

Effect of Parecoxib, A Novel Intravenous Cyclooxygenase Type-2 Inhibitor, on the Postoperative Opioid Requirement and Quality of Pain Control

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Background: The analgesic efficacy and side effect profile of intravenous parecoxib, a novel cyclooxygenase type-2 (COX-2) inhibitor, was assessed in a double-blinded, placebo-controlled study involving patients undergoing major gynecologic surgical procedures.

Methods: After Institutional Review Board approval, 60 consenting women, American Society of Anesthesiologists (ASA) physical status I-III, undergoing lower abdominal surgery with a standardized general anesthetic technique were randomly assigned to receive one of three study medications: group 1 (control) received normal saline; group 2 received intravenous parecoxib, 20 mg; and group 3 received intravenous parecoxib, 40 mg. The initial dose of study medication was administered when the patient first requested pain medication after surgery. All patients had access to patient-controlled analgesia (PCA) with intravenous morphine, 1 or 2 mg, with a 6-min lockout period. Subsequent doses of the same study medication were administered at 12-h and 24-h intervals after the initial dose. The postoperative opioid analgesic requirement (PCA morphine usage), pain scores, pain relief scores, side effects, and need for supplemental medications (e.g., antiemetics, antipruritics, laxatives) were recorded.

Results: Compared with saline, intravenous parecoxib, 20 mg and 40 mg every 12 h, significantly decreased the PCA morphine usage during the first 6 h postoperatively (group 1, 25 ± 13 mg; group 2, 16 ± 11 mg; group 3, 17 ± 10 mg) and at 12 h (group 1, 34 ± 18 mg; group 2, 24 ± 14 mg; group 3, 23 ± 13 mg) and 24 h (group 1, 51 ± 27 mg; group 2, 34 ± 20 mg; group 3, 33 ± 21 mg) after surgery. However, there were no significant differences in the patients' global evaluation of the study medications at 12 h and 24 h between those who received intravenous parecoxib (20 or 40 mg) and saline. Moreover, the postoperative pain scores and side effect profiles were similar in the three treatment groups.

Conclusion: Intravenous parecoxib (20 or 40 mg) was effective in decreasing the PCA opioid requirement after lower ab-

dominal surgical procedures. However, it failed to improve pain management or reduce opioid-related side effects in the early postoperative period.

DESPITE their well-known side effects,¹ opioid analgesics remain the primary therapy for moderate-to-severe pain after surgery. Nonsteroidal antiinflammatory drugs (NSAIDs) have been used adjunctively in the management of pain after a variety of surgical procedures.^{2,3} The mechanism of action of NSAIDs is related to inhibition of the cyclooxygenase (COX) enzyme,⁴ which exists as two distinct isoforms: COX-1 and COX-2.^{5,6} COX-1 is constitutively active throughout the body and is responsible for mediating routine physiologic functions, such as maintaining gastric mucosal integrity⁷ and vascular hemostasis.⁸ However, the inducible COX-2 enzyme is expressed in association with inflammation and pain.⁶

The classic NSAIDs inhibit the COX-1 and COX-2 isoenzymes⁹ and, therefore, have an antiinflammatory and analgesic effect and the ability to produce adverse effects on the gastrointestinal tract, kidney, and platelets. It has been suggested that the newer NSAIDs that are more specific for the COX-2 isoenzyme may produce antiinflammatory and analgesic effects while avoiding the adverse effects on the body's homeostatic mechanisms. Previous studies comparing the oral COX-2 inhibitors rofecoxib¹⁰ and celecoxib¹¹ with the classic NSAIDs have reported similar analgesic effects when used to manage post-dental surgery pain. Recently, Reuben and Connelly¹² demonstrated significant opioid-sparing effects with celecoxib and rofecoxib when used in conjunction with patient-controlled analgesia (PCA) with morphine after spinal fusion surgery.

Parecoxib, a water-soluble prodrug of valdecoxib, is a high-selective COX-2 inhibitor that is available for intravenous administration. A preliminary study in rats suggested that parecoxib produced comparable analgesic efficacy to ketorolac.¹³ Therefore, we designed a study to test the hypothesis that parecoxib could produce an opioid-sparing effect, thereby decreasing opioid-related side effects when administered during the early postoperative period after lower abdominal surgery.

