COX-2 Selective Inhibitors in the Treatment of Osteoarthritis

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Objectives: To assess the efficacy of cyclooxygenase-2 selective inhibitors (coxibs) in osteoarthritis (OA) and their gastrointestinal, cardiovascular, renovascular, and hepatic side effects compared with traditional nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen.

Methods: Bibliographic database searches for randomized controlled trials, meta-analyses, and literature reviews.

Results: Coxibs are comparable to traditional NSAIDs, providing moderate benefit for OA patients in pain and function versus placebo. NSAIDs, including coxibs, are superior to acetaminophen for OA, particularly in patients with moderate to severe pain. Coxibs decrease gastroduodenal ulcers (74% relative risk reduction) and ulcer complications (61% reduction) versus traditional NSAIDs. Meta-analysis of randomized trials indicates that coxibs increase the risk of myocardial infarctions approximately twofold versus placebo and versus naproxen, but do not increase the risk versus nonnaproxen NSAIDs. NSAIDs, including coxibs, commonly cause fluid retention and increase blood pressure and uncommonly induce congestive heart failure or significant renal dysfunction; risk factors include advanced age, hypertension, and heart or kidney disease. NSAIDs are a rare cause of clinical hepatotoxicity (<1 liver-related death per 100,000 NSAID users in clinical studies). Increased rates of aminotransferase elevations occur with rofecoxib (2%) and high-dose lumiracoxib (3%), and postmarketing cases of clinical liver injury with lumiracoxib have been reported recently.

Conclusions: Coxibs are as effective as traditional NSAIDs and superior to acetaminophen for the treatment of OA. Coxibs cause fewer gastrointestinal complications than traditional NSAIDs. Coxibs increase cardiovascular risk versus placebo and naproxen—but probably not versus nonnaproxen NSAIDs. Blood pressure commonly increases after initiation of selective or nonselective NSAIDs, especially in hypertensive patients.

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Nonsteroidal antiinflammatory drugs (NSAIDs) are a mainstay of treatment for patients with osteoarthritis (OA). However, despite their efficacy and widespread availability, NSAIDs also may cause negative effects. The most common side effects limiting the use of NSAIDs are gastrointestinal (GI), although adverse events also occur in other organ systems. NSAID product information includes "black box" warnings about serious GI and cardiovascular (CV) events, as well as ad-

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Abbreviations	
ACE	Angiotensin-converting enzyme
ALT	Alanine aminotransferase
APTC	Anti-Platelet Trialists' Collaboration
AST	Aspartate aminotransferase
BP	Blood pressure
CI	Confidence interval
CLASS	Celecoxib Long-Term Arthritis Safety Study
COX	Cyclooxygenase
Coxib	Cyclooxygenase-2 selective inhibitor
CV	Cardiovascular
ES	Effect size
FDA	Food and Drug Administration
GI	Gastrointestinal
HAQ	Health Assessment Questionnaire
HR	Hazard ratio
MEDAL	Multinational Etoricoxib and Diclofenac Arthritis Long-Term
MI	Myocardial infarction
NHANES	National Health and Nutrition Examination Survey
NNT	Number needed to treat
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OR	Odds ratio
PG	Prostaglandin
PPI	Proton pump inhibitor
RR	Relative risk
RRR	Relative risk reduction
TARGET	Therapeutic Arthritis and Gastrointestinal Event Trial
$TRPV_1$	Transient receptor potential vanilloid-1
ULN	Upper limit of normal
VIGOR	Vioxx Gastrointestinal Outcomes Research
WOMAC	Western Ontario MacMaster Osteoarthritis Index

ditional warnings and precautions about hypertension, edema, renal injury, and hepatic injury. Thus, choosing an agent as seemingly "simple" as an NSAID requires consideration of a variety of potential benefits and risks. With 14% of the U.S. population using NSAIDs or acetaminophen nearly every day for at least a month (1), understanding the benefits and risks of these agents is crucial for physicians and their patients.

Cyclooxygenase (COX)-2 selective NSAIDs were developed with the goal of providing the antiinflammatory and analgesic efficacy of traditional NSAIDs but with a decrease in the GI injury and in the antiplatelet activity associated with traditional NSAIDs. Initial trials documented efficacy in patients with OA as well as a decrease in ulcers and upper GI clinical events such as bleeding. However, placebo-controlled trials documented that COX-2 selective inhibitors (coxibs) increase the risk of CV events, particularly myocardial infarctions (MIs), leading to the withdrawal of 2 of the 3 coxibs available in the United States, and uncertainty among clinicians regarding their role in the treatment of pain and inflammation.

We therefore performed an evidence-based assessment of the benefits and risks of COX-2 selective NSAIDs as compared with traditional NSAIDs and the most commonly used non-NSAID analgesic, acetaminophen. We explore the efficacy of COX-2 selective NSAIDs in the treatment of patients with OA as well as the potential GI, CV, renovascular, and hepatic risks. By summarizing the overall benefits and risks, we hope to provide practicing clinicians a framework to integrate the risks and benefits of these agents to make appropriate therapeutic choices for individual patients.

METHODS

In performing this review, we developed 5 focused clinical questions: As compared with placebo/no therapy, traditional NSAIDs, or acetaminophen, (1) what is the efficacy of coxibs in the treatment of patients with OA?; (2) what are the GI effects of coxibs?; (3) what are the CV effects of coxibs?; (4) what are the renovascular effects of coxibs (defined as renal dysfunction/failure, hypertension, edema, and congestive heart failure)?; and 5) what are the hepatic effects of NSAIDs?

We then developed a literature search strategy designed to address these focused questions. To collect all relevant studies a MEDLINE search for randomized controlled trials, meta-analyses, systematic reviews, and review literature of COX-2 inhibitors (including the specific agents celecoxib, rofecoxib, valdecoxib, etoricoxib, and lumiracoxib) from 1950 through February 2007 was performed. The search was not restricted to OA. MEDLINE searches for clinical trials, meta-analyses, systematic reviews, and review literature of acetaminophen combined with GI tract, CV system/diseases, kidney/kidney diseases, hypertension, or liver/liver diseases were also performed to collect additional studies related to efficacy and side effects of acetaminophen.

RESULTS

Efficacy of Coxibs in Osteoarthritis

The prevalence of symptomatic OA is approximately 12% among adults aged 25 to 74 years in the U.S., based on data from the First National Health and Nutrition Examination Survey (NHANES I), corresponding to an estimated 27 million persons aged 25 years and above with symptomatic OA at any joint (2). The prevalence of symptomatic OA in specific joint groups has been estimated in several studies conducted in the U.S. The prevalence of symptomatic knee OA was about 5% among adults aged ≥26 years in the Framingham OA Study, 17% among adults aged ≥45 in the Johnston County OA Study, and 12% among adults aged ≥60 in the NHANES III study (2). The prevalence of symptomatic hip OA was about 10% among adults aged ≥45 in the