A SPECIAL ARTICLE

Protecting Patients’ Stomachs and Hearts While Managing Their Osteoarthritis

Management of osteoarthritis (OA) often involves concerns about the gastrointestinal (GI) toxicity associated with non-steroidal anti-inflammatory drugs (NSAIDs) and/or low-dose salicylates versus the need for cardioprotection in select patients with cardiovascular risks. Newer treatment options may offer ways to improve GI safety while maintaining cardioprotection. However, only the cyclooxygenase-(COX) 2 specific inhibitors, celecoxib and rofecoxib, and the combination of misoprostol/NSAIDs have been evaluated in large-scale, randomized, controlled trials. These trials have largely confirmed the GI benefits of these treatments. But, methodological differences between the studies may have affected the rate of upper GI events (with the use of salicylates in the celecoxib study) and, unexpectedly, the higher rate of myocardial infarction (without the use of low-dose salicylates in the rofecoxib study). These findings require careful consideration before planning therapy in patients at risk.

INTRODUCTION

Despite their well-known gastrointestinal (GI) toxicities, the non-steroidal anti-inflammatory drugs (NSAIDs) have long been relied upon for effective relief of pain and inflammation in patients with osteoarthritis (OA). For many patients, the risk of GI bleeding, ulcers, perforation, and intestinal obstruction with NSAID therapy has been preferable to the therapeutic alternatives: the many, varied side effects of steroidal or opioid therapies. However, approximately 20% of patients with OA take long-term salicylate therapy due to a history of concurrent cardiovascular (CV) disease or the presence of CV risk factors. Gastroenterologists may find themselves facing questions about how best to manage trade-offs between GI

Norman Gitlin, M.D., Professor of Medicine, Emory University, Atlanta, Georgia.
safety and CV safety in OA patients who require analgesic/anti-inflammatory therapy with concomitant salicylate therapy. The purpose of this paper is to review options for managing both the GI and CV health of patients with OA.

AVOIDING ULCER COMPLICATIONS

The most widely accepted approach to minimizing treatment-related GI risks in any patient with OA is to start with acetaminophen. Treatment guidelines have traditionally advocated this approach, followed by a switch to, or the addition of, an NSAID for non-response to acetaminophen (1–3). However, growing evidence from clinical trials strongly suggests that acetaminophen is not as effective or as safe as has long been assumed. In recent clinical trials, acetaminophen was less effective in providing pain relief and improving functionality and was perceived as less valuable than NSAIDs by patients with OA (1,4,5). Additionally, the risk of upper GI complications (Figure 1) has been shown to be higher with acetaminophen >2 g/day (3.6-fold greater risk versus non-acetaminophen use) than with low-medium doses of NSAIDs (2.4-fold greater risk versus non-NSAID use), although not as high as with high-dose NSAIDs (4.9-fold greater versus non-NSAID use) (6). Patients who used acetaminophen ≥2 g/day with concomitant NSAIDs had substantially increased risks of GI complications (13.2-fold greater risk versus non-use of acetaminophen/NSAIDs) (6). In addition, patients who consume excessive quantities of alcohol (>40 g/day) and/or have advanced decompensated liver disease need to be cautioned to avoid acetaminophen entirely.

Many clinicians, and nearly all gastroenterologists, are reluctant to prescribe traditional NSAIDs or recommend non-prescription NSAIDs in patients with any degree of GI risk. The newer treatment options to NSAIDs—COX-2 specific inhibitors (e.g., celecoxib, rofecoxib, and valdecoxib), gastroprotection through exogenous prostaglandin-replenishment with misoprostol, and the reduction of hydrochloric acid utilizing proton-pump inhibition, have been able to effectively reduce the risk of upper GI complications compared with traditional NSAIDs. Of these alternatives, currently only the COX-2 specific inhibitors, celecoxib and rofecoxib, and misoprostol have actually been confirmed to reduce upper GI complications, such as perforation, ulcers, bleed, and obstruction, in large, prospective, randomized, controlled clinical trials (7–9).

