Review

THE USE OF KETOROLAC IN THE MANAGEMENT OF POSTOPERATIVE PAIN

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ABSTRACT

Ketorolac tromethamine (Toradol) is a nonsteroidal antiinflammatory drug (NSAID) available in intramuscular (IM) and oral formulations for the management of acute pain. Intramuscular ketorolac is the only parenteral NSAID available for analgesic use in the US. The clinical profile is reviewed, and clinical studies most applicable to a postoperative patient are discussed in detail. The results of a clinical study performed at Emory University School of Medicine are presented. In this single-dose study, 176 patients received either 10 mg of oral ketorolac, 5 mg or 10 mg of IM morphine, or placebo after orthopedic surgery. The analgesic efficacy of ketorolac was comparable to both doses of morphine and significantly superior to placebo. Ketorolac, when administered intramuscularly or orally, is a safe and effective analgesic agent for the short-term management of acute postoperative pain and can be used as an alternative to opioid therapy.

Ketorolac tromethamine (Toradol) is a nonsteroidal antiinflammatory (NSAID) drug which is available in the United States for both intramuscular (IM) and oral use for the treatment of acute pain. The IM formulation is the only parenteral NSAID available in the US for analgesic use. Opioid analgesics are commonly used to treat postoperative pain, as well as a variety of other acute pain states, even though they may be associated with undesirable side effects such as respiratory depression and somnolence. IM ketorolac, which acts peripherally, can be used as an alternative to parenteral opioid analgesics, which act centrally, for the relief of moderate to severe pain. IM ketorolac is associated with a lower incidence of side effects typically seen with opioids. In several published, randomized, double-blind, single and multi-dose trials, IM ketorolac has been compared to morphine and other opioid analgesics. Intramuscular ketorolac has been shown to be effective compared to morphine, meperidine (pethidine), and pentazocine, with a dose of 30 mg ketorolac providing analgesic efficacy comparable to 12 mg of IM morphine, 100 mg of IM meperidine or 30 mg of IM pentazocine. Intramuscular ketorolac, when used in conjunction with morphine or other opioids, has an opioid-sparing effect leading to a reduction in opioid requirements after major surgery.

The oral formulation of ketorolac can be used after IM ketorolac at the point in a patient's postoperative course when oral medications can be tolerated. Several studies have demonstrated that oral ketorolac at a dose of 10 mg has equal or greater efficacy compared to acetaminophen.
Table 1

<table>
<thead>
<tr>
<th>Pharmacokinetic Values</th>
<th>Ketorolac Oral 10 mg</th>
<th>Ketorolac Oral 15 mg</th>
<th>Ketorolac IM 30 mg</th>
<th>Ketorolac IM 60 mg</th>
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<td>Volume of Distribution</td>
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(paracetamol) alone or in combination with codeine, pentazocine, aspirin, and ibuprofen.18-20

In this review, the pharmacology, pharmacokinetics, dosing, drug interaction, and adverse events associated with ketorolac will be examined. Additionally, various clinical trials comparing ketorolac to other analgesics will be discussed, and the results of a clinical trial performed at the Emory University School of Medicine comparing oral ketorolac to IM morphine will be presented.

CLINICAL PHARMACOLOGY

Ketorolac, like other NSAIDs, blocks cyclooxygenase in the arachidonic acid cascade, thereby inhibiting the formation of prostaglandins. Consequently, ketorolac displays the analgesic, antinflammatory, and antipyretic properties of other NSAIDs. Tissue trauma results in increased prostaglandin production, and prostaglandins have been implicated in enhancing the sensitization of peripheral pain pathways to the effects of bradykinin, serotonin, and histamine. Because ketorolac inhibits the production of prostaglandins, sensitization to these pain mediators is reduced and pain perception is diminished. Various animal assays have shown that the analgesic activity of ketorolac is more pronounced than the antiinflammatory action.27,28

The lipooxygenase pathway of the arachidonic acid cascade is not affected by ketorolac, nor does ketorolac appear to affect opiate receptors (Syntex Laboratories, unpublished data).

