Review

Current state of therapy for pain and inflammation

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs), including both traditional nonselective NSAIDs and the selective cyclo-oxygenase (COX)-2 inhibitors, are among the most widely used medications in the USA. Traditional NSAIDs, although effective at relieving pain and inflammation, are associated with a significant increase in the risk for gastrointestinal adverse events. Throughout the 1990s these events were estimated to result in approximately 100,000 hospitalizations and 16,500 deaths each year nationally. Recent studies have indicated that the risk for serious NSAID gastropathy has declined substantially during the past decade as a result of a number of factors, including lower doses of NSAIDs, the use of gastroprotective agents such as proton pump inhibitors and misoprostol, and the introduction of the selective COX-2 inhibitors. One therapeutic approach that may reduce the risk for gastrointestinal side effects associated with traditional NSAIDs while retaining their efficacy is the inclusion of co-therapy with a proton pump inhibitor; these agents inhibit acid secretion and have been demonstrated to promote ulcer healing in patients with NSAID-related gastric ulcers. Alternatively, COX-2 selective agents have been used to treat patients at high risk for such events. Both nonselective and selective COX-2 inhibitors have now been shown to be associated with an increased risk for cardiovascular events. These studies, together with the outcomes of the recent US Food and Drug Administration decision to require 'black box' warnings regarding potential cardiovascular risks associated with NSAIDs, suggest that the use of COX-2 inhibitors as the sole strategy for gastroprotection in patients with arthritis and other pain syndromes must be reconsidered, particularly among those at risk for cardiovascular events.

Introduction

The nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications in the USA because of their demonstrated efficacy in reducing pain and inflammation. In the year 2000 patients in the USA alone received more than 111 million prescriptions for these agents. In addition, NSAIDs are the most commonly used over-the-counter medications, with more than 30 billion tablets sold annually. More than one-third of the elderly take NSAIDs daily, and 70% report taking NSAIDs at least once a week [1].

A major limiting factor in the use of traditional NSAIDs is gastrointestinal toxicity. Endoscopic studies have demonstrated that gastric or duodenal ulcers develop in 15–30% of patients who regularly take NSAIDs [2]. Throughout the 1990s clinically important NSAID-related events (e.g. bleeding, obstruction, and perforation) were estimated to result in approximately 100,000 hospitalizations and 16,500 deaths each year nationally. Recent studies have indicated that the risk for serious NSAID gastropathy has declined 67% over the past decade as a result of a number of factors, including lower doses of NSAIDs, use of gastroprotective agents such as proton pump inhibitors (PPIs), and the introduction of the selective cyclo-oxygenase (COX)-2 inhibitors [3-5]. Studies suggest that between US$0.66 and US$1.25 is spent on the treatment of gastrointestinal side effects for each US$1 spent on NSAIDs; furthermore, it has been estimated that one-third of the cost of managing arthritis is associated with the treatment of NSAID-related adverse effects [6-8]. Because these agents are so widely used, the potential scope of the health problem associated with NSAID related gastrointestinal adverse events is substantial.

Therapeutic approaches are available that may reduce the risk for gastrointestinal side effects associated with traditional NSAIDs. Co-therapy with a nonselective NSAID (such as naproxen) and a PPI, which inhibits acid secretion, has been demonstrated to promote ulcer healing in patients with NSAID-related gastric ulcers. Prophylactic use of PPIs in patients with previous gastrointestinal events or in those at high risk for such events is considered appropriate by major treatment guidelines [9]. Clinical studies also support the efficacy of misoprostol, a stable prostaglandin that reduces gastric acid secretion, as a strategy to prevent NSAID dependent gastropathy [10,11]. However, it should be noted

ACR = American College of Rheumatology; COX = cyclo-oxygenase; FDA = Food and Drug Administration; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; PPI = proton pump inhibitor.

that in the report by Graham and coworkers [10], at the studied dosage of misoprostol (800 mg/day) a significant proportion of patients in the misoprostol group reported treatment-related adverse events and discontinued the medication.

