

Nonsteroidal anti-inflammatory drugs in postoperative pain management

PIERRE BEAULIEU MD, PHD, FRCA

Management of acute postoperative pain remains suboptimal; nearly 80% of patients report moderate to extreme pain following surgery. The use of balanced analgesia – a combination of opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and local anesthesia – improves the efficacy of pain relief and decreases the risk of side effects.¹ Nonselective NSAIDs have a role in postoperative pain management, but concerns about adverse events such as increased bleeding have limited their use. Cyclooxygenase (COX)-2 selective inhibitors (coxibs) offer the pain-relieving benefits of nonselective NSAIDs, but with fewer adverse effects.²⁻⁴ Clinical trials have also demonstrated the efficacy and safety of celecoxib and rofecoxib for postoperative pain and for preemptive analgesia. Newer agents such as valdecoxib and etoricoxib have also demonstrated efficacy in these settings, although some studies have not shown this benefit. Factors, in addition to side effects such as time to onset, duration of action, maximum pain relief, and others relevant to postoperative pain, may be important in determining the overall analgesic efficacy of these compounds.

The goal of postoperative pain relief is to achieve optimal analgesia, facilitating a quick return to normal physiological organ function with minimal side effects. Furthermore, the effective treatment of acute postoperative pain may reduce the incidence of chronic pain after surgery.

INFLAMMATORY PAIN

Surgical trauma leads to a well-described systemic response. The arachidonic cascade metabolites, from which the prostaglandins originate, may play an important role in mediating some of these responses.¹ Recent advances in the neurobiology of inflammatory pain have shown that many mediators and systems may activate and sensitize nociceptors such as: potassium and hydrogen ions, kinins, peptides, prostaglandins (PGE₂, PGI₂), histamine, serotonin, proinflammatory cytokines, neurotrophins, nitric oxide, proteases, excitatory amino acids, etc. The resultant prostaglandin-mediated inflammatory process is characterized by vasodilatation and increased vascular permeability, followed by hyperalgesia and a resultant decrease in the pain threshold.²

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Many NSAIDs have been developed since aspirin was discovered in 1853. In fact, over 50 NSAIDs and over 200 aspirin-containing compounds are currently available in the United States. More than 13 million people use an NSAID daily and the annual number of NSAID prescriptions in Canada is 10 million.

NSAIDs include a variety of different agents from different chemical classes: salicylates (aspirin, diflunisal), indol derivatives (indomethacin, ketorolac), oxicams (piroxicam, meloxicam), propionic acid derivatives (ibuprofen, ketoprofen, naproxen), and fenamates (mefenamic acid). Acetaminophen (paracetamol in Europe), an acetanilide derivative and strictly speaking not an NSAID, is used as an analgesic for the relief of pain of mild to moderate severity and as an antipyretic agent. An intravenous formulation is available in some European countries in the form of a prodrug (propacetamol) and should soon be available in Canada.

Most NSAIDs exhibit 3 major types of effects: analgesic effects, anti-inflammatory effects, and antipyretic effects. Virtually all are analgesic and antipyretic, but the degree of anti-inflammatory activity varies.

EICOSANOIDS AND PROSTAGLANDINS

Eicosanoids are produced from arachidonic acid after its liberation from the cell membrane by phospholipase A₂ in response to diverse stimuli.³ Arachidonic acid is then metabolized by arachidonate cyclooxygenase (COX) to produce prostaglandins and thromboxanes. In 1990, two

Committee for Continuing Medical Education
Department of Anesthesiology
University of Montreal

Pierre Drolet, MD
Chairman and Editor
Maisonneuve-Rosemont Hospital

Jean-François Hardy, MD
Chairman of the Department of Anesthesiology,
University of Montreal

François Donati, MD
Maisonneuve-Rosemont Hospital

Edith Villeneuve, MD
Ste-Justine Hospital

Robert Blain, MD
Montreal Heart Institute

Normand Gravel, MD
CHUM

Robert Thivierge, MD
Vice-Dean
Continuing Education
University of Montreal

University of Montreal
Department of Anesthesiology
Faculty of Medicine
C.P. 6128, Succursale Centre-Ville
Montréal (Québec) H3C 3J7
Pavillon principal, bureau S-712
Tel: (514) 343-6466
Fax: (514) 343-6961
E-mail: anesth@medclin.umontreal.ca

Université de Montréal
Faculty of Medicine
Department of Anesthesiology

The editorial content of *Anesthesiology Rounds* is determined solely by the Department of Anesthesiology of the University of Montreal Faculty of Medicine

