Role of COX-2 Inhibitors in the Evolution of Acute Pain Management

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Abstract

Management of acute postoperative pain remains suboptimal: nearly 80% of patients report moderate to extreme pain following surgery. New pain management paradigms incorporate multimodal analgesia, using a combination of analgesics throughout the perioperative period to control nociceptive and centrally-stimulated pain. Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) have a role in postoperative pain management, but concerns about increased bleeding and inhibited wound healing and bone fusion have limited their use. Cyclooxygenase (COX)-2-selective inhibitors (coxibs) offer the peripheral pain-relieving benefits of nonselective NSAIDs but with fewer adverse GI effects; they also may have a role in central sensitization. Clinical trials have demonstrated the efficacy and safety of celecoxib and rofecoxib for postoperative pain and for preemptive analgesia, and newer agents such as valdecoxib and etoricoxib also have demonstrated efficacy in these settings. In addition to their selectivity for the COX-2 isozyme overall, unique differences among the coxibs, such as in plasma half-life, may impart certain clinical advantages.

Key Words

Acute pain, celecoxib, coxibs, cyclooxygenase (COX)-2-selective inhibitors, preemptive analgesia, postoperative pain, rofecoxib

Introduction

A better understanding of pain mechanisms has encouraged the development of new paradigms of pain management based on preemptive and multimodal strategies. Although cyclooxygenase (COX)-2-selective inhibitors (coxibs) were originally developed as chronic pain medications, and have demonstrated efficacy similar to conventional, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), their role has expanded to include postsurgical and acute medical pain. Rofecoxib (50 mg), for example, was similar to ibuprofen after dental surgery in terms of overall analgesic effect, onset of analgesia, and peak effects, although notably, rofecoxib exhibited significantly longer duration of action. The efficacy and safety of both rofecoxib and celecoxib, the other first-generation coxib, administered prior to surgery have been demonstrated in several settings, including orthopedic procedures, abdominal surgery, and outpatient ear, nose, and throat surgery.

The addition of coxibs to pain management paradigms is an important advancement be-
cause postsurgical and acute pain management are often suboptimal. It was noted nearly three decades ago that approximately 73% of patients reported moderate-to-severe pain following medical and surgical procedures.\textsuperscript{10} Although technologic advances in understanding pain have been made, nearly 80% of patients across two recent studies nevertheless experienced pain they described as moderate to extreme following surgery.\textsuperscript{11,12} These results raise issues other than undertreatment of pain, such as fear of addiction/dependence among patients and physicians alike, and use and impact of more complex surgical procedures. Furthermore, there is a widely held belief among patients that pain is normal. Modified strategies of pain management may alleviate much of this suffering.

The consequences of analgesic undermedication are considerable. Unrelieved acute pain is often associated with sleeplessness, anxiety, fear, or demoralization and may lead to the development of chronic pain syndromes. Furthermore, pain has a pathophysiologic effect on body systems that may lead to an increased incidence of myocardial ischemia, atelectasis, and impaired wound healing (Figure 1). Heightened awareness of the influence of unrelieved pain on outcomes has led to new strategies to optimize pain relief including the development of acute and chronic pain service units in healthcare institutions, broadening roles of nurses, and expanding education.

Current management strategies for acute and surgical pain employ multimodal and preemptive approaches with emphasis on preventing algesic flare prior to surgery and moderating or preventing development of hyperalgesic states after surgery. In the postoperative setting, use of intravenous (IV) anesthesia, epidural patient-controlled analgesia (PCA), and controlled-release opioids has become commonplace. Tactics to prevent preoperative flares (e.g., knee pain that returns on discontinuation of nonselective NSAIDs prior to total joint replacement) are becoming more prominent and are increasingly utilizing COX-2 selective inhibitors. Clearly, traditional, nonselective NSAIDs have a demonstrated role in postoperative pain management, but concerns about their effects on platelets have limited their use in the immediate preoperative period. Coxibs may offer benefits in the pre- and perioperative settings because of their selective inhibition of COX-2. This article will review strategies for acute and perioperative pain management and the evidence for the role of coxibs in improving outcomes.