PHARMACOKINETICS

Some key pharmacokinetic parameters regarding ketorolac are summarized in Table 1. Following oral or intramuscular dosing, the pharmacokinetics of ketorolac are linear, with plasma levels increasing as the dose increases. However, there appears to be a non-linear dose response curve, as with other NSAIDs, where higher doses of ketorolac may not result in a corresponding increase in analgesic activity.4

Absorption and Distribution. Ketorolac is rapidly and completely absorbed following intramuscular and oral administration.29 Following a 30 mg IM injection, ketorolac reaches a mean peak plasma level of 2.2-3.0 µg/mL after an average of 50 minutes. A 10 mg dose of oral ketorolac reaches peak plasma levels of 0.7-1.1 µg/mL after an average of 44 minutes. Ketorolac is highly protein bound with 99% of the drug bound in plasma.30 In healthy adults, steady state plasma levels are reached in 24 hours following dosing four times daily.

Therapeutic plasma levels ranging between 0.3 and 5.0 µg/mL appear to correlate with analgesic activity, with 0.3 µg/mL being the minimal level needed to achieve a significant analgesic effect and 5.0 µg/mL being the level beyond which side effects occur more frequently.31 Ketorolac does not cross the blood-brain barrier; with cerebrospinal fluid levels are approximately 0.2% of plasma levels.31

The pharmacokinetic profile of ketorolac has characteristics of a two-compartment model. Following a rapid distribution phase, IM ketorolac has an average terminal half-life of nearly 5.3 hours (range: 3.5 to 9.2) in normal subjects, and oral ketorolac also has an average half life of 5.3 hours (range: 2.4 to 9.0).31

Metabolism and Excretion. Ketorolac is metabolized by the liver and is eliminated as inactive glucuronide metabolites and excreted through the kidneys (91%) within 2 days or feces (6%) within 3 days, probably by biliary elimination.29,30 A minor metabolic pathway yields a slightly active para-hydroxy ketorolac metabolite with less than 20% of the antiinflammatory and less than 1% of the analgesic activity.29

Effect of Age and Disease on Pharmacokinetics. Elderly (mean age: 72 years; range: 65 to 78) and young subjects received a single dose of 30 mg of IM ketorolac and 10 mg of ketorolac orally on separate days. The elderly subjects had significantly longer half-lives of IM ketorolac: 6.95 hours in the elderly vs 4.45 hours in the young, and oral ketorolac 6.14 hours in the elderly compared to 4.69 hours in the young.32

In nine patients with renal impairment (serum creatinine values ranging from 1.9-5.0 mg/dL), the elimination of ketorolac was significantly reduced compared to healthy subjects. The mean plasma half-life in the renally impaired patients increased 10.3 hours (range: 8.1 to 15.7).

INDICATIONS

Intramuscular ketorolac is indicated for the short-term management (up to 5 days) of pain and can be used as an alternative to parenteral opioid therapy. Likewise, oral ketorolac is indi-
cated for the limited duration (average: 5 to 14 days) management of pain and can be used as an alternative to oral opioids.31

DOSING

Intramuscular ketorolac may be given on a scheduled basis or as needed for pain. Therapy is usually initiated with a 60 mg IM loading dose followed by 30 mg IM every 6 hours or a 30 mg loading dose followed by 15 mg every 6 hours. Elderly patients (greater than 65 years old), patients with decreased renal function, or those patients weighing less than 50 kg should be dosed at the lower end of the dosing range. When administering ketorolac on a prn schedule, the dosage should be individualized based on duration of pain relief from the previous injection. Intramuscular ketorolac should not be used for periods longer than 5 days because the frequency and severity of adverse events may increase with longer use. The maximum recommended dose is 150 mg for the first day and 120 mg on subsequent days.31

The recommended dose for oral ketorolac is 10 mg every 4 to 6 hours as needed for the treatment of pain. However, oral ketorolac should only be used for the limited duration management of pain (average: 5 to 14 days). When oral ketorolac is used as follow-up therapy to IM ketorolac, 20 mg may be given as the first oral dose if the last IM dose was 30 mg. On the day of transition, the minimum dosing intervals should be observed, i.e., 6 hours between IM doses and 4 hours between oral doses.31