Available on the Internet
www.anesthesiologyrounds.ca

isoforms of COX (COX-1 and COX-2) were discovered and later cloned. COX-1 is constitutively present in almost all tissues. It produces prostaglandins and related substances, maintaining cell-cell signalling and homeostasis in many organs (eg, stomach, lung, kidney, and others). On the other hand, COX-2 appears to be expressed constitutively in the central nervous system and the urogenital tract where it has low basal activity. During inflammatory disease states, COX-2 production is induced in macrophages, endothelial cells, and synoviocytes by inflammatory mediators, including cytokines and lipopolysaccharides. Inhibition of COX-1 is thought to account for the adverse gastrointestinal and renal effects of traditional NSAIDs, whereas COX-2 inhibition produces the anti-inflammatory effects. Most NSAIDs in current use are inhibitors of both isoenzymes, though the degree of inhibition may vary (Table 1).⁴

COMMON SIDE EFFECTS OF NSAIDS

NSAIDs are responsible for nearly a quarter of the adverse drug reactions officially reported. The recent introduction of COX-2 inhibitors provides the potential means to reduce the side effects of NSAIDs. The rates of upper gastrointestinal (GI) bleeding, congestive heart failure, and acute renal failure associated with NSAID use are estimated at 18, 22, and 10 episodes, respectively, per 100,000 patients each year.⁵ The large number of patients with complications is an under-recognized problem.

Gastrointestinal disturbances

COX-1 is responsible for the synthesis of the prostaglandins that normally inhibit gastric acid secretion, protect the mucosa, and modulate its blood flow. The most prevalent and significant adverse outcomes of NSAID use are GI ulceration and serious GI complications (eg, perforation and bleeding). Estimates show that in the United States, approximately 107,000 patients (3,900 in Canada) are hospitalized each year for NSAID-related GI complications and 16,500 (365 in Canada) NSAID-related deaths occur in arthritis patients alone.⁶ Furthermore, the mortality rate among patients hospitalized for serious NSAID-related bleeding complications is 10% to 15%.⁷ There are often no warning signs for serious GI complications, and prospective studies show that more than 80% of patients with these complications had no previous GI illness.

Epidemiological and clinical studies have identified important risk factors for NSAID-related gastropathy: advancing age, high NSAID dose, prior GI complications, *Helicobacter pylori* infection, and use of anticoagulants or corticosteroids.

Outcome studies of the GI safety of COX-2 inhibitors have been performed recently. Rofecoxib (VIGOR⁸ and ADVANTAGE⁹) and celecoxib (CLASS¹⁰ and SUCCESS¹¹) studies in over 39,000 patients with osteoarthritis or rheumatoid arthritis, have demonstrated efficacy equivalent to nonselective NSAIDs with lower rates of GI side effects. Selective COX-2 inhibitors provided effective treatment of pain and inflammation while reducing the risk of gastropathy. However, in the CLASS study (celecoxib), concomitant use of aspirin for cardiovascular prophylaxis offset the GI benefits of the coxib compared to nonselective NSAIDs. Furthermore, the trend favouring celecoxib in that study was no longer apparent at the end of the study (12 months), whereas it was present at 6 months.¹²

TABLE 1: Selectivity of NSAIDs for COX-1 and COX-2.⁴

Preferential COX-1 inhibitor	– aspirin, indomethacin, piroxicam;
Nonselective COX inhibitor	– diclofenac, ibuprofen, naproxen;
Preferential COX-2 inhibitor	– meloxicam, nimesulide;
Selective COX-2 inhibitor	– celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib.

Skin reactions

Skin reactions are the second most common unwanted side effect of NSAIDs, particularly with mefenamic acid (10%-15% frequency) and sulindac (5%-10% frequency). Patients may present with skin conditions varying from mild rashes, urticaria, and photosensitivity, to more serious and potentially fatal, although rare, diseases.

Cardiovascular adverse effects

Thrombotic cardiovascular effects

Aspirin is a more potent inhibitor of COX-1 than of COX-2, and at low doses, it selectively inhibits thromboxane A₂ (TXA₂) formation without inhibiting prostacyclin (PGI₂) synthesis. In contrast to aspirin, other conventional NSAIDs inhibit both cyclooxygenases more equally. However, the cardioprotective effects of these agents are unclear. The consequences of inhibiting prostacyclin activity in the absence of concomitant inhibition of TXA₂ (like the coxibs) are not currently clear. Data from one clinical trial (VIGOR study) revealed a 5-fold divergence in rates of myocardial infarction between a coxib and a conventional NSAID.⁸

Cardiac function

One of the concerns about the use of NSAIDs is the apparent association with congestive heart failure.¹³ NSAID-associated congestive heart failure is most likely to occur in patients with a history of any form of heart disease.¹⁴ The use of NSAIDs by elderly patients taking diuretics is associated with a 2-fold increased risk of hospitalization for congestive heart failure compared with diuretic therapy alone.¹⁵

Blood pressure and edema

NSAIDs have potential effects on systemic blood pressure and peripheral edema via the renin-angiotensin pathway, causing alterations in sodium and water retention in the kidneys and inhibition of vasodilating prostaglandins. In 2 meta-analyses, NSAIDs were found to have small, but significant effects on blood pressure, most notably in hypertensive patients on antihypertensive medication where NSAIDs cause small (< 5 mmHg) elevations in systolic blood pressure.^{16,17} The incidence and levels of hypertension associated with COX-2 inhibitors are within the range of those observed with nonspecific NSAIDs.¹⁸ Peripheral edema is an occasional side effect associated with all NSAIDs. The degree of edema is typically minor and reversible with discontinuation of the drug.