### Understanding Preemptive Analgesia

The notion of preemptive analgesia, raised more than 50 years ago, recently has received greater attention. The underlying principle of preemptive analgesia is therapeutic intervention prior to pain rather than in response to it.\textsuperscript{13} While there is little disagreement that the concept is successful in animal models, data from human studies suggest a positive effect on the course of postoperative pain only when

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**Fig. 1.** Harmful effects of unrelieved acute pain.
therapy is started early and pain is prevented from becoming overwhelming.

Inflammatory pain associated with surgery is characterized by a decrease in the threshold of sensitivity whereby, following a period of unrelied pain, patients experience algesia as a result of stimuli that normally would not be perceived as painful. Furthermore, this lowering of the pain threshold is accompanied by an exaggerated response to painful stimuli (primary hyperalgesia) and a spread of the hyperalgesic area to nearby uninjured tissues (secondary hyperalgesia). Primary hyperalgesia occurs in the presence of an excess of inflammatory mediators and cytokines, which in turn increases the sensitivity of high-threshold nociceptor primary sensory neurons at their peripheral terminals. This change is known as peripheral sensitization; a major action of NSAID treatment is the prevention of peripheral sensitization. Secondary hyperalgesia results from a change in the excitability threshold of dorsal horn neurons, a phenomenon known as central sensitization (Figure 2).

Severe pain can result in peripheral and central sensitization and instigation of a process known as wind-up. Wind-up refers specifically to the prolonged overstimulation of sensory neurons, which respond nonlinearly to repetitive stimulation of the unmyelinated axons, C-fibers. It has been suggested that since the repetitive and synchronized sensory input needed to produce the phenomenon are unlikely outside of an experimental setting, wind-up may have little clinical relevance. Nevertheless, wind-up is often a precursor of central sensitization. Central sensitization, with or without wind-up, however, is common and results in secondary hyperalgesia. Dorsal horn neurons become hyperexcitable and produce a pain response outside the area of actual injury.

Preemptive analgesic strategies are designed to control or prevent central sensitization, and the rationale for therapeutic intervention considers: (1) differentiating between analgesic states that eliminate all physiologic pain and those that eliminate only abnormal hypersensitivity; (2) specifically targeting the induction or maintenance of central sensitization by particular treatments; and (3) preventing or reducing postoperative pain with strategies designed to inhibit the establishment of central sensitization during surgery.

Glutaminergic neurotransmission is ubiquitous in the central nervous system (CNS), primarily mediating excitatory functions. A drug that can block this type of transmission/response might prevent central sensitization, but the value of glutaminergic inhibition as a therapeutic target is diminished precisely because it affects synaptic transmission throughout the CNS. Other potential therapeutic targets include pathways involving substance P receptors, neurokinin receptors, N-methyl-D-aspartate (NMDA) receptors, and various neuromodulators.

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**Fig. 2.** Central sensitization occurs as a result of a change in the sensory processing of the central nervous system (CNS) so that low-threshold neurons that ordinarily produce painless signals (e.g., a touch) deliver painful signals. Thus, nociceptor input produces pain directly and, by producing hyperexcitability in the spinal cord, indirectly as well.
these receptor targets is an ideal approach to blocking pain mediation, though among these, NMDA receptors seem the most promising: NMDA is integral to cellular potassium and calcium metabolism. Dysfunction here is at the root of hyperexcitability.

Approaches to Preemptive Analgesia

Clinical approaches to preventing central sensitization may include preemptive analgesia using regional anesthesia with pre- and perioperative nerve blocks, IV and epidural opioids prior to incision, and postoperative maintenance therapy, but NSAIDs may also have a role.

