PAIN MEDICINE
Volume 2 • Number 4 • 2001

REVIEW ARTICLE

Ketorolac in the Era of Cyclo-Oxygenase-2 Selective Nonsteroidal Anti-Inflammatory Drugs: A Systematic Review of Efficacy, Side Effects, and Regulatory Issues

Alex Macario, MD, MBA,* and Arthur G. Lipman, PharmD†

*Department of Anesthesia, Stanford University School of Medicine, Stanford, California; †College of Pharmacy and Pain Management Center, University of Utah Health Sciences Center, Salt Lake City, Utah

ABSTRACT

Objective. The recent introduction of oral COX-2 selective NSAIDs with potential for perioperative use, and the ongoing development of intravenous formulations, stimulated a systemic review of efficacy, side effects, and regulatory issues related to ketorolac for management of postoperative analgesia.

Design. To examine the opioid dose sparing effect of ketorolac, we compiled published, randomized controlled trials of ketorolac versus placebo, with opioids given for breakthrough pain, published in English-language journals from 1986–2001. Odds ratios were computed to assess whether the use of ketorolac reduced the incidence of opioid side effects or improved the quality of analgesia.

Results. Depending on the type of surgery, ketorolac reduced opioid dose by a mean of 36% (range 0% to 73%). Seventy percent of patients in control groups experienced moderate-severe pain 1 hour postoperatively, while 36% of the control patients had moderate to severe pain 24 hours postoperatively. Analgesia was improved in patients receiving ketorolac in combination with opioids. However, we did not find a concomitant reduction in opioid side effects (e.g., nausea, vomiting). This may be due to studies having inadequate (to small) sample sizes to detect differences in the incidence of opioid related side effects. The risk for adverse events with ketorolac increases with high doses, with prolonged therapy (>5 days), or invulnerable patients (e.g. the elderly). The incidence of serious adverse events has declined since dosage guidelines were revised.

Conclusions. Ketorolac should be administered at the lowest dose necessary. Analgesics that provide effective analgesia with minimal adverse effects are needed.

Key Words. Ketorolac; Odds Ratio; Opioid Sparing; Analgesia; NSAIDS; Acute Pain

The introduction of oral cyclo-oxygenase-2 selective nonsteroidal anti-inflammatory drugs (COX-2 NSAIDs) and the development of an intravenous COX-2 selective NSAID have heightened interest in the potential perioperative use of parenteral NSAIDs. Anesthesiologists, surgeons, and pharmacists are particularly interested in improved parenteral drug risk-benefit ratios in the care of surgical patients. Whereas the only parenteral NSAID currently available in the United States is ketorolac, other parenteral NSAIDs are commercially available in other countries.

We review the analgesic efficacy, side effects, and regulatory issues related to ketorolac for the management of analgesia for patients undergoing surgery.

Reprint requests to: Alex Macario, MD, MBA, Department of Anesthesia, Stanford University School of Medicine, Stanford, CA 94305-5640. Tel: 650-723-6411; Fax: 650-725-8544; E-mail: amaca@stanford.edu.

An educational grant was provided by Pharmacia.

Need for Improvement in Postoperative Analgesia

Clinicians document [1] and patients continue to fear [2] postoperative pain. A recent U.S. survey of

 1526-2375/01/$15.00/336 336–351

250 patients receiving usual postoperative care confirmed other studies' findings that as many as 40% to 60% of patients experience moderate, severe, or extreme pain [3,4]. Another study of 10,008 patients reported the incidence of severe pain as 5% in the recovery room and 5.3% 24 hours postoperatively [5]. Despite new techniques and increased emphasis on relieving acute pain, postoperative pain remains undertreated. Reasons for this include confusion about who is responsible for analgesia, providers' lack of knowledge regarding the effective dose ranges and duration of action of opioids, and fears of respiratory depression and addiction [6,7].

Adequate analgesia has become an even more important outcome with the implementation of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) standards for pain management, which became effective in January 2001 [8]. These new pain management standards were published in 2000 for all seven categories of facilities accredited by the JCAHO. Heightened awareness of pain as the fifth vital sign suggests that pain management must be assessed regularly during treatment and, when indicated, be addressed in discharge planning, using standardized, internally developed guidelines [9]. Systems to ensure that pain management is provided must also be in place.

Internationally, results of a national audit in Great Britain [10] further highlight the increasing importance being given to more aggressive management of acute postoperative pain. The audit recommended establishing performance standards for levels of pain relief in contracts, having patients' pain scores be a quality indicator reported regularly to the board, and developing evidence-based guidelines on effective analgesic therapies.

The choice of a particular postoperative pain management regimen depends on the anticipated pain intensity, type of surgery performed, and capacity for postoperative monitoring and supervision. The evolving role of NSAIDs, and in particular ketorolac, is aimed at providing pain relief while minimizing side effects of other analgesics.

Ketorolac

Historically, NSAIDs were used to treat rheumatological diseases. They were then introduced to relieve pain after tooth extraction. NSAIDs are now considered drugs of choice in the management of pain and inflammation. NSAIDs are the most widely used drugs in the world. In fact, physicians rated NSAIDS as the 15th most important medical innovation in the past 30 years, ranking between cardiac enzymes and laparoscopic surgery [11].

The development of an injectable NSAID, ketorolac, provided an increased opportunity for the use of this class of drugs in patients unable to take enteral drugs, most notably in postoperative pain management. This is reflected in the 1992 federal Agency for Health Care and Policy Research Acute Pain Guideline, in which the recommended options for postoperative pain explicitly include systemic administration of NSAIDs [12].

NSAIDs are useful for postoperative pain management because surgery causes both pain and inflammation. NSAIDs provide both analgesic and anti-inflammatory activity. Opioids, in contrast, do not provide clinically useful anti-inflammatory activity in this setting. Also, opioids have a narrow therapeutic index.

This creates a delicate relationship between analgesia and side effects that can be altered by changes in pain intensity with changing activity (e.g., the patient who is somnolent at rest but very uncomfortable when moving or coughing). In patients experiencing postoperative pain for whom physical therapy and unimpaired cognition is essential, NSAIDs would be an attractive option if they lacked other side effects.

When used as analgesic monotherapy, NSAIDs can effectively relieve minor to moderate pain (e.g., after minor orthopedic procedures). In these settings, opioids may be unnecessary, and discharge may be accelerated because opioid side effects are avoided. For more severe acute pain, concurrent use of NSAIDs provides an opioid dose-sparing effect that should lessen the risk of opioid-associated adverse events. Thus, there is great clinical and scientific interest in using NSAIDs as adjuncts for postoperative analgesia.

Ketorolac tromethamine was introduced into general clinical practice in the United States a decade ago. The tromethamine salt enhances water solubility, which allows formulation of a parenteral product. Ketorolac was marketed as a safer intravenous alternative to opioid analgesics. Although the use of ketorolac increased rapidly, reports describing serious NSAID-type gastrointestinal, renal, and hematological adverse reactions also increased [13], leading to the withdrawal of the drug from distribution in some European countries and the U.S. Food and Drug Administration (FDA) mandating a cautionary "black box" warning in the package labeling of ketorolac (Appendix).

Because the use of a parenteral NSAID in the postoperative setting is valuable, many clinicians

consider the risk-benefit ratio of ketorolac to be favorable and continue to use it after surgery when patients are unable to take oral NSAIDs. When ketorolac was introduced, all NSAIDs were believed to act by inhibiting the COX enzyme. More recent research has demonstrated that COX is not a single enzyme but exists as two isoforms, COX-1 and COX-2 which are discussed in more detail later in the Clinical Pharmacology section.

COX-2 Selective NSAIDs

Currently, in the United States, COX-2 selective NSAIDs are only available in oral dosage forms of celecoxib and rofecoxib. Celecoxib is approved for use in osteoarthritis and rheumatoid arthritis, whereas rofecoxib is approved for osteoarthritis, acute pain in adults, and primary dysmenorrhea. Rofecoxib and celecoxib are available outside the United States.

Clinical advantages of oral formulations of COX-2 selective NSAIDs highlight the potential for intraoperative use. For example, at dosages higher than those listed in the FDA-approved labeling, celecoxib was associated with a lower incidence of symptomatic ulcers (2.08% vs. 3.54%, $P = .02$), as well as other clinically important complications, than what occurred with nonselective NSAIDs at standard dosages [14].

For surgical patients, COX-2 selective NSAIDs are receiving more attention. For example, 60 inpatients undergoing spine stabilization were divided into three groups: those receiving preoperative oral celecoxib, 200 mg, rofecoxib, 50 mg, or placebo [15]. Both agents demonstrated an opioid-sparing effect. Celecoxib resulted in decreased morphine use for the first 8 hours after surgery, whereas rofecoxib demonstrated less morphine use throughout the 24-hour study period.