Materials and Methods

Sixty consenting patients undergoing total abdominal hysterectomy or myomectomy procedures were entered

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into this Institutional Review Board–approved, randomized, double-blinded, placebo-controlled study at Cedars-Sinai Medical Center in Los Angeles, California. Study entry criteria included body weight of at least 50 kg and no more than 50% above ideal body weight, age 18–70 yr, and ability to understand the use of pain assessment scales and the PCA device. Exclusion criteria included known allergy, sensitivity, or contraindication to opioid and nonopioid analgesic drugs; history of bleeding disorders, peptic ulceration, or anticoagulant use within the past month; current pregnancy or breastfeeding; history of known or suspected drug abuse; and NSAIDs use within 24 h before surgery.

After receiving a standardized general anesthetic technique consisting of propofol (1.5–2 mg/kg) and fentanyl (1–2 μ g/kg) for induction, and desflurane (3–6% end tidal) with nitrous oxide 60–70% in oxygen for maintenance of anesthesia. Supplemental bolus doses of intravenous fentanyl, 25–50 μ g, were administered for persistent tachycardia not responding to increases in the desflurane concentration or a bolus of intravenous fluid. After surgery, patients were randomly assigned to one of three study groups (group 1 [control] received normal saline; group 2 received intravenous parecoxib, 20 mg; group 3 received intravenous parecoxib, 40 mg) according to a computer-generated table. The initial dose of study medication was administered when the patient first requested an analgesic medication in the postanesthesia care unit (PACU). Subsequent doses of the same study medication were administered at 12-h and 24-h intervals after the initial dose. The study medications were prepared by a hospital pharmacist who was not involved in the data collection process. Each study medication was reconstituted to a total volume of 2 ml with sterile 0.9% normal saline in identical-appearing plastic syringes. All the patients were allowed access to a PCA pump (Abbott Lifecare-PCA plus II, Chicago, IL) in the PACU after administration of the first dose of study medication. The PCA device was programmed to deliver 1- to 2-ml bolus doses of morphine (1 mg/ml) “on demand,” with a minimum lock-out interval of 6 min and a total morphine dose not to exceed 20 mg during any 4-h interval.

A 4-point verbal rating scale (VRS), with 0 = none, 1 = mild, 2 = moderate, and 3 = severe, was used to evaluate the pain intensity just before the first dose of study drug and subsequently at 2-, 4-, 6-, 9-, 12-, 18-, and 24-h intervals. Patients' global evaluation of the analgesic efficacy of the study medication was obtained at 12 h and 24 h using a 4-point satisfaction scale (1 = poor, 2 = fair, 3 = good, and 4 = excellent). Patients were also asked to assess the maximum pain on a 4-point VRS (0 = none, 1 = mild, 2 = moderate, and 3 = severe) and the maximum pain relief on a 5-point VRS (0 = none, 1 = a little, 2 = some, 3 = a lot, and 4 = complete) at the end of the study period (*i.e.*, 12 h after the last dose of study

medication). The total dosages of morphine administered *via* the PCA delivery system were recorded at 6 h, 12 h, and 24 h after the first dose of study medication. During the study period, the patients were not permitted to ambulate for 15 min before each pain assessment.

Systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate were recorded immediately before administration of the study medication and at 1-, 2-, and 4-h intervals after the first dose of study drug. Standard clinical laboratory tests were ordered before surgery, before the first dose of the study medication, and 12 h after the last dose of study medication. Adverse events and the need for supplement medications (*e.g.*, antiemetics, antipruritics, laxatives) were recorded throughout the 36-h study period.

Statistical Analysis

An *a priori* power analysis was performed to determine the minimum power group sizes ($n = 19$), based on the assumption that (1) parecoxib, 40 mg, achieved a maximal analgesic effect,¹⁴ (2) parecoxib, 20 mg and 40 mg, would produce 20% and 35%, respectively, decreases in the PCA morphine requirement ($SD = 19$), and (3) an $\alpha = 0.05$ and $\beta = 0.8$.^{15,16} Statistical analyses of these data were performed using one-way analysis of variance (ANOVA) for continuous variables, and when significant differences were determined, a *post hoc* intergroup comparison was performed using a Newman-Keuls multiple-comparison test. Two-way ANOVA was used for repeated measures, and when significant differences were noted, a *post hoc* test was used to compare the post-treatment with the baseline values using Bonferroni correction. Categorical data were analyzed using chi-square or Fisher exact test as appropriate. All tests were two-sided, and P values less than 0.05 were considered statistically significant.