Role of Nonselective NSAIDs. Nonselective NSAIDs affect peripheral sensitization through the inhibition of COX-mediated prostaglandin (PG) release, in turn, possibly making them helpful in preventing secondary hyperalgesia. Thus, nonselective NSAIDs could decrease afferent input in a way that would limit the worst expression of NMDA and thereby prevent central sensitization. The ability of coxibs to prevent central sensitization has been researched in animal studies and more recently in human clinical trials.

Multimodal Analgesia. Multimodal analgesia refers to the use of two or more agents throughout the pain cycle. Individual agents given at high enough doses may achieve analgesic results, but a multimodal approach maximizes the benefits of each agent while minimizing the adverse events associated with higher doses. The guiding principle is that a balance of agents will provide optimal pain control.

In this strategy, coxibs would be used for peripheral sensitization, local anesthetics and opioids would be used during and immediately after surgery, and an agent like ketamine could be introduced as an NMDA-receptor antagonist to minimize central sensitization. An effective model seamlessly couples preemptive analgesia with postoperative maintenance therapy. This was demonstrated in a trial that compared epidural bupivacaine or fentanyl (along with standard anesthesia) with placebo before, during, and after radical prostatectomy. Patients receiving the epidural agents experienced 33% less pain during hospitalization.

Rationale for NSAIDs/Coxibs in Acute Pain Management/Multimodal Analgesia

Nonselective NSAIDs have well recognized adverse effects that contraindicate their use in the immediate pre- or perioperative setting, in particular, their effects on platelet aggregation. Bleeding during hip arthroplasty increased 1- to 2-fold compared with controls when nonselective NSAIDs were used in the immediate preoperative period. Other specific concerns include wound hematomas and a possible increase in gastric ulcers as a result of the combination of nonselective NSAID side effects and the stress associated with surgery.

Many of the side effects that limit the role of nonselective NSAIDs in the peri- or immediately preoperative setting are related to their nonselective inhibition of the COX isoenzymes. Briefly, COX-1, a constitutively expressed enzyme, plays a role in platelet aggregation, hemostasis, and the protection of gastric mucosa. COX-2, an inducible enzyme, is a crucial mediator of pain, inflammation, and fever. Coxibs selectively inhibit COX-2 without compromising the constitutive role of COX-1. They have been shown to have a minimal effect on platelet aggregation and gastric mucosa, while exerting a major effect on pain and inflammation (Figure 3).

Prostaglandin, the primary noxious mediator released from injured tissue, is responsible for activation of primary afferents and sensitization of nociceptors to secondary and tertiary mediators (substance P, bradykinin, and histamine) (Figure 4). Hyperalgesia occurs when PG recruits secondary mediators to adjacent afferent fibers or sympathetic nerves.

Both forms of COX regulate the synthesis of PGs in general, which impact wound healing through their effect on platelet aggregation. However, PG synthesized by COX-2 activity (primarily PGE₂) mediates a pain response that includes inflammation; the specific interruption of the COX-2 pathway disrupts this process. While nonselective NSAIDs inhibit PG broadly, inhibiting both COX-2 and COX-1 isoenzymes, coxibs inhibit only COX-2. Therefore, by inhibiting COX-2, the primary noxious mediator can be blocked and the action of second- and third-order downstream mediators may be reduced. In relation to its role in pain,
COX-2 is expressed in glial cells and dorsal horn neurons, so COX-2-selective inhibition may minimize central sensitization, altered neural connections, and cell death in the dorsal horn.\textsuperscript{16}

NSAIDs have a potentially major role in acute pain management because of their primary action in peripheral sites of sensitization—\textit{nociceptor transduction}. Peripheral sensitization is an efficient and selective target for

![Diagram of NSAID mechanism of action](image)