DRUG INTERACTIONS

Ketorolac is highly bound to plasma protein, and consequently may affect the binding of other drugs, especially those that bind to plasma proteins in a highly specific manner. Conversely, other drugs might affect ketorolac binding. However, in vitro studies have shown that therapeutic concentrations of digoxin, ibuprofen, naproxen, acetaminophen, phenytoin, tolbamidine, and piroxicam did not alter ketorolac binding at clinically significant plasma concentrations. When therapeutic concentrations of aspirin (300 μg/mL) are present, the binding of ketorolac is decreased (92.2% to 97.5%), representing a two-fold increase in free drug concentrations. Ketorolac does not alter digoxin binding. The in vitro binding of warfarin was slightly reduced in the presence of ketorolac (99.5% vs 99.3%) (Syntex Laboratories, unpublished data).

Patients receiving ketorolac with warfarin in one study and with subcutaneous heparin in another study demonstrated no significant changes in the pharmacokinetics or pharmacodynamics of warfarin or heparin (Syntex Laboratories, unpublished data).33

Other drugs that can be affected by NSAIDs, although no effect has been studied with ketorolac, include lithium (increased lithium levels) and methotrexate (increased methotrexate levels). The diuretic response of furosemide was reduced in normotensive, healthy subjects who received ketorolac. Co-administration of ketorolac (10 mg orally) and probenecid (500 mg orally four times daily) resulted in decreased clearance of ketorolac, significantly increased ketorolac plasma levels, and an increased terminal half-life. Additionally, information from the manufacturer indicates a possible interaction between ketorolac and non-depolarizing muscle relaxants (enhanced effect of the muscle relaxant) that was discovered from post-marketing reports.31

There is no evidence in animal or human studies that ketorolac induces or inhibits the cytochrome P-450 enzymes. Thus, ketorolac would not be expected to alter the pharmacokinetics of other drugs due to enzyme induction.31

CLINICAL STUDIES

Intramuscular ketorolac has been studied in several pain states including orthopedic, abdominal, and gynecologic surgery and renal colic. The studies are, for the most part, double-blind, controlled, and single or multi-dose in design. All of the studies reviewed followed standard analgesic methodology where patients rate their pain intensity at baseline and their pain intensity and pain relief at intervals periodically during the study. In addition, overall evaluations of the study medication are made by the patients and investigators at the end of the study. A variety of pain scores are calculated from these data.

For example, pain intensity scores at each post-dose interview are subtracted from the baseline pain intensity score yielding a pain intensity difference (PID). A summed pain intensity difference (SPID) is the area under the PID curve over time. A higher SPID score represents greater analgesic efficacy. Efficacy is also measured by pain relief scores and total pain relief—TOTPAR (defined as the area under the pain relief curve over time). Additional measures of analgesic efficacy include the number of patients terminating from the study due to inadequate pain relief, the time to onset of analgesia, and the duration of analgesia. Analgesic studies often have placebo groups to validate the pain model that is used because active study medications with previously established efficacy should separate from placebo.

Two single-dose IM investigations examined
the use of ketorolac in a variety of surgery types, mainly gynecologic, abdominal, and orthopedic. One of the studies, by Yee et al., compared several doses of IM ketorolac (10 mg, 30 mg, and 90 mg) to IM morphine 6 mg and 12 mg in 241 patients. Pain measurements were taken over a 6-hour time period after the dose of study medication. Intramuscular ketorolac doses of 10 mg, 30 mg, and 90 mg were similar in efficacy to 12 mg of morphine, and were clearly superior to morphine 6 mg. Each of the ketorolac doses had an onset of analgesic activity similar to morphine, and the duration of action tended to be longer than both doses of morphine. The same design was duplicated in a study by O’Hara et al., in 155 postoperative patients recovering from major abdominal and orthopedic surgery. The authors found that ketorolac 90 mg and 30 mg was as effective as morphine 12 mg for up to 3 hours, and more effective thereafter. They also found that ketorolac 30 mg and 90 mg and morphine 12 mg were consistently more efficacious than ketorolac 10 mg and morphine 6 mg.