Results

Sixty patients were initially enrolled in this study, although only 55 patients successfully completed the entire study. There were four consented patients who voluntarily withdrew from the study before the initial dose of study medication was administered, and one patient in group 3 who failed to complete all the postoperative evaluations. The three study groups were comparable with respect to age, weight, height, ASA physical status, and type and duration of surgery (table 1). In addition, the total intraoperative fentanyl dosages were similar in the three treatment groups.

After the administration of the study medication, the cumulative doses of morphine were significantly decreased at the 6-, 12-, or 24-h testing intervals in patients receiving intravenous parecoxib, 20 mg and 40 mg, when compared to the control group receiving normal

Table 1. Demographic Characteristics, Surgical Times, and Intraoperative Opioid Dosages of the Three Study Groups

	Control (Saline)	Parecoxib 20 mg	Parecoxib 40 mg
Number (n)	18	19	18
Age (yr)	49 ± 10	52 ± 9	47 ± 9
Height (cm)	165 ± 7	164 ± 6	164 ± 7
Weight (kg)	77 ± 22	75 ± 14	75 ± 15
ASA class (I/II/III) (n)	6/9/3	9/8/2	6/10/2
Surgical procedures			
Myomectomy (n)	3	4	8
Hysterectomy (n)	15	15	10
Surgery time (min)	121 ± 42	115 ± 41	131 ± 39
Fentanyl (μg)	228 ± 91	175 ± 83	211 ± 108

Values are mean ± SD. No significant differences were noted among the three study groups.

n = number.

saline (table 2). However, the morphine dosages did not differ significantly between the two parecoxib groups. The time interval from the first dose of study medication to the first PCA morphine dose was also similar among the three study groups (table 2). Postoperative VRS pain scores were similar among the three groups at all of the time intervals studied (fig. 1). With respect to the patients' global evaluation of the analgesic efficacy of the study medication at 12 h and 24 h after the first dose of study medication, there were no significant differences between patients in the parecoxib groups compared with the control group (table 3). Moreover, at 12 h after the last dose of the study medication, patients' evaluation of their maximum postoperative pain score and the magnitude of the pain relief produced by the study medication did not differ significantly among the three groups (table 3).

Compared with the baseline vital sign values, blood pressure, heart rate, and respiratory rate values immediately before and after study drug administration were not significantly different in any of the groups (data not shown). Postoperative side effects were also similar in the three study groups (table 4). No postoperative wound complications or bleeding problems were reported in any of the study groups. Finally, clinical labo-

ratory testing revealed no abnormalities related to the study medications (data not reported).

Discussion

The concept of balanced analgesia suggests that a combination of opioid and nonopioid analgesic drugs will enhance analgesic efficacy and reduce side effects after surgery.^{2,3} The use of a parenteral NSAID (e.g., ketorolac) in combination with PCA morphine has been reported to produce an opioid-sparing effect after major surgical procedures.¹⁵⁻¹⁷ For example, when ketorolac was administered as an adjuvant to PCA morphine after lower abdominal surgery, it produced a 20-30% decrease in the postoperative opioid dosage.^{16,17} Although intravenous ketorolac is an effective analgesic, its use may be associated with increased operative site and gastrointestinal bleeding and renal toxicity.^{18,19} Serious NSAID-associated complications after surgery have been alleged to occur without warning.²⁰ Concern regarding these adverse effects of ketorolac resulted in its withdrawal from clinical practice in several European countries²¹ and a limitation of its use to 5 days after surgery in the United States.²²

The availability of a parenterally active COX-2 specific inhibitor with potent analgesic properties would represent a significant therapeutic advance in the management of acute postoperative pain. Although parecoxib is an inactive prodrug of valdecoxib, pharmacokinetic studies have demonstrated that parecoxib is rapidly converted to valdecoxib after intravenous administration.²³ Using an animal model of acute pain, parecoxib was found to produce comparable analgesic efficacy and a more rapid onset of action than ketorolac.¹³ In a preliminary study evaluating intravenous parecoxib (20-80 mg) when administered before oral surgery, Desjardins *et al.*¹⁴ reported that parecoxib was superior to placebo in preventing pain. These investigators also suggested that fewer adverse events and higher global assessment of pain control was found in the parecoxib-treated patients compared with those receiving the