**Fig. 3.** Schematic of NSAID mechanism of action. COX-1, a constitutive enzyme, plays a major role in the release of PG to protect gastric mucosa and regulate hemostasis. COX-2, an inducible enzyme, releases PG that mediates pain, inflammation, and fever. Nonselective NSAIDs inhibit both forms of COX. Coxibs such as rofecoxib or celecoxib selectively inhibit COX-2, resulting in control of pain and inflammation with a minimal effect on bleeding and gastric mucosa.\textsuperscript{21,22}

![Diagram of peripheral responses to acute trauma](image)

**Fig. 4.** Peripheral responses to acute trauma: (1) Following tissue injury, potassium (K\textsuperscript{+}), serotonin, and histamine (H\textsuperscript{+}) released from damaged cells, and bradykinin (BK) released from damaged vessels activate the terminal endings of sensory afferent fibers (nociceptors). Bradykinin initiates prostaglandin (PG) release at nociceptive endings. Prostaglandin has been implicated in nociceptor sensitization, further increases in vascular permeability, and primary hyperalgesia. (2) Orthodromic transmission in sensitized afferents results in the release of substance P (sP) in and around the site of injury. Substance P is responsible for further release of BK. (3) Substance P also stimulates histamine release from mast cells and 5-hydroxytryptamine (5HT) from platelets, which, in turn, activate additional nociceptors and exacerbate the inflammatory response. (4) Reflexes mediated by sympathetic efferents may sensitize nociceptors directly via secretion of noradrenaline (NA) indirectly via further release of BK and PG, and mediate peripheral vasoconstriction.\textsuperscript{23}
multimodal analgesia. NSAIDs can provide an effective adjunctive benefit to opioid therapy and improve outcomes, not only by allowing pain relief, but also by sparing patients some of the adverse effects associated with opioid use (possibly reducing undertreatment of pain resulting from those adverse effects).

Fear of the addictive potential of opioid analgesics appears to contribute to the undermedication of postsurgical pain. Clinically speaking, opioids, particularly morphine, are a leading cause of ileus in postsurgical patients using a combination of nonopioid and opioid analgesics has been shown to shorten the duration of ileus. In a landmark study, the use of IV ketorolac, a nonselective NSAID, resulted in a 40% reduction in the use of patient-controlled epidural fentanyl. Patients who received adjunctive ketorolac also reported less pain with movement and a more rapid recovery of bowel function. There were no differences between study groups in terms of blood loss, transfusion requirements, platelets, or temperature.

**Safety and Efficacy of COX-2-Selective Inhibitors in Multimodal Analgesia**

Partly because of the specific action of COX-2 on PGE₂, COX-2-selective inhibitors can be used up to and immediately following surgery. When nonselective NSAIDs are discontinued 5 to 10 days before surgery, many patients experience algesic flare as pain medication levels wane; surgery is subsequently performed on inflamed nerve endings. Because coxibs can be safely administered immediately prior to incision, they can help prevent algesic flare and resulting central sensitization.

**Reduction of Algesic Flare**

COX-2-selective inhibitors can be used prior to certain types of surgery; they have been shown to be safe and effective in minimizing algesic flare and in reducing the use of opioid PCA.

Rofecoxib versus placebo was evaluated for the perioperative management of pain after total knee arthroplasty (TKA) to determine whether algesic flare could be eliminated with no adverse effects on postsurgical bleeding. In this study, patients discontinued nonselective NSAIDs 10 days before TKA; rofecoxib (25 mg) was initiated three days before TKA. Following surgery, patients continued on placebo or rofecoxib for 48 hours and received warfarin (standard procedure in TKA patients). Pain was measured (visual analog scale [VAS] scores at rest and during movement) on preoperative Day 3 and the day of the surgery. As might be expected, rofecoxib significantly decreased pain scores compared with placebo on both preoperative Day 3 and day of surgery (Figure 5). Notably, no differences between the groups in intraoperative or 24-hour blood loss were observed, nor were there any differences in the number of patients requiring transfusions. Other hematologic measures showed rofecoxib to be as safe as placebo.

