Intranasal Ketorolac for the Treatment of Postoperative Pain

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ABSTRACT

Objective: Ketorolac is a non-opiate analgesic for management of moderate-to-severe acute pain. Ketorolac is a mixed COX1/2 inhibitor with potent analgesia when administered as an IV or IM injection. An intranasal (IN) ketorolac formulation (ROX-888) is in clinical development as an easy-to-administer alternative to opiate analgesics for ambulatory pts with acute pain. This Phase 3 randomized, double-blind, placebo-controlled study evaluated the analgesic efficacy and tolerability of ROX-888 in major surgery pts expected to remain in hospital for 2-5 days.

Methods: Adult men and women who underwent major surgery were randomly assigned 2:1 to receive ROX-888 (30 mg) or placebo. The study consisted of two parts, a multidose arm with background morphine sulfate (MS) via PCA and a single dose arm without PCA. Pts in the multidose arm received study drug 3x daily for up to 5 d with access to PCA for 48 hr. Efficacy assessments in the multidose arm included global evaluation of pain control and mean total MS use. In the single dose arm, pts were removed from PCA 3hr prior to the first study dose the day after surgery and received a single dose of ROX-888 or placebo without other analgesia when VAS scores were ≥40. The primary efficacy variable in the single dose arm was the 6-hour summed pain intensity difference (SPID6) score. Safety was assessed from spontaneously reported adverse events and measurement of vital signs.

Results: Three hundred surgery pts (n=199 ROX-888, n=101placebo) were enrolled. Mean age was 52 yr and 69% of pts were women. Major surgeries included abdominal (52%) and orthopaedic (46%) procedures. Of the 300, 189 (n=115 ROX-888, n=74 placebo) entered the single dose arm. Single dose SPID6 was significantly higher (indicating better analgesia) in pts treated