In contrast, in a prospective, randomized, double-blinded, placebo-controlled trial of 30 patients undergoing radical prostatectomy, preoperative oral rofecoxib, 50 mg, did not decrease postoperative pain or morphine consumption [16]. It is unclear why the studies showed different opioid-sparing results, but the anticipated pain intensity and the type of surgery performed may affect whether adding NSAIDS actually are shown to yield a benefit.

Currently, parenteral COX-2 selective NSAIDs are under study for postoperative pain management; one such agent is parecoxib [17,18]. Clinical trials indicate that parecoxib, 20 mg, provides analgesia comparable to ketorolac, 30 mg [19,20], but without endoscopic evidence of upper gastrointestinal mucosal injury that is associated with ketorolac [21]. The introduction of parenteral COX-2 selective NSAIDs in the near future may increase the ability of clinicians to manage acute pain more effectively and safely.

Thus, the recent introduction of oral COX-2 selective NSAIDs with potential for use in the perioperative period and the pending availability of an intravenous formulation [22] provide an impetus for clinicians to review efficacy, side effect, and regulatory issues related to ketorolac and the management of analgesia for patients undergoing surgery.

Efficacy

Postoperative care encompasses three levels of recovery: early recovery as the patient emerges from anesthesia; intermediate recovery when the patient achieves criteria for discharge home; and late recovery at home when the patient returns to full and normal activity level after surgery and anesthesia.

A key part of all three phases of recovery is adequate control of pain during rest (rest pain) and pain with activity (incident pain). Rest pain is generally easier to alleviate. Incident pain is difficult to manage, and many studies of postoperative pain (and in decisions by physicians as to what analgesic to prescribe) do not assess incident pain.

In clinical trials, intramuscular (IM) ketorolac, 10 to 30 mg, has been shown to be equianalgesic to morphine, 6 to 12 mg, meperidine, 50 to 100 mg, and propacetamol, 2 g [23–27]. Propacetamol is a prodrug of acetaminophen (paracetamol). Propacetamol is used clinically in several other countries but is not available in the United States [28].

Like all other NSAIDs, ketorolac has an analgesic dose ceiling effect. Therefore, its effectiveness as analgesic monotherapy is usually insufficient for moderately severe to severe pain after major surgery (e.g., orthopedic, abdominal, thoracic procedures). In most studies, a daily ketorolac dose of 120 mg was not exceeded, and the duration of treatment was usually 5 days or less [29].

Ketorolac can be combined with opioids as part of a balanced analgesia regimen [30]. For example, during bilateral tubal ligation with regional anesthesia, preemptive analgesia using IV ketorolac 60, metoclopramide, and infiltration with local anesthetic enabled nine of 10 patients to recover with no pain, nausea, vomiting, or cramping and to maintain good analgesia for 7 days postoperatively [31]. In patients who underwent major cancer surgery, ketorolac reduced total postoperative mor-

phine use as well as nausea, vomiting, and pruritus compared with morphine alone [32].

However, many clinicians hesitate to combine ketorolac with opioids because of potential adverse effects of ketorolac, especially in patients with risk factors for gastropathy and bleeding. In fact, ketorolac administration before surgery is contraindicated according to the FDA-approved package labeling (i.e., the package insert).

Ketorolac as an Opioid-Sparing Agent: Systematic Review of Published Studies

Systematic reviews apply strategies that limit bias to the assembly, appraisal, and synthesis of relevant studies on a specific topic [33]. We followed published guidelines [34,35] in compiling published, randomized controlled trials on the opioid dose-sparing effect of ketorolac. A number of different search strategies were used to identify eligible studies in MEDLINE (Knowledge Server, Silver Platter). English-language journals with studies conducted on adult humans from 1986 to January 2001 were included.

The search terms used were ketorolac, nonsteroidal anti-inflammatory, postoperative pain, intravenous, IM, rectal, dose-response, efficacy. Additional studies were identified from the reference lists of retrieved papers, review articles, and medical textbooks. Abstracts, letters, and nonevaluative review articles as well as unpublished reports were not considered. Any study in which the numbers of patients per treatment group was fewer than 10 was excluded.

The primary inclusion criteria were double-blind, randomized, controlled trials (RCTs) that included parenteral ketorolac versus placebo, with opioids given for breakthrough pain [36,37]. The contents of 85 abstracts and full-text articles identified during our literature search were read in full. In addition, a manual search performed by screening citation lists in review articles yielded another 18 articles. Each trial was reviewed for design details. Data extraction was performed by Alex Macario.

The following study characteristics were recorded: first author's name, year of publication, and country of origin; mean age, age range, total number, and gender of patients; presence of coexisting disease; design details, including blinding (open, single, or double) and type of control treatment; and study duration. Methodologically invalid trials (e.g., retrospective chart audits) were not considered. The primary outcome was the percentage of opioid dose spared that was associated with ketorolac use. This was computed as the mean total amount of opioid used for the surgery for the placebo group divided by the mean total amount of opioid administered for the case in the group receiving ketorolac.

Ketorolac Decreases Opioid Requirements

Depending on the type of surgery, ketorolac had an opioid dose-sparing effect of a mean of 36% (Table 1).

Quality of Postoperative Analgesia Is Improved by Adding Ketorolac

In a second analysis, we computed the odds ratios for opioid side effects and quality of analgesia for the studies listed in Table 1.

Compiling the data for all studies provides more power than would be available from single trials. This was done to determine whether pooling data provided evidence that ketorolac use was associated with a decreased incidence of the following opioid-related outcomes: vomiting, nausea, whether an antiemetic was given, and whether urinary retention, oxygen supplementation, or pruritus occurred. Quality of analgesia was evaluated as the fraction of patients in the experimental group versus the fraction of patients in the placebo group who reported moderate to severe pain at 1 hour after surgery and moderate to severe pain 24 hours after surgery.

The odds ratio was computed from a 2×2 classification table that displays the predicted and observed classification of cases for a binary dependent variable (e.g., had moderate severe pain after surgery or not). The odds ratio distills the results of systematic reviews into one number. For example, for patients experiencing nausea after surgery, the 2×2 table appears as follows. Then, the odds ratio would equal AD/BC.

	NSAID–yes	NSAID–no
nausea–no	A	B
nausea–yes	C	D

Our analysis of the data suggests that the level of analgesia may have been better in patients receiving ketorolac (odds ratio < 0.6) in combination with opioids than with either analgesic alone, in particular 1 hour after surgery (Table 2). Seventy percent of patients in control groups experienced moderate to severe pain 1 hour postoperatively, whereas 36% of the control patients had moderate to severe pain 24 hours postoperatively.

However, we did not find a concomitant reduction in opioid side effects (e.g., nausea, vomiting). The odds ratio for vomiting, nausea, urinary reten-

Table 1 Use of ketorolac to improve analgesia and reduce opioid use in surgical patients

Reference	Ketorolac dose (mg)	Time administered	No. patients	Rescue opioid used	Procedure type	Percentage reduction versus placebo	*P*	Side effects reduced
Tarkkila [38]	IV 30	Intraoperative and postopertive	20	Oxycodone	Tonsillectomy	42%	<.05	No
Fredman [39]	IIM 60	Intraoperative	60	PCA morphine	Prostate surgery	10%	ns	No
Vanlersberghe [40]	IV 30	30 min preoperative	60	IV morphine	Minor orthopedic surgery	0%	ns	No
Parker [41]	IV 60/3	Preoperative and every 6 h postoperative	198	IV morphine IV meperidine	Abdominal hysterectomy	25% (first night only)	<.05	Less Flatus, antiemetic, sedation
Green [42]	IV 60	Intraoperative	80	Fentanyl	Diagnostic laparotomy	0	ns	Less ponv, ambulation improved
Green [42]	IV 60	Intraoperative	46	Fentanyl	Tubal ligation	10%	ns	No
Blackburn [43]	IV 120 Infustion 24 hr	Postoperative	60	Morphine	Lower abdominal surgery	22%	<.02	Less hypoxemia
Reuben [44]	IV 10	Postoperative q 6×6	70	Morphine	Lumbar fusion	33%	<.05	Yes
Etches [45]	IV 30	Postoperative and infusion	174	Morphine	Knee/hip replacement	40%	<.01	Less sedated, less antiemetic
O'Hara [46]	IV 30	Bolus infusion	191	Morphine	Major abdominal surgery	73%	<.002	Yes
Rogers [47]	IV 10	Intraoperative and postoperative	90	Diamorphine	Abdominal hysterectomy	20%	<.01	Yes
Rogers [47]	IV 10	Intraoperative and postoperative	90	Diamorphine	Abdominal hysterectomy	20%	<.01	Yes
Ding [48]	IV 60	Preoperative	136	Fentanyl	Outpatient Laparoscopy	62%	*	Yes
Ding [49]	IV 30–60	Intraoperative	109	Fentanyl	Outpatient gynecological surgery	54%	*	No

ND, no difference.
*Tests of significance were not reported for the fentanyl vs. fentanyl/ketorolac group.

tion, and pruritus ranged from 0.63 to 1, suggesting no large effect by ketorolac. This apparent lack of reduction of side effects despite opioid sparing may be due to the low overall incidence of some opioid-related side effects. For example, for patients in control groups the incidence of pruritus equaled 24% and for urinary retention 24%. Alternatively, the apparent lack of reduction of side effects despite opioid sparing may be due to the multifactorial etiology of some side effects (e.g., postoperative nausea is caused by other factors besides opioid use).

