

Perioperative COX-2 Inhibitors: Knowledge and Challenges

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It has been nearly a century since the possibility of synergism between analgesic drugs was first proposed (1). Although later research differentiated this initial proposition into additivity and synergy, the fundamental strategy behind such combinations remains unchanged: enhanced analgesia with minimization of adverse effects. The classic analgesic combination is aspirin, phenacetin, and codeine (1).

Application of analgesic combinations to perioperative pain ["balanced analgesia" (2)], specifically the combination of opioids with analgesic-antipyretic and nonsteroidal antiinflammatory drugs (NSAIDs), is decades old (3). Early investigations simply reported analgesic efficacy, whereas later ones specifically evaluated opioid-sparing effects. IV lysine acetyl salicylate decreased postoperative opioid requirements by about half, and also decreased attendant sedation (4). Laparotomy patients receiving the first nonaspirin NSAID, indomethacin, experienced less postoperative pain, required less morphine and for a shorter period of time, and had less respiratory depression compared with those receiving placebo (5). Indeed, the investigation was stopped early because of the overwhelmingly greater efficacy of the opioid-oral NSAID combination. Nevertheless, the adverse effects of this combination were also recognized, with a greater incidence of postoperative hemorrhage. Ketorolac was the first parenteral NSAID available in the United States, and initial studies showed a significant opioid-sparing effect and a reduction in respiratory depression (6). Ketorolac essentially introduced the widespread use of perioperative NSAIDs in this country. More than two decades of research has clearly established the perioperative analgesic efficacy and opioid-sparing effect of NSAIDs.

A major scientific discovery was the identification of multiple isoforms of cyclooxygenase (COX), most pertinently COX-1 and COX-2, and development of isoform-selective inhibitors (7). Simplistically, COX-1 is ubiquitously and constitutively expressed and has a homeostatic role in platelet aggregation, gastrointestinal mucosal integrity, and renal function, whereas COX-2 is inducible and expressed mainly at sites of injury (and kidney and brain) and mediates pain and inflammation (7,8). The recent past has seen an exponential increase in publications and the growing use of COX-2 inhibitors in the perioperative period (8–10).

In this issue of the journal, Sinatra et al. (11) present the results of a randomized, double-blinded, placebo-controlled study of the COX-2 inhibitor rofecoxib in patients recovering from a midline laparotomy. According to the authors, it is the first to evaluate rofecoxib oral suspension in abdominal surgery patients and to determine rofecoxib's effects on morphine consumption and pain associated with respiratory effort. The primary outcome measures were postoperative morphine requirements and pain (resting and effort-dependent). The authors also tested the hypothesis that a reduction in effort-dependent pain would correlate with improvements in pulmonary function. The secondary outcome measure was postoperative pulmonary function, measured as 1-s forced expiratory volume and forced vital capacity (FVC). Subjects received 25 or 50 mg of rofecoxib or placebo, 1 h before anesthetic induction, a standardized general anesthetic, and postoperative morphine via IV patient-controlled analgesia (PCA).

Morphine requirements in the recovery room were unaffected by rofecoxib. Postoperative morphine requirements (12 h and 24 h) were significantly diminished 42%–44% and 59%–60%, respectively, by single preoperative doses of 25 and 50 mg of rofecoxib. Resting and effort-dependent (after measurement of 1-s forced expiratory volume and FVC) pain scores were also significantly and dose-dependently diminished by rofecoxib at 12 h, but not 24 h. The secondary outcome measures were minimally affected by rofecoxib, which diminished postoperative changes only in FVC, and only at 12 h and at the larger rofecoxib dose. These results show that a single preoperative

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dose of rofecoxib can reduce postoperative pain scores, despite patient control of their own morphine dosing, and reduce postoperative morphine consumption.

The findings of Sinatra et al. (11), like numerous antecedent publications, provide a compelling body of evidence that the COX-2 inhibitors, like their predecessors the nonselective NSAIDs, in general, 1) decrease postoperative pain (even in patients using PCA), 2) decrease opioid requirements by 20%–50%, and 3) provide greater patient satisfaction compared with placebo. Nevertheless, the primary advantage of COX-2 inhibitors compared with NSAIDs is their lack of effect on platelet function and bleeding and hence the opportunity for pre- and perioperative administration.

These are critical findings, representing intensive research efforts. The field of COX-2 inhibitor research should now move beyond this seminal phase. The novelty of additional studies simply showing analgesia and opioid-sparing will soon wane. The challenge of future research will be to elucidate the mechanisms of COX-2 inhibitor analgesia and their functional significance. By analogy to economics, the science of COX-2 inhibitors and their perioperative use can be divided into questions of micropharmacology and of macropharmacology.

