American Journal of Hematology 46:43–47 (1994)

# Enhancement of Pain Control With Ketorolac Tromethamine in Patients With Sickle Cell Vaso-Occlusive Crisis

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**Twenty one patients with sickle cell disease admitted to the hospital with the pain of vaso-occlusive crisis (VOC) were treated by continuous IV infusion of ketorolac or normal saline for up to 5 days. All patients received supplemental IM injections of meperidine, 100 mg, as necessary, but not more frequently than every 3 hr. Over the 5 days the ketorolac treated patients (KT) required 33% less meperidine than did the placebo treated patients (PL), $P = 0.04$, and had significantly better pain relief as assessed by categorical, visual analog, and pain relief scales. By the end of 5 days infusions had been discontinued in six KT and one PL. The time to discontinuation of the infusion was significantly shorter in KT, ($P = 0.009$). The median duration of hospital stay from the start of treatment was 3.3 days for KT and 7.2 days for PL, $P = 0.027$. Adverse events were mainly related to the digestive system. This study showed that continuous infusion of ketorolac significantly reduced total meperidine requirement and that the analgesia produced by this combination was superior to that produced by meperidine alone. Further evaluation of this drug in the management of sickle cell VOC is warranted.** © 1994 Wiley-Liss, Inc.

**Key words: sickle cell disease, ketorolac, pain crisis**

## INTRODUCTION

Achievement of adequate analgesia for moderate to severe vaso-occlusive crisis (VOC) in sickle cell disease continues to be a difficult problem. Each VOC painful crisis lasts 4–6 days on average [1] and treatment with a parenteral analgesic, usually an opioid every 3 hr, may require the patients to remain in the hospital for 7 days or more [2].

In many facilities treating VOC, meperidine is the opioid of choice but IM injections every 3 hr may produce abscesses and fibrosis at the repeatedly used injection sites while IV administration of doses of 30 mg given at intervals of 10 min can lead to significant respiratory depression [3]. Prolonged use of meperidine also may cause constipation and central nervous system excitability, resulting in seizures when toxic levels of its major metabolite, normeperidine, are reached [4]. Other opioid analgesics have their own limitations.

Over the past several years we have been attempting to improve the management of the pain of VOC. For example, we have described the successful use of patient-controlled analgesia for sickle cell patients using IV meperidine [5,6]. In an earlier study [7] we found that diflunisal, a nonsteroidal anti-inflammatory drug (NSAID), was ineffective as an opioid sparing agent in the management of VOC. In the present study we have evaluated a more powerful NSAID, ketorolac, which is injectable and has activity comparable to the opioids but which does not bind to the mu, kappa, or delta opioid receptors [8]. Thirty milligrams of ketorolac has been shown to be as effective as 12 mg of morphine or 100 mg of meperidine in the management of postoperative pain [9–11].

Received for publication March 22, 1993; accepted October 27, 1993.

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It has been reported recently that IM ketorolac may also be useful for the treatment of VOC [12], although a single dose given in the Emergency Room was not opioid sparing [13]. The effectiveness of ketorolac as an opioid sparing agent when given by IV infusion has not been evaluated, although one report suggests that it is safe [14]. We therefore decided to evaluate the IV infusional use of ketorolac in a double-blind, placebo-controlled study.

## PATIENTS AND METHODS

### Patients

The study was a randomized, double-blind placebo comparison of parallel-group design in patients with electrophoretically proven sickle cell disease who were experiencing moderate to severe pain as a result of an acute VOC. Patients under 15 years of age were ineligible, as were those with active peptic ulcer disease, systemic bleeding disorders, impaired renal function (BUN > 20 mg/dL and/or serum creatinine > 1 mg/dL), or other medical condition likely to complicate their participation in the study, and those with a history of hypersensitivity to the NSAID group of drugs. Pregnant women were also excluded. All of the patients were ketorolac naive.

Patients received a pretreatment physical examination and laboratory evaluation which measured red blood cell count, hemoglobin, hematocrit, white blood cell count with differential count, platelet count, BUN, uric acid, total and direct bilirubin, total protein and albumin, total cholesterol, glucose, SGOT, SGPT, alkaline phosphatase, LDH, calcium, phosphorus, chloride, bicarbonate, potassium, sodium, stool occult blood, and urinalysis. The BUN and serum creatinine were measured daily throughout the study and on completion of the study all patients received another physical examination and laboratory evaluation.

All patients had been admitted to hospital before enrollment in the study and had received routine treatment which included IM injections of meperidine and oral hydroxyzine pamoate in addition to adequate oral and/or IV hydration. The study was approved by the Howard University Institutional Review Board and all patients consented in writing to their participation.

### Study Description

The study drugs were prepared by a designated hospital pharmacist (J.P.) and allocated according to a predetermined, computer generated random code, balanced in blocks of four. Ketorolac was diluted in $D_5$ in 1/2 normal saline and the placebo was normal saline.