Adverse renal effects

Therapeutic doses of NSAIDs in healthy individuals pose little threat to kidney function. However, in some

susceptible patients, they cause acute renal failure due to inhibition of the biosynthesis of those prostaglandins (PGE₂, PGI₂) involved in maintaining renal blood flow, and more particularly in the PGE₂-mediated compensatory vasodilation that occurs in response to the action of norepinephrine or angiotensin II. The patients at risk of developing renal dysfunction are elderly patients and those with diabetes, hypertension, or congestive heart failure. Both isoforms of COX are expressed in the kidney in constitutive and inducible forms. Therefore, COX-2 inhibitors can cause sodium retention and decrease the glomerular filtration rate similar to nonselective NSAIDs.¹⁷

Effect of NSAIDs on hemostasis

Bleeding during hip arthroplasty increased 1- to 2-fold compared with controls when nonselective NSAIDs were used in the immediate preoperative period.¹⁹ Due to their reversible inhibition of COX activity, NSAIDs can inhibit platelet aggregation. However, this may not be the case with the new COX-2 inhibitors. Indeed, COX-2 inhibition with coxibs may increase the risk of vascular thrombus formation by upsetting the balance of pro- and antiplatelet aggregation effects: TXA₂ synthesis is primarily a COX-1-induced effect, while PGI₂ synthesis is a COX-2 effect. This side effect is unreported with nonselective COX inhibitors. Although platelet dysfunction occurs with COX-1 inhibition, there has been no prospective, randomized, controlled, clinical trial demonstrating an increase in hemorrhage in patients who have received NSAIDs.²⁰

Effects on osteogenesis and wound healing

Osteogenesis

Some orthopedic centres do not allow the use of NSAIDs for postoperative analgesia after fractures or orthopedic surgery because they are thought to interfere with bone healing. The only evidence that NSAIDs inhibit bone healing comes from animal experiments and from a retrospective series in humans using high doses of intramuscular ketorolac after spinal fusion,²¹ plus a small case-controlled study looking at the failure of fractured femurs to heal.²² Preclinical data showed that rofecoxib does not inhibit osteogenic activity. Currently, there is an ongoing trial to verify that rofecoxib does not interfere with spinal fusion. Additionally, a retrospective trial involving more than 300 patients who underwent spinal fusion surgery demonstrated that rofecoxib was associated with a non-union rate similar to placebo.²³

Wound healing

There are no specific data on the effect of nonselective NSAIDs or coxibs on the tensile strength of wounds, thus uncertainty remains concerning the effects of NSAIDs on wound healing. However, based on the results of many clinical trials in surgical patients, there is no reason to suspect that either class of agents would delay or prevent healing.²⁴

EFFICACY OF NSAIDS IN TREATING POSTOPERATIVE PAIN

Use of acetaminophen and synergy between acetaminophen and NSAIDs

Any attempt to improve postoperative pain control should include the optimal use of acetaminophen.²⁵ This agent can be given by mouth, rectally, and in many countries, intravenously as well. Too often, clinicians use acetaminophen in too small a dose, especially with rectal

administration. At least 1 g orally, every 6 hours, is needed for adult patients. Ideally, the maximum dose is 4 g daily, but doses up to 6 g daily have been used without problems in healthy individuals. At this dose, acetaminophen reduces morphine consumption and adverse effects, improves analgesia, and increases overall patient satisfaction.²⁶ Rectal administration is widely used in many countries, but absorption is slow and variable. For this reason, some have advocated the use of an initial rectal dose of 2 g, followed by 1 g every 4 hours. Intravenous administration of propacetamol is preferable and at 1 g, 4 times/24 hours, it reduces PCA morphine consumption by almost 40% after orthopedic surgery.²⁷

Children also tend to be given doses of acetaminophen that are much too low. The recommended dose, for rectal administration is 40 mg/kg for the initial dose, with subsequent doses of 20 mg/kg every 6 hours to a maximum of 120 mg/kg over 24 hours.²⁸

Co-administration of drugs that affect the same process via different mechanisms of action is likely to obtain additive or even synergistic effects. Animal studies have documented synergistic effects between acetaminophen and traditional NSAIDs.^{29,30}

A recent systematic review of 33 clinical trials examined the effects of rectal and parenteral acetaminophen with or without NSAIDs for postoperative analgesia.³¹ Evidence of a clinically relevant analgesic effect attributed to rectal and parenteral acetaminophen was found. Furthermore, the concurrent use of acetaminophen and an NSAID was superior to acetaminophen alone, although the combination was not deemed superior to an NSAID alone.

