Controversial Issues in the Perioperative Use of Non-steroidal Anti-inflammatory Drugs for Orthopedic Surgery

a report by

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Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the synthesis of prostaglandins both in the spinal cord and at its periphery, thus diminishing the hyperalgesic state after surgical trauma.1,2 NSAIDs are useful as the sole analgesic after minor surgical procedures3 and may have a significant opioid-sparing effect after major orthopedic surgery.4 NSAIDs are currently recommended for a multimodal analgesic approach to the management of perioperative pain.4 Recent practice guidelines for acute pain management in the perioperative setting specifically state that “unless contraindicated, all patients should receive around-the-clock regimen of NSAIDs, coxibs, or acetaminophen”.5 However, several controversial issues have arisen regarding the routine perioperative administration of NSAIDs for orthopedic surgery. These include a possible deleterious effect on fracture and tendon healing, an increased risk of perioperative bleeding, and concerns regarding cardiovascular (CV) safety.

Cyclo-oxygenase Inhibitors

The cyclo-oxygenase (COX)-2 inhibitors (coxibs) are the newest class of NSAIDs with analgesic efficacy comparable with conventional NSAIDs, but they are associated with reduced gastrointestinal (GI) side effects and an absence of anti-platelet activity.6,7 These COX-2 NSAIDs can therefore be administered preemptively to surgical patients without the added risk of increased perioperative bleeding that has been reported with conventional NSAIDs.8,9 The author believes that coxibs offer a significant advantage compared with non-specific NSAIDs for a variety of musculoskeletal and orthopedic surgical procedures including total joint arthroplasty (TJA), anterior cruciate ligament (ACL) reconstruction, and spinal fusion surgery.

Prior to the introduction of coxibs, all of the author’s patients undergoing elective TJA were instructed to discontinue their use of NSAIDs seven to 10 days prior to surgery. Continuing conventional NSAIDs before TJA has been associated with a two-fold increase in the incidence of perioperative bleeding, resulting in higher transfusion requirements.7 The use of NSAIDs has been associated with other postoperative complications, including wound hematoma, upper GI tract bleeding, and hypotension.9 The

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The most common adverse events reported in clinical studies (>10%) were: decreased oxygen saturation, hypotension, urinary retention, vomiting, constipation, nausea, pruritus, pyrexia, anemia, headache, and dizziness. As with all opioids, the chief hazard of morphine sulfate is respiratory depression, especially in elderly and debilitated patients and in those with compromised respiratory function; therefore, patients must be monitored for at least 48 hours and the facility must be equipped to resuscitate patients.

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studies showed that morphine is non-mutagenic in the mouse micronucleus test and to induce chromosomal aberrations in murine lymphocytes and spermatids. Some of the clastogenic effects reported with morphine in mice may be directly related to increases in glucocorticoid levels that are known to be causally related to increases in DNA fragmentation when incubated with murine erythrocytes. Contrary to these results, morphine was found to increase DNA fragmentation when incubated in vitro with a human lymphoma cell line. In vivo, morphine has been reported to produce an increase in the frequency of sister chromatid exchanges and chromosomal aberrations in bone marrow cells and consequently an increase in the frequency of micronuclei in bone marrow cells in mice. Similar evidence of chromosomal alterations when incubated with murine erythrocytes. Contrary to these results, morphine was found to increase DNA fragmentation when incubated in vitro with a human lymphoma cell line. In vivo, morphine has been reported to produce an increase in the frequency of sister chromatid exchanges and chromosomal aberrations in bone marrow cells and consequently an increase in the frequency of micronuclei in bone marrow cells in mice. Similar

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The likelihood of developing these complications was found to be 5.8 times greater for patients using NSAIDs 24 hours before surgery than without such usage. The author has observed that discontinuing NSAIDs before TJA results in an arthritic flare not only in the operative joint but also in other arthritic joints leading to increased pre-operative pain. Increased pain before TJA is the leading cause for increased post-operative pain, prolonged hospital admission, and impaired rehabilitation. The administration of perioperative coxibs for TJA has demonstrated a reduction in perioperative pain and improvement in outcomes without an added risk of increased perioperative bleeding.

Prostaglandins have been known for many years to have potent effects on bone metabolism, including both osteoblastic and osteoclastic activity, as well as being essential in bone repair. Prostaglandins have been known for many years to have potent effects on bone metabolism, including both osteoblastic and osteoclastic activity, as well as being essential in bone repair. The exact mechanism by which NSAIDs impair spinal fusion has not yet been elucidated. It has been hypothesized that the effect may be mediated by an inhibition of the inflammatory process with concomitant reduction in blood flow in the early period of osteogenesis, decreased mesenchymal cell proliferation, or through inhibition of the calcification of the bone matrix.