Alternatively, selective COX-2 NSAIDs may be used to treat patients at high risk for gastrointestinal events. The COX-2 inhibitors have approximately half the associated gastrointestinal risks compared with nonselective NSAIDs. However, important concerns have recently been raised regarding the potential cardiovascular toxicity of the entire NSAID class, including selective and nonselective agents [12-14].

Cardiovascular safety review of COX-2 inhibitors

In response to an emerging body of data underscoring the possible cardiovascular risks associated with the use of COX-2 inhibitors, a joint meeting of the US Food and Drug Administration (FDA) Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee was held in February 2005 to examine the safety of COX-2 inhibitors and NSAIDs [15].

Safety review

The primary purpose of this hearing was to examine data on rofecoxib, celecoxib, valdecoxib, etoricoxib, lumiracoxib, and naproxen to determine whether these agents pose a cardiovascular safety risk, to evaluate the risks and benefits of each drug, and to identify actions needed for the safe use of these agents.

Clinical trials and population-based studies of rofecoxib indicated that this agent is associated with increased cardiovascular risk, particularly at higher doses [15]. Risk for cardiovascular events is highest among patients receiving the 50 mg dose, and less so among patients receiving the 25 mg dose and not detected among those receiving 12.5 mg. The issue of potential cardiovascular events came into sharper focus with the release of the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial [12], which demonstrated a significant difference between rofecoxib 50 mg/day and naproxen 500 mg twice daily in risk for cardiovascular thrombotic events. The subsequent withdrawal of rofecoxib on 30 September 2004 was triggered in part by the results of the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial [16], which found that the long-term use of the COX-2 inhibitor at 25 mg/day was associated with an increased risk for thrombotic events, first observed after 18 months of therapy.

For celecoxib, controlled clinical trials conducted to date suggest that low dose celecoxib is not associated with increased cardiovascular risk [15]. However, the majority of these trials were of short duration; longer exposures may be associated with increased risk. The Adenoma Prevention with Celecoxib (APC) trial [17], which randomly assigned patients to placebo or high dose celecoxib (400–800 mg/day) for 3 years, demonstrated dose related increases in cardiovascular events. An additional trial, conducted by the National Institute on Aging in patients with Alzheimer's disease, was suspended after preliminary data showed a trend toward increased risk for cardiovascular events, although the study was too small to provide conclusive results [18]. Active comparator trials using diclofenac or ibuprofen demonstrated that celecoxib was not associated with increased risk compared with these agents [14].

In contrast, the use of valdecoxib and its intravenous prodrug parecoxib was associated with increased cardiovascular risk in short-term studies of patients undergoing coronary artery bypass graft surgery [15]. In one recent trial patients receiving these agents were at 3.7-fold increased risk compared with placebo. It should be noted that all patients in this study received low-dose aspirin, indicating that the increased risk occurred in the setting of dual inhibition of both COX-1 and COX-2. Meta-analyses of short-term trials enrolling more than 12,000 patients who required treatment for arthritis or pain did not find increased cardiovascular risk for valdecoxib in comparison with other NSAIDs; however, higher rates of edema and hypertension were detected at the higher doses.

For the newer agents lumiracoxib and etoricoxib, data suggest that there may be some increase in cardiovascular risk [15]. In a study that compared lumiracoxib with ibuprofen, no statistical differences in cardiovascular risk were observed, although numerically more events were observed on ibuprofen [19]. However, more cardiovascular events were observed with lumiracoxib in comparison with naproxen. Among patients who took concomitant low-dose aspirin, variable and inconsistent effects on cardiovascular outcomes were observed. Similarly, etoricoxib had a similar rate of cardiovascular events to that of non-naproxen NSAIDs; direct comparison with naproxen showed that etoricoxib was associated with increased cardiovascular risk compared to naproxen [15].

Although data on the cardiovascular risks of traditional NSAIDs are incomplete, unpublished studies presented at the recent US FDA meeting [15] suggest an increase in risk for cardiovascular events. The naproxen data are at odds with meta-analyses suggesting that it might reduce risk for cardiovascular events.