A systematic qualitative review of postoperative pain studies comparing acetaminophen (minimum 1 g) with NSAIDs in a double-blind, randomized manner was also recently reported.³² The authors demonstrated that acetaminophen had analgesic efficacy comparable to that of NSAIDs in many of the studies reviewed. However, overall, NSAIDs seemed to be superior for postoperative pain management, although there were apparent differences in the efficacies of acetaminophen and NSAIDs depending on the type of surgery performed. In major and orthopedic surgery, the efficacy of NSAIDs and acetaminophen seems to be comparable, while in dental surgery NSAIDs seem to be superior.

The very low apparent risk of acetaminophen therapy suggests a highly favourable risk:benefit ratio that might justify a role for acetaminophen as a near-routine postoperative background analgesic. When the additional analgesic properties of an NSAID are particularly desirable (eg, after relatively minor or ambulatory surgery) and when the perceived risks from NSAIDs are low, NSAIDs may be preferred as background analgesics.

It is noteworthy that, unlike ibuprofen, the COX-2 specific inhibitor, rofecoxib, did not show additive analgesic effects with acetaminophen in a double-blind, placebo-controlled, analgesic study on tonsillectomy in children.³³

Use of traditional NSAIDs

The efficacy of NSAIDs for postoperative pain relief is well-established, if adequate dose regimens are used in relation to the type of surgery and the specific drug chosen.³⁴ After minor surgery, NSAIDs are as effective as opioids for pain control. They are particularly effective in relieving pain following orthopedic and dental surgery. Although it is widely accepted that NSAIDs are less potent than opioids

for treatment of visceral pain, they may reduce by 40%-70% the amount of opioids needed after abdominal surgery, when administered concurrently.³⁴ Indeed, several NSAIDs provide morphine-sparing effects and improve analgesia when co-administered with PCA morphine. This interaction may be pharmacokinetic as well as pharmacodynamic. NSAIDs transiently decrease renal function and the co-administration of morphine and NSAIDs impedes renal excretion of active morphine metabolites. This increases the plasma concentration of morphine and intensifies opioid effects and side effects if doses are not markedly reduced.^{35,36}

How do the NSAIDs compare with each other in terms of serious adverse effects after elective major surgery? To answer this question, a recent, multicenter study in over 11,000 patients showed that ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery.³⁷ Note that in this large cohort (with no difference between the study drugs), 155 patients (1.38%) had a serious adverse outcome consisting of 19 deaths (0.17%), surgical site bleeding (1%), allergic reactions (0.12%), acute renal failure (0.09%) and gastrointestinal bleeding (0.04%).

The preoperative use of NSAIDs in adults, reported in the literature, is inconclusive, although most studies involving outpatients undergoing ambulatory surgery suggest that preoperative administration of NSAIDs will decrease the requirements for opioid analgesics in the early postoperative period.² However, a qualitative and quantitative systematic review has recently evaluated the role of NSAIDs in preemptive analgesia for postoperative pain relief.³⁸ The authors concluded that some aspects of postoperative pain control were improved by preemptive treatment in 4 of the 20 trials reviewed. Overall, the data demonstrated preemptive NSAIDs to be of no analgesic benefit when compared with post-incisional administration of these drugs.

Use of coxibs

In an effort to minimize the potential for operative-site bleeding complications, as well as the GI and renal damage associated with classical NSAIDs, the more specific COX-2 inhibitors are being increasingly used as nonopioid adjuvants for minimizing pain during the perioperative period.³⁹

Dental pain: Several studies in acute, postoperative, dental pain have been performed recently.⁴⁰⁻⁴⁴ The results of these studies show that rofecoxib is superior to placebo and compares with commonly used non-selective NSAIDs as well as codeine plus acetaminophen. Similar results may hold for parecoxib compared with ketorolac. Time to onset, peak effect, and duration of analgesia are important factors.⁴⁵ Furthermore, valdecoxib has been found to be more efficacious than rofecoxib in relieving pain associated with oral surgery.⁴⁶

For ambulatory surgery, preliminary data suggest that celecoxib (200 mg PO) is equivalent to acetaminophen (2 g PO) when administered before outpatient otorhinolaryngologic surgery.⁴⁷ However, in the ambulatory setting, rofecoxib (50 mg PO) produced significantly more effective analgesia than acetaminophen (2 g PO) and the pain relief was more