Intramuscular meperidine 100 mg was compared to IM ketorolac, 10 mg and 30 mg, and placebo in a single-dose study by Folsland et al., in 129 patients who had undergone major abdominal surgery. This study demonstrated that the overall analgesic efficacy of 30 mg of IM ketorolac was approximately the same as 100 mg of IM meperidine for the treatment of moderate to very severe postoperative pain. The authors also found that meperidine had a slightly faster onset of action than the ketorolac groups, but the duration of action of the 30 mg ketorolac dose was longer. Stanski et al. compared single doses of IM ketorolac 30 mg or 90 mg with meperidine 50 mg or 100 mg in 125 postoperative patients. Both doses of ketorolac were significantly superior in efficacy to the 50 mg dose of meperidine, and comparable to the 100 mg meperidine dose. All four groups had similar onset of analgesia, peak analgesic effects, and side effect profiles. The ketorolac groups had longer durations of action than the meperidine groups. A study by Oosterlinck et al. evaluated the efficacy of IM ketorolac 10 mg or 90 mg compared to IM meperidine 100 mg in 121 patients with renal colic pain. The results of this study show that IM ketorolac was very efficacious in treating renal colic pain and 10 mg of IM ketorolac was equivalent in efficacy to 100 mg of meperidine. Side effects were minimal in all three groups, but were slightly higher in the meperidine group.

Multiple dose studies, in general, reproduce typical clinical situations more closely than single dose analgesic evaluations. One such study was conducted by Brown et al., with a total of 542 postoperative (various orthopedic, gynecologic, and abdominal procedures) patients who experienced moderate to severe pain. Multiple IM doses of ketorolac 30 mg were compared to multiple IM doses of morphine, 6 mg and 12 mg, all administered as needed every 2 hours for up to 20 doses during no more than 5 days of dosing. There were no statistically significant differences between the ketorolac and morphine 12 mg groups in pain intensity scores, and both groups were superior to the morphine 6 mg group. Additionally, the ketorolac group experienced fewer adverse events causing withdrawal from the study than did the two morphine groups. The authors concluded that 30 mg of IM ketorolac can be used safely in a variety of postoperative pain states and is comparable in efficacy to 12 mg of IM morphine.

A second multi-dose study comparing IM ketorolac to IM morphine in patients after an elective cholecystectomy was conducted by Power et al. One hundred patients received 30 mg of ketorolac IM or 10 mg morphine IM initially followed by 30 mg ketorolac IM or 10 mg morphine IM every 2 hours for up to 6 doses in 24 hours. The authors found that ketorolac patients experienced less pain relief immediately after the surgery compared to the morphine patients. However, the groups had similar SPID and pain relief scores by postoperative day.

Ketorolac has been used concomitantly with IM morphine in two clinical trials, which are reviewed here. In the first study, by Gillies et al., ketorolac 1.5 mg/hr, ketorolac 3.0 mg/hr, or placebo were administered by continuous intramuscular infusion to 61 upper abdominal surgery patients. All of the patients received additional intravenous morphine on demand during the 24-hour study period. Patients in the ketorolac group used significantly less morphine during the study period compared to the placebo group: 78 mg of morphine/24 hours (placebo), 53 mg of morphine/24 hours (ketorolac 1.5 mg/hr), and 55 mg of morphine/24 hours (ketorolac 3.0 mg/hr). Additionally, the patients in both ketorolac groups had significantly better visual analogue pain scores as well as lower postoperative increases in arterial carbon dioxide tension. The authors concluded that ketorolac is a safe and effective analgesic when combined with morphine in abdominal surgery patients.