Many investigators recommend that NSAIDs should not be utilized in the multimodal management of acute pain for patients undergoing spinal fusion surgery. Despite the fact that data is conflicting, a large body of literature derived from laboratory animal studies suggests that COX-2 inhibitors either delay or inhibit bone healing. However, in these studies, NSAIDs were administered over several weeks to months at doses greater than those approved for acute pain. Recently, it has been suggested that the deleterious effects of COX-2 inhibitors on fracture healing may be reversible with short-term treatment. Gerstenfeld and Einhorn have concluded that “management of fracture-associated pain with inhibitors of COX-2 should neither impair nor delay healing as long as the duration of treatment is consistent with current standards of care”. In addition, when limiting the use of NSAIDs for short-term use, physicians should prescribe the lowest effective dose for bone surgeries. In a retrospective study of 434 consecutive patients undergoing elective, decompressive, posterior lumbar laminectomy with instrumented spinal fusion by a single surgeon within...
an eight-year period, they revealed that the short-term perioperative administration of celecoxib, rofecoxib, or low-dose ketorolac (≤110mg/d) had no significant deleterious effect on non-union. In contrast, higher doses of ketorolac (120–240mg/d), even when administered for less than one week, resulted in a significant increase in the incidence of non-union following spinal fusion surgery.

Further evidence for the safety of coxibs following spinal fusion surgery was demonstrated in a recent prospective, double-blind, randomized study in humans. This was the first prospective study in humans demonstrating that the perioperative administration of celecoxib for five consecutive days following spinal fusion surgery resulted in no increased incidence of non-union at a one-year follow-up compared with placebo. In addition, the author has reported that patients who were administered celecoxib showed a significantly (p<0.01) lower incidence of chronic donor site pain (4/40; 10%) in the celecoxib group compared with the placebo group (12/40; 30%) at one year post-surgery.

A more recent concern about the perioperative administration of NSAIDs, and coxibs in particular, for orthopedic surgery has been their possible role in increasing CV morbidity.

although intravenous (IV) ketorolac can provide an effective analgesia for ACL surgery, it is currently contraindicated for use as a pre-emptive analgesic. The author has observed increased perioperative bleeding with the pre-emptive administration of either ketorolac or ibuprofen for out-patient ACL surgery, and has since discontinued its use. The author is currently performing a prospective, randomized, double-blind study assessing the effect of administering COX-2 NSAIDs on bone and ligament healing in patients following ACL surgery.

A more recent concern about the perioperative administration of NSAIDs, and coxibs in particular, for anterior cruciate ligament (ACL) repair surgery. In a retrospective study of 1,200 patients undergoing ACL surgery, the pre-emptive administration of coxibs demonstrated a reduction in the incidence of pain, opioid use, post-operative nausea and vomiting, recovery room length of stay, and unplanned admission to the hospital. In addition to providing short-term analgesic benefits, the use of pre-emptive multimodal analgesia including coxibs resulted in a significant reduction in long-term patellofemoral complications following ACL surgery. These included a reduction in the incidence of anterior knee pain, scar tissue, flexion contracture, and complex regional pain syndrome. Furthermore, patients receiving pre-emptive coxibs were more likely to return to their pre-injury level of activity including full sports participation.

The Advantages and Disadvantages of Perioperative Coxib Administration

perioperative coxib administration offers significant advantages for anterior cruciate ligament (ACL) repair following spinal fusion surgery. In a retrospective study of 1,200 patients undergoing ACL surgery, the pre-emptive administration of coxibs demonstrated a reduction in the incidence of pain, opioid use, post-operative nausea and vomiting, recovery room length of stay, and unplanned admission to the hospital. In addition to providing short-term analgesic benefits, the use of pre-emptive multimodal analgesia including coxibs resulted in a significant reduction in long-term patellofemoral complications following ACL surgery. These included a reduction in the incidence of anterior knee pain, scar tissue, flexion contracture, and complex regional pain syndrome. Furthermore, patients receiving pre-emptive coxibs were more likely to return to their pre-injury level of activity including full sports participation.

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for orthopedic surgery has been their possible role in increasing CV morbidity.6 Theoretical concerns relating to this risk were borne out when a five-fold increase in the incidence of myocardial infarction (MI) was seen in the Vioxx Gastrointestinal Outcome Research (VIGOR) study.36 This study utilized rofecoxib 50mg daily for a median of nine months in a high-risk rheumatoid arthritis (RA) patient population in which the use of aspirin was precluded. It was argued at the time that the findings did not represent an increased CV risk due to rofecoxib, but rather a protective effect of naproxen in the control population, as well as precluding the use of aspirin.

Other clinicians attributed the increased adverse CV events to a pro-thrombotic state caused by selective COX-2 inhibitors.37 COX-1 mediates the production of thromboxane A2 in platelets, leading to platelet aggregation and vasoconstriction. In contrast, COX-2 catalyzes endothelial prostacyclin syntheses, which counteracts thromboxane A2 leading to vasodilation, and is an inhibitor of platelet aggregation. Since selective COX-2 inhibitors decrease prostacyclin formation, these NSAIDs may potentially disrupt homeostasis and create a pro-thrombotic effect.37 Epidemiological database studies that reflected actual drug use and included higher risk patients also found a correlation between normal- or high-dose rofecoxib use and adverse CV outcomes.38,39

Merck & Co. voluntarily withdrew rofecoxib from the worldwide market on September 30 2004 after examining the interim results from the Adenomatous Polyyp Prevention on Vioxx (APPROVe) study.34 This long-term, randomized, prospective, placebo-controlled, double-blind multicenter study was designed to investigate the effects of three years of treatment with rofecoxib 25mg daily, at the risk of recurrent neoplastic polyps of the large bowel in patients with a history of colorectal adenomas. This study revealed a 1.7-fold increased risk of MI or cerebrovascular accident with rofecoxib compared with placebo, which became apparent after 18 months of treatment. During the first 18 months, the event rates were similar in the two groups.

