GUEST EDITORIAL

Does the opioid-sparing effect of NSAIDs benefit the patient in the postoperative period?

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Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce pain intensity[1] and improve patient satisfaction after surgery.[2] They work by inhibition of cyclo-oxygenase (COX) enzymes that catalyse the production of prostaglandins.[3] Nonselective NSAIDs (e.g., diclofenac[4] and piroxicam[5]) inhibit COX-1 and COX-2 enzymes, whereas selective NSAIDs (e.g., rofecoxib[6]) inhibit only COX-2 enzymes.

In randomized controlled trials (RCTs), it has been shown that pain relief after administration of NSAIDs is associated with a significant reduction in opioid consumption.[1] The expectation, therefore, is that there should be a concomitant improvement in opioid-related effects such as nausea, vomiting, sedation, and gastrointestinal ileus. Obviation of these factors is necessary to facilitate convalescence in the recovery period.

In some RCTs, patients who received NSAIDs experienced significantly less postoperative nausea and vomiting than those who had opioids. For instance, in a quantitative systematic review of use of NSAIDs after tonsillectomy, the relative risk [RR, 95 percent confidence interval (CI)], for postoperative nausea and vomiting in favor of NSAIDs compared with opioids was 0.73 (range, 0.63 to 0.85).[7] In another systematic review of patients undergoing abdominal, orthopedic, dental, and gynecological procedures, it was shown that morphine 10 mg intramuscular, but not ketorolac 10 to 30 mg intramuscular, is associated with an increased relative risk of postoperative nausea and vomiting compared with placebo.[8]

Furthermore, sedation is a dose-dependent effect of opioids and may be minimized by NSAIDs. For instance, in an RCT of pain relief after abdominal hysterectomy, total sedation score was significantly lower in patients receiving rectal diclofenac 75 mg bd than placebo.[1] This difference was attributable to the significantly lower opioid consumption in the treatment group compared with placebo.

Opioid administration is also associated with delayed gastric emptying and gastrointestinal ileus.[9] It is likely that NSAIDs may minimize these effects by reducing opioid consumption. To test this hypothesis, formal methods (e.g., radio-opaque markers, measurement of gastric emptying, and assessment of intestinal motility) would have to be used.[10]

Despite minimizing opioid-related effects, NSAIDs are associated with adverse effects themselves. They may impair renal function[11] and precipitate bronchospasm in susceptible patients. Furthermore, nonselective NSAIDs are associated with gastric irritation[12] and hemorrhage,[13] which restrict their use.

In recent years, selective NSAIDs or COX-2 inhibitors have been introduced and have been shown to be opioid sparing.[14] Compared with nonselective NSAIDs, they are associated with a reduced risk of gastric irritation,[12] bleeding after surgery,[15,16] and of possible delay in fracture healing.[17] Despite these advantages, however, it would seem that selective NSAIDs are linked to an increased risk of cardiovascular events, in particular myocardial infarction. Evidence on this issue first came to light in the year 2000, from the findings of the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, in which the relative risk of myocardial infarction in patients with rheumatoid arthritis was significantly higher when they received rofecoxib compared with naproxen, a nonselective NSAID.[18] Subsequently, in a retrospective study, Ray[19] showed that this effect may be dose dependent. In a comparison of nonusers and celecoxib users, the RR (95 percent CI) of a serious cardiovascular event was 1.93 (range, 1.09 to 3.43) and 2.20 (range, 1.17 to 4.10), respectively, in patients taking rofecoxib in doses exceeding 25 mg.[19] This finding has been confirmed by a meta-analysis of 63 reports including 18 RCTs[20] in which the RR (95 percent CI) of a cardiovascular event was 2.83 (range, 1.24 to 6.43) and 1.37 (range, 0.52 to 3.61) in patients receiving rofecoxib 50 mg and 25 mg, respectively, when compared with control.

In September 2004, rofecoxib was withdrawn from the market. This decision came after analysis of the results of the Adenomatous Polyp Prevention on Vioxx (APROVe) RCT, which was designed to evaluate the effect of rofecoxib on recurrence of polyps in patients with a history

of colorectal adenoma.[21] Over a three-year period, there was an increased relative risk of myocardial infarction and stroke in patients taking rofecoxib 25 mg compared with placebo. There has been much criticism of the regulating bodies and manufacturer for not withdrawing rofecoxib sooner.[22] Indeed, in the cumulative meta-analysis of publications from 1997 to 2001, it would appear that the risk of cardiovascular events compared with control became significantly higher in the year 2000.[20]

The important question is whether the cardiovascular events associated with rofecoxib are specific to itself, or whether they may be generalized to other COX-2 inhibitors (e.g., celecoxib and valdecoxib). Celecoxib has been investigated extensively. In a case-control study, it would appear that these cardiovascular events are associated with rofecoxib but not with celecoxib. The odds ratio (95 percent CI) of myocardial infarction in patients receiving rofecoxib versus celecoxib was 2.72 (range, 1.24 to 5.95).[23] Similarly, in another case-control study, the odds ratio (95 percent CI) of myocardial infarction and sudden cardiac death in patients who had rofecoxib versus celecoxib was 1.59 (range, 1.10 to 2.32).[24] This elevated risk appears to occur during the first 90 days of exposure, but not thereafter.[25] Despite these reassuring results, a five-year RCT, the Adenoma Prevention with Celecoxib (APC) study, has been stopped by the National Institutes of Health.[26] In comparison with placebo, a daily dose of celecoxib 400 mg and 800 mg over an average of 33 months was associated with a hazard ratio (95 percent CI) of a major cardiovascular event of 2.5 (range, 1.0 to 6.4) and 3.4 (range, 1.4 to 8.5), respectively.[27,28]

In addition, adverse events have been associated with the consumption of valdecoxib and its prodrug, parecoxib, after cardiac surgery. In comparison with placebo, the risk ratio (95 percent CI) of cardiovascular events in patients receiving a combination of parecoxib and valdecoxib for 10 days postoperatively was 3.7 (range, 1.0 to 13.5).[29] In another RCT, this combination for 14 days after coronary revascularization was associated with a significantly higher incidence of sternal wound infections but not adverse cardiovascular events.[30]

Over the past year, many precautionary measures have been taken. In December 2004, the National Institutes of Health suspended another study, the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), in which celecoxib 200 mg bd, naproxen 220 mg bd, and placebo were evaluated.[31] Furthermore, after discussion with the European Medicines Agency, Pfizer announced in February 2005 that it would be revising safety information on celecoxib, valdecoxib, and parecoxib. These drugs are now contraindicated in patients with ischemic heart disease, cerebrovascular disease, and New York Heart Association II to IV congestive heart failure. In addition, it has been declared that valdecoxib and parecoxib should not be used for treatment of pain after coronary artery bypass surgery.[32]

In the postoperative period, the clinician would need to weigh the risks and benefits of nonselective NSAIDs and COX-2 inhibitors. Both analgesic adjuncts are associated with similar reductions in opioid consumption and pain intensity. Despite these benefits, both groups of drugs are contraindicated in patients with asthma and renal failure. Although COX-2 inhibitors may be useful after tonsillectomy in healthy patients when there is a propensity to hemorrhage, they are contraindicated after coronary revascularization, when the probability of a serious cardiovascular thrombotic event is high.[33] The opioid-sparing effects of nonselective NSAIDs and COX-2 inhibitors have not come without risk, and we await further safety data on COX-2 inhibitors to clarify whether some of them may continue to be administered postoperatively. Currently, it would seem that opioids remain a reasonable choice for management of moderate to severe pain intensity in the postoperative period.

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