Three oral COX-2-specific inhibitors are currently marketed, there are tablet and suspension formulations, and a parenteral COX-2 inhibitor is available in many countries outside the United States. What is the optimal time of preoperative oral COX-2 inhibitor administration? Typically, studies administer the drugs 1 h before anesthetic induction. Yet in awake patients, maximal plasma concentrations (T_{max}) do not occur until 2–4 h after oral dosing. Should oral COX-2 drugs be administered earlier? Are there differences between oral COX-2 inhibitors in their absorption kinetics? T_{max}? Efficacy? Are the absorption kinetics in supine anesthetized patients the same as in awake patients?

Neuronal plasticity, central sensitization, and COX-2 upregulation in the central nervous system (CNS) are considered important in the pathogenesis of postoperative pain (12,13). Nevertheless, whether CNS COX-2 is actually upregulated in patients after surgery is presently unknown. It has been proposed that COX-2 drugs exert their analgesic effects in part by preventing central sensitization (14). Yet it remains untested in patients whether they even reach the CNS, and in sufficient concentrations. Are there clinically relevant differences between various COX-2 inhibitors in their CNS concentrations and kinetics? What are the effects of COX-2 inhibitors on concentrations of prostanoids and inflammatory mediators? What is the optimal duration of perioperative use?

Opioid sparing may be challenged as an inconsequential benefit of NSAIDs or COX-2 inhibitors; opioids are effective and inexpensive. Nevertheless, opioid side effects (nausea, vomiting, constipation, etc.)

are deleterious and expensive, and often a major cause of patient dissatisfaction and underdosing which diminishes analgesic benefit. There is some evidence that opioid sparing by COX-2 inhibitors also spares opioid side effects (15,16). Nevertheless, more information on opioid side effect sparing, including patient populations and operations of benefit, is needed. Also important is the risk of respiratory depression. For example, there is still a risk (and likely higher than generally realized) of clinically significant respiratory depression with opioid PCA (17–19). Does the use of COX-2 inhibitors spare such PCA-related respiratory depression?

It is increasingly recognized that there is an unacceptably frequent (approaching or exceeding 50%) incidence of chronic persistent pain after surgery, for which acute postoperative pain is a significant risk factor (20). What is the influence of perioperative COX-2 inhibitors on the incidence and severity of chronic postsurgical pain? On other long-term outcome measures? Are there economic benefits of COX-2 inhibitor use that mitigate the cost of their increased use? Fewer nursing interventions? Faster return to work?

Safety concerns regarding the perioperative use of COX-2 inhibitors, somewhat different from generalized COX-2 inhibitor controversies (21), remain unresolved. COX-2 inhibitors, albeit less so than NSAIDs, impair bone healing in animal fracture models (22,23). Ketorolac was associated with a fivefold greater incidence of nonunion after spinal fusion in patients (24); however, spinal fusion was not inhibited by celecoxib in rabbits (25) or by rofecoxib in patients (26). Based on these limited animal and human data, one set of recommendations suggests that COX-2 drugs not be avoided in orthopedic surgery (except in implantation of prostheses requiring bone ingrowth), but limited in duration of use (10–14 days) (27). Nonetheless, there is a paucity of randomized controlled clinical studies on bone and wound healing to guide rational pharmacology. It is well known that long-term use of some COX-2 inhibitors can increase blood pressure and cause peripheral edema (28), and concerns abound regarding their propensity to cause cardiovascular events (29,30). One recent investigation in coronary artery bypass grafting patients suggested a proportionately, but not significantly, greater incidence of cardiac and cerebrovascular serious adverse events in patients taking COX-2 inhibitors (31). Nonetheless, the cardiovascular effects of perioperative COX-2 inhibitors, particularly with short-term use, remain virtually unknown. These merit large, carefully controlled investigations. Similarly, the renal effects of perioperative COX-2 inhibitors, particularly in populations susceptible to NSAID nephropathy (volume depletion, renal insufficiency, heart failure, diabetes, elderly) merit further definition (32).

In contrast to the above, other potential safety issues such as platelet effects and increased bleeding seem moot. NSAIDs can increase the risk of postoperative bleeding, particularly in specific cases, such as tonsillectomy, plastic, and other ear, nose, and throat surgery, and are suggested to be used cautiously or avoided (33,34). COX-2 inhibitors, unlike nonselective NSAIDs, do not impair platelet function or increase bleeding time (35), and do not increase blood loss (36).

Having recognized the challenge to move beyond simply demonstrating diminished postoperative pain and opioid requirements in future COX-2 inhibitor research, it is nonetheless important to ask, Are these benefits alone sufficient to justify incorporating COX-2 inhibitors into perioperative anesthetic regimens? It is meritorious to remember the century-old goal of enhancing analgesia while minimizing adverse effects. If we can, we should.

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