FDA Advisory Committee recommendations

Based on the data summarized above, the Committee voted unanimously that all COX-2 inhibitors that have been approved for use in the USA, including celecoxib, valdecoxib, and rofecoxib, significantly increase the risk for cardiovascular events [15]. The Committee noted that the benefits of celecoxib outweigh potential cardiovascular risks, and voted unanimously in favor of keeping celecoxib on the market. In contrast, opinion was only slightly in favor of keeping valdecoxib on the market. Just over half of the Committee voted in favor of permitting the reintroduction of rofecoxib,

and many members argued that the 50 mg dosage of rofecoxib should not be marketed. The panelists were unanimous in recommending the addition of a 'black box' warning to the labeling of all COX-2 inhibitors. It was also agreed that product labels for all traditional NSAIDs should contain a warning regarding cardiovascular risk.

FDA mandated labeling changes

On 7 April 2005, the FDA requested that valdecoxib be removed from the market and recommended a series of changes to the labeling for COX-2 inhibitors and NSAIDs. A 'black box' warning will be added to the celecoxib label highlighting the potential for increased cardiovascular and gastrointestinal risk; the labels for prescription NSAIDs will be revised to include a similar boxed warning. The labels will also contain specific information on the potential for cardiovascular and gastrointestinal risk. In addition, all prescribed NSAIDs will be required to include a medication guide for patients to advise them of the risk for cardiovascular and gastrointestinal events. The FDA also requested that over-the-counter NSAIDs add a warning about potential skin reactions. In a recently issued Executive Summary Report [20], the FDA noted that it was deemed reasonable to conclude that there is a 'class effect' for increased cardiovascular risk for all NSAIDs, pending the availability of data from long-term controlled clinical trials that more clearly delineate risks associated with individual agents. Data at this point do not allow one to conclude that currently available COX-2 selective drugs confer an increased risk over nonselective NSAIDs in chronic use.

Current treatment for pain and inflammation

The American College of Rheumatology (ACR) and the American Pain Society have issued practice guidelines for the management of patients with rheumatoid arthritis, osteoarthritis (OA), and chronic pain. Although these guidelines require revision on the basis of the recommendations of the FDA Advisory Committees regarding the NSAIDs, including the COX-2 inhibitors, it is worthwhile presenting them here to provide a context in which to discuss treatment decisions in light of recent regulatory events.

Current recommendations for the use of NSAIDs and COX-2 inhibitors

Recommendations for the medical management of OA of the hip and knee have been published by the ACR [21]. Nonpharmacologic management strategies are first-line therapy for all patients. The ACR recommends that, when necessary, pharmacologic therapy should be added to continuing nonpharmacologic approaches. Recommendations vary for patients with mild, moderate, or severe disease. Acetaminophen is considered first-line pharmacologic therapy for mild to moderate OA based on cost, efficacy, and toxicity profile. Although NSAIDs can be effective, the guidelines indicate that the relief of mild to moderate pain afforded by acetaminophen is comparable to that achieved using over-the-counter NSAIDs.

Currently, the ACR recommends acetaminophen as first-line treatment for OA of the knee or hip. This is largely because of the perception that acetaminophen is safer than NSAIDs and is equally effective [22,23]. Until recently, few comparison data were available with which to assess the therapeutic equivalence of acetaminophen and NSAIDs. Results from two older comparison studies, one comparing acetaminophen with ibuprofen [24] and the other comparing acetaminophen with naproxen [25], suggested that acetaminophen had similar efficacy to NSAIDs. The results of these trials influenced current ACR guidelines recommending first-line use of acetaminophen.

