Intranasal Ketorolac for the Treatment of Postoperative Pain

John Moodie[1], Colin Brown[1], Eileen Bisley[1], Lincoln Bynum[2]

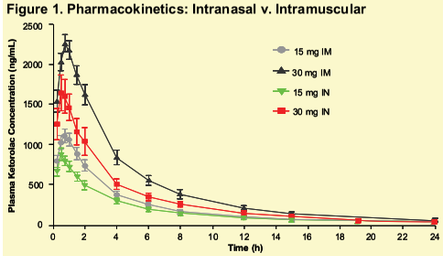
INTRODUCTION

Ketorolac tromethamine is a water soluble nonsteroidal, anti-inflammatory drug (NSAID) with potent analgesic and moderate anti-inflammatory activity (1, 2). The parenteral formulation is used IM or IV for the treatment of moderate to severe pain. The analgesic efficacy of ketorolac has been extensively evaluated in the postoperative setting, in both hospital inpatients and outpatients, and in patients with various other acute pain states. Ketorolac has been reported to provide relief from moderate to severe pain in a majority of patients and has similar analgesic efficacy to that of standard doses of morphine and meperidine.

An alternative parenteral formulation would be desirable once a patient is ambulatory when an IV line is no longer available and to avoid the discomfort of IM injections. The nasal route of administration is an alternative to parenteral injections and has been increasingly explored for systemic applications. The intranasal (IN) route has the advantages of relative ease of administration and the potential for rapid absorption of the drug across the nasal mucous membrane.

Evaluation of the 15- and 30-mg doses in a Phase 1 trial demonstrated that the bioavailability of IN ketorolac (ROX-888) was approximately 70% compared to IM administration and T_{max} was equivalent (3). The efficacy of ketorolac by various routes of administration has been established between 10 and 30mg. The purpose of the present study was to determine the efficacious dose in postoperative pain for further testing in Phase 3 efficacy studies.

Figure 1. Pharmacokinetics: Intranasal v. Intramuscular



PATIENTS AND METHODS

Eligibility Criteria

Inclusion: Age ≥ 18 years; body weight 100-300 lb; negative serum pregnancy test; able to provide written informed consent. Exclusion: allergy to ketorolac or EDTA; allergy to aspirin or other NSAIDs; a respiratory tract condition that could interfere with absorption of drug or assessment of safety; use of any IN product within 24 hours prior to study entry; clinically significant abnormality on screening laboratory tests; history of peptic ulcer disease or gastrointestinal bleeding; advanced renal impairment; allergy or significant reaction to opioids.

Study Design and Treatment Plan

This study was randomized, double-blind, and placebo-controlled. Following a screening visit, eligible subjects who had undergone major surgery (primarily orthopedic or abdominal) had a 2-day treatment period and a follow-up visit. When subjects reported a pain intensity (PI) rating of at least 40 on a 100-mm visual analog scale (VAS), they received a dose of IN ketorolac, 10 mg or 30 mg, or placebo. Thereafter, subjects received study drug every 8 hours until 40 hours. The last pain assessments occurred at 48 hours. Subjects had access to morphine sulfate (MS) by patient-controlled analgesia (PCA) throughout the study.

One hundred twenty subjects were to be randomly and in equal numbers assigned to 1 of 3 treatment groups: IN ketorolac 10 mg, IN ketorolac 30 mg, or IN placebo.

Baseline and Treatment Assessments

Subjects were assessed immediately before receiving the study drug and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 h after the first dose. Assessments included PI and quality of analgesia. PI was measured on a 100-mm VAS (0 = no pain; 100 = worst pain possible). Quality of analgesia was measured on a 5-point categorical scale (0 = poor; 4 = excellent). A global evaluation was completed once daily at bedtime on a 5-point categorical scale (0 = poor; 4 = excellent). The total MS dose by PCA was measured in milligrams and collected at 8-hour intervals.