Table 2. Dosages of PCA Morphine and Time to First PCA Rescue Dose During the Postoperative Study Period in the Three Study Groups

	Control (Saline)	Parecoxib 20 mg	Parecoxib 40 mg
Number (n)	18	19	18
PCA morphine consumption			
0-6 h (mg)	25 ± 13	16 ± 11*	17 ± 10*
6-12 h (mg)	9 ± 6	7 ± 8	8 ± 8
12-24 h (mg)	25 ± 17	17 ± 13	18 ± 16
Cumulative morphine dosages			
0-12 h (mg)	34 ± 18	24 ± 14*	23 ± 13*
0-24 h (mg)	51 ± 27	34 ± 20*	33 ± 21*
Time to first PCA rescue bolus (min)	33 ± 37	34 ± 33	34 ± 40

Values are mean ± SD. * $P < 0.05$ versus control group. No significant differences were noted among the three study groups.

PCA = patient-controlled analgesia; n = number.

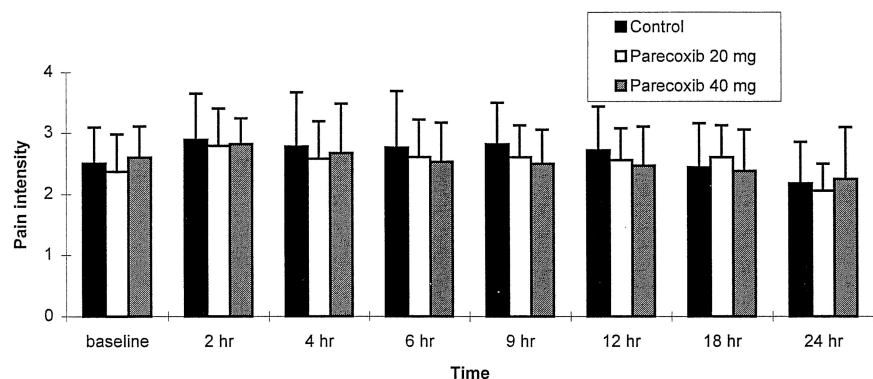


Fig. 1. Pain intensity scores during the first 24-h period after administering the initial dose of the study medication using a 4-point verbal rating scale, with 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Solid black bars represent the control group (n = 18), white bars represent the 20-mg parecoxib group (n = 19), and cross-hatched bars represent the 40-mg parecoxib group (n = 18). Values are means \pm SD. There were no statistically significant differences among the three treatment groups.

placebo. However, to date no published data exist regarding the clinical benefit(s) of using this novel COX-2 inhibitor to manage postsurgical pain.

Based on the information provided by the study sponsor (G.D. Searle & Co. Skokie, IL), doses of intravenous parecoxib less than 20 mg were ineffective when studied in a post-dental surgery pain model. Therefore, parecoxib doses of 20 mg and 40 mg were selected to evaluate its analgesic effects after major surgical procedures. These doses were found to reduce PCA morphine use by approximately 30% during the first 24 h after surgery compared with the control group. However, the primary opioid-sparing effect was noted in the first 6 h after administering the parecoxib. These findings are similar to earlier studies involving the use of ketorolac as an adjuvant to postoperative PCA morphine.^{15,16}

Compared with the control group, administration of intravenous parecoxib (20 or 40 mg) failed to improve the patients' global evaluation of the study medication's analgesic efficacy. Moreover, the interval between the

initial dose of study drug and the time to the first PCA rescue dose of morphine, the maximal pain intensity, and the maximum pain relief after surgery failed to demonstrate any significant differences between the intravenous parecoxib- (20 or 40 mg) and saline-treated patients. These findings are analogous to those of Dahl and Kehlet,²⁴ who demonstrated that the adjunctive use of NSAIDs decreased the opioid analgesic requirement without improving pain relief postoperatively. Our inability to confirm the recent findings of Desjardins *et al.*¹⁴ suggests that parecoxib may be more effective in the prevention (*vs.* management) of acute pain. Alternatively, oral (dental) surgery may not be an optimal model for studying postoperative pain. In the current study, we failed to find any difference between parecoxib doses of 20 mg and 40 mg. This finding may be the result of an inadequate number of patients being enrolled in the study or may be related to the plateau effect that occurs with parecoxib doses above 20 mg in this postsurgical pain model.

