials not designed to measure the cardiovascular outcome in question. Rather, the trials were designed to measure the frequency of gastrointestinal events (bleeding, ulceration, and perforation) in patients taking COX-2 inhibitors compared with nonselective NSAIDs. Data on serious cardiovascular adverse events were collected in a retrospective poststudy analysis.

One problem is that the information may have been gathered inconsistently. To be valid, the outcomes that a trial is to measure must be specified in advance and defined precisely.

Regulations from the Food and Drug Administration (CFR 312.32)² require that serious adverse events that occur during clinical trials be reported to the agency as they happen. A serious

adverse event is defined as any experience that is fatal, life-threatening, or permanently disabling, or that requires hospitalization. However, the data generated carry with them any inconsistencies and misinterpretations entered at the trial site. Appropriate clinical screening for cardiovascular disease and parameters of disease activity were not in place.

In addition, any background factors that may affect the outcome being measured need to be addressed up front. The inclusion and exclusion criteria in the studies analyzed by Mukherjee et al addressed the issues of potential gastrointestinal adverse events but did not address cardiovascular events.

A retrospective analysis, as in the paper by Mukherjee et al, will see only the results of the interpretation of the metrologist compiling the data with respect to both inclusion and exclusion criteria and the description of the adverse event itself and the coding of data. Consequently, the data presented are inadequate for use by the internist in daily clinical practice.

The study population was not homogeneous

The analysis included patients with rheumatoid arthritis, patients with osteoarthritis and, presumably, patients with neither disease, although these groups differ in their risk for cardiovascular events.

Patients with inflammatory diseases have a shortened life expectancy, and cardiovascular events account for approximately half of all deaths in patients with rheumatoid arthritis.³ Wolfe et al⁴ observed twice the number of deaths expected in a cohort of patients with rheumatoid arthritis (361 actual vs 161 expected). In a trial in the United Kingdom, Symmons et al⁵ reported a standardized mortality ratio of 2.2 for patients with rheumatoid arthritis, with 34% of deaths due to cardiovascular causes.

Although the explanation for these findings is unknown, the inflammatory mediators present in these



diseases may contribute to the pathogenesis of the atherosclerotic lesion.

We therefore cannot compare these patients with age-matched controls who have no rheumatic disease.

The study lacked statistical power

The number of cardiovascular events seen was not sufficient to show a significant difference between the groups. Moreover, the duration of these trials was much shorter than the aspirin meta-analysis used for comparison.

It was calculated that for the CLASS trial to demonstrate the cardioprotective benefits of aspirin in reducing primary cardiovascular events or to demonstrate that a selective COX-2 inhibitor causes cardiovascular events, the study would have had to include more than 20,000 patients treated for 5 years.⁶

Other studies did not show a difference

In a study comparing rofecoxib vs placebo in patients with Alzheimer disease, the rate of adverse cardiovascular events was similar in both groups, 2.8 and 3.3 per 100 patient-years, respectively. The duration of the trial was more than 12 months.⁷

THE DILEMMA

Practicing internists constantly need to scan the available literature for material applicable to their practice. Preferably, we find conclusive data to validate or change our current practice standards. Unfortunately, we are faced all too often with conjecture, speculation, and "further investigation is needed."

How can the practicing internist interpret and apply inconclusive data? As practitioners, we deal with an "n of 1," the patient in front of us. The dilemma is how to apply the population study data to our clinical practice. Can and should we apply the conclusions of studies comprising disparate groups?

WE NEED THESE DRUGS

NSAIDs are a necessary adjunctive therapy in inflammatory diseases, relieving pain and suppressing inflammation via an anti-eicosanoid effect. They are used as cotherapy with all of the disease-modifying regimens available. COX-2 inhibitors afford a relatively safe alternative to the high-dose salicylates and gastrotoxic, nonselective NSAIDs of the past.

Given that patients with rheumatic diseases are at increased cardiovascular risk to begin with, it remains conjectural if COX-2 inhibitors inflict any associated

insult to the cardiovascular system. The rheumatology community is aware of the potential prothrombotic effects of these drugs, noted by Lipsky et al.⁸

Investigators continue to gather information to examine the question in clinical trials. The FDA mandates quarterly and annual reports by the manufacturer, monitoring the adverse events possibly to be included in labeling and as a warning to the prescriber.

WHAT DO THE DATA SUPPORT?

For patients with an existing risk for cardiovascular events, the data support giving low-dose aspirin for cardioprotection. The same patient's primary disease demands the relief afforded by a COX-2 inhibitor. I do not believe there is sufficient support for avoiding these drugs. Both drugs, a COX-2 inhibitor and low-dose aspirin, should be used in patients with rheumatoid arthritis, with appropriate gastrointestinal protection if indicated.

Patients with rheumatoid arthritis suffer daily pain and discomfort. The drug of choice should have anti-inflammatory, analgesic, and gastroprotective properties. COX-2 inhibitors afford a safe, effective treatment to satisfy these criteria. In my opinion, it would be a disservice to patients to deny them the benefit of these newer agents. Until a clear cause-and-effect relationship is established between cardiovascular events and the use of COX-2 inhibitors, these drugs should remain in use.

REFERENCES

1. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001; 286:954-959.
2. Code of Federal Regulations, Part 312. Federal Register May, 1997.
3. Reilly PA, Cosh JA, Maddison PJ, Rasker JJ, Silman AJ. Mortality and survival in rheumatoid arthritis: a 25 year prospective study of 100 patients. *Ann Rheum Dis* 1990; 49:363-369.
4. Wolfe F, Mitchell DM, Sibley JT, et al. The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994; 37:481-494.
5. Symmons DP, Jones MA, Scott DL, Prior P. Longterm mortality outcome in patients with rheumatoid arthritis: early presenters continue to do well. *J Rheumatol* 1998; 25:1072-1077.
6. Steering Committee of the Physicians' Research Study Group. Final report on the aspirin component of the ongoing Physicians Health Study. *N Engl J Med* 1989; 321:129-135.
7. Needleman P, Geiss SG, Lefkowitz J, Silverstein F. Celecoxib long term arthritis safety study (CLASS). FDA Advisory Committee, 2/7/01. www.fda.gov/ohrms/dockets/ac/01/slides/3677s1.htm.
8. Lipsky PE, Brooks P, Crofford LJ, et al. Unresolved issues in the role of cyclooxygenase-2 in normal physiologic processes and disease. *Arch Intern Med* 2000; 160:913-920.

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