sustained in the postdischarge period.⁴⁸ More recently, a parenterally active COX-2 inhibitor, parecoxib (20-40 mg IV), has been proposed as an alternative to ketorolac⁴⁹ and diclofenac.⁵⁰ Furthermore, in orthopedic surgery, celecoxib (200 mg, 3 times daily) was superior to hydrocodone (10 mg) plus acetaminophen (1 g) in reducing maximum pain intensity and fewer patients taking celecoxib experienced adverse events.⁵¹ Both preoperative⁴⁹ and postoperative⁵⁰ administration of this investigational drug seem to exert significant opioid-sparing effects. However, in a recent study of patients undergoing lower abdominal surgery, despite the fact that IV parecoxib decreased the PCA opioid requirement significantly, it failed to improve pain management or reduce opioid-related side effects in the early postoperative period.⁵⁰ The authors suggested that parecoxib might be more effective in the prevention (versus management) of acute pain. Another recent study has just demonstrated that valdecoxib is an efficacious opioid-sparing analgesic in patients undergoing hip arthroplasty and that it provided greater analgesic efficacy compared to morphine alone.⁵² The degree of opioid-sparing effectiveness of valdecoxib shown in that study was comparable to other COX-2 specific inhibitors. Current data also confirm findings from previous studies that examined the opioid-sparing effects of parecoxib sodium.^{53,54} Parecoxib demonstrated postsurgical opioid-sparing effects in women who had undergone gynecologic surgery through lower transverse and midline abdominal incisions⁵⁵ and in patients who had undergone orthopedic surgery.⁵³

In conclusion, the quality of recovery and patient satisfaction with postoperative pain management may be improved by the coxibs. However, further comparative clinical studies are needed to define the optimal role of COX-2 inhibition in ambulatory surgery. The use of long-lasting analgesics before surgery may help avoid the establishment of a sensitized state, thus resulting in diminished postoperative pain.

Preemptive analgesia: Data on coxibs in preemptive analgesia extracted from recent studies have shown that a single dose of rofecoxib, celecoxib, or parecoxib before surgery diminished both postoperative pain and postsurgical morphine use.^{44,47,49,56-59} Rofecoxib was more effective than celecoxib for preemptive analgesia. Both drugs were similarly analgesic over the initial postoperative period, but one preoperative dose of rofecoxib provided enduring relief. Furthermore, oral premedication with a combination of acetaminophen (2 g) and celecoxib (200 mg) was effective in decreasing pain and improving patient satisfaction after otolaryngologic surgery, however acetaminophen or celecoxib alone were not significantly more effective than placebo in reducing postoperative pain.⁴⁷

For postsurgical pain, rofecoxib 50 mg was superior to placebo and similar to naproxen for all single-dose measures of pain relief following orthopedic surgery.⁶⁰ Furthermore, the rofecoxib group used less narcotic analgesia and reported less pain on global evaluation than did the placebo group. Another study showed that preoperative oral rofecoxib did not

decrease postoperative pain or morphine consumption in patients after radical prostatectomy.⁶¹ Finally, parecoxib (20 or 40 mg IV) has been shown to be equivalent to ketorolac (30 mg IV), but better than morphine IV (although at a single dose of 4 mg) or placebo in relieving acute postoperative pain following gynecologic laparotomy.⁶²

EVIDENCE-BASED MEDICINE IN PAIN MANAGEMENT WITH NSAIDS

Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. Systematic reviews and large randomized trials constitute the most reliable sources of evidence that can be gathered and can be found on the web at www.ebando.com/index.htm. Analgesic efficacy is expressed as the number-needed-to-treat (NNT): the number of patients who need to receive the active drug in order to achieve at least 50% relief of pain compared with placebo over a 6-hour treatment period. The most effective drugs have a low NNT of about 2.

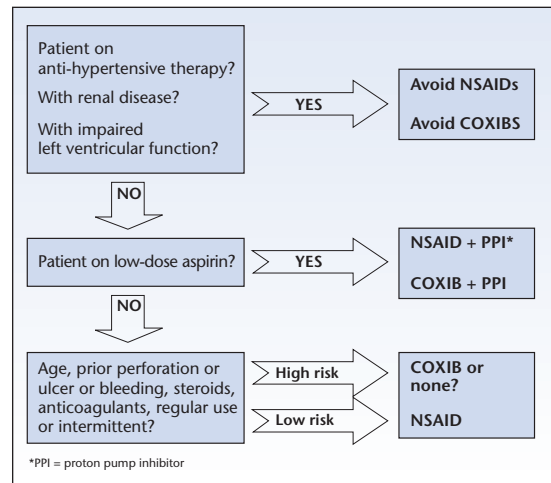
For the relief of postoperative pain, a single oral dose of aspirin is effective. A dose of 600/650 mg has an NNT of 4.4 (from a population of 6550 patients), but it is associated with increased adverse effects (gastric irritation and nausea). A single dose of 1 g of acetaminophen is also effective with an NNT of 3.8, based on information from 2759 patients. It is not associated with increased adverse effects. Piroxicam is an effective analgesic with a single dose of 20 mg giving an NNT of 2.7, while a dose of 40 mg has an NNT of 1.9 (from 310 patients). Ketorolac has also been evaluated and oral doses of 10 or 20 mg have an NNT of 2.6 and 1.8, respectively, while 30 mg administered IM or IV has an NNT of 3.4. A single dose of 550 mg of naproxen has an NNT of 3.0 compared with placebo in 607 patients. A single-dose administration of 50 mg of diclofenac has an NNT of 2.3 (from 738 patients), whereas the NNT is 2.4 with a single administration of 400 mg of ibuprofen (from 6358 patients).