Statistical Analyses

The primary efficacy variable was total MS use in milligrams through 24 hours. The treatment groups were compared with the Kruskal-Wallis test. Secondary variables included MS use through 48 hours and MS use from 24-48 hours. The PI ratings were tested with a 1-way ANOVA. An hourly PID was calculated by subtracting the hourly score from the baseline score. A SPID was calculated and analyzed at 4, 6, and 8 hours by adding the weighted PID scores over those intervals. Data on the quality of analgesia at 6, 24, and 48 hours and the once-daily global evaluation of analgesia were compared among the treatment groups using the Mantel-Haenszel test.

RESULTS

Subject Disposition and Characteristics

A total of 127 subjects enrolled. Table 1 shows that the majority of subjects received all 6 study drug doses: 90.5% in the placebo group, 74.4% in the 10-mg IN ketorolac group, and 76.2% in the 30-mg IN ketorolac group. There were no early withdrawals due to death, unsatisfactory response, protocol violation, or "lost to follow-up". The proportions of subjects discontinuing the study early because of an adverse event were similar among the 3 treatment groups.

Most baseline characteristics were similar in the 3 treatment groups, except for a trend toward a higher mean age and higher percentage of men in the placebo group. Overall, the mean age was 53 years, 33.1% were men, 76.4% were Caucasian, 21.3% were Polynesian, mean height was 167 cm, and mean weight was 80.1 kg.

Analgesic Response

The mean MS consumption during the first 24 hours was 56.5 mg in the placebo group, 54.3 mg in the 10-mg IN ketorolac group, and 37.8 mg in the 30-mg IN ketorolac group. As shown in Table 2, the difference between the 30-mg IN ketorolac group and the placebo group was statistically significant (P = .0165). The difference between the two IN ketorolac groups was also significant (P = .0289), but the difference between the IN 10-mg ketorolac and the placebo group was not.

The mean MS consumption during the intervals of 24–48 and 0–48 hours was significantly lower in the 30 mg IN ketorolac than in the placebo group (Table 2). The differences between the 10-mg IN ketorolac and the placebo group and between the 2 IN ketorolac groups were not statistically significant for these intervals.

Measurements of MS use by 8-hour intervals over 48 hours showed a lower MS use in the IN ketorolac groups than in the placebo group for nearly all of these intervals, as the following mean values (in mg) show:

Dose Group	0–8 h	8–16 h	16–24 h	24–32 h	32–40 h	40–48 h
Placebo	25.4	15.0	16.1	10.6	10.4	11.6
IN KET 10 mg	26.1	14.2	13.9	11.9	8.6	7.7
IN KET 30 mg	18.3	8.9	10.6	8.2	7.2	7.7

At 6 hours postdose, the mean PI values were 13.1 in the 30-mg IN ketorolac group and 22.3 in the placebo group (P = .0024). The differences between the 10-mg IN ketorolac and placebo groups and between the 2 IN ketorolac groups were not significant, and none of the intergroup differences were significant at 24 hours. At 48 hours, mean PI was 4.4 in the 30-mg IN ketorolac group and 14.2 in the placebo group (P = .0179); mean PI was 13.3 in the 10-mg IN ketorolac group, not significantly different from placebo but significantly different from the IN ketorolac 30-mg group (P = .0099).

As shown in Table 2, the SPID values at 4, 6 and 8 hours were significantly different between the IN ketorolac 30 mg and the placebo group. Comparing the 2 IN ketorolac groups also showed significant differences in favor of IN ketorolac 30 mg for SPID at 4 h (P = .0183), at 6 h (P = .0293) , and at 8 h (P = .0327).

Ratings of the quality of analgesia showed IN ketorolac 30 mg to be significantly superior to the placebo group at 6 hours (P = .0028). IN Ketorolac 30 mg also tended to be superior to IN ketorolac 10 mg (P = .0591). At 24 hours, none of the differences were significant. At 48 hours, the difference between the 2 IN ketorolac groups was significant (P = .0193), and the difference between the IN ketorolac 30 mg and the placebo group was nearly significant (P = .0558).