Despite older clinical data suggesting that acetaminophen is as effective as NSAIDs, a survey of 1799 patients found that the majority of patients with OA (>60%) prefer NSAIDs over acetaminophen in the symptomatic treatment of OA based on perceived better efficacy [26]. Results from recent blinded, randomized, placebo controlled trials comparing the efficacy of acetaminophen and NSAIDs are consistent with this patient preference for NSAIDs and may necessitate the reassessment of the ACR guidelines. Results from a meta-analysis conducted by Lee and colleagues [27] indicate that NSAIDs are statistically superior to acetaminophen in reducing OA pain. Using data from seven clinical trials that evaluated both traditional and COX-2-selective agents in the treatment of OA pain, the authors found that scores for overall pain at rest and walking pain favored the NSAID group. There were slightly, but not significantly, more withdrawals due to adverse events in the NSAID group. A second trial, conducted by Zhang and colleagues [28], found that while acetaminophen was effective in relieving arthritis pain, NSAIDs were significantly better in terms of pain relief, patient preference, and clinical response.

A 2001 study of patients with OA of the hip or knee randomly assigned to 75 mg diclofenac plus 200 μg misoprostol twice daily or 1000 mg acetaminophen four times daily [29] showed that the diclofenac/misoprostol combination yielded significantly greater improvement in all primary outcome measures (Western Ontario and McMaster Universities Osteoarthritis Index and the visual analog pain scale of the Multidimensional Health Assessment Questionnaire; $P < 0.001$) over a 6 week period.

Recently, Geba and colleagues [30] reported that rofecoxib 25 mg/day provided greater therapeutic benefits than maximal daily doses of 4000 mg/day of acetaminophen in patients with OA of the knee for all prespecified end-points (night pain, composite pain subscale, stiffness subscale, and physical functioning subscale) and was more effective than rofecoxib 12.5 mg/day and celecoxib 200 mg/day.

The Patient Preference for Placebo, Acetaminophen (paracetamol) or Celecoxib Efficacy Studies (PACES) [31] also demonstrated that 200 mg/day celecoxib was more effective

Table 1

Guidelines for NSAID use

	NSAID alone	NSAID + PPI	COX-2	COX-2 + PPI
Appropriate	Age <65 years, no aspirin and no previous gastrointestinal event	On aspirin Previous gastrointestinal event	On aspirin and no previous gastrointestinal event Not on aspirin and previous gastrointestinal event	Previous gastrointestinal event and on aspirin On aspirin and steroids/warfarin
Inappropriate	Previous gastrointestinal event On aspirin, steroids, or warfarin	Age <65 years, not on aspirin and no previous gastrointestinal event	–	Not on aspirin and no previous gastrointestinal event Age <65 years, on aspirin but no previous gastrointestinal event Age <65 years, previous uncomplicated gastrointestinal event and not on aspirin, steroids, or warfarin

Shown are guidelines for nonsteroidal anti-inflammatory drug (NSAID) use prior to rofecoxib withdrawal [9]. COX, cyclo-oxygenase; PPI, proton pump inhibitor. Reproduced with permission from [9].

than acetaminophen at a dosage of 1000 mg four times daily, with approximately twice as many patients preferring the COX-2 inhibitor compared with acetaminophen or placebo ($P = 0.001$ and $P = 0.009$; two 6 week crossover trials).

Prescription NSAIDs are recommended for the treatment of moderate to severe OA; however, the guidelines strongly recommend co-therapy with gastroprotective agents in patients at increased risk for gastrointestinal adverse events. COX-2 selective inhibitors are associated with a somewhat better toxicity profile, but they are still categorized as NSAIDs, with the same risks and warnings. Patients with moderate to severe OA may receive prescription NSAIDs with gastroprotective agents, or COX-2 selective inhibitors as first-line therapy.

Recommendations for the treatment of pain in OA have also been released by the American Pain Society [32]. The guidelines indicate that acetaminophen is the medication of first choice for mild pain. For the person with moderate to severe pain and/or inflammation, a COX-2 inhibitor is considered first-line therapy unless the patient is thought to be at high risk for hypertension or renal disorder. In patients at risk for hypertension and edema, the guidelines recommend caution when using NSAIDs because of the risk for exacerbating these conditions. Nonselective NSAIDs should be considered only if the person is not responsive to or unable to take COX-2 selective NSAIDs and/or acetaminophen up to 4000 mg/day, and only after a risk analysis is done to determine the risk for a significant NSAID induced gastrointestinal complication. If such risk factors exist, then a prophylactic agent such as a PPI or misoprostol should be given along with the nonselective NSAID. Among patients at cardiovascular risk, low-dose aspirin is recommended; however, it should be accompanied by a gastroprotective agent, regardless of whether the patient is treated with a nonselective or COX-2 selective NSAID.