Subsequently, on December 17 2004, Pfizer Inc. informed the US Food and Drug Administration (FDA) that it was halting its Adenoma Prevention with Celecoxib (APC) trial because of an increase in the incidence of CV events. The APC trial examined the efficacy of celecoxib (200mg or 400mg twice-daily) with placebo for 33 months for the prevention of colorectal adenoma.35 Celecoxib was associated with a dose-related 2.3- to 3.4-fold increase in serious adverse CV events. Similar to the APPRove study, the increased risk did not become apparent until after 12 months of treatment. It was argued that these results were not consistent with the extensive database or with two other large long-term placebo-controlled studies.

The Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial included patients taking 400mg of celecoxib or placebo daily for an average of 32 months. The Alzheimer’s Disease Anti-Inflammatory Prevention Trial (ADAPT)36 found no increased risk with celecoxib 200mg daily but did find a statistically significant increase in CV risk with naproxen. This study is of significant clinical importance since previous prospective, long-term coxib studies used placebo for comparison, while this is the first trial to use a non-specific NSAID as a comparator drug.

Valdecoxib and the parenteral pro-drug parecoxib have also been associated with the potential risk of adverse post-operative CV events, including an increase in cerebrovascular events (2.9% versus 0.7%) and MIs (1.6% versus 0.7%) after administering a supramaximal dose (40mg twice daily) for 14 days following coronary artery bypass grafting (CABG) surgery. However, no increase in CV events was observed with a therapeutic dosing of parecoxib followed by valdecoxib for general and orthopedic surgeries.

The question of whether the increased cardiac risk associated with COX inhibition is unique to COX-2 inhibitors, or is characteristic for all NSAIDs, now arises. A joint meeting of the FDA’s Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee convened on February 16–18 2005 to discuss the safety of COX-2 inhibitors and non-specific NSAIDs. The FDA Advisory Committee reaffirmed that COX-2 inhibitors are important treatment options for pain management and the preponderance of data demonstrates that the CV risk associated with celecoxib is similar to those associated with commonly used, older, non-specific NSAIDs. The rationale behind this was that COX-2 inhibitors collectively increased CV risk compared with placebo but not when compared with non-selective NSAIDs. The Committee commented that the short-term use of NSAIDs otherwise does not appear to increase CV risk and that rigorous scientific studies are needed to characterize the longer-term CV risks of these analgesics.

Subsequently, on April 7 2005, the FDA announced a series of changes to the entire class of NSAIDs. These included an FDA boxed warning for the potential increased risk of CV events and GI bleeding associated with all prescription NSAIDs, including celecoxib. The manufacturers were asked to revise their labeling to include a medication guide for patients in order to help make them aware of the potential for CV and GI adverse events. In addition, the FDA is asking the manufacturers of all over-the-counter (OTC) NSAIDs to revise their labels to include more specific information about the potential CV and GI risks, and information to assist consumers in the safe use of these drugs. Finally, the FDA concluded that the overall risk compared with benefit profile of valdecoxib is unfavorable, and has requested that Pfizer voluntarily withdraw valdecoxib from the market. This request was based on:

• the lack of adequate data on the CV safety of long-term use of valdecoxib, along with the increased risk of adverse CV events in short-term CABG trials, which the FDA believes may be relevant to chronic use;

• reports of serious and potentially life-threatening skin reactions, including death, in patients taking valdecoxib. The risk of these reactions in individual patients is unpredictable, occurring in patients with and without a prior history of sulfa allergy, and after both short- and long-term use; and

• lack of demonstrated advantages for valdecoxib compared with other NSAIDs. Pfizer agreed to suspend sales and marketing of valdecoxib, pending further discussions with the FDA.

Conclusions

In summary, the author believes that the short-term perioperative administration of coxibs for orthopedic surgery poses no significant increased CV risk. It has been observed that COX-2 selective NSAIDs should probably be avoided in patients after recent CABG surgery or with severe CV disease (CVD). Celecoxib continues to be utilized for a wide variety of musculoskeletal and orthopedic surgeries. These selective NSAIDs have no effect on platelet aggregation and can be continued throughout the perioperative period without an increased risk of bleeding. Furthermore, the author has observed that the short-term administration of coxibs demonstrates no deleterious effect on ligament or bone healing. For those patients requiring long-term NSAID administration, these drugs are reinstated after six weeks, after which time bone healing will have already occurred.

The author believes that denying patients these medications may pose a greater risk than non-union. The fact that unreheved acute pain may be associated with significant morbidity, including chronic post-surgical pain that may be reduced with perioperative coxib administration, should be kept in mind. Furthermore, the perioperative administration of NSAIDs may reduce the incidence of potentially serious side effects from other analgesic modalities.