The second study, by Kinsella et al., evaluated 75 patients who had undergone major or minor orthopedic surgery. The patients were administered 30 mg of IM ketorolac or placebo every 6 hours, and could receive supplemental...
IM morphine every 2 hours on demand during the 24-hour study period. The major surgery patients in the ketorolac group were administered an average of 10 mg of morphine postoperatively compared to the placebo group, which received an average of 30 mg of morphine. The pain evaluations were similar in both treatment groups. In the minor orthopedic surgery group, ketorolac patients used less morphine than placebo patients (0 mg and 10 mg, respectively), but this difference was not statistically significant. However, the pain scores were significantly better in the patients who received ketorolac.17

Oral ketorolac has been compared to several oral analgesics, including: acetaminophen/codeine, pentazocine, aspirin, ibuprofen, and acetaminophen. In a clinical trial by Kagi,18 comparing 10 mg of oral ketorolac to 100 mg oral pentazocine in abdominal or orthopedic surgery pain, 100 patients were randomly assigned to receive either drug four times daily. Ketorolac was found to be equally effective compared to pentazocine, yet had a much lower incidence of adverse events.18

Three studies reviewed here compared oral ketorolac to acetaminophen/codeine. Vangen et al21 performed a study involving 107 patients who had just undergone gynecologic surgery. Kotorolac 10 mg was compared to acetaminophen/codeine (1000 mg/60 mg). This study consisted of two phases, a first dose analysis followed by a multidose period. During each study period, pain was equally controlled in both treatment groups with a majority of investigators and patients rating the medications as “excellent” or “very good.” Two studies were performed by Forbes et al, evaluating the use of ketorolac after oral surgery (removal of impacted third molars). The first study compared oral ketorolac 10 mg, aspirin 650 mg, and acetaminophen 600 mg/codeine 60 mg given up to four times daily in 128 outpatients. The authors found that the ketorolac patients had significantly superior pain relief compared to both aspirin and acetaminophen/codeine immediately after the surgery. In the second dental study, Forbes et al23 measured the analgesic efficacy of ketorolac 10 mg and 20 mg, acetaminophen 600 mg/codeine 60 mg, acetaminophen 600 mg, and ibuprofen 400 mg in 206 outpatients. Overall, both doses of ketorolac were significantly more efficacious than acetaminophen 600 mg/codeine 60 mg, acetaminophen 600 mg, and placebo. Oral ketorolac, 10 mg and 20 mg, demonstrated numerically superior analgesic efficacy values to ibuprofen 400 mg on some evaluations, but the differences were not statistically significant. Few adverse events were reported in any of the active treatment groups, and those reported were transitory and consistent with the pharmacologic activity of the study medications.24

SAFETY

In published studies with both formulations of ketorolac, digestive and nervous system complaints occurred at the highest rates.126 As with other NSAIDs, ketorolac given by IM injection or orally has the potential to produce serious gastrointestinal adverse events. An endoscopy study by Lanza et al35 was performed comparing various doses of ketorolac (90 mg IM, 30 mg IM, 10 mg IM, and 10 mg orally all given four times daily for 17 doses) to aspirin 650 mg four times daily for 17 doses. Ketorolac 30 mg IM, 10 mg IM, and 10 mg orally caused significantly less gastric mucosal damage than aspirin 650 mg orally and ketorolac 90 mg IM.35

A study evaluating long-term use compared ketorolac 10 mg up to four times daily to aspirin 650 mg up to four times daily in 823 patients suffering from chronic pain conditions such as osteoarthritis, fibrositis, miscellaneous soft tissue pain, and headaches.25 During this 1-year trial, the patients were evaluated at various times and received a mean daily dose of 30 mg of ketorolac and 1850 mg of aspirin. The incidence of peptic ulcer disease was slightly higher in the ketorolac group, but other adverse events occurred at similar rates in both groups.25

Ketorolac, as opposed to injectable narcotic analgesics, causes no detectable respiratory depression. Brandon Bravo et al36 administered either ketorolac IM 10 mg or 90 mg or morphine 10 mg IM in a randomized, blinded, crossover design to volunteers and measured respiratory function. The authors found that, while the morphine dose caused significant respiratory depression for up to 4 hours after administration, the ketorolac groups demonstrated no significant change in ventilatory function.36

NSAIDs have varying degrees of effect on hemostasis and platelet function. As with other NSAIDs, ketorolac inhibits platelet aggregation by inhibiting production of thromboxane A2. Bleeding time is prolonged slightly for 24 to 48 hours following a single IM injection, but remains within the normal clinical range for most patients.33 When results from several clinical trials were pooled, the incidence of clinically significant bleeding associated with the postoperative use of ketorolac was 0.4% compared to 0.2% in the opioid comparative groups.31