Three large GI-outcomes studies, conducted at the request of the United States Food and Drug Administration, were intended to evaluate reductions in the risk of upper GI complications with misoprostol plus NSAIDs (the MUCOSA trial), celecoxib (the CLASS trial), or rofecoxib (the VIGOR trial) versus traditional NSAIDs (Table 1). While these trials have confirmed the GI safety of these agents, differences among these trials in study designs, patient populations, and clinical outcomes have led to discussion and controversy over

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how best to apply these findings to clinical practice. A brief review of these studies, their results, and application to clinical practice follows.

The MUCOSA study of misoprostol plus traditional NSAIDs, the first of the large GI outcomes studies, served as the model for the two subsequent trials. In MUCOSA, misoprostol at doses up to 800 mcg/day plus NSAIDs (principally naproxen 75 50 mg/day, diclofenac 100 mg/day, ibuprofen 1200 mg/day, and piroxicam 20 mg/day) reduced the incidence of upper GI complications by 40% compared with NSAIDs alone (7). The GI benefit of misoprostol has since been confirmed in endoscopy studies of the combination formulation of misoprostol plus diclofenac (Arthrotec®) versus traditional NSAIDs (10,11). Since misoprostol replenishes prostaglandin E1 in the gastric mucosa, it is not surprising that this agent is particularly effective at reducing the risk of gastric ulcers. The reduction in hydrochloric acid by misoprostol also reduces the risk of duodenal ulcers.

Interpretation of the GI outcomes in the CLASS and VIGOR trials is more challenging. These trials were similar in that they each enrolled approximately 8,000 patients and created “worst-case” scenarios by requiring doses that were two- to four-fold higher than the maximum recommended doses for rheumatoid arthritis (RA) and OA (8,9). But, the trials were different in several important ways. The CLASS trial further increased the potential for upper GI complications among patients receiving celecoxib or NSAID comparator by allowing the use of salicylates for cardioprotection in 21% of patients, whereas VIGOR specifically did not allow salicylate therapy (8,9). The CLASS trial evaluated celecoxib 400 mg/day versus ibuprofen 800 mg TID or diclofenac 75 mg BID as comparator NSAIDs, whereas VIGOR evaluated rofecoxib 50 mg/day versus naproxen 500 mg BID (8,9). And, the CLASS trial enrolled patients with OA or RA, whereas VIGOR enrolled only patients with RA, who have greater potentials for medical complications (8,9).

Overall, celecoxib and rofecoxib each decreased the risk of upper GI events by approximately 50% versus comparator NSAIDs in these studies (8,9). In CLASS, the reduction in upper GI events with celecoxib 400 mg/day was borderline statistically significant versus comparator NSAIDs in the overall study population (47% risk reduction versus ibuprofen, \( p = 0.09 \)). However, there were significantly fewer GI events in the major sub-population of patients not taking salicylates (65% risk reduction versus ibuprofen).
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$p = 0.04$), which is more comparable to the approach taken in VIGOR (8,9). In the VIGOR trial, rofecoxib 50 mg/day reduced the risk of upper GI complications by 50% versus naproxen 500 mg BID ($p < 0.001$) (9). However, rofecoxib was unexpectedly associated with a four-fold higher rate of CV events, specifically myocardial infarction, compared with naproxen (9). The potential implications of these cardiovascular observations will be discussed in greater detail below. A recent meta-analysis has shown that the newest COX-2 inhibitor, valdecoxib, significantly reduced the risk of GI events, including gastric ulceration, compared to non-selective NSAIDs in 10 OA and RA clinical trials of up to 26 weeks in duration. (12). This finding was particularly striking for three reasons: valdecoxib was used at doses of up 80 mg once daily (eight times greater than the approved daily dosage in OA and RA) in these studies; risk reductions with valdecoxib versus the non-selective NSAIDs were observed in patients 55 years of age and older, as well as in patients under 55 years of age, who were found to be at increased risk of NSAID-related toxicity; and, the overall incidence of GI events was similar among patients treated with valdecoxib or placebo.