Studies are needed to document that opioid/NSAID combinations help patients reach recovery milestones in the inpatient setting and discharge criteria in the outpatient setting more quickly.

Obstetrics

The transfer of ketorolac into breast milk has been quantified and is considered to be safe for use during lactation [50,51]. Only one study investigated the effect of IV ketorolac after cesarean delivery. Advantages compared with IM administration include less discomfort and better patient acceptance. Fifty healthy parturients, status postelective cesarean delivery under combined spinal-epidural anesthesia, received either meperidine patient-controlled

Table 2 Odds ratio for opioid side effects and analgesia in patients receiving ketorolac

No. patients	Vomiting	Nausea	Moderate-severe pain 24 hr postoperatively	Moderate-severe pain 1 hr postoperatively	Antiemetic given	Urinary retention	Oxygen supplement	Pruritus
1,384	1.00	0.86	0.55*	0.34	0.56	0.72	0.51	0.63

*The odds ration of 0.55 suggests a protective effect of ketorlac, such that when being treated with opioids post-operatively, the risk of having moderate-severe pain 24 hours after surgery is almost half as likely when taking ketorolac than when not taking ketorolac.

epidural analgesia (PCEA) plus either IV ketorolac (15 mg initial dose and 105 mg IV over 24 hours) or saline. Patients receiving ketorolac had a meperidine dose-sparing effect of approximately 30% but did not exhibit significantly improved pain relief or reduced opioid-related side effects [52].

Pediatrics

There is an increasing body of published data on the use of IV ketorolac perioperatively for pediatric analgesia [53]. Pediatric clinical studies provide evidence that adding ketorolac to opioids improves quality of pain relief and reduces the incidence of opioid-related adverse effects [54]. For example, IV ketorolac, 0.9 mg/kg, given to children having strabismus surgery produced similar analgesic effects as meperidine, 0.5 mg/kg [55]. In children undergoing orthopedic surgery, concurrent administration of ketorolac with morphine using a patient-controlled analgesia (PCA) pump enhanced analgesia resulting in decreased total opioid doses [56].

In tonsillectomy patients, the frequency of postoperative hemorrhage did not differ among children receiving ketorolac versus a control group [57]. Time to discharge was shorter in ketorolac patients (8.5 hours vs. 12.5 hours, $P < .0001$), and the frequency of overnight hospital stays was lower in ketorolac patients (16.0% vs. 31.6%, respectively, $P < .01$). A separate randomized, double-blind, placebo-controlled study of 60 children admitted for tonsillectomy confirmed that ketorolac, 1 mg/kg IV, improved postoperative analgesia without evidence of increased incidence of bleeding compared with a control group [58].

The pediatric literature confirms that hemorrhagic events in the postoperative period occur. However, the association between perioperative use of NSAIDs and disordered hemostasis is inconclusive.

Analgesic Dose–Response Evidence for Ketorolac

The published studies suggest that the analgesic efficacy of ketorolac increases as the dose increases. However, increasing the IM ketorolac dose above 60 mg does not increase analgesic efficacy [59]. The challenge for the clinician is to select a ketorolac dose that balances the risk of bleeding and gastropathy with analgesic effectiveness. Because of the risk of drug-induced toxicity, patients should always be given the lowest effective ketorolac dose.

Dose-ranging efficacy studies of oral and IM ketorolac were conducted in postoperative patients [60]. This single article described multiple studies.

In the first study, adults undergoing dental extraction received ketorolac (oral doses ranging from 2.5–200 mg or IM doses ranging from 5–90 mg). Pain levels improved at 3, 5, and 6 hours after 200 mg oral doses of ketorolac, which was comparable to naproxen, 500 mg.

The second study (N = 60) documented a statistically significant improvement in pain control after a smaller dose of ketorolac (12.5 mg orally) compared with placebo. Patients in the ketorolac group also had fewer requests for rescue pain medication.

A third study compared oral ketorolac, 2.5 and 10 mg, to oral naproxen sodium, 550 mg, morphine, 10 mg IM, or placebo. One-half hour after dosing, morphine was significantly more effective than all groups. There was no statistically significant difference between the effectiveness of ketorolac, 10 mg, and morphine and naproxen sodium at 1, 2, 3, and 4 hours after dosing. Ketorolac was statistically significantly superior to morphine at 5 and 6 hours after dosing. There was no significant difference between the lower 2.5-mg ketorolac dose and placebo.

These data suggested that the onset of action of ketorolac is slower than that of morphine, the effectiveness similar, and the duration longer.

No direct comparisons were made between the 15-mg dose now recommended in ketorolac labeling and the 12.5-mg, 100-mg, and 200-mg doses used in the first two studies. The authors concluded that the upper range for the oral ketorolac dose–response curve lies between 100 and 200 mg when given orally. However, higher doses and intermediate doses were not evaluated to determine whether a true plateau is observed within this dose range [59].

Two studies compared IM ketorolac with opioids. One study compared ketorolac, 10, 30, and 90 mg, to morphine, 6 and 12 mg, for postoperative pain (N = 241). Ketorolac, 90 mg, was superior to both doses of morphine and to ketorolac, 30 mg, for overall pain relief, whereas no significant differences were demonstrated between the 10-mg and 30-mg ketorolac doses and the 12-mg morphine dose. Both doses of ketorolac were significantly more effective than the 6-mg morphine dose. The number of patients withdrawing from the trial because of inadequate pain relief in the 12-mg morphine, 10-mg ketorolac, and 30-mg ketorolac groups was similar.

The other study compared ketorolac, 5, 10, and 30 mg, and meperidine, 50 and 100 mg, for dental extraction pain (N = l54). No significant difference was reported between 10- and 30-mg ketorolac doses for overall pain relief. Both the 10- and 30-mg ketorolac doses were significantly more effective than ketorolac, 5 mg, meperidine, 50 mg, and meper-

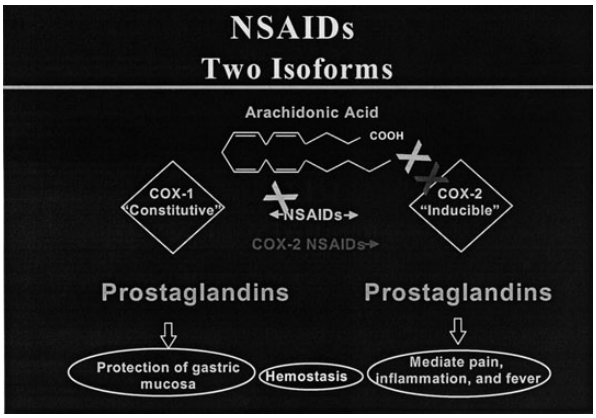

Figure 1 Differentiated arachidonic acid pathways for COX-1 and COX-2. Salicylates and all other NSAIDs are nonselective COX selective NSAIDs (i.e., those drugs inhibit both COX-1 and COX-2 to varying degrees) [117]. COX-1 is the constitutive isoform that is present in gastric mucosa, vascular endothelium, and platelets. Therefore, inhibiting COX-1 increases risk of ulceration and decreases platelet-mediated blood clotting. The analgesic and anti-inflammatory effects of ketorolac are derived from inhibition of the COX-2 isoform (inhibiting the production of prostaglandins that mediate pain and inflammation), whereas the adverse gastrointestinal and hematological effects of these agents arise from inhibition of COX-1 enzyme activity.

idine, 100 mg, for overall pain relief. No direct comparison of the relative effectiveness of 15-mg and 30-mg ketorolac doses was described.

Based on these studies, the labeling for ketorolac dosing was established as oral doses of 10 mg every 6 hours and IM doses of up to 30 mg every 6 hours. Although the ketorolac, 90-mg IM, dose was significantly more effective than the lower ketorolac doses, increased risk of gastrointestinal toxicity with multiple doses was a sufficient concern to preclude recommending the higher dose [61].