A systematic review of rofecoxib in adults with acute postoperative pain examined its analgesic efficacy over 6 hours, as well as the amount and quality of the evidence on the extended duration of analgesia and the quality and quantity of evidence on adverse events.⁶³ The review concluded that rofecoxib, at 2-4 times the standard daily dose for chronic pain, is an effective single-dose oral analgesic in acute pain. The NNT for rofecoxib 50 mg is 2.3. The limitations in trial reporting constrain conclusions about longer durations of analgesia and the adverse event profile.

CONCLUSION

NSAIDs are important adjuvants for the treatment of postoperative pain. They can be combined with opioids and local anesthetics to form a multimodal approach to pain treatment. They are effective in reducing pain and morphine consumption, but traditional NSAIDs are not effective when given preemptively. Acetaminophen alone or in combination is also effective. Initial prescription of oral NSAIDs can be supplemented with acetaminophen. As pain wanes, the prescription should be acetaminophen-based,

FIGURE 1: The use of NSAIDs and selective inhibitors of COX-2 in current therapeutics



supplemented if necessary by NSAIDs. Acetaminophen should be prescribed at adequate doses and regular intervals. NSAIDs are associated with important adverse effects and their prescription should be targeted to a very specific group of patients, (ie, those without a history of GI symptoms, with normal cardiac and renal function, and not taking anticoagulants or steroids.) The new COX-2 inhibitors, despite the sound pharmacological basis for their development and the large publicity around their use, are not “miracle” drugs. They also seem to be associated with adverse effects and, although they may represent a safer alternative to nonselective NSAIDs, their definitive place in postoperative pain management is not yet settled. The clinical use of NSAIDs and coxibs in therapy today is summarized in Figure 1.

References

- Dahl JB, Kehlet H. Non-steroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. *Br J Anaesth* 1991;66:703-12.
- Souter AJ, Fredman B, White PF. Controversies in the perioperative use of nonsteroidal antiinflammatory drugs. *Anesth Analg* 1994;79:1178-90.
- Funk CD. Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science* 2001;294:1871-5.
- Bertolini A, Ottani A, Sandrini M. Dual acting anti-inflammatory drugs: a reappraisal. *Pharmacol Res* 2001;44:437-49.
- Bandolier, Evidence-based health care: <http://www.ebando.com/index.htm>
- Laine L. Nonsteroidal anti-inflammatory drug gastropathy. *Gastrointest Endosc Clin North Am* 1996;6:489-504.
- Peura DA. Gastrointestinal safety and tolerability of non-selective non-steroidal anti-inflammatory agents and cyclooxygenase-2-selective inhibitors. *Clev Clin J Med* 2001;69(SI):31-39.
- Bombardier C, Laine L, Reicin A, et al. for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; 343:1520-8.
- Geba GP, Lisse JR, Polis AB, et al. Gastrointestinal tolerability in primary care patients treated with naproxen or rofecoxib for osteoarthritis (OA): the ADVANTAGE trial [abstract]. *European League Against Rheumatism, Prague, Czech Republic, June 13-16, 2001.*
- Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomised controlled trial. *JAMA* 2000;284:1247-55.
- Goldstein JL, Eisen G, Bensen W, et al. SUCCESS in osteoarthritis (OA) trial: celecoxib significantly reduces the risk of upper gastrointestinal (UGI) hospitalisations compared to diclofenac and naproxen in 13,274 randomized patients with OA [abstract]. *European League Against Rheumatism, Prague, Czech Republic, June 13-16, 2001.*
- FDA Arthritis Advisory Committee, available at : www.fda.gov/ohrms/dockets/ac/
- Hillis WS. Areas of emerging interest in analgesia: cardiovascular complications. *Am J Ther* 2002;9:259-69.
- Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. *Arch Int Med* 2000;160:777-84.