Pain intensity over the preceeding 24 hr was assessed daily, at approximately the same time each morning, using a Verbal Categoric Scale (VCS: where 0 = no pain, 1 = mild, 2 = moderate, 3 = severe pain), a 100 mm Visual Analog Scale (VAS: where 0 = no pain and 100 = worst possible pain), and a Pain Relief Verbal Scale where 0 = none, 1 = a little, 2 = some, 3 = a lot, and 4 = complete. The infusion of ketorolac or placebo was given through a peripheral invravenous line. Central intravenous lines were not used.

Over the first 40 min of the infusion, patients allocated to ketorolac received a loading dose of 30 mg and thereafter received an infusion of 120 mg at 5 mg/hr, for a total dose of 150 mg ketorolac on the first day; for the remainder of the study patients received 120 mg/day. Patients allocated to placebo received their infusion at the same ml/hr rate as those receiving ketorolac. Commercially available meperidine 100 mg IM was administered every 3 hr, if patients reported moderate pain to the staff nurse and requested relief. Since the recommended maximum duration of treatment for intramuscular injection of ketorolac is 5 days, the intravenous infusion in this study was also limited to 5 days. Patients who continued to require analgesia beyond the 5 days of infusion received IM meperidine and oral hydroxyzine pamoate.

The primary efficacy variable was a comparison of the quantity of meperidine required by and administered to the patients in the two groups over the 5-day period of the study.

Secondary efficacy variables were the quality of analgesia, evaluated by the VCS and the VAS, the Pain Relief Assessment and a Global Assessment. When data from a particular patient were not available, the last valid measurement or evaluation was carried forward in an attempt to minimize the bias inherent in basing comparisons solely on those patients remaining in the study at a given time. The duration of hospital stay, measured from the day of enrollment in the study to the day of discharge, was also recorded for all patients. At the end of the study a Global Assessment was obtained by asking each patient to compare the analgesic regimen just received with that received for previous sickle cell crises (where Much Worse = 1, Worse = 2, Same = 3, Better = 4, and Much Better = 5).

During the study all adverse events that were reported spontaneously or in response to nonspecific questions were noted.

### Statistical Analyses

Statistical comparisons were performed with respect to total meperidine dose, mean daily meperidine dose, number of days of meperidine dosing, change from baseline in VCS and VAS, Pain Relief Assessment, Global Assessment, and time to termination of analgesia. Student's t-test or Wilcoxon Rank Sum test were used to compare the continuous variables, the Cochran-Mantel-Haenszel row-mean scores were used to test for categorical variables, and the log-rank test was used for the time-to-event variable. The level of significance was 0.05.

**TABLE I. Patient Demographic Data**

| | | Treatment group | |
|---|---|---|---|
| | | Ketorolac (%) | Placebo (%) |
| No. of patients enrolled | | 10 | 11 |
| No. of patients withdrawn prematurely | | 1 | 2 |
| Sex | | | |
| Males | | 5 (50) | 6 (55) |
| Females | | 5 (50) | 5 (45) |
| Age (yrs) | | | |
| Under 25 | | 7 (70) | 1 (9) |
| 25–34 | | 3 (30) | 6 (55) |
| 35–44 | | 0 | 4 (36) |
| Mean (± SD) | | 24 (5.4) | 32 (6.5) |
| Range | | 19–34 | 21–41 |
| Weight (lb) | | | |
| Mean (± SD) | | 132 (17.0) | 149 (22.5) |
| Range | | 100–161 | 116–183 |
| Height (inches) | | | |
| Mean (± SD) | | 65 (3.2) | 68 (3.1) |
| Range | | 62–71 | 65–74 |
| Baseline VCS | | | |
| Moderate (2) | | 5 (50) | 4 (36) |
| Severe (3) | | 5 (50) | 7 (64) |
| Baseline VAS (mm) | | | |
| Mean (± SD) | | 76 (11.2) | 79 (10.4) |
| Range | | 63–93 | 60–94 |
| Days in hospital prior to start of study | | | |
| 0–1 | | 1 | 1 |
| 2–3 | | 9 | 9 |
| 4–5 | | 0 | 1 |
| Mean (median) | | 2.3 (2) | 2.3 (2) |
| Range | | 1–3 | 1–5 |
| In years 1990 and 1991 | | | |
| No. of admissions | Mean | 10 | 8 |
| Days in hospital | Mean (± SD) | 8.2 (1.9) | 10.2 (3.4) |

**TABLE II. Use of Meperidine**

| | Treatment group | |
|---|---|---|
| | Ketorolac | Placebo |
| No. of patients | 9 | 11 |
| Mean total dose of meperidine required (mg) (± SD) | 1,866.7 (1,112.4) | 2,804.5* (795.1) |
| Mean daily dose of meperidine required (mg) (± SD) | 523.6 (222.1) | 662.4 (68.6) |

*Difference between ketorolac and placebo significant ($P < 0.05$).