Toxicity and Side Effects of Ketorolac

The most common side effects associated with NSAIDs are gastrointestinal irritation, nausea, and impairment of platelet aggregation [62]. The risk associated with ketorolac is higher and more clinically important when ketorolac is used in higher doses, in older patients, and for more than 5 days.

Clinical Pharmacology

NSAIDs inhibit COX, the enzyme responsible for conversion of arachidonic acid to prostaglandins [63]. COX exists in two isoforms [64], now designated COX-1 and COX-2. Figure 1 illustrates the different pathways of the two isoforms.

In animal models, ketorolac has a greater analgesic/anti-inflammatory ratio than other NSAIDs. For instance, ketorolac was found to be 50 times more potent than naproxen in analgesia models but only three times more potent in inflammation models. This dissociation between analgesic and anti-inflammatory effects made the drug attractive as an analgesic in clinical settings [65].

Some clinicians have questioned whether COX-2 selective agents would be as effective as nonselective NSAIDs, but comparable efficacy of these two types of drugs has been clearly demonstrated in two large controlled studies: the CLASS and VIGOR trials [14,66].

The timing of ketorolac administration may be clinically important because onset may be delayed by 30 to 60 minutes while the opioid-sparing effect may not be apparent until 4 hours after administration. The graphic presentation of data in a randomized double-blind study of abdominal surgery patients shows a dose-related decrease in morphine requirements that became noticeable about 4 hours after initiation of the combined analgesia and continued to increase over the 24-hour period [67]. A second report supports those conclusions [68]. These findings may be explained by the pharmacokinetic behavior of ketorolac. For example, ketorolac has an intermediate half-life (5 hours) compared with diclofenac (1 hour) and piroxicam (50 hours).

Bone and Soft Tissue Healing

For surgical patients, there is a concern that ketorolac use, as with any NSAID, may adversely impact wound healing. In an animal model, large doses of ketorolac may affect the mechanical properties of the bone matrix or affect bone osteogenesis during fracture healing [69,70]. In a rat model of posterior spine fusion, indomethacin given for 12 weeks postoperatively produced a fusion rate of 10% versus 45% in controls [71]. A separate study of indomethacin and the growth of the femur in rats found no significant effect on osteoblast activity [72].

For the clinical orthopedic population, two retrospective studies specifically address the relationship between NSAIDs and rate of spinal fusion. A retrospective study found that patients who took NSAIDs for more than 3 months after posterolateral spine fusion had lower successful fusion rates (44% vs 37%) [73]. Another retrospective study found that nonunion was five times more likely in patients who had undergone posterior spinal fusion and received ketorolac postoperatively (n = 167 patients) compared with those who had not received NSAIDs postoperatively (n = 121 patients) [74].

Those studies were conducted with nonselective NSAIDs. The challenge for the clinician remains evaluating this potential healing risk in any individual patient relative to the analgesic benefit of ketorolac.

Studies of oral COX-2 selective NSAIDs and healing have been performed in animals. For example, rabbits were randomized to celecoxib (>10 mg/kg), indomethacin (>10 mg/kg), or placebo daily for 8 weeks after single-level intertransverse posterolateral fusions using autologous iliac crest. The celecoxib and control groups were similar for fusion rate and remodeling. In contrast, the indomethacin group had a higher incidence of nonunion (50%) [75].

More clinical studies are necessary to evaluate how COX-2 selective NSAIDs affect healing.

Bleeding

After introduction into general clinical use a decade ago, ketorolac has produced a higher incidence of adverse events, including bleeding, than was anticipated based on premarketing studies and the adverse event rates associated with other NSAIDs [76]. In the first 3 years after ketorolac was approved in the United States (in 1990), more than 16 million patients received the drug and 97 fatalities were reported [77]. More than half of these were associated with gastrointestinal bleeding. In fact, gastroduodenal ulcers can be demonstrated by endoscopy in 10% to 20% of patients who take NSAIDs on a regular basis, and the annual incidence of clinically important gastrointestinal complications approaches 2% [78].

The effect of ketorolac on bleeding has been studied in animal models, healthy volunteers, children undergoing surgery, and adult medical and surgical patients.

NSAIDs do not directly affect blood clotting, but they inhibit thromboxane A_2 (normally measured as thromboxane B_2 levels) and prostacyclin. Both are important for clot formation. Animals injected with ketorolac had decreased platelet aggregation (10% vs. 75% for controls) and significant prolongation of bleeding time (291 ± 5 seconds) [79].

In healthy volunteer studies, a randomized, double-blind, placebo-controlled study had 26 patients receive ketorolac IM 30 mg four times a day for 5 days, and oral placebo capsules for the last 2 days. The effects of that regimen were compared with those induced by an identical-appearing schedule of intramuscular placebo and oral aspirin, 650 mg, given to eight volunteers. Aspirin at a mean serum concentration of 84 μg/mL did not affect prothrombin time, partial thromboplastin time, platelet count, or bleeding time. Ketorolac, however, significantly prolonged bleeding time from 4.9 ± 1.1 minutes to 7.8 ± 4 minutes [80].

Single oral doses ranging from 2.5 to 200 mg taken by 40 volunteers increased bleeding time and inhibition of platelet aggregation 3 hours after administration [81]. There was no observable dose response. Twenty-four hours after the single doses were taken, bleeding time was still elevated in patients taking doses greater than 15 mg.

In 14 healthy male volunteers, ketorolac prolonged bleeding time (bleeding time did remain within the normal range in almost all patients) and inhibited platelet aggregation and platelet thromboxane production [82].

Because the half-life of ketorolac is 6 hours, platelet function returns to normal 24 to 30 hours (five half-lives) after a single dose [83]. The authors concluded that when postoperative hematoma formation is a particular concern, ketorolac probably should not be used.

Tonsillectomy is a useful model for studying the effects of drugs on bleeding because of the high vascularity of the peritonsillar tissues and the frequency of this operation in children. Both preoperative use and intraoperative use of ketorolac increases the risk of postoperative bleeding [84]. Intravenous ketorolac increased blood loss compared with rectal acetaminophen. In a comparative study of 50 tonsillectomy patients, 25% of patients who received ketorolac required additional measures to provide hemostasis versus 4% of the patients receiving acetaminophen [85]. In adult surgical patients, similar results have been documented [86]. More recently, in 1997, two postoperative hemorrhages were reported in patients who received ketorolac, 30 mg IM, after plastic surgery [87].

Although the effects of ketorolac on bleeding may be inconsistent, this effect can become more important if patients have other risk factors for bleeding. Because platelet effects of NSAIDs are COX-1 mediated, COX-2 selective NSAIDs may be safer from this perspective.

Hypertension

Over the last two decades, there has been growing interest in adverse drug interactions between NSAIDs and antihypertensive agents. For example, cases of hypertensive emergency have been reported in patients taking the NSAIDs piroxicam and indomethacin, possibly mediated by reduced synthesis of prostaglandins, in patients with previously well-controlled

hypertension [88,89]. A comprehensive literature search failed to identify published reports of this type of toxicity in surgical patients. NSAIDs also may affect sodium and water metabolism, resulting in risk of sodium retention, lower extremity edema, and exacerbation of hypertension [90,91].

Liver Failure

Hepatic toxicity has not been found to be a significant issue in surgical patients [92].

Renal Failure

The clinical consequences of NSAIDs on renal function are heterogeneous, and whether there are clinically important differences between nonselective and COX-2 selective NSAIDs on human renal function is not yet well defined [93]. Acute renal failure is mostly a concern for elderly patients with congestive heart failure, hepatic cirrhosis, hypovolemia, or an underlying renal disorder [94]. Unlike bleeding disorders, however, these reactions may occur at low doses.

Acute renal failure has been reported after ketorolac administration, but this toxicity usually reverses after discontinuation of the drug [95–97]. However, the pharmacological effects of prostaglandins on renal function suggests that this is a dose-related phenomenon. Relative risk for acute renal failure with ketorolac when administered for more than 5 days was 2.08 (confidence interval [CI]: 1.08–4.00; $P = .03$) compared with opioids [97]. Ketorolac administered for 5 days or less did not increase the rate of renal failure.

Meta-analyses can be useful as the primary data in safety evaluations [98]. An electronic meta-analysis search yielded eight randomized and quasirandomized controlled trials [99]. This work showed that, as a group, NSAIDs reduced creatinine clearance by 18 mL/min (95% CI: 6–31) and potassium output by 38 mmol/day (95% CI: 19–56) on the first day after surgery compared with placebo. There was no significant difference in serum creatinine in the early postoperative period between patients receiving ketorolac and diclofenac in one trial. No cases of postoperative renal failure requiring dialysis were described. The authors concluded that NSAIDs caused a clinically unimportant transient reduction in renal function in the early postoperative period and suggested that NSAIDs should not be withheld from adults with normal preoperative renal function because of concerns about postoperative renal impairment.