15. Heerdink ER, Leufkens HG, Herings RM, et al. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. *Arch Int Med* 1998;158:1108-12.
16. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? *Ann Intern Med* 1994;121:289-300.
17. Brater DC. Renal effects of cyclooxygenase-2 selective inhibitors. *J Pain Symptom Manage* 2002;23:515-20.
18. Frishman WH. Effects of nonsteroidal anti-inflammatory drug therapy on blood pressure and peripheral edema. *Am J Cardiol* 2002;89(suppl):18D-25D.
19. Robinson CM, Christie J, Malcom-Smith N. Nonsteroidal anti-inflammatory drugs, perioperative blood loss, and transfusion requirements in elective hip arthroplasty. *J Arthroplasty* 1993;8:607-10.
20. McCrory CR, Lindahl SGE. Cyclooxygenase inhibition for postoperative analgesia. *Anesth Analg* 2002;95:169-76.
21. Glassman SD, Rose SM, Dimar JR, et al. The effect of postoperative nonsteroidal anti-inflammatory drug administration on spinal fusion. *Spine* 1998;23:834-8.
22. Giannoudis PV, MacDonald DA, Matthews SJ, et al. Nonunion of the femoral diaphysis. The influence of reaming and nonsteroidal anti-inflammatory drugs. *J Bone Joint Surg Br* 2000;82:655-8.
23. Reuben SS. Effect of nonsteroidal anti-inflammatory drugs on osteogenesis and spinal fusion. *Reg Anesth Pain Med* 2001;26:590-1.
24. Sinatra R. Role of COX-2 inhibitors in the evolution of acute pain management. *J Pain Symptom Manage* 2002;24:S18-27.
25. Breivik H. Postoperative pain: toward optimal pharmacological and epidural analgesia. *Pain 2002 – An Updated Review: Refresher Course Syllabus*, edited by MA Giamberardino, IASP Press, Seattle, 2002;337-49.
26. Schug SA, Sidebotham DA, McGuinness M, Thomas J, Fox L. Acetaminophen as an adjunct to morphine by patient-controlled analgesia in the management of acute postoperative pain. *Anesth Analg* 1998;87:368-72.
27. Delbos A, Boccard E. The morphine-sparing effect of propacetamol in orthopedic postoperative pain. *J Pain Symptom Manage* 1995;10:279-86.
28. Birmingham PK, Tobin MJ, Fisher DM, et al. Initial and subsequent dosing of rectal acetaminophen in children. *Anesthesiology* 2001;94:385-9.
29. Wong S, Gardocki JF. Anti-inflammatory and antiarthritic evaluation of acetaminophen and its potentiation of tolmetin. *J Pharmacol Exp Therapeut* 1983;226:625-32.
30. Fletcher D, Benoist JM, Gautron M, Guilbaud G. Isobolographic analysis of interactions between intravenous morphine, propacetamol, and diclofenac in carrageenin-injected rats. *Anesthesiology* 1997;87:317-26.
31. Romsing J, Moiniche S, Dahl JB. Rectal and parenteral paracetamol, and paracetamol in combination with NSAIDs, for postoperative analgesia. *Br J Anaesth* 2002;88:215-26.
32. Hyllested M, Jones S, Pedersen JL, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. *Br J Anaesth* 2002;88:199-214.
33. Pickering AE, Bridge HS, Nolan J, Stoddart PA. Double-blind, placebo-controlled analgesic study of ibuprofen or rofecoxib in combination with paracetamol for tonsillectomy in children. *Br J Anaesth* 2002;88:72-7.
34. Rorarius MGF, Baer GA. Nonsteroidal anti-inflammatory drugs for postoperative pain relief. *Curr Opin Anaesth* 1994;7:358-62.
35. Hobbs GJ. Ketorolac alters the kinetics of morphine metabolites. *Br J Anaesth* 1997;78:95.
36. Tighe KE, Webb AM, Hobbs GL. Persistently high plasma morphine-6-glucuronide levels despite decreased hourly patient-controlled analgesia morphine use after single-dose diclofenac: potential for opioid related toxicity. *Anesth Analg* 1999;88:1137-42.
37. Forrest JB, Camu F, Greer IA, et al. for the POINT Investigators. Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery. *Br J Anaesth* 2002;88:227-33.
38. Moiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief. *Anesthesiology* 2002;96:725-41.
39. White PF. The role of non-opioid analgesic technique in the management of pain after ambulatory surgery. *Anesth Analg* 2002;94:577-85.
40. Morrison BW, Christensen S, Yuan S, et al. Analgesic efficacy of the cyclooxygenase-2-specific inhibitor rofecoxib in post-dental surgery pain: a randomised, controlled trial. *Clin Ther* 1999;21:943-53.
41. Malmstrom K, Daniels S, Kotey P, et al. Comparison of rofecoxib and celecoxib, two cyclooxygenase-2 inhibitors, in postoperative dental pain: a randomised, placebo- and active-comparator-controlled clinical trial. *Clin Ther* 1999;21:1653-63.
42. Chang DJ, Fricke JR, Bird SR, et al. Rofecoxib versus codeine/acetaminophen in postoperative dental pain: a double-blind, randomised, placebo- and active-comparator-controlled clinical trial. *Clin Ther* 2001;23:1446-55.
43. Daniels SE, Grossman EH, Kuss ME, et al. A double-blind, randomised comparison of intramuscularly and intravenously administered parecoxib sodium versus ketorolac and placebo in a post-oral surgery pain model. *Clin Ther* 2001;23:1018-31.