## RESULTS

### Patients

Twenty-one patients were enrolled in the study, 10 assigned to ketorolac and 11 assigned to placebo. One patient in the ketorolac treated group had SC genotype and one had S/Th; the remainder had SS. One patient in the placebo treated group had S/Th and the remainder had SS. One SS male patient, randomized to ketorolac, was already receiving warfarin at the same time and therefore inappropriately enrolled. Data from this patient who received ketorolac for 1.5 hr were excluded from all the analyses of efficacy but were included in the safety analysis.

The demographic characteristics of the 21 patients are shown in Table I. The KT patients were younger (mean 24 years) and lighter (mean 132 lb) compared with the PL patients (32 years and 149 lb respectively), and these differences were significant. No significant differences were found with regard to other characteristics. All the patients in the study had been treated in our hospital in the past and there was no significant difference between the average number of admissions and the average duration of hospital stay for these patients in the years 1990 and 1991. Thus, we believed that the difference in mean age between the two treatment groups would have little impact on the outcome of the study.

In addition to the inappropriately enrolled patient described above, two PL patients (both SS) were withdrawn prematurely, one at his own request at the end of the second day because of lack of adequate analgesia and the other by the investigators at the end of the third day because of elevated SGOT and alkaline phosphatase levels. It was subsequently determined that these laboratory abnormalities were the result of sickle cell liver disease.

### Evaluation of Efficacy

The results of the primary efficacy evaluation (use of meperidine) is shown in Table II and those of the secondary efficacy variables (quality of analgesia) in Tables III and IV.

For the 5 days of the study the KT patients required less meperidine compared with the PL patients (Table II). This difference (938 mg,33% reduction) in the total mean dose of meperidine was significant, $P = 0.04$.

The mean VCS pain intensity scores for the KT group compared with those in the PL group are shown in Table III. After day 1 all the differences between the two groups were statistically significant. Similarly, the differences between the two groups with respect to the VAS were statistically significant on days 1, 3, and 4.

Mean scores for the Pain Relief Assessment also are shown in Table III. Only two patients reported complete relief of pain, by the end of the third day, and both were in the KT group. Although the mean scores for pain relief every day after the first day were higher in the KT group than in the PL group, these differences reached statistical significance only on day 3.

Also shown in Table III is the comparison with previous analgesic therapy (Global Assessment) and it can be seen that the overall mean score for KT was significantly higher than that for PL.

From the start of treatment in the study to the time of discharge from hospital, the median duration for the KT

**TABLE III. Quality of Analgesia**

| | Treatment group | |
|---|---|---|
| | Ketorolac | Placebo |
| No. of patients | | |
| Mean pain intensity, VCS (0–3) | | |
| Baseline | 2.5 | 2.6 |
| Day 1 | 2.0 | 2.4 |
| Day 2 | 1.3 | 2.1* |
| Day 3 | 1.1 | 1.8* |
| Day 4 | 1.0 | 1.7* |
| Day 5 | 1.1 | 1.7* |
| Mean pain intensity, VAS (0–100 mm; 95% confidence interval) | | |
| Baseline | 77.7 (69.1–86.2) | 79.1 (72.1–86.0) |
| Day 1 | 58.6 (48.6–68.5) | 72.6 (62.4–82.8)* |
| Day 2 | 48.7 (33.0–64.4) | 64.6 (53.7–75.6) |
| Day 3 | 37.0 (16.3–57.7) | 60.8 (49.2–72.4)* |
| Day 4 | 32.0 (12.7–51.3) | 54.7 (41.8–67.6)* |
| Day 5 | 32.4 (11.7–53.2) | 52.9 (38.0–67.8) |
| Mean pain relief score, verbal scale (0–4) | | |
| Day 1 | 1.8 | 1.9 |
| Day 2 | 2.1 | 1.9 |
| Day 3 | 2.8 | 2.0* |
| Day 4 | 2.8 | 2.3 |
| Day 5 | 2.7 | 2.4 |
| Comparison with previous treatment (no. patients) | | |
| Much worse (1) | 0 | 0 |
| Worse (2) | 0 | 1 |
| Same (3) | 3 | 6 |
| Better (4) | 3 | 4 |
| Much better (5) | 3 | 0 |
| Mean score | 4.0 | 3.3* |

*Difference between ketorolac and placebo significant ($P < 0.05$).