Another study supported these conclusions because it found no significant changes in urine oxygen tension, erythropoietin, β_2-microglobulin, serum creatinine, urea, or urine output in women receiving 30 mg of ketorolac IM for breast surgery compared with a control group [100].

We reexamined the studies listed in Table 1 to quantify the occurrence of adverse drug events (ADEs) in patients receiving ketorolac. These data are summarized in Table 3.

Many of the toxic indices (i.e., ADEs) were not reported in most studies. This may be due to the

Table 3 Studies often do not report on toxicity

Reference	No. patients	Postoperative blood loss	Need for transfusion	Hemoglobin drop	Creatinine	Blood urea nitrogen	Protein drop below normal range
Tarkkila [38]	20	2 in placebo* 1 in ketorolac	NR	NR	NR	NR	NR
Fredman [39]	60	NR	NR	NR	NR	NR	NR
Vanlersberghe [40]	60	NR	NR	NR	NR	NR	NR
Parker [41]	198	NR	NR	ND	ND	NR	NR
Green [42]	80	NR	NR	NR	NR	NR	NR
Green [42]	46	NR	NR	NR	NR	NR	NR
Blackburn [43]	60	NR	NR	1 with placebo† 4 with ketorolac	ND	ND	16 with placebo 22 with ketorolac
Reuben [44]	70	NR	NR	NR	NR	NR	NR
Etches [45]	174	ND	ND	NR	NR	NR	NR
O'Hara [46]	191	NR	NR	ND	NR	NR	NR
Rogers [47]	90	‡Greater in ketorolac group	NR	NR	NR	NR	NR
Ding [48]	136	NR	NR	NR	NR	NR	NR

NR = not reported; ND = no difference.
*Three patients (two in the placebo group, one in the ketorolac group) were withdrawn because of postoperative bleeding requiring reoperation.
†Hemoglobin decreased below 100 g/L in four patients in the ketorolac group and one patient in the placebo group.
‡The proportion of patients with blood loss more than 600 mL was greater in the group given ketorolac preoperatively.

lower doses used in the studies, resulting from updated recommendations and indications as described in the next section. An alternative explanation for the absence of reported ADEs may be that the sample sizes for any one study are too small to detect rare adverse events.

Another possible explanation may be inadequate reporting. To scrutinize the completeness of reporting of specific adverse effects and frequency and reasons for withdrawals as a result of toxic effects, 192 randomized drug trials in seven diverse topics with sample sizes of at least 100 patients and at least 50 patients in a study arm (N = 130,074 patients) were studied [101]. That study found that, in general, severity of clinical adverse effects and laboratory-determined toxicity was adequately defined in only 39% and 29% of trial reports, respectively. Only 46% of trials stated the frequency of specific reasons for discontinuation of study treatment because of toxicity.

There are limitations to analysis of pooled controlled trials. Although such studies may produce useful insights about toxicities, assemblages of randomized trials are at risk of biased selection because of publication bias. Also, not all studies follow standards of reporting to allow proper evaluation of the quality and completeness of analyses of multiple studies [102].

Regulatory Issues

FDA regulations already require overviews of data on safety and effectiveness in marketing applications [103]. However, Phase III clinical (premarketing) trials frequently do not have sufficient power to reliably detect important ADEs [104], and adequate postmarketing surveillance may not be conducted to detect ADEs after the introduction of the drug into general clinical practice [105].

Approval of a new drug does not exclude the possibility of serious ADEs. In recent years, three oral NSAIDs that were fully approved and marketed were subsequently withdrawn form the market because of serious, potentially fatal, ADEs: zomepirac, suprofen, and most recently bromfenac. To determine drug safety after introduction into general clinical practice release of any drug, including ketorolac, the FDA evaluates information from multiple sources, including postmarketing surveillance, observational studies, and case reports.

In general, adverse drug reactions can be divided into two categories: events that otherwise occur rarely in the population and events that represent an increased frequency over a relatively common rate in the general population. These two categories of ADEs may be further subdivided by the length of time after administration that detrimental outcomes occur.

Spontaneous Reporting

When an adverse event is rare and its rate is increased by use of a drug, spontaneous reporting is generally necessary to detect the existence of a problem. Spontaneous reporting systems (e.g. MEDWATCH; website: http://www.fda.gov/medwatch/) can be effective in revealing unusual or rare adverse events and may be sufficient to establish a hypothesis of causality. Reporting is easiest when the event is typical of drug reactions and when it occurs soon after the drug use. However, ADEs that occur after discharge from hospital may be missed. For spontaneous reporting to be effective, health professionals must become aware of the event, recognize it as an adverse drug effect, identify the possible/probable cause of the effect, and report it.

Serious adverse events are those that lead to death, hospitalization, significant or permanent disability, or congenital anomaly or that require medical or surgical intervention [106]. Serious adverse drug events are underreported by physicians, pharmacists, and nurses to both pharmaceutical manufacturers and the FDA [107]. By 1993, after 41 million uses of ketorolac, gastrointestinal, hematological (e.g., operative site bleeding), and renal ADEs included 143 deaths. However, these spontaneous reports would not have been expected to detect ADEs that occurred long after ketorolac was first used [108] nor to determine that the ADE occurred primarily only after prolonged exposure (more than 5 days in the case of ketorolac). Spontaneous reports were the first pieces of evidence in changing how ketorolac was perceived and used.

Epidemiological Studies in Postmarketing Surveillance

Spontaneous reports triggered interest in establishing epidemiological studies to define the increase in risk of ADEs in persons receiving the drug. Data from computerized databases of medication users and nonusers were analyzed.

A retrospective closed cohort study of ketorolac conducted in 35 U.S. hospitals compared 10,272 courses of parenteral ketorolac therapy with matched patients who received 10,247 courses of a parenteral opioid analgesia [84]. The authors determined the odds ratio for clinically serious gastrointestinal bleeding to be 1.30 (1.11–1.52). The highest risk was for patients older than 75 years (odds ratio 1.66), those receiving daily doses greater than 120 mg (odds

ratio 7.34), and those with more than 5 days of treatment (odds ratio 2.20).

A dose–response relationship was evident between daily ketorolac dosing and the risk of gastrointestinal or operative site bleeds ($P > .001$, trend test). On the basis of this study, in 1997 the sole American manufacturer of ketorolac at that time, Roche Laboratories, made alterations to the package labeling for Toradol to reflect more stringent guidelines for doses, duration, and age-based dosing [109].

To further define the impact of ketorolac on gastroduodenal lesions, 600 outpatients with ulcer or erosion were matched with 6,000 community controls [110]. Among NSAIDs, ketorolac was the only drug that showed a distinctly elevated risk of gastroduodenal lesions (odds ratio 4.2). The increase in risk associated with ketorolac was more dramatic for ulcers (odds ratio 10.5) than for erosions. In most cases, ketorolac was administered for 6 days or less.

Another study of 1,505 patients hospitalized because of upper gastrointestinal bleeding matched to 20,000 controls found a relative risk for gastrointestinal tract bleeding and perforation in NSAID users compared with nonusers of 4.4 [111]. Ketorolac was found to have the highest risk (relative risk 24.7); it was five times more gastrotoxic than all other NSAIDs (relative risk 5.5). Ketorolac risk remained high at lower doses (i.e., 20 mg or less). The risk of hospitalization for gastroduodenal ulcer associated with the use of ketorolac and other NSAIDs was further examined [112]. In patients who had received at least one NSAID prescription, the highest rate of lesions for current NSAID use was observed for piroxicam (relative risk 4.6) and ketorolac (relative risk 3.4).

More recently, information from a database of 200 hospitals and 1.5 million discharges in 1998 showed that surgical patients receiving parenteral ketorolac had total hospital costs more than 20% higher than patients not receiving ketorolac despite equivalent length of stay [113]. Additional analysis of these data is necessary to determine whether there is a causal relationship.

Changes in Recommended Use of Ketorolac

Epidemiological studies and spontaneous reports provide a scientific foundation for regulatory actions. In Europe, the Committee for Proprietary Medicinal Products (CPMP), the scientific body of the European Medicines Evaluation Agency, reevaluated indications for ketorolac use. The manufacturer ceased supplying the drug in Germany in 1993, and the license to market ketorolac was suspended in France [114]. Other European countries had varying degrees of restrictions [115].

Recommendations on the use of ketorolac were changed to emphasize contraindications, restrict the indication to short-term management of postoperative pain, and include restrictions on dose and duration of treatment. The recommended starting dose for parenteral (both IM and IV) administration was reduced to 10 mg, and the maximum daily dose was reduced to 90 mg for nonelderly patients and 60 mg for elderly patients. The duration of treatment for parenteral ketorolac was reduced to 2 days.