Another study compared the effects of identical doses of rofecoxib given either prior to, or immediately after, arthroscopic knee surgery. Patients were randomized to three groups: 50 mg rofecoxib 1 hour before surgery, placebo 1 hour before surgery, or 50 mg rofecoxib 15 to 30 minutes after surgery. Pain was assessed using VAS measurements. Compared with placebo (318 ± 108 min), a significantly longer duration of analgesia was observed for patients who received rofecoxib prior to surgery (803 ± 536 minutes) and for those who received rofecoxib after surgery (461 ± 344 minutes). Six of 20 patients who received rofecoxib prior to surgery required no rescue analgesics, compared with 2 of 20 patients who received rofecoxib after surgery and 0 of 20 patients who received placebo. This study provides powerful proof of concept that preventing algesic flare is impor-

![Fig. 5. Preoperative rofecoxib prevents algesic flare after discontinuation of NSAIDs prior to total knee arthroplasty.](image-url)
tant in the successful postoperative management of acute pain.

In a study of the use of celecoxib following minor orthopedic surgery, single doses (200 mg) of this agent over an 8-hour period were shown to be as effective as hydrocodone plus acetaminophen in patients with moderate to severe pain. 6

**Possible Synergy of Coxibs With Acetaminophen**

Acetaminophen may be synergistic with coxibs in providing pain relief. In two studies, the effects of rofecoxib and celecoxib, alone and in combination with acetaminophen, were compared in an outpatient ear, nose, and throat surgery population (Table 1). The combination groups received 2 g acetaminophen plus either 50 mg rofecoxib or 200 mg celecoxib prior to surgery (comparison arms were placebo, 2 g acetaminophen alone, or coxib alone). Visual analog scale measurements were used to assess postoperative pain. Recovery time, use of rescue analgesics, and side effects were also recorded.

Both studies found that rofecoxib and celecoxib in combination with acetaminophen produced a significant reduction in fentanyl use and a significant improvement in patient satisfaction. When acetaminophen use was excluded, rofecoxib, in contrast to celecoxib, achieved significant reductions in fentanyl use and improvement in patient satisfaction. The results of these studies support the concept that preemptive analgesia with an effective coxib or coxib/acetaminophen combination can reduce postoperative pain. A new and possibly more effective IV acetaminophen preparation is under investigation and may offer additional options in the management of this type of pain.

**Postoperative Effects of Preemptive Coxib Administration in Abdominal Surgery**

Preoperatively administered rofecoxib was also evaluated for its effect on postoperative pain and reduction of PCA morphine in patients undergoing abdominal surgery. Patients were randomized to receive 50 mg or 25 mg rofecoxib or placebo 1 hour prior to surgery. An interim analysis of 25 of 60 patients found no differences among the groups in terms of demographics, length of surgery, or intraoperative morphine dose. Patients in both rofecoxib groups required less morphine than those in the placebo group. Furthermore, PCA morphine use in patients who received 50 mg rofecoxib was 44% less at 12 hours and 47% less at 24 hours, and they had improved effort-dependent pain and pulmonary function measurements following spirometric effort at 12 hours. Preoperatively administered rofecoxib reduced the magnitude of decline in FEV1 (the amount that can be forcefully exhaled in the first second from a full inspiration) and VC (vital capacity) compared with that of the placebo group, indicators that patients experienced less abdominal pain with this agent.