Evidence based consensus guidelines

Recently, evidence based consensus guidelines were published for the use of NSAIDs, COX-2 inhibitors, and co-therapy with PPIs in patients who require chronic anti-inflammatory therapy [9]. These guidelines were based on a literature review performed by the authors on the risks, benefits, and costs of each therapy. Use in particular clinical scenarios was rated as 'appropriate', 'uncertain', or 'inappropriate' on a 9 point scale by a physician panel consisting of rheumatologists, internists, gastroenterologists, and cardiologists.

The guidelines are summarized in Table 1 [9]. Briefly, the panel recommended treatment with NSAIDs alone in patients aged less than 65 years who do not have gastrointestinal risk factors. Co-therapy with a PPI or treatment with a COX-2 inhibitor was considered unnecessary in these patients. The use of an NSAID alone was considered inappropriate in any patient with a previous gastrointestinal event and in those who concurrently receive aspirin, steroids, or warfarin; these patients should receive either a COX-2 inhibitor or an NSAID plus a PPI. Use of a COX-2 inhibitor with PPI co-therapy was considered appropriate only in patients at very high risk, such as those with a previous gastrointestinal event who are taking aspirin and those who are taking aspirin plus steroids or warfarin. Among patients aged 65 years or older considered at low risk for gastrointestinal events, there was uncertainty regarding whether an NSAID or a COX-2 inhibitor could be used alone.

Conclusion

Taken together, the results of recent clinical trials and evidence presented at the US FDA Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee hearing [33] suggest that there is an

increase in cardiovascular risk associated with the use of NSAIDs as a class. These findings have substantial implications for public health, patient education, and therapeutic decision making on the part of rheumatologists and other physicians charged with managing arthritis and related conditions.

Current guidelines for the management of pain and inflammation in patients with OA and rheumatoid arthritis must be revised to encompass not only the regulatory changes proposed for COX-2 inhibitor therapy but also the lack of benefit – and questionable safety – of acetaminophen. The recommendations should also reflect the emerging role of co-therapy with a nonselective NSAID and a PPI, a combination that may offer effective pain control along with optimal gastroprotection. Furthermore, the guidelines should integrate assessment of cardiovascular and gastrointestinal risk before initiation of NSAIDs or COX-2 inhibitors.

A key concern is the interaction between aspirin and NSAIDs. Although low-dose aspirin is cardioprotective, evidence suggests that concomitant use with certain NSAIDs – in particular ibuprofen – may reduce its cardioprotective benefits and increase gastrointestinal risk. Although not sanctioned by a medical society, a clinician's guide to NSAID therapy following the withdrawal of rofecoxib and valdecoxib provides initial guidance for the treatment of patients who require NSAID therapy [34]. This treatment algorithm accounts for recent evidence that cardiovascular risk is increased in patients who receive NSAIDs and for data suggesting that an NSAID plus a PPI is comparable to a COX-2 selective agent in terms of gastrointestinal safety. The key aspects of this algorithm are those that address gastroprotection, especially with regard to recognition of the added risk of ASA-induced gastric injury. Specific cardiovascular recommendations are premature at this time, given the increased risk imparted by both traditional NSAIDs and COX-2 selective agents [35].

It is clear from recent data and FDA decisions that the use of both traditional NSAIDs and COX-2 selective agents must be reconsidered. This supplement considers the evidence for and against the use of NSAIDs, including COX-2 inhibitors, with regard to gastrointestinal and cardiovascular safety, and presents a summary of current management options for the prevention of gastrointestinal complications in light of these recent developments.

Competing interests

SBA has served as a consultant to Pfizer, Novartis and TAP Pharmaceuticals. ALW is on advisory boards, and is a speaker and consultant for Merck, Novartis, Pfizer and TAP.

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