In the United States, the maximum aggregate duration for parenteral and oral ketorolac use was reduced to not more than 5 days in the FDA-approved labeling that became effective in 1995 (see Appendix). Current parenteral dosing recommendations require consideration of the patient's age, renal function, and weight [116].

For adults younger than 65 years and weighing more than 50 kg with normal renal function, single IM doses of 60 mg may be given. Repeated IM or IV doses should not exceed 30 mg every 6 hours for a total not to exceed 120 mg daily. For patients older than 65 years who weigh less than 50 kg or who have moderate renal impairment, the approved dose is one half the listed amounts.

The labeling reflects the fact that oral ketorolac should be reserved for continuation of parenteral therapy once the patient is able to take medications orally. The initial oral dose is two tablets (20 mg) for a patient previously receiving 60 mg parenterally, followed by 10 mg every 4 to 6 hours not to exceed 40 mg per day. The dose should be limited to 10 mg for patients who are older than 65 years or who have impaired renal function. With the maximum recommended daily dose remaining at 40 mg, it is noteworthy that the labeling recommends changing to a different analgesic if therapy is required for more than 5 days.

Because of the high association with adverse events, ketorolac is contraindicated in patients with a history of peptic ulcer disease or a current gastrointestinal bleed. It also is labeled as contraindicated for patients with significant renal impairment and those at risk of renal failure because of volume depletion. Patient factors that increase risk of hemorrhage also are listed as contraindications. These include intraoperative use, cerebrovascular bleeding, coagulation disorder, and concurrent use of other NSAIDs. Patients with contraindications to other NSAIDs may have an increased incidence of

ADEs, most notably renal failure and gastrointestinal hemorrhage, with ketorolac.

Current dosing recommendations are based on data from both Phase 3 (premarketing) clinical trials and postmarketing surveillance and trials. Because of clinically important ADEs and the revised labeling for the drug, ketorolac is often used at an initial parenteral dose of 30 mg followed by doses of 15 mg today.

Conclusions

There is a need to improve postoperative analgesia. NSAIDs for acute postoperative pain relief can be part of an effective multimodal protocol that includes patient education (e.g., instructing the patient to take pain medication as soon as discomfort occurs).

For ketorolac, a dose–response effect exists with single doses up to 90 mg IM and 100 to 200 mg orally. Parenteral ketorolac doses of 10 to 30 mg are comparable to 10 to 12 mg parenteral morphine in single-dose trials. However, risks of gastrointestinal bleeding, platelet inhibition, and renal impairment limit the routine use of ketorolac in surgical patients. The published literature suggests that the risk for adverse events increases with high doses, with prolonged therapy (>5 days), or in vulnerable patients (e.g., the elderly).

The incidence of serious adverse events has declined since dosage guidelines were revised, but adverse drug-related events still do occur.* New injectable COX-2 selective NSAIDs may change the clinical relevance of ketorolac.

If the use of ketorolac is considered, careful patient selection is essential. Contraindications to ketorolac use include a history or current risk of gastrointestinal bleeding, risk of renal failure, compromised hemostasis, hypersensitivity to aspirin or other NSAIDs, labor, delivery, and nursing. Ketorolac should be prescribed at the lowest dose necessary to control pain, and the duration of therapy should be limited to as few days as possible.

New analgesics that provide effective pain relief with minimal potential for adverse effects are needed.

References

1 Macario A, Weinger M, Truong P, Lee M. Which clinical anesthesia outcomes are both common and important to avoid? The perspective of a panel of expert anesthesiologists. Anesth Analg 1999;88:1085–91.

2 Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. Anesth Analg 1999; 89:652–8.

3 Apfelbaum J, Gan TJ, Chen C. Patient perception of post-operative pain experience after outpatient surgery: Patient survey. Anesthesiology 2000;A1.

4 Beauregard L, Pomp A, Choiniere M. Severity and impact of pain after day surgery. Can J Anaesth 1998;45:304–311.

5 Chung F, Ritchie E, Su J. Postoperative pain in ambulatory surgery. Anesth Analg 1997;85:808–16.

6 Abbott F, Gray-Donald K, Sewitch M, et al. The prevalence of pain in hospitalized patients and resolution over six months. Pain 1992;50:15.

7 Phillips DM. JCAHO pain management standards are unveiled. JAMA 2000;284:428–9.

8 Moore JD. An issue of "quality": Hospitals will soon have to meet new pain-management standards set by JCAHO. Modern Healthcare 2000, May 29:14–5.

9 Joint Commission on Accreditation of Healthcare Organizations. http://www.jcaho.org. Retrieved November 20, 2000.

10 National Report: Anesthesia Under Examination. London, England: Royal College;1998.

11 Fuchs V, Sox H. Physician's views of the relative importance of thirty medical innovations. Health Affairs 2001;20:30–42.

12 Acute Pain Management Guideline Panel. Acute Pain Management: Operative or Medical Procedures and Trauma; Clinical Practice Guideline (AHCPR Publication Number 92-0032). Rockville MD: Agency for Health Care Policy and Research, U.S. Department of Health and Human Services, Public Health Service; 1992.

13 Choo V, Lewis S. Ketorolac doses reduced. Lancet 1993;342:109.

14 Silverstien 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 randomized controlled trial. JAMA 2000;284:1247–55.

15 Reuben SS, Connelly NR. Postoperative analgesic effects of celecoxib or rofecoxib after spinal fusion surgery. Anesth Analg 2000;91:1221–5.

16 Huang JJ, Taguchi A, Hsu H, Andriole GL, Kurz A. Preoperative oral rofecoxib does not decrease postoperative pain or morphine consumption in patients after radical prostatectomy: A prospective, randomized, double-blinded, placebo-controlled trial. J Clin Anesth 2001;13:2:94–7.

17 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.

*Practitioners should be familiar with label warnings that recommend ketorolac therapy for no more than 5 days regardless of the route of administration.

18 Daniels SE, Grossman EH, Kuss ME, Talwalker S, Hubbard R. A double-blind, randomized 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.
19 Mehlisch D, Kuss M, Baumann A, Baum D, Hubbard R. Onset and duration of analgesia of single IM doses of parecoxib and Toradol in postoperative pain. Abstract presented at the IASP 9th World Congress on Pain, Vienna, 1999.
20 Daniels S, Kuss M, Mehlissch DR, et al. Pharmacokinetic and efficacy evaluation of IV parecoxib in a postsurgical dental pain model. Abstract presented at the American Society for Clinical Pharmacology and Therapeutics, 2000.
21 Hubbard R, Kuss M, LeComte D, Talwalker S, Geis GS. An endoscopic study of the gastroduodenal effects of parecoxib sodium and injectable COX-2 specific inhibitor in the elderly. Gastroenterology 2000;118(suppl 2):A250.
22 Karim A, Aziz L, Kuss M, Hubbard R, Qian J. Single dose tolerability and pharmacokinetics of parecoxib sodium, a COX-2 specific inhibitor following IM administration. Abstract presented at the meeting of the ASA, 2000.
23 Perez-Urizar J, Granados-Soto V, Castaneda-Hernandez G, et al. Analgesic efficacy and bioavailability of ketorolac in postoperative pain: a probability analysis. Arch Med Res 2000;31:191–6.
24 O'Hara D, Fragen R, Kinzer M, Pemberton D. Ketorolac tromethamine as compared with morphine sulfate for treatment of postoperative pain. Clin Pharmacol Ther 1987;41:556–61.
25 Varrassi G, Marinangeli F, Agro F, et al. A double-blinded evaluation of propacetamol versus ketorolac in combination with patient-controlled analgesia morphine: Analgesic efficacy and tolerability after gynecologic surgery. Anesth Analg 1999;88:611–6.
26 Zhou TJ, Tang J, White PF. Propacetamol versus ketorolac for treatment of acute postoperative pain after total hip or knee replacement. Anesth Analg 2001;92:1569–75.
27 Yee J, Koshiver J, Allbon C, Brown C. Comparison of intramuscular ketorolac tromethamine and morphine sulfate for analgesia of pain after major surgery. Pharmacotherapy 1986;6:253–61.
28 Jarde O, Boccard E. Parenteral versus oral route increases paracetamol efficacy. Clin Drug Invest 1997;14:474–81.
29 Gillis JC, Brogden RN. Ketorolac: A reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. Drugs 1997;53:139–88.
30 Acute Pain Management Guideline Panel. Acute Pain Management: Operative or Medical Procedures and Trauma. Clinical Practice Guideline. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services; 1992.
31 Wittels B, Faure EA, Chavez R, et al. Effective analgesia after bilateral tubal ligation. Anesth Analg 1998;87:619–23.
32 Bosek V, Miguel R. Comparison of morphine and ketorolac for intravenous patient-controlled analgesia in postoperative cancer patients. Clin J Pain 1994;10:314–8.
33 Mulrow CD, Cook DJ, eds. Systematic Reviews: Synthesis of Best Evidence for Health Care Decisions. Philadelphia: American College of Physicians; 1998.
34 Cook DJ, Sackett DL, Spitzer WO. Methodological guidelines for systematic reviews of randomized control trials in healthcare from the Potsdam consultation on meta-analysis. J Clin Epidemiol 1995;48:167–71.
35 Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. JAMA 2000;283:2008–12.
36 O'Hara DA, Fragen RJ, Kinzer M, Pemberton D. Ketorolac tromethamine as compared with morphine sulfate for treatment of postoperative pain. Clin Pharmacol Ther 1987;41:556–61.
37 DeAndrade J, Maslanka M, Reines H, et al. Ketorolac versus meperidine for pain relief after orthopaedic. Clin Orthop 1996;325:301–12.
38 Tarkkila P, Saarnivaara L. Ketoprofen, diclofenac or ketorolac for pain after tonsillectomy in adults? Br J Anaesth 1999;82:56–60.
39 Fredman B, Olsfanger D, Flor P, Jedeikin R. Ketorolac does not decrease postoperative pain in elderly men after transvesical prostatectomy. Canadian Journal of Anaesthesia 1996;43:438–41.
40 Vanlersberghe C, Lauwers MH, Camu F. Preoperative ketorolac administration has no preemptive analgesic effect for minor orthopaedic surgery. Acta Anaesthesiologica Scandinavica 1996; 40:948–52.
41 Parker RK, Holtmann B, Smith I, White P. Use of ketorolac after lower abdominal surgery. Effect on analgesic requirement and surgical outcome. Anesthesiology 1994;80:6–12.
42 Green CR, Pandit SK, Levy L, Kothary SP, Tait AR, Schork M. Intraoperative ketorolac has an opioid-sparing effect in women after diagnostic laparoscopy but not after laparoscopic tubal ligation. Anesth Analg 1996;82:732–7.
43 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.
44 Reuben SS, Connelly NR, Lurie S, Klatt M, Gibson C. Dose-response of ketorolac as an adjunct to patient-controlled analgesia morphine in patients after spinal fusion surgery. Anesth Analg 1998;87:98–102.