**Table 1**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Postoperative Fentanyl Dose (g)</th>
<th>Patient Satisfaction (0–100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofecoxib 5</td>
<td>101 ± 133</td>
<td>73 ± 9</td>
</tr>
<tr>
<td>Placebo 101</td>
<td>183 ± 133</td>
<td>81 ± 13</td>
</tr>
<tr>
<td>Rofecoxib alone (50 mg)</td>
<td>22 ± 42a</td>
<td>98 ± 4a</td>
</tr>
<tr>
<td>Celecoxib 9</td>
<td>46 ± 80a</td>
<td>96 ± 5a</td>
</tr>
<tr>
<td>Placebo 114</td>
<td>114 ± 183</td>
<td>81 ± 13</td>
</tr>
<tr>
<td>Celecoxib alone (200 mg)</td>
<td>86 ± 83</td>
<td>88 ± 17</td>
</tr>
<tr>
<td>Celecoxib (200 mg) + acetaminophen (2 g)</td>
<td>61 ± 60a</td>
<td>90 ± 17</td>
</tr>
</tbody>
</table>

*P* < 0.05 compared with placebo.
hours) (Figure 6). Pain scores in the rofecoxib group were also significantly lower at two of six intervals compared with both celecoxib and placebo. While both rofecoxib and celecoxib were safe in this setting and did not increase bleeding, the longer duration of action of rofecoxib may be desirable as a component of preoperative pain management strategies for spinal fusion surgery. Additional dosing is possible for some agents, but many patients cannot tolerate another oral dose of medication 8 to 12 hours postsurgery, making agents with a longer duration of action more attractive.

**Role of Coxibs in Bone and Wound Healing**

Concerns about the use of coxibs and their effect on bone and wound healing have been raised based on studies of nonselective NSAIDs in animal models. The nonselective NSAID ketorolac inhibits both COX-1 and COX-2, although it is somewhat more selective for COX-2. In a rabbit model, only 35% of the animals that received ketorolac achieved fusion, compared with 75% of the surviving controls. One study in humans found that nonunion was five times more likely to occur in patients treated postoperatively with ketorolac, than in patients who did not receive the drug. An analysis of data on coxibs in spinal fusion surgery, on the other hand, found no difference in fusion rates among the rofecoxib, celecoxib, and placebo arms of the trial. Patients were followed for 6 months after surgery, as were those in the ketorolac study. Although the mechanism by which nonselective NSAIDs inhibit bone fusion is not clear, it appears that the coxibs may not share that mechanism and may therefore be useful in orthopedic procedures.

The effects of rofecoxib on biochemical markers of bone formation and resorption were compared with those of ibuprofen in 304 osteoarthritis patients. After three months, neither drug affected bone mineral density at measured points in the lumbar spine, femoral neck, or body, and indices of bone turnover were similar in both groups. At six months, the rofecoxib group had a slight decrease in a marker of bone resorption, but no difference in markers for bone formation.

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 nonselective 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 agent would delay or prevent healing.

**Conclusion**

A better understanding of pain mechanisms has brought about a new paradigm of pain management based on preemptive and multimodal strategies. Preemptive strategies involve
therapeutic intervention prior to pain. Multimodal strategies emphasize nonopioid analgesics, reserving opioids for extreme pain or breakthrough pain (potentially minimizing concerns about opioid-related side effects and possible dependence).

A major contribution to this “paradigm shift” has been the development of the COX-2-selective inhibitors, which allow safe and effective analgesia immediately prior to surgery. Rofecoxib has been approved for use in acute pain since it was introduced in 1999 and celecoxib recently received such approval. Rofecoxib has demonstrated significant efficacy in the preemptive setting; the addition of acetaminophen does not significantly increase its efficacy. Furthermore, rofecoxib administered prior to surgery was significantly more effective at controlling postoperative pain than when administered at identical doses immediately following surgery.

Notable to this finding is the 24-hour duration of effect of rofecoxib. This allows not only the advantage of once-daily dosing but also preoperative administration that maintains pain relief until the day after surgery, by which time many patients are more likely able to take a second oral dose. While there may be some psychologic benefit to taking a second dose of pain medication, if only so patients feel proactive in their pain management, individual preferences should be considered. In many cases, patients express a preference for drugs that can be taken once or twice daily, and furthermore, patients tend to be more compliant with once-daily dosing.