The bedtime global ratings were not significantly different on either day between the IN ketorolac 30 mg and the placebo group, but were significantly different between the 2 IN ketorolac groups on day 2 (P = .0268).

Safety

The numbers of serious adverse events occurring in the 48-hour period of dosing were zero, 2, and 1 in the placebo, 10 mg, and 30-mg groups, respectively. Adverse events were frequently reported in all treatment groups (Table 3). The distribution of most of these events was similar among the 3 treatment groups; significant differences between IN ketorolac 30 mg and placebo were seen in the rates of pyrexia (P = .0088) and tachycardia (P = .0317), and the rates of pruritus, somnolence, and hypotension tended to be lower with IN ketorolac. Adverse events typically associated with NSAID use (ie, abdominal pain, dyspepsia, hematemesis, fluid retention, and oliguria) were all reported by a total of 4 (3.1%) or fewer subjects with similar rates in all groups.

Table 1. Subject Disposition & Baseline Characteristics

	Placebo	Ketorolac 10 mg	Ketorolac 30 mg	Total
Number of patients				
Enrolled	42	43	42	127
Received all 6 doses	38 (90.5%)	32 (74.4%)	32 (76.2%)	102 (80.3%)
Early withdrawal	6 (14.3%)	11 (25.6%)	11 (26.2%)	28 (22.0%)
–for adverse events	4 (9.5%)	5 (11.6%)	3 (7.1%)	12 (9.4%)
–for "other" reasons	2 (4.8%)	6 (14.0%)	8 (19.0%)	16 (12.6%)
Age				
Mean (SEM)	56.7 (2.5)	49.7 (2.1)	52.8 (2.5)	53.0 (1.4)
Median (range)	61 (19–78)	47 (22–78)	53 (24–80)	54 (19–80)
Sex				
Male	18 (42.9%)	11 (25.6%)	13 (31.0%)	42 (33.1%)
Female	24 (57.1%)	32 (74.4%)	29 (69.0%)	85 (66.9%)
Ethnicity				
Asian	0	2 (4.7%)	0	2 (1.6%)
Caucasian	32 (76.2%)	31 (72.1%)	34 (81.0%)	97 (76.4%)
Hispanic	0	0	1 (2.4%)	1 (0.8%)
Polynesian	10 (23.8%)	10 (23.3%)	7 (16.7%)	27 (21.3%)
Height (cm)				
Mean (SEM)	167 (1.6)	167 (1.5)	167 (1.3)	167 (0.8)
Median	167	165	166	166
Range	135–183	152–197	150–188	135–197
Weight (kg)				
Mean (SEM)	79.7 (2.6)	81.4 (2.8)	79.2 (2.4)	80.1 (1.5)
Median	77	83	78	80
Range	49–115	50–124	50–117	49–124

Table 2. Mean (SEM) Analgesic Responses by Treatment Group

	Placebo	Ketorolac 10 mg	Ketorolac 30 mg	*P* Value*
MS use (mg)				
0-24 h	56.5 (4.8) (n = 41)	54.3 (6.4) (n = 41)	37.8 (5.0) (n = 41)	.0165
24-48 h	32.6 (4.8) (n = 39)	28.3 (5.7) (n = 38)	23.1 (5.3) (n = 35)	.0182
0-48 h	87.9 (9.4) (n = 39)	78.7 (11.2) (n = 38)	61.4 (10.8) (n = 35)	.006
SPID				
4 hour	75.9 (10.1) (n = 42)	89.6 (10.5) (n = 43)	120.1 (9.3) (n = 42)	.0017
6 hour	130.6 (10.1) (n = 42)	154.8 (15.5) (n = 43)	195.5 (12.1) (n = 42)	.0015
8 hour	190.1 (18.8) (n = 42)	213.8 (21.0) (n = 43)	269.3 (15.4) (n = 42)	.0025

