Intranasal Ketorolac (ROX-888) for Postoperative Pain: A Phase 3, Double-Blind, Randomized Study

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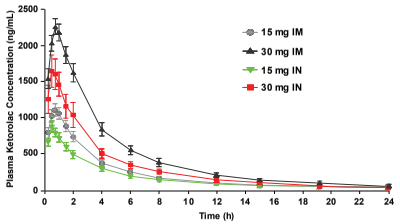
INTRODUCTION

Ketorolac tromethamine is a water soluble, nonsteroidal, anti-inflammatory drug (NSAID) with potent analgesic and moderate anti-inflammatory activity (1, 2). IM or IV parenteral ketorolac formulations are currently used for the treatment of moderate to severe acute 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. Previous studies have shown that ketorolac provides relief from moderate to severe pain in a majority of patients and has similar analgesic efficacy to standard doses of morphine and meperidine.

A convenient non-injectable parenteral formulation of ketorolac would be desirable to reduce the use of opioid analgesics in the ambulatory setting. 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 rapid absorption across the nasal mucous membrane.

Evaluation of 15-mg and 30-mg ketorolac doses in a Phase 1 trial demonstrated that the bioavailability of IN ketorolac was approximately 70% compared to IM administration and had Tmax at least comparable to the IM route (3) *(see Figure 1)*.

Figure 1. Pharmacokinetics: Intranasal v. Intramuscular



The efficacy of IN ketorolac 30 mg (ROX-888) was previously established in multiple studies, including a Phase 3 trial in patients undergoing major orthopedic or abdominal surgery. In that trial, patients receiving IN ketorolac 30 mg up to 3 times daily experienced significantly better analgesia while consuming significantly less morphine compared to placebo.

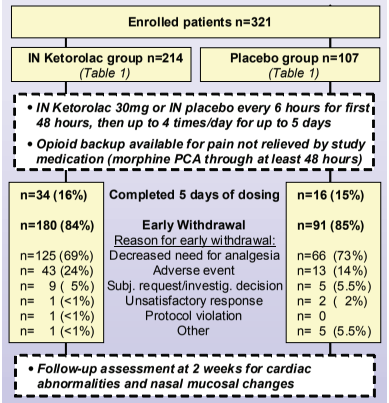
The current study was designed to further assess the safety and efficacy of IN ketorolac 30 mg dosed up to four times daily (the current dosing regimen for IM ketorolac) in patients undergoing major abdominal surgery.

RESULTS

Patients

- Men or women age 18 through 64 years undergoing major abdominal surgery by an open procedure who were expected to remain in the hospital for at least 48 hours and up to 5 days

Study Design and Treatment Plan



Baseline and Treatment Assessments

- Subjects were assessed immediately before receiving the study drug and at 20, 40, and 60 minutes, and 2, 3, 4, 5, 6, 12, 18, 24, 36, 42, and 48 hours after the first dose
- Pain intensity (PI) 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 morphine sulfate (MS) dose by PCA was measured in milligrams and collected at 2-hour intervals for the first 12 hours and 6-hour intervals for the remainder 72 hours
- Safety was assessed by spontaneously reported AEs, physical examinations including cardiovascular examination and evaluation of the nasal mucosa at the end of dosing, and routine clinical laboratory tests. A final safety visit included cardiovascular and nasal evaluations 14 days after the end of dosing.

RESULTS, Cont.

Results

Statistically significant superiority for ketorolac was demonstrated for:

- The primary endpoint, SPID6, as well as SPID4 *(Figure 2)*
- Morphine consumption for the time intervals 0-24 hours, 24-48 hours and 0-48 hours *(Figure 3)*
- Mean PID Scores at 20 minutes, 60 minutes, 2 hours and 3 hours *(Figure 4)*
- Quality of analgesia (LOCF analysis) at all timepoints through 6 hours, except 40 minutes *(Figure 5)*
- Day 1 global assessment of pain control ($P = 0.009$)

Safety

- The most common AEs are shown in Table 2
- The overall rates of treatment-emergent AEs were similar in the 2 treatment groups and were consistent with patients undergoing major abdominal surgery. No deaths occurred.
- The rates of subjects experiencing SAEs were similar (12 subjects (5.6%) in the ketorolac group and 6 (5.6%) in the placebo group)
- Mild events of rhinalgia and nasal irritation occurred more frequently in the IN ketorolac group
- There was a trend for reduction in opioid-related side effects in the ketorolac group compared to the placebo group
- There were no differences in treatment-emergent cardiovascular at the end of the study at the 14-day follow-up

Table 1. Subject Disposition & Baseline Characteristics

	Placebo	IN Ketorolac 30 mg
No. of Patients	107	214
Age		
Mean (SE)	46 (0.9)	46 (0.6)
Range	22-64	28-70
Sex		
Male	4 (4%)	8 (4%)
Female	103 (96%)	206 (96%)
Ethnicity		
Non-hispanic	88 (82%)	182 (85%)
Hispanic	19 (18%)	32 (15%)
Race		
Black	11 (10%)	23 (11%)
White	76 (71%)	154 (72%)
All other	20 (19%)	37 (17%)
Weight (kg)		
Mean (SE)	80 (1.7)	77 (1.3)
Range	49-126	45-141
Height (cm)		
Mean (SE)	165 (0.8)	164 (0.5)
Range	147-191	145-188
Baseline Pain Intensity		
Mean (SE)	61 (1.1)	63 (1.6)
Median	58	59
Range	33-100	40-100

Table 2. Most Commonly Reported (>10%) Adverse Events

	Placebo + Opioid	IN Ketorolac 30 mg + Opioid
No. of Patients	107	214
Nausea	66 (62%)	122 (57%)
Constipation	35 (33%)	59 (28%)
Vomiting	24 (22%)	51 (24%)
Headache	25 (23%)	47 (22%)
Rhinalgia	0 (0%)	43 (20%)
Flatulence	23 (22%)	39 (18%)
Pyrexia	36 (34%)	34 (16%)
Anemia	11 (10%)	33 (15%)
Pruritus	19 (18%)	31 (15%)
Insomnia	16 (15%)	30 (14%)
Epistaxis	17 (16%)	29 (14%)
Nasal Discomfort	3 (3%)	24 (11%)
Tachycardia	15 (14%)	20 (9%)

Figure 2. Pain Intensity
Primary Endpoint: SPID6

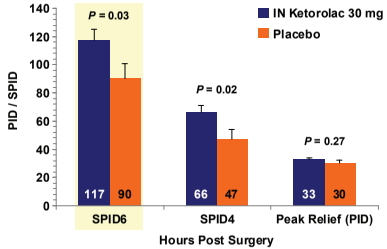


Figure 3. PCA Morphine Consumption

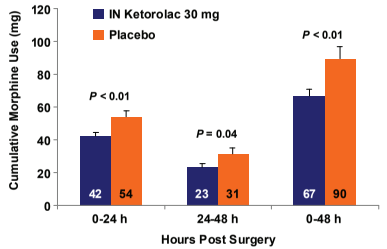
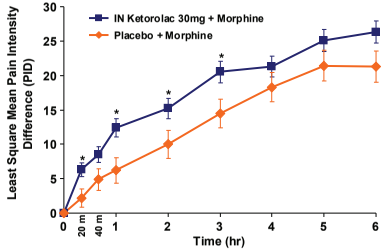
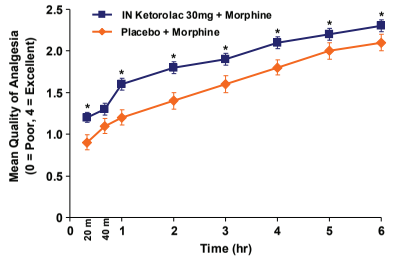


Figure 4. Mean Pain Intensity Difference (PID) through 6-hours



** Significantly different from placebo, P<0.05*

Figure 5. Mean Quality of Analgesia through 6-hours (LOCF)



** Significantly different from placebo, P<0.05*

CONCLUSION

- **IN ketorolac 30 mg (ROX-888) self-administered up to four times a day was effective and well tolerated in patients who were in moderate-to-severe acute pain after abdominal surgery**
- **IN ketorolac reduced opioid use and improved quality of analgesia**
- **IN ketorolac may provide a new, non-opioid analgesic alternative for ambulatory patients**

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