The incidence of adverse events in different clinical trials may vary widely depending on dosing regimens and pain models. For example, in a single dose trial comparing several different doses of ketorolac (90 mg, 30 mg, and 10 mg) to
morphine (6 mg and 12 mg) all given intramuscularly, adverse events were reported infrequently. In this study, 8% of the morphine patients reported somnolence and 0% reported nausea vs 1% of the ketorolac patients with somnolence and 3% with nausea. However, in a multiple dose trial comparing 30 mg of IM ketorolac to 6 mg and 12 mg of IM morphine, 7% of patients left the trial because of side effects in the ketorolac group vs 10% and 17% in the 6 mg and 12 mg morphine groups. Somnolence was reported by 23% of the ketorolac patients, 27% of the morphine 6 mg patients and 44% of the morphine 12 mg patients. This study also revealed differences in the incidence of nausea: 7% in the ketorolac group, 15% in the morphine 6 mg group, and 44% in the morphine 12 mg group.

Side effects have been reported by the manufacturer following IM and oral administration of ketorolac. Events that have occurred during clinical trials in 12% to 17% of patients were nausea, dyspepsia, abdominal pain, and headache. Adverse events that occurred in 3% to 9% of patients enrolled in clinical trials include edema, pruritus, diarrhea, drowsiness, and dizziness. Side effects that occurred in 1% to 3% of patients include: hypertension, rashes, injection site pain, constipation, vomiting, purpura, and stomatitis. Side effects reported in less than 1% of patients from both clinical trials and postmarketing surveillance include: hypersensitivity reactions such as anaphylaxis, palpitation, hypotension, syncope, urticaria, gastritis, peptic ulceration, gastrointestinal hemorrhage and perforation, melena, epistaxis, anemia, postoperative wound bleeding, thrombocytopenia, convulsions, dyspnea, pulmonary edema, asthma, oliguria, nephritis, and acute renal failure.

Because ketorolac shares the toxic potential of other NSAIDs, certain precautions should be discussed. Although rare, the most significant risks with ketorolac are gastrointestinal (including ulceration, bleeding, and perforation), renal (including renal failure), bleeding, and hypersensitivity reactions (including anaphylaxis). Patients must be screened carefully for anything in their histories that may predispose them to these or other complications. Patients with underlying renal disease should be given reduced doses of ketorolac, as prostaglandins are partly responsible for maintaining renal perfusion. Patients with underlying coagulation problems (ie, concurrent warfarin or heparin use, von Willebrand's disease, or thrombocytopenia) should be monitored closely; the drug should be used very cautiously in these patients. Additionally, the drug should be used cautiously in situations in which strict hemostasis is critical. Finally, ketorolac should not be administered to patients with a known hypersensitivity to NSAIDs. Patients in whom aspirin or other NSAIDs precipitate a complete or partial syndrome of angioedema, bronchospasm, and nasal polytis should not receive ketorolac because acute allergic reactions have occurred.

**Single Dose Study**

*Materials and Methods.* A single-dose study of oral ketorolac vs IM morphine and placebo after orthopedic surgery conducted at the Emory University School of Medicine compared 10 mg of oral ketorolac to either 5 mg or 10 mg of IM morphine or placebo in 176 patients experiencing moderate or severe pain following knee (64% of patients) or hip (36% of patients) surgery. The study was double-blind, parallel, placebo-controlled, and single dose in design. Patients entered the study within 48 hours of surgery, and no analgesics were allowed during the 3-hour period prior to study entry. Patients were randomly assigned to one of four groups: 1) ketorolac 10 mg po plus placebo IM (50 patients); 2) morphine 10 mg IM plus placebo po (51 patients); 3) morphine 5 mg IM plus placebo po (50 patients); and 4) placebo IM plus placebo po (25 patients). Patients who had inadequate pain relief could receive an alternate analgesic, but were withdrawn from the study at that time.