45 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.
46 O'Hara DA, Fanciullo G, Hubbard L, Maneatis T, Seuffert P, Bynum L, Shefrin A. Evaluation of the safety and efficacy of ketorolac versus morphine by patient-controlled analgesia for postoperative pain. Pharmacotherapy 1997;17:891–9.
47 Rogers JE, Fleming BG, Macintosh KC, Johnston B, Morgan-Hughes J. Effect of timing of ketorolac administration on patient-controlled opioid use. BJA 1995;75:15–8.
48 Ding Y, White PF. Comparative effects of ketorolac, dezocine, and fentanyl as adjuvants during outpatient anesthesia. Anesth Analg 1992;75:566–71.
49 Ding Y, Fredman B, White PF. Use of ketorolac and fentanyl during outpatient gynecologic surgery. Anesth Analg 1993;77:205–10.
50 Rathmell JP, Viscomi CM, Ashburn MA. Management of nonobstetric pain during pregnancy and lactation. Anesth Analg 1997;85:1074–87.
51 Wischnik A, Manth SM, Lloyd J, et al. The excretion of ketorolac tromethamine into breast milk after multiple oral dosing. Eur J Clin Pharmacol 1989;36:521–4.
52 Pavy T, Michael J. Paech MJ, Sharon F, Evans SF. The effect of intravenous ketorolac on opioid requirement and pain after cesarean delivery. Anesth Analg 2001;92:1010–4.
53 Romsing J, Wakther-Larsen S. Peri-operative use of nonsteroidal anti-inflammatory drugs in children: Analgesic efficacy and bleeding. Anaesthesia 1997;52:673–83.
54 Forrest JB; Heitlinger EL, Revell S. Ketorolac for postoperative pain management in children. Drug Safety 1997;16:309–29.
55 Shende D, Das K. Comparative effects of intravenous ketorolac and pethidine on perioperative analgesia and postoperative nausea and vomiting (PONV) for paediatric strabismus surgery. Acta Anaesthesiol Scand 1999;43:265–9.
56 Sutters KA, Shaw BA, Gerardi JA, Hebert D. Comparison of morphine patient-controlled analgesia with and without ketorolac for postoperative analgesia in pediatric orthopedic surgery. Am J Orthop 1999;28:351–8.
57 Agrawal A, Gerson CR, Seligman I, Dsida RM. Postoperative hemorrhage after tonsillectomy: Use of ketorolac tromethamine. Otolaryngol Head Neck Surg 1999;120:335–9.
58 Romsing J, Ostergaard D, Walther-Larsen S, Valentin N. Analgesic efficacy and safety of preoperative versus postoperative ketorolac in paediatric tonsillectomy. Acta Anaesthesiol Scand 1998;42: 770–5.
59 Gillis JC, Brogden RN. Ketorolac: A reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. Drugs 1997;53:139–88.
60 Brown CR, Moodie JE, Dickie G, et al. Analgesic efficacy and safety of single-dose oral and intramuscular ketorolac for postoperative pain. Pharmacotherapy 1990;10:59S–70S.
61 Tong D, Chung F. Post-operative pain control in ambulatory surgery. Surg Clin North Am 1999; 79:401–30.
62 Niemi TT, Taxell C, Rosenberg PH. Comparison of the effect of intravenous ketoprofen, ketorolac, and diclofenac on platelet function in volunteers. Acta Anesthesiol Scand 1997;41:1353–58.
63 Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for the aspirin-like drugs. Nat New Biol 1971;231:235–9.
64 Crofford LJ, Lipsky PE, Brooks P, Abramson SB, et al. Basic biology and clinical application of specific cyclooxygenase-2 inhibitors. Arthritis Rheum 2000;43:4–13.
65 Spickler W. Ketorolac (Toradol): A new analgesic or an old NSAID? Can Med Assoc J 1993;148: 1693–5.
66 Bombadier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343:1520–8.
67 Gillies GWA, Kenny GNC, Bullingham RES, McCardle CS. The morphine sparing effect of ketorolac tromethamine. Anaesthesia 1987;42: 727–31.
68 Kenny NC, McArdie CS, Aitken HH. Parenteral ketorolac: opiate-sparing effect and lack of cardiovascular depression in the perioperative patient. Pharmacotherapy 1990:10;127S–31S.
69 Ho ML, Chang JK, Wang GJ. Antiinflammatory drug effects on bone repair and remodeling in rabbits. Clin Orthop 1995;313:270–8.
70 Allen HL, Wase A, Bear WT. Indomethacin and aspirin: Effect of nonsteroidal antiinflammatory agents on the rate of fracture repair in the rat. Acta Orthop Scand 1980;51:595–600.
71 Dimar JR II, Ante WA, Zhang YP, Glassman SD. The effects of nonsteroidal anti-inflammatory drugs on posterior spinal fusions in the rat. Spine 1996; 21:1870–6.
72 Sudman E, Tveital T, Hald J. Lack of effect of indomethacin on growth of the femur in rats. Acta Orthop Scand 1982;53:43–9.
73 Deguchi M, Rapoff AJ, Zdeblick TA. Posterolateral fusion for isthmic spondylolisthesis in adults: A study of fusion rate and clinical results. J Spinal Disord 1998;11:459–64.
74 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.
75 Lewis SJ, Long J, Kuklo TR, Riew KD. The effect

of COX-2 inhibitors on spinal fusion. Proceedings from the 15th Annual Meeting of the North American Spine Society, October 26, 2000:64–5.
76 Anomymous. New ketorolac dosage recommendations. Pharm J 1993;251:49.
77 Reinhart DJ. Minimizing the adverse effects of ketorolac. Drug Safety 2000;22:487–97.
78 Wolfe M, Lichtenstein D, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med 1999;340:1888–99.
79 Buckle RC, Davidson SF, Das SK. Effects of ketorolac tromethamine (Toradol) on a functional model of microvascular thrombosis. Br J Plast Surg 1993;46:296–9.
80 Conrad KA, Fagan TC, Mackie MJ, Mayshar PV. Effects of ketorolac tromethamine on hemostasis in volunteers. Clin Pharmacol Ther 1988;43:582–6.
81 Roe RL, Bruno JJ, Ellis DJ. Effects of a new nonsteroidal anti-inflammatory agent on platelet function in male and female subjects (abstract). Thromb Haemost 1981;46:412.
82 Greer IA. Effects of ketorolac tromethamine on hemostasis. Pharmacotherapy 1990;10:71S–6S.
83 Williams RL, Upton RA. The clinical pharmacology of ketoprofen. J Clin Pharmacol 1988;28:S13–22.
84 Strom BL, Berlin JA, Kinman JL, et al. Parenteral ketorolac and risk of gastrointestinal and operative site bleeding. A postmarketing surveillance study. JAMA 1996;275:376–82.
85 Rusy IM, Houek CS, Sullivan LJ, et al. A double-blind evaluation of ketorolac tromethamine versus acetaminophen in pediatric tonsillectomy and adenoidectomy. Anesth Analg 1995;80:226–9.
86 Pallapies D, Peskar BA, Brune K, et al. Effects on platelet function and pharmacokinetics of azapropazone and ketorolac tromethamine given as single parenteral doses. Br J Clin Pharmacol 1994: 37;335–9.
87 Marin-Bertolin S, De Andres J, Gonzalez-Martinez R, et al. A controlled, randomized, double-blind study of ketorolac for postoperative analgesia after plastic surgery. Ann Plast Surg 1997;38: 478–84.
88 Oates JA. Antagonism of antihypertensive drug therapy by nonsteroidal anti-inflammatory drugs. Hypertension 1988;11:2S–4S.
89 Mousavy SM. Indomethacin induces hypertensive crisis in pre-eclampsia irrespective of prior anti-hypertensive drug therapy. Am J Obstet Gynecol 1991;165:1577.
90 Merck & Company. VIOXX package insert. West Point PA: Merck & Co; 1998.
91 G. D. Searle and Company. Celebrex package insert. Chicago: G.D. Searle and Co; 1999.
92 Hennessy S, Kinman JL, Berlin JA, et al. Lack of hepatotoxic effects of parenteral ketorolac in the hospital setting. Arch Intern Med 1997;157:2510–4.
93 Swan SK, Rudy DW, Lasseter KC, et al. Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet. Ann Intern Med 2000;133:1–9.
94 Camu F, Lauwers MH, Vanlersberghe C. Side effects of NSAIDs and dosing recommendations for ketorolac. Acta Anaesthesiol Belg 1996;47:143–9.
95 Buck ML, Norwood VF. Ketorolac-induced acute renal failure in a previously healthy adolescent. Pediatrics 1996;98:294–6.
96 Buller GK, Perazella MA. Acute renal failure and ketorolac. Ann Intern Med 1997;127:493–4.
97 Feldman HI, Kinman JL, Berlin JA, et al. Parenteral ketorolac: The risk for acute renal failure. Ann Intern Med 1997;126:193–9.
98 Temple R. The regulatory evolution of the integrated safety summary. Drug Inf J 1992;25:485–92.
99 Lee A, Cooper MG, Craig JC, Knight JF, Keneally JP. Cochrane. Effects of nonsteroidal anti-inflammatory drugs on post-operative renal function in adults (Cochrane Review). Database Syst Rev 2000;4:CD002765.
100 Laisalmi M, Eriksson H, Koivusalo A, et al. Ketorolac is not nephrotoxic in connection with sevoflurane anesthesia in patients undergoing breast surgery. Anesth Analg 2001;92:1058–63.
101 Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: An evaluation of 7 medical areas. JAMA 2001;285:437–43.
102 Berlin JA, Colditz GA. The role of meta-analysis in the regulatory process for foods, drugs, and devices. JAMA 1999;281:830–4.
103 Center for Drug Evaluation and Research. Guideline for the Format and Content of the Clinical and Statistical Sections of an Application. Rockville, MD: Food and Drug Administration, U.S. Department of Health and Human Services; 1998.
104 Anello C, O'Neill RT. Does research synthesis have a place in drug regulatory policy? Synopsis of issues: Assessment of safety and postmarketing surveillance. Clin Res Reg Aff 1996;13:13–21.
105 Sills JIM, Tanner A, Milstein JB. Food and Drug Administration monitoring of adverse drug reactions. Am J Hosp Pharm 1986;43:2764–70.
106 Kessler DA. Introducing MEDWATCH: A new approach to reporting medication and device adverse effects and product problems. JAMA 1993;269:2765–8.
107 Scott HD, Thacher-Renshaw A, Rosenbaum SE, et al. Physician reporting of adverse drug reactions: Results of the Rhode Island adverse drug reaction reporting project. JAMA 1990;263:1785–8.
108 Brewer T, Colditz GA. Postmarketing surveillance and adverse drug reactions: Current perspectives and future needs. JAMA 1999;281:824–9.
109 Song K, Roche Laboratories. Personal communication, September 19, 2000.
110 Traversa G, Walker AM, Ippolito FM, et al. Gastroduodenal toxicity of different nonsteroidal antiinflammatory drugs. Epidemiology 1995;6:49–54.
111 Garcia Rodriguez LA, Cattaruzzi C, Troncon MG, Agostinis L. Risk of hospitalization for upper gas-

trointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. Arch Intern Med 1998;158:33–9.
112 Menniti-Ippolito F, Maggini M, Raschetti R, Da Cas R, Traversa G, Walker AM. Ketorolac use in outpatients and gastrointestinal hospitalization: A comparison with other non-steroidal anti-inflammatory drugs in Italy. Eur J Clin Pharmacol 1998;54:393–7.
113 Chen C, Dedhiya S, Morton D, Wester LM. Characteristics of parenteral ketorolac in the surgical population. Abstract presented at the meeting of the American Pain Society, 2000.
114 Lewis S. Ketorolac in Europe. Lancet 1994;343:784.
115 De Abajo FJ. Ketorolac and gastrointestinal toxicity. A perspective from 1998. http://www.hsph.harvard.edu/organizations/ddil/ketorolac.html. Retrieved September 1, 2000.
116 Roche Laboratories. Toradol (ketorolac tromethamine injection) and Toradol (ketorolac tromethamine tablets) package labeling. Nutley, NJ: Roche Laboratories; 1997.
117 Gierse JK, Hauser SD, Creely DP, et al. Expression and selective inhibition of the constitutive and inducible forms of human cyclooxygenase. Biochem J 1995;305:479–84.

APPENDIX

Warning

Toradol, an NSAID, is indicated for the short-term (up to 5 days) management of moderately severe, acute pain that requires analgesia at the opioid level. It is not indicated for minor or chronic painful conditions. Toradol is a potent NSAID analgesic, and its administration carries many risks. The resulting NSAID-related adverse events can be serious in certain patients for whom Toradol is indicated, especially when the drug is used inappropriately. Increasing the dose Toradol beyond the label recommendations will not provide better efficacy but will result in increasing the risk of developing serious adverse events.

Gastrointestinal Effects

Toradol can cause peptic ulcers, gastrointestinal bleeding, and perforation. Therefore, Toradol is contraindicated in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation, and in patients with a history of peptic ulcer disease or gastrointestinal bleeding.

Renal Effects

Toradol is contraindicated in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion (see Warnings).

Risk of Bleeding

- Toradol inhibits platelet function and is, therefore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diatheses, patients with incomplete hemostasis, and those at high risk of bleeding (see Warnings and Precautions).
- Toradol is contraindicated as prophylactic analgesic before any major surgery and is contraindicated intraoperatively when hemostasis is critical because of the increased risk of bleeding.

Hypersensitivity

Hypersensitivity reactions, ranging from bronchospasm to anaphylactic shock have occurred, and appropriate counteractive measures must be available when administering the first dose of Toradol IV/IM (see Contraindications and Warnings). Toradol is contraindicated in patients with previously demonstrated hypersensitivity to Toradol or allergic manifestations to aspirin or other NSAIDs.

Concomitant Use With NSAIDs

Toradol is contraindicated in patients currently receiving acetylsalicylic acid or NSAIDs because of the cumulative risk of inducing serious NSAID-related side effects.

Dosage and Administration

Toradol^{ORAL}

- Toradol^{ORAL} is indicated only as continuation therapy to Toradol IV/IM, and the combined duration of use of Toradol IV/IM and Toradol^{ORAL} is not to exceed 5 days because of the increased risk of serious adverse events.
- The recommended total daily dose of Toradol^{ORAL} (maximum 40 mg) is significantly lower than for Toradol IV/IM (maximum 120 mg) (see Dosage and Administration and Transition from Toradol IV/IM to Toradol^{ORAL}).

SPECIAL POPULATIONS

- Dosage should be adjusted for patients 65 years or older, for patients weighing less than 50 kg (110 lb) of body weight (see Dosage and Administration) and for patients with moderately elevated serum creatinine (see Warnings). Doses of Toradol IV/IM are not to exceed 60 mg (total dose per day) in these patients.