**TABLE IV. Duration of Infusions and Days in the Hospital**

| | Treatment group | |
|---|---|---|
| | Ketorolac | Placebo |
| No. of patients | 9 | 11 |
| Median duration in hospital for infusion (days) | 3.0 | 5.0 |
| Median duration in hospital post-infusion (days) | <1 | 3.0 |
| Median duration in hospital for study (days) | 3.3 | 7.2* |
| No. of patients requiring infusion: | | |
| Day 1 | 10[a] | 11 |
| Day 2 | 9 | 11 |
| Day 3 | 8 | 10[b] |
| Day 4 | 4 | 9[c] |
| Day 5 | 3 | 8* |

[a]One patient was inappropriately enrolled and was treated for only 1.5 hr.
[b]One patient was withdrawn because of lack of analgesia.
[c]One patient was withdrawn because of adverse event.
*Difference between ketorolac and placebo significant ($P < 0.05$).

group (3.3 days) was shorter than that for the PL group (7.2 days), $P = 0.027$ (Table IV). The median duration of time spent in the hospital post infusion was also longer for the PL patients.

**TABLE V. Adverse Events Reported During the Study Stratified by Body System***

| | Treatment group | |
|---|---|---|
| | Ketorolac | Placebo |
| Total patients enrolled | 10 | 11 |
| Digestive system: | 5 | 4 |
| Constipation | 2 | 2 |
| Nausea | 3 | 1 |
| Vomiting | 2 | 2 |
| Diarrhea | 2 | 0 |
| Dyspepsia | 2 | 0 |
| Dysphagia | 0 | 1 |
| Liver function tests abnormal | 0 | 1 |
| Body as a whole: | 3 | 5 |
| Fever | 1 | 2 |
| Abdominal pain | 1 | 1 |
| Headache | 1 | 1 |
| Chest pain | 0 | 2 |

*In addition, one KT reported epistaxis and one reported pruritus; one PL reported insomnia.

By the end of the scheduled 5-day infusion period, six of the KT patients but only one of the PL patients had discontinued treatment because it was no longer needed. The time to the termination of the infusion was significantly shorter in the KT group, ($P = 0.009$). Those patients who continued to require relief from their pain were treated with the standard regimen of IM meperidine and hydroxyzine pamoate until they were pain free and could be discharged from the hospital.

### Evaluation of Safety

All the adverse events reported during the study are shown in Table V, stratified by body system. As can be seen, most of these involved the digestive system. In particular, no renal effects were noted. Two patients who received placebo and meperidine developed the acute chest syndrome, mapped to "chest pain" in Table V. There were no drug related abnormal laboratory values.

## DISCUSSION

Other nonsteroidal anti-inflammatory drugs have been used to treat VOC [1]. As already noted, we have evaluated the oral NSAID, diflunisal, with respect to a meperidine sparing effect, but found that there was no reduction in opioid requirement and no difference in analgesia compared with placebo [7]. In this study we have evaluated ketorolac, a more potent NSAID analgesic, and found that the IV infusion of ketorolac resulted in a significant reduction in the mean total meperidine requirement with respect to placebo.

Moreover, the results from a variety of pain measurements showed that the quality of analgesia obtained from the ketorolac-meperidine combination was superior to that of the placebo-meperidine regimen. Recognizing that these patients are very experienced in the use of

meperidine and other opiates for the treatment of their pain, it was of interest that six of the eleven who received placebo-meperidine rated it no better than their previous therapy, (i.e., meperidine and hydroxyzine), while six of the nine who received ketorolac-meperidine rated it "much better" or "better" than previous therapy.

Patients in the PL group spent a median of 7.2 days in hospital which is close to their personal average over the past 2 years and similar to the average of other patients [2]. The shorter duration in hospital stay of 3.3 days from the start of the infusion for the KT patients was an important finding. Measurement of the total days in the hospital from admission to discharge showed that the KT patients also stayed fewer days compared with the average duration of their admissions over the past 2 years.

The pain of VOC is probably a result of both ischemia and post infarction inflammation. Therefore it is reasonable to expect that a drug such as ketorolac would be effective in the management of VOC since it has antinociceptive and anti-inflammatory properties. That the pain in VOC, at least in part, results from inflammation is supported by results from a recent study of children with VOC in which treatment with high dose methylprednisolone was shown to shorten the duration of hospital stay [15]. However, steroid administration could be undesirable in patients with sickle cell disease who may be harboring infections and inhibition of prostaglandins probably could be accomplished more safely with ketorolac.

While it is unlikely that ketorolac alone will be adequate to control the pain of sickle cell VOC, from the results of this pilot study it appears to be safe and effective adjunctive therapy. Further investigation of this drug in the management of sickle cell VOC is warranted.

## ACKNOWLEDGMENTS

The authors thank the nursing staff for their help with this study and Anne Ling, MAS, for the statistical analyses. The study was supported in part by a grant from Syntex Research, a division of Syntex (USA), Inc., who manufacture ketorolac as Toradol™.

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