** Kruskal-Wallis test for difference between ketorolac 30 mg and placebo*

Table 3. Most Common Adverse Events by MedDRA Preferred Term

	Placebo	Ketorolac 10 mg	Ketorolac 30 mg	Total
Number of patients	42	43	42	127
Patients reporting AEs	41 (97.6%)	43 (100.0%)	40 (95.2%)	127 (97.6%)
Pyrexia	26 (61.9%)	24 (55.8%)	14 (33.3%)	64 (50.4%)
Nausea	20 (47.6%)	25 (58.1%)	19 (45.2%)	64 (50.4%)
Anemia	14 (33.3%)	12 (27.9%)	11 (26.2%)	37 (29.1%)
Vomiting	11 (26.2%)	12 (27.9%)	12 (28.6%)	35 (27.6%)
Headache	9 (21.4%)	15 (34.9%)	9 (21.4%)	33 (26.0%)
Tachycardia	17 (40.5%)	7 (16.3%)	8 (19.0%)	32 (25.2%)
Constipation	10 (23.8%)	8 (18.6%)	11 (26.2%)	29 (22.8%)
Pruritus	10 (23.8%)	8 (18.6%)	4 (9.5%)	22 (17.3%)
Dizziness	5 (11.9%)	7 (16.3%)	6 (14.3%)	18 (14.2%)
Nasal passage irritation	5 (11.9%)	6 (14.0%)	7 (16.7%)	18 (14.2%)
Somnolence	5 (11.9%)	9 (20.9%)	1 (2.4%)	15 (11.8%)
Hypotension	6 (14.3%)	4 (9.3%)	3 (7.1%)	13 (10.2%)

Figure 2. Cumulative PCA Morphine Usage by Time

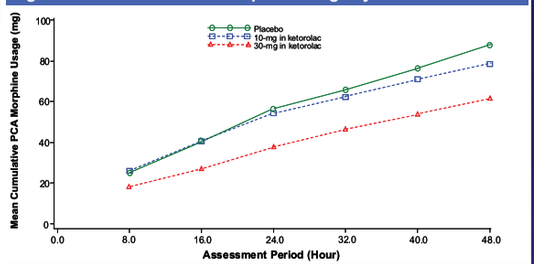
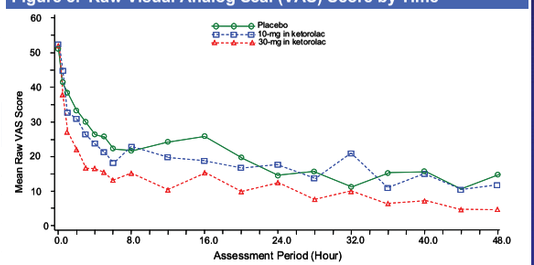


Figure 3. Raw Visual Analog Scal (VAS) Score by Time



DISCUSSION

The analgesic efficacy of IN ketorolac in 30-mg doses was evident in the significantly lower morphine consumption in this treatment group compared to either the 10-mg IN ketorolac or the placebo treatment group at multiple time points. Pain severity, quality of pain control, and global pain relief measurements all favored the 30-mg IN ketorolac group over the other treatment groups. Thus, even though the subjects in the 30-mg IN ketorolac group used less morphine, they experienced superior pain relief. The safety analyses showed that the 30-mg IN ketorolac group was associated with a side-effect profile at least as favorable as that observed in the other two treatment groups.

CONCLUSION

We conclude that IN ketorolac (ROX-888) is well tolerated by patients with postoperative pain following major surgery and has good analgesic efficacy, which reduces the need for opioid use. Ketorolac administered as an IN formulation appears to have analgesic efficacy similar to the IM and IV formulations. Thirty mg was selected as the dose for subsequent Phase 3 trials now underway.

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[1]Waikato Clinical Research, Hamilton, New Zealand; [2]ICON Clinical Research, Redwood City, California

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