Table 3. Patient's Global Evaluation of the Study Medication, Maximum Pain, and Pain Relief Scores in the Three Study Groups

	Control (Saline)	Parecoxib 20 mg	Parecoxib 40 mg
Number (n)	18	19	17
Global evaluation of the study medication at 12 hr			
Excellent [n (%)]	2 (11)	4 (21)	7 (41)
Good [n (%)]	10 (56)	15 (79)	8 (47)
Fair [n (%)]	5 (27)	0 (0)	2 (12)
Poor [n (%)]	1 (6)	0 (0)	0 (0)
Global evaluation of the study medication at 24 hr			
Excellent [n (%)]	4 (22)	5 (26)	7 (41)
Good [n (%)]	8 (44)	13 (69)	8 (47)
Fair [n (%)]	5 (28)	1 (5)	2 (12)
Poor [n (%)]	1 (6)	0 (0)	0 (0)
Maximum pain score at 36 hr			
None [n (%)]	0 (0)	0 (0)	0 (0)
Mild [n (%)]	0 (0)	0 (0)	0 (0)
Moderate [n (%)]	9 (50)	11 (58)	10 (59)
Severe [n (%)]	9 (50)	8 (42)	7 (41)
Maximum pain relief score at 36 hr			
None [n (%)]	0 (0)	0 (0)	0 (0)
A little [n (%)]	0 (0)	1 (5)	0 (0)
Some [n (%)]	5 (28)	2 (11)	3 (18)
A lot [n (%)]	9 (50)	14 (73)	10 (59)
Complete [n (%)]	4 (22)	2 (11)	4 (23)

Values are numbers (n) and percentages (%). No significant differences were noted among the three study groups.

Table 4. Incidence of Postoperative Side Effects and Surgical Complications in the Three Study Groups

	Control (Saline)	Parecoxib 20 mg	Parecoxib 40 mg
Number (n)	18	19	18
Nausea [n (%)]	10 (56)	12 (63)	11 (61)
Vomiting [n (%)]	1 (6)	2 (11)	0
Itching [n (%)]	5 (28)	4 (21)	3 (17)
Fever [n (%)]	3 (17)	0	2 (11)
Ileus >24 hr (n)	0	0	0
Wound hematoma (n)	0	0	0

Values are number (n) and percentages (%); No significant differences were noted among the three study groups.

The opioid-sparing effect of a nonopioid analgesic is most beneficial when it also results in a reduction in postoperative side effects. Despite its opioid-sparing effects, parecoxib did not significantly alter the overall incidence of opioid-related side effects (e.g., postoperative nausea, vomiting, urinary retention, constipation, or ileus). Interestingly, previous lower abdominal studies involving the use of ketorolac as an adjuvant to PCA morphine have also failed to find clinically relevant differences in postoperative side effects compared with a placebo group.^{16,17} Because the COX-2 inhibitors lack an antiplatelet effect,^{5,11,25} it has been suggested that parecoxib may be associated with an improved perioperative safety profile compared with non-specific NSAIDs like ketorolac.¹⁵ Although we failed to detect any postoperative bleeding problems or wound complications, the relatively small group sizes (n = 18 or 19) precluded us from drawing any conclusions regarding the safety profile of parecoxib with respect to bleeding diathesis. This study and the early study by Desjardins *et al.*¹⁴ can be criticized for failing to include an active NSAID comparator (e.g., ketorolac) and for not quantifying the perioperative blood loss.

In conclusion, intravenous parecoxib (20 or 40 mg) was effective in decreasing the PCA opioid requirement after major gynecologic surgical procedures without increasing postoperative side effects or wound complications. However, parecoxib failed to improve postoperative pain control or the global assessment of the analgesic medication when compared with a placebo. Further studies are needed to assess the comparative analgesic efficacy of parecoxib and the classic NSAIDs, as well as their effects on clinically important outcome variables, such as blood loss, wound complications, recovery of bowel and bladder function, and resumption of oral alimentation and physical activities.