Neither COX-2 selective inhibition with meloxicam nor hydrochloric acid/proton-pump inhibition with omeprazole or similar agents has been documented to reduce the incidence of upper GI complications versus traditional NSAIDs in large-scale clinical trials, such as MUCOSA, CLASS, and VIGOR. This is a critical distinction, because the findings from endoscopic studies alone with these or any other medications are poor predictors of subsequent upper GI complications. Short-term reductions in lesions with medication cannot be extrapolated to reductions in the morbidity and mortality associated with GI toxicity of NSAID therapy. Additionally, the GI risks with the COX-2 selective inhibitor, meloxicam, are minimized only at the lowest dose of 7.5 mg/day (13,14). A comprehensive literature review of randomized clinical trials showed that there is currently no convincing evidence that the GI safety of meloxicam is maintained at higher, therapeutic and clinically effective doses (14).

Recently, the use of proton pump inhibitors (PPIs) in combination with traditional NSAIDs has become increasingly popular, despite the absence of substantial clinical evidence of a reduction in upper GI complications. Currently available information suggests that the PPI, omeprazole, is more effective than eradication of Helicobacter pylori in preventing recurrent upper GI bleeds (15). The role of PPIs in healing or preventing gastric or duodenal ulcers and preventing ulcer complications associated with NSAID therapy in H. pylori-negative patients has not been fully evaluated or defined. There is evidence from at least one major clinical trial, however, that omeprazole is inferior to misoprostol 400 mcg/day for the prevention of ulcer relapse among H. pylori-negative patients (16).

AVOIDING CV COMPLICATIONS

Salicylate therapy has earned a place in the management of a wide array of patients with a history of CV disease or risk factors for the development of CV disease. But even at low doses (325 mg/day), salicylates require a balance between an increased risk of upper GI complications and a decreased risk of thrombotic events. No daily dosage of salicylate is entirely risk-free. In healthy subjects, salicylates at a dose of 300 mg daily have been associated with a four-fold greater risk of peptic ulcer bleeding compared with non-use of salicylates, and even low doses of 75 mg daily had double the risk of bleeding compared with placebo (Figure 2) (17). Unfortunately, patients are more likely to take the 325-mg tablets of salicylate because they are typically much less expensive than the 81-mg tablets marketed for cardioprotection. Since salicylates bind irreversibly to the COX-1 enzyme on platelets and provide sustained protection against platelet aggregation throughout the life of the platelet population, they could be taken less frequently than daily to improve gastric tolerability/safety. However, the extent of reduction of gastric complications and the degree to which patients will comply with less than daily dosing of low-dose salicylates have not been extensively evaluated.

Controversies continue regarding the potential CV risks and GI benefits of conventional NSAIDs versus COX-2 specific inhibitors. The VIGOR trial described above has stoked many of these controversies. In that trial, significantly fewer RA patients receiving naproxen 500 mg BID experienced an myocardial

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apathy may have a potentially important effect on increasing blood pressure and edema in a subset of all treated patients (21). Rofecoxib 50 mg/day was associated with a higher incidence of the development of hypertension in previously normotensive patients than was naproxen 500 mg twice daily in the VIGOR trial (9.7% versus 5.5%, respectively) (21). This may be important because hypertension, especially systolic hypertension, is a key risk factor for the development of many manifestations of CV disease, including MI. Peripheral edema, which may be frequently observed in patients with hypertension, was also more common with rofecoxib than naproxen in VIGOR (5.4% versus 3.6%, respectively) (21).

In contrast to rofecoxib, celecoxib has generally been associated with incidences of hypertension and edema that were similar to, or less than, incidences associated with traditional NSAIDs (21). Moreover, in head-to-head analyses, celecoxib has been found to be less likely than rofecoxib to cause hypertension or impair blood pressure control achieved with antihypertensive medication (especially angiotensin converting enzyme inhibitors or beta-blockers) (22–25). The CV risk potential for newer COX-2 specific inhibitors, such as valdecoxib, has not been fully evaluated and defined.

