REVIEW

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Gastrointestinal and Cardiovascular Risks of Nonsteroidal Anti-inflammatory Drugs

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed but can have serious gastrointestinal (GI) and cardiovascular side effects, which have led to the withdrawal of some of these drugs and continuing uncertainty about the best approach to patients requiring NSAID therapy, particularly in those with GI or cardiovascular risk factors. To define the risks to the GI and cardiovascular systems associated with NSAID therapy, we have undertaken a series of systematic reviews of original articles published between January 1995 and December 2006. In this article we describe the mechanisms and patterns of GI and cardiovascular side effects in NSAID-taking patients and identify a range of drug and patient factors that contribute to an increased risk of adverse events. We conclude that NSAID therapy should not be started unless it is essential, and that *Helicobacter pylori* eradication should be considered in patients at increased GI risk. We discuss the use of gastroprotective agents and provide practical advice to help physicians assess and balance both cardiovascular and GI risks and benefits in their prescribing decisions.
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KEYWORDS: Cardiovascular symptoms; Gastrointestinal symptoms; Gastroprotection; Morbidity; Mortality; Nonsteriodal anti-inflammatory drugs; Risks

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed of all therapeutic agents, but their therapeutic efficacy comes at a price. Damage to the upper gastrointestinal (GI) tract was the first unwanted effect to be recognized clinically,[1] but other organ systems can be affected by NSAIDs.[2,3] The gastrointestinal damage caused by the nonselective NSAIDs can be ameliorated—either by discontinuing the drug or by adding a second drug to protect against further gastrointestinal damage.[4] These drugs include H_2-receptor antagonists, proton pump inhibitors, and prostaglandin analogues.[5,6]

The introduction of the cyclooxygenase-2 (COX-2)-specific NSAIDs[7] in the late 1990s promised a revolution in NSAID therapy because of their much higher specificity for the COX-2 system, but evidence of cardiovascular side effects including an increased risk of myocardial infarction began to emerge,[8] and some of the COX-2 NSAIDs were eventually withdrawn from general use in Europe and North America.[9,10]

Confusion about the best approach to the management of patients requiring NSAID treatment, particularly for more complex patients, has been made worse by recent concerns about ibuprofen and diclofenac, which were previously regarded as having excellent safety records but also have been associated with a significantly increased risk of myocardial infarction.[11] Long-term NSAID therapy may, of course, have benefits, including reducing the risk of some cancers.[12]

This review provides clinicians with evidence-based guidance on NSAID treatment. We briefly review the differences

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and similarities between the nonselective and COX-2 selective NSAIDs, the range of GI and cardiovascular side effects with different NSAIDs, and the impact of dosing and other drug factors affecting toxicity. We discuss the agents available to provide protection against NSAID-induced gastrointestinal damage, and consider approaches to the estimation and stratification of NSAID risks. Finally, we look at key questions for prescribing these agents—when not to prescribe them, prescription in low- and high-risk patients, when NSAIDs should be discontinued, and the role of *Helicobacter pylori* infection eradication. Our recommendations are based largely on medium- to long-term studies which show that increased rates of thrombotic side effects of NSAIDs become significant after about 18 months, although an increased incidence of congestive heart failure is apparent in as early as 5 months.[13] Although duration of therapy is a risk factor, serious gastrointestinal and cardiovascular side effects may develop even during short-term treatment, particularly in patients with preexisting risk factors.[14-16]

CLINICAL SIGNIFICANCE

- Nonsteroidal anti-inflammatory drugs (NSAIDs) have significant cardiovascular and gastrointestinal toxicity.
- *Helicobactor pylori* eradication reduces the risk of gastrointestinal complications of NSAIDs.
- Patients at normal cardiovascular risk may receive nonselective and COX-2 selective NSAIDs, with or without proton pump inhibitor cover.
- Patients at increased cardiovascular risk should receive naproxen with or without proton pump inhibitor co-prescription.
- A COX-2 NSAID plus proton pump inhibitor is recommended in patients with previous gastrointestinal bleeding.

METHODS

We systematically searched the Cochrane Library, Medline, and EMBASE for publications between 1995 and December 2006. We used the search terms "non steroidal anti inflammatory agent" or "NSAID" or "COX," and also searched under the pharmaceutical names of available NSAIDs, combining this search with the terms "GI," "gastro$," "gastric" AND "protection," "prevent$," "prophylaxis," "co-medication" OR "proton pump inhibitor," "proton pump inhibitor" AS WELL AS "safety," "side effect," "complication," "event," "symptoms," "intolerance," "toxicity," "tolerability," "risk" for both ("GI," "gastro$," "gastric") and ("cardiovascular," "coronary," "myocardial"), limiting our search to human studies. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. In discussing treatment and prevention, we have concentrated on randomized controlled trials and meta-analyses, and have not included information derived from less powerful studies.

These searches identified over 2000 articles, which, after checking for relevance and duplication, were reduced to 97 for GI complications of NSAIDs, 131 for NSAIDs and the cardiovascular system, and 47 for NSAIDs and gastroprotective agents. Selected references are included in the text and a full list of references is available from the authors.

NSAIDS

Terminology

A variety of terms has been applied to the NSAID class of drugs. For consistency we use only 2 terms—nonselective NSAIDs and COX-2 selective NSAIDs—although we recognize a spectrum of COX-2 selectivity across the range of NSAIDs.

Mechanisms of Action

Cells synthesize prostaglandins in response to tissue injury, and inhibition of prostaglandins inhibits inflammation. NSAIDs exert their anti-inflammatory action by inhibition of cyclooxygenase activity, which transforms phospholipid-derived arachidonic acid into prostaglandins. COX-1, which is not stimulated by proinflammatory cytokines such as IL-1, is a *constitutive* enzyme, present in most cells, and is associated with the regulation of hemostasis, the integrity of the gastrointestinal and renal tracts, platelet function, and macrophage differentiation (Figure 1). Although inhibition of COX-1 by NSAIDs may have some anti-inflammatory effect, the adverse effects of NSAIDs are predominantly related to the inhibition of the other important functions of COX-1. COX-2, by contrast, is an *inducible* enzyme and is more specifically associated with inflammation. Specific inhibition of COX-2 leads to reduction of inflammation without these adverse effects. However, all NSAIDs have some inhibitory effects on COX-1 and COX-2 activities, so that none is absolutely selective for COX-2. The adverse effects reported for COX-2 NSAIDs can occur with the older, COX-1 NSAIDs, and there also is a dose effect for the COX-2 agents, with greater COX-1 effects at higher doses. The recently described COX-3 system has opened up further avenues of therapeutic opportunity in the treatment of inflammatory conditions, not least because of the ability of paracetamol to inhibit COX-3 activity.[17,18]

NSAIDs can be divided into a number of groups. The nonselective NSAIDs are mostly derived from carboxylic and enolic acids. The first COX-2 selective NSAIDs were celecoxib and rofecoxib, with the subsequent development of "second generation" COX-2-specific NSAIDS, including lumiracoxib and etoricoxib (Table 1).

Mechanisms of Damage

The mechanisms underlying the damage caused by NSAIDs to the gastrointestinal tract include disruption of the protective mucus layer, inhibition of protective bicar-