44. Khan AA, Ibrahim JS, Rowan JS, Dionne RA. In vivo selectivity of a selective cyclooxygenase 2 inhibitor in the oral surgery model. *Clin Pharmacol Ther* 2002;72:44-9.
45. Katz WA. Cyclooxygenase-2-selective inhibitors in the management of acute and perioperative pain. *Clev Clin J Med* 2002;69(S1):65-75.
46. Fricke J, Varkalis J, Zwillich S, et al. Valdecoxib is more efficacious than rofecoxib in relieving pain associated with oral surgery. *Am J Therapeut* 2002;9:89-97.
47. Issioui T, Klein KW, White PF, et al. The efficacy of premedication with celecoxib and acetaminophen in preventing pain after otolaryngologic surgery. *Anesth Analg* 2002;94:1188-93.
48. Issioui T, Klein KW, White PF, et al. Analgesic efficacy of rofecoxib alone or in combination with acetaminophen in the ambulatory setting [abstract]. *Anesthesiology* 2001;94:A35.
49. Desjardins PJ, Grossman EH, Kuss ME, et al. The injectable cyclooxygenase-2-specific inhibitor parecoxib sodium has analgesic efficacy when administered preoperatively. *Anesth Analg* 2001;93:721-7.
50. Tang J, Li S, White PF, et al. Effect of parecoxib, a novel intravenous cyclooxygenase type-2 inhibitor, on the postoperative opioid requirement and quality of pain control. *Anesthesiology* 2002;96:1305-9.
51. Gimbel J, Brugger AM, Zhao W, et al. Efficacy and tolerability of celecoxib versus hydrocodone / acetaminophen in the treatment of pain after ambulatory orthopedic surgery in adults. *Clin Ther* 2001;23:228-241.
52. Camu F, Beecher T, Recker DP, Verburg KM. Valdecoxib, a COX-2-specific inhibitor, is an efficacious, opioid-sparing analgesic in patients undergoing hip arthroplasty. *Am J Therapeut* 2002;9:43-51.
53. Camu F, Kuss M, Talwalker S, et al. The COX-2 specific inhibitor parecoxib sodium is an effective, opioid-sparing agent in patients undergoing knee replacement surgery. *American Society Anesthesiology Annual Congress*, New Orleans, LA, October 13-17, 2001.
54. Malan TP, Marsh G, Grossman E, et al. Parecoxib sodium, a new injectable COX-2 specific inhibitor, is opioid-sparing and improves pain relief in postoperative hip arthroplasty patients. *American Pain Society Annual Congress*, Phoenix, AZ, April 19-22, 2001.
55. Wender RH, Desai PM, Snabes MC, et al. Parecoxib sodium demonstrates opioid sparing effects in post-laparotomy surgical patients. *American Society of Reproductive Medicine Annual Congress*, Orlando, FL, 2001.
56. Reuben SS, Fingerth R, Krushell R, Maciolek H. Evaluation of the safety and efficacy of the perioperative administration of rofecoxib for total knee arthroplasty. *J Arthroplasty* 2002;17:26-31.
57. Reuben SS, Connelly NR. Postoperative analgesic effects of celecoxib or rofecoxib after spinal fusion surgery. *Anesth Analg* 2000;91:1221-5.
58. Shen Q, Sinatra R, Luther M, Halaszynski T. Preoperative rofecoxib 25 mg and 50 mg: effects on post-surgical morphine consumption and effort dependent pain. [abstract] *Anesthesiology* 2001;95:A961.
59. Reuben SS, Bhopatkar S, Maciolek H, Joshi W, Sklar J. The preemptive analgesic effect of rofecoxib after ambulatory arthroscopic knee surgery. *Anesth Analg* 2002;9:55-9.
60. Reicin A, Brown J, Jove M, et al. Efficacy of single-dose and multidose rofecoxib in the treatment of post-orthopedic surgery pain. *Am J Orthop* 2001;30:40-8.
61. Huang JJ, Taguchi A, Hsu H, et al. Preoperative oral rofecoxib does not decrease postoperative pain or morphine consumption in patients after radical prostatectomy: a prospective, randomised, double-blinded, placebo-controlled trial. *J Clin Anesth* 2001;1:94-7.
62. Barton SF, Langeland FF, Snabes MC, et al. Efficacy and safety of intravenous parecoxib sodium in relieving acute postoperative pain following gynaecologic laparotomy surgery. *Anesthesiology* 2002;97:306-14.
63. Barden J, Edwards JE, McQuay HJ, Moore RA. Single-dose rofecoxib for acute postoperative pain in adults: a quantitative systematic review. *BMC Anesthesiology* 2002;2:4. (This article is available from www.biomedcentral.com/1471-2253/2/4)

Upcoming Scientific Meetings

31 January – 02 February 2003

41st Clinical Conference in Pediatric Anesthesiology
Anaheim, California

CONTACT: Herbert Zarco, Conference coordinator
Tel: 323 669-2262
Fax: 323 660-8983
Email: hzarco@chla.usc.edu

18-23 February 2003

**American Academy of Pain Medicine
Annual Meeting**
New Orleans, LA

CONTACT: American Academy of Pain Medicine
Tel: 847 375-4731
Fax: 877 734-8750
Email: aspm@amctec.com

Change of address notices and requests for subscriptions to *Anesthesiology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Anesthesiology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above.

This publication is made possible by an educational grant from

Organon Canada Limited