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BALANCING GI AND CV RISKS

There are currently no treatment guidelines specifically for patients with OA and pre-existing CV disease or for patients with risk factors requiring low-dose salicylate therapy. By the time these patients see a gastroenterologist, they typically have tried with no success acetaminophen and were taking traditional NSAIDs when they developed GI symptoms. Although current treatment options involve some compromise between risks for GI and CV complications, it is prudent to provide all of these patients with low-dose salicylate therapy and change their analgesic/anti-inflammatory therapy. Ideally, patients should take a low-dose of enteric-coated salicylate (eg, 81 mg/day) to minimize their GI risks. Comparative studies in healthy volunteers showed similar platelet thromboxane inhibition over 12 weeks with daily salicylate doses of 81 mg and 325 mg. Thus, the 81-mg daily dose of enteric-coated salicylates is currently advocated for use by patients with cardiovascular risks.

An option to minimize the potential for both GI and CV complications in these patients involves a COX-2 inhibitor, such as celecoxib, that has well-defined GI and cardiovascular safety profiles with low-dose salicylate therapy. The GI safety profile of celecoxib has been documented in the CLASS study, which showed significantly fewer upper GI events with celecoxib versus traditional NSAIDs among OA and RA patients not on low-dose salicylate therapy. Although the findings of this study suggest that concomitant salicylate therapy diminishes the gastroduodenal benefit of celecoxib, there was no evaluation of GI risks according to salicylate dose level (low-dose [325 mg/day] versus very-low-dose [81 mg/day]). Since the GI risks of salicylates are dose-related, it would be anticipated that the combination of celecoxib with very-low-dose salicylate would provide GI outcomes superior to those reported in CLASS. Additionally, there was no other evidence of a trade-off between GI and CV safety (eg, no increase in MI, hypertension, or edema) with celecoxib in CLASS.

Rofecoxib improved GI safety but increased the rate of MI versus naproxen among RA patients not on low-dose salicylate in the VIGOR trial. The incidences of hypertension and edema with rofecoxib have also been reported to be higher than with celecoxib in direct comparative trials (22–25). Additionally, other comparative studies showed that rofecoxib was associated with more moderate GI symptoms, such as nausea, vomiting, dyspepsia, and abdominal pain, than celecoxib in OA and RA patients taking low-dose salicylates (3–25 mg/day) (26,27). Taken together, these findings favor the use of celecoxib in patients with OA and CV disease or CV risk factors requiring low-dose salicylates.

Patients who do not respond to, or are intolerant of their initial COX-2 inhibitor should be switched to an alternative COX-2 inhibitor, such as valdecoxib, that has not been associated with adverse CV findings. Patients who require a subsequent change due to lack of response or intolerance can be switched to gastroprotective therapy with the combination formulation of diclofenac/misoprostol. Misoprostol has been shown to reduce the risk of NSAID-associated upper GI events to a degree similar to that of the COX-2 specific inhibitors. Additionally, the gastroprotective effect of misoprostol counters the potential ulcerative effects of low-dose salicylates on the gastric mucosa. Most patients tolerate this combination therapy well, especially following an initiation of treatment at low doses (eg, diclofenac 50 mg/misoprostol 200 mcg once or twice daily) with titration to higher doses, as needed, for greater pain relief. The incidence of loose stools/diarrhea with misoprostol has possibly been overemphasized in clinical practice, and may be less of an issue among elderly OA patients who frequently present with complaints of the opposite problem—constipation. This side effect is dose-dependent and does not usually occur until misoprostol doses of 600 or 800 mcg are administered on a daily basis.

The combination of a PPI plus a traditional NSAID may be helpful but does not appear to be as effective as diclofenac/misoprostol in preventing NSAID-associated gastric lesions, particularly in *H. pylori*-positive patients. Ideally, experience from a large-scale clinical trial would clarify how best to use this regimen in patients with OA, and particularly in patients with OA who have CV disease or risk factors requiring low-dose salicylate therapy.

Despite its limitations, acetaminophen may continue to play a supportive role in the management of OA patients on low-dose salicylate therapy. This medication is most beneficial at doses up to 2 g/day on its own as initial therapy in patients with mild OA or as a
supplement to the therapies discussed above in patients with more moderate-severe OA.

References