Pain intensity and pain relief were rated by patients at 30 minutes, 1 hour, and hourly thereafter until the study ended at 6 hours after drug administration. Pain intensity was rated on a five-point categorical scale and also on a 100 mm horizontal visual analog scale (VAS). Pain relief was measured using a five-point categorical scale. Additionally, the patients and investigators were asked at the end of the study to give several overall ratings of the pain medication. Drug safety was evaluated by analyzing overall drug tolerability, as rated by the patients and investigators, by recording any adverse events that occurred during the study and all early withdrawals due to adverse events.

Continuous variables, including demographic data (ie, age, height, etc), baseline pain intensity on a VAS, and efficacy variables were analyzed using the one-way Analysis of Variance model. If significant differences were found among treatment groups, a two-tailed least significant difference test was performed. Additionally, nonparametric methods (Kruskal-Wallace test) were used to confirm the results of the analysis of variance. Categorical data, demographic information (ie, sex, race, etc), and baseline pain intensity (categorical) were compared using the likelihood ratio chi-square tests. Categorical

162
Table 2

<table>
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<tr>
<th></th>
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<th>Mo10 (51 pts)</th>
<th>Mo5 (50 pts)</th>
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*Pairwise comparison P-values are from the one-way Analysis of Variance with factor of treatment, and were performed using two-tailed least significant difference tests.
†Overall P-value is from the one-way Analysis of Variance, and is the probability of a difference among the four treatment groups.
‡Pain intensity rated: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe. PID = pain intensity difference: baseline-each subsequent pain intensity value. SPID = Weighted sum of PIDs from hour 0.5 through hour i.
§Visual analog scale (VAS) from 0 mm = no pain to 99 mm = worst possible pain. VPID = pain intensity difference: baseline-each subsequent VAS value. VSPIRD = Weighted sum of VPIDs from hour 0.5 through hour i.
**Pain relief scores rated: 0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete. TOTPAR = Weighted sum of pain relief scores from hour 0.5 through hour i.
Ket = ketorolac; Mo10 = morphine 10 mg; Mo5 = morphine 5 mg; Plac = placebo; Pts = patients

assessments of efficacy (pain intensity and pain relief), distributions of patients terminating early, and numbers of patients reporting adverse events were analyzed by the Cochran-Mantel-Haenszel procedure.37

Results. Of the 105 patients remaining in the study for 6 hours, 33 (66%) were in the ketorolac group, 33 (66%) were in the 10 mg morphine group, 32 (64%) were in the 5 mg morphine group, and 7 (28%) were in the placebo group. The difference in the percentage of patients in the three active drug groups remaining in the study compared to the placebo group was statistically significant (P<.01). A total of 71 patients terminated from the study prematurely. Sixty-four of these patients were given supplemental analgesic or medication precluded by the protocol; 16 (32%) were in the ketorolac group, 14 (28%) were in the 10 mg morphine group, 17 (34%) were in the morphine 5 mg group, and 17 (34%) received placebo. There were no significant differences between the active treatment groups for withdrawal due to inadequate efficacy.37

Ketorolac and both doses of morphine were each significantly superior to placebo (P<.01) and not significantly different from each other in each of the following assessments: SPIDs and TOTPARs (Table 2), categorical PIDs (Fig 1), and categorical pain relief scores (Fig 2). Even though the 10 mg morphine group had numerically higher values than the ketorolac and 5 mg morphine groups for all SPID and TOTPAR scores and the ketorolac group had consistently higher values than the 5 mg morphine group, none of these differences were statistically significant (Table 2). The 10 mg morphine group was significantly superior to the ketorolac group for peak VAS PID (P = .04) and for peak pain relief scores (P = .01). The time of onset of pain relief was comparable among all active treatment groups (Table 3).37

Adverse Events. Of the 176 patients included in the safety analysis in this study, only five withdrew from the study because of adverse events: two after 10 mg of IM morphine and one from each of the remaining groups. In only two of these five patients was the adverse event causing study withdrawal considered to be related to the study medication by the investigator: nausea in one of the 10 mg morphine patients and in one of the placebo patients. Sixty-six patients (38%) reported at least one adverse event (Table 4), and the overall differences among treatments approached statistical significance (P = .06). The only pairwise comparison that showed a statistically significant difference was a higher proportion of patients in the morphine 10 mg group with adverse events than the placebo group (P = .01).

The number of patients in the morphine 10 mg group experiencing somnolence was higher than the other three groups, and the differences between the morphine 10 mg group and placebo group regarding this symptom was statistically significant (P < .01). There were no significant differences between treatment groups in the ratings of drug tolerability by patients or investigators.

Discussion. In the Emory University study, a
Fig 1. Categorical PIDS.

Fig 2. Categorical pain relief scores.
single 10 mg dose of oral ketorolac provided effective pain relief, with SPID and TOTPAR scores comparable to those achieved with IM morphine at doses of 5 mg and 10 mg, although the 10 mg morphine group had higher peak analgesic effects. A dose response between 5 mg and 10 mg of morphine was not seen in this study to the extent that would be expected, which could be explained by the fact that these orthopedic surgery patients may have been experiencing less pain at the point in their postoperative course when they were able to take oral medication.

Many orthopedic surgery patients will tolerate oral medications and nutrition sooner than abdominal and other surgical patients, and a potent oral analgesic with efficacy comparable to parenteral opioids but associated with fewer side effects would be very useful. The Emory University study shows that oral ketorolac would be an appropriate agent to use in this clinical situation. Furthermore, ketorolac is available in an intramuscular form, which could be used in orthopedic or other surgical patients early in their postoperative course. As discussed previously in this review, it has been demonstrated that 30 mg of ketorolac IM is comparable in analgesic efficacy to 12 mg of IM morphine and 100 mg of IM meperidine. In the early postoperative period when pain is most severe, parenteral opioids could also be safely added, if needed, to a regimen of IM ketorolac because of their different sites of activity, i.e., peripheral with ketorolac and central with opioids. With the documented opioid-sparing properties of ketorolac, as discussed previously, significantly less opioid would be used when added to a regimen of ketorolac than if an opioid alone were used to manage the patient's pain.

When the patient is able to tolerate oral medication, a smooth transition from IM to oral ketorolac could take place without the necessity of switching to a different analgesic.

**CONCLUSION**

Ketorolac is a safe and effective analgesic as evidenced by the data presented in this review, including the Emory University study. The intramuscular and oral forms can be used as alternatives to parenteral and oral opioids, respectively, in the short-term management of acute postoperative pain.

**REFERENCES**


**Table 3**

<table>
<thead>
<tr>
<th>Treatment (N)</th>
<th>Peak Effect Measured Over 6 Hours</th>
<th>Pain Relief</th>
<th>Onset of Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PIDs Mean ± SD</td>
<td>VAS PIDs Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>1.6 ± 0.8</td>
<td>45.8 ± 22.1</td>
<td>2.8 ± 1.3</td>
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<tr>
<td>Morphine 10 mg</td>
<td>1.9 ± 0.8</td>
<td>54.1 ± 16.1</td>
<td>3.4 ± 0.8</td>
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<tr>
<td>Morphine 5 mg</td>
<td>1.7 ± 0.8</td>
<td>48.5 ± 20.3</td>
<td>3.1 ± 0.9</td>
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<td>Placebo</td>
<td>0.7 ± 0.8</td>
<td>24.2 ± 20.7</td>
<td>1.4 ± 1.2</td>
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</table>

**Table 4**

<table>
<thead>
<tr>
<th>Total Patients</th>
<th>Ket</th>
<th>Mo10</th>
<th>Mo5</th>
<th>Plac</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>No. Reporting (%) AEs</td>
<td>50</td>
<td>51</td>
<td>50</td>
<td>25</td>
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<tr>
<td>No. AEs Reported</td>
<td>18 (36)</td>
<td>26 (52)</td>
<td>17 (34)</td>
<td>5 (20)</td>
<td>66 (38)</td>
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<tr>
<td>No. of Patients (%) with Somnolence</td>
<td>20</td>
<td>28</td>
<td>17</td>
<td>6</td>
<td>71</td>
</tr>
</tbody>
</table>

Ket = ketorolac; Mo10 = morphine 10 mg; Mo5 = morphine 5 mg; Plac = placebo