Is there a central COX-2 pathway for pain relief? Samad and colleagues have demonstrated significant upregulation of COX-2 in CNS parenchyma in response to acute peripheral inflammatory pain. Increased synthesis of PG is known to increase neuronal excitability and may play a role in CNS remodeling. In an animal model, rofecoxib has been shown to have excellent CNS penetration, as CSF concentration of drug was 35% of that detected in plasma. This finding suggests that rofecoxib is able to penetrate and possibly reduce CNS responses to locally synthesized PG.

The COX-2-selective inhibitors are safe and effective in the pre- and perioperative settings and improve outcomes in postsurgical pain. Along with epidural analgesics and a potential IV acetaminophen formulation, coxibs will form the base of the multimodal analgesia triangle in the future, allowing potent, short-duration opioids to be reserved for breakthrough pain. Within this new paradigm, alleviation of postsurgical pain should be greatly improved.

References

13. Woolf CJ, Chong MS. Preemptive analgesia—
treating postoperative pain by preventing the estab-
lishment of central sensitization. Anesth Analg 1993;
77:362–379.
14. Woolf CJ. An overview of the mechanisms of hy-
16. Mannion RJ, Woolf CJ. Pain mechanisms and man-
17. Brinkmann A, Seeling W, Wolf CF, et al. The im-
pact of prostanoids on pulmonary gas exchange
during abdominal surgery with mesenteric traction.
18. Gotshalk A, Smith DS, Jobs DR, et al. Pre-
emptive epidural analgesia and recovery from radi-
19. Robinson CM, Christie J, Malcolm-Smith N. Non-
steroidal antiinflammatory drugs, perioperative
bleed loss, and transfusion requirements in elective
20. Fitzgerald GA, Patrono C. The coxibs, selective
345:433–442.
21. Vane JR, Bakkle YS, Botting RM. Cyclooxygen-
ase 1 and 2. Annu Rev Pharmacol Toxicol 1998;38:
97–120.
22. Vane JR, Botting RM. New insights into the mode of action of anti-inflammatory drugs. Inflamm
23. Sinatra RS, Bigham M. The anatomy and patho-
Raven; 1997.
24. Ferraz AAB, Cowles VE, Condon RE, et al. Non-
optic analgesics shorten the duration of postopera-
25. Frantzides CT, Cowles V, Salaymeh B, Tekin E, Condon RE. Morphine effects on human colonic
26. Grass JA, Sakima NT, Valley M, et al. Assessment of ketorolac as an adjuvant to fentanyl patient-con-
trolled epidural analgesia after radical retropubic
27. Reuben SS, Maciolek H, Parker RK, et al. Evalu-
atation of the safety and efficacy of the perioperative
administration rofecoxib for total knee arthroplasty
SD. The effects of nonsteroidal anti-inflammatory
drugs on posterior spinal fusions in the rat. Spine
29. Dimar JR. A new class of COX-2 inhibitors offers
an alternative to NSAIDs in pain management after
30. Martin GJ Jr, Boden SD, Titus L. Recombinant human bone morphogenetic protein-2 overcomes
the inhibitory effect of ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), on postero-
lateral lumbar intertransverse process spine fusion. Spine
1999;24:2188–2193.
31. Glassman SD, Rose SM, Dimar JR, et al. The ef-
fect of postoperative nonsteroidal anti-inflammatory
drug administration on spinal fusion. Spine 1998;
32. Holt, data on file, Merck.
33. Samad TA, Moore KA, Sapirstein A, et al. Inter-
leukin-1beta-mediated induction of Cox-2 in the
CNS contributes to inflammatory pain hypersensitiv-
34. Buvanendran A, Luk P, Kroin JS, Rodger IW, McCarthy RJ. Central nervous system penetration of
oral rofecoxib, a selective cyclooxygenase-2 (COX-2)