References

- Melzack R, Abbott FV, Zackon W, Mulder DS, Davis MW: Pain on a surgical ward: A survey of the duration and intensity of pain and the effectiveness of medication. *Pain* 1987; 29:67-72
- Kehlet H, Dahl JB: The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg* 1993; 77:1048-56
- Souter AJ, Fredman B, White PF: Controversies in the perioperative use of nonsteroidal antiinflammatory drugs. *Anesth Analg* 1994; 79:1178-90
- Vane JR: Inhibition of prostaglandin synthesis as a mechanism of action of aspirin-like drugs. *Nat New Biol* 1971; 231:232-5
- Hawkey CJ: COX-2 inhibitors. *Lancet* 1999; 353:307-14
- Xie W, Chipman JG, Robertson DL, Erikson RL, Simmons DL: Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. *Proc Natl Acad Sci U S A* 1991; 88:2692-6
- Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane RJ: Non-steroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci U S A* 1999; 96:7563-8
- Moncada S, Gryglewski R, Bunting S, Vane JR: An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature* 1976; 263:663-5
- Mitchell JA, Akaraseenont P, Thiemermann C, Flower NJ, Vane JR: Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc Natl Acad Sci U S A* 1993; 90:11693-7
- Morrison BW, Christensen S, Yuan W, Brown J, Amlani S, Seidenberg B: Analgesic efficacy of the cyclooxygenase-2-specific inhibitor rofecoxib in post-dental surgery pain: A randomized, controlled trial. *Clin Ther* 1999; 21:943-53
- Clemett D, Goa KL: Celecoxib: A review of its use in osteoarthritis, rheumatoid arthritis and acute pain. *Drugs* 2000; 59:957-80
- Reuben SS, Connelly NR: Postoperative analgesic effects of celecoxib or rofecoxib after spinal fusion surgery. *Anesth Analg* 2000; 91:1221-5
- Talley JJ, Bertenshaw SR, Brown DL, Carter JS, Graneto MJ, Kellogg MS, Koboldt CM, Yuan J: N-[[[(5-methyl-3-phenylisoxazol-4-yl)-phenyl]sulfonyl] propanamide, sodium salt, parecoxib sodium: a potent and selective inhibitor of COX-2 for parenteral administration. *J Med Chem* 2000; 43:1661-3
- Desjardins PJ, Grossman EH, Kuss ME, Talwalker S, Dhadda S, Baum D, Hubbard RC: The injectable cyclooxygenase-2-specific inhibitor parecoxib sodium has analgesic efficacy when administered preoperatively. *Anesth Analg* 2001; 93:721-7
- Etches RC, Warriner CB, Badner N, Buckley DN, Beattie WS, Chan VW, Parsons D, Girard M: Continuous intravenous administration of ketorolac reduces pain and morphine consumption after total hip or knee arthroplasty. *Anesth Analg* 1995; 81:1175-80
- Parker RK, Holtmann B, Smith I, White PF: Use of ketorolac after lower abdominal surgery. Effect on analgesic requirement and surgical outcome. *ANESTHESIOLOGY* 1994; 80:6-12
- Blackburn A, Stevens JD, Wheatley RG, Madej TH, Hunter D: Balanced analgesia with intravenous ketorolac and patient-controlled morphine following lower abdominal surgery. *J Clin Anesth* 1995; 7:103-8
- Kenny GN: Potential renal, haematological and allergic adverse effects associated with nonsteroidal anti-inflammatory drugs. *Drugs* 1992; 44:31-6
- Cashman J, McAnulty G: Nonsteroidal anti-inflammatory drugs in perisurgical pain management. Mechanism of action and rationale for optimum use. *Drugs* 1995; 49:51-70
- Armstrong CP, Blower AL: Nonsteroidal antiinflammatory drugs and life threatening complications of peptic ulceration. *Gut* 1987; 28:527-32
- Lewis S: Ketorolac in Europe. *Lancet* 1994; 343:784
- Choo V, Lewis S: Ketorolac doses reduced. *Lancet* 1993; 342:109
- Jain KK: Evaluation of intravenous parecoxib for the relief of acute post-surgical pain. *Expert Opin Investig Drugs* 2000; 9:217-23
- Dahl JB, Kehlet H: Non-steroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. *Br J Anaesth* 1991; 66:703-12
- Ehrich EW, Dallob A, De Lepeleire I, Van Hecken A, Riendeau D, Yuan W, Porras A, Wittreich J, Seibold JR, DeSchepper P, Mehlich DR, Gertz BJ: Characterization of rofecoxib as a cyclooxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain modal. *Clin Pharmacol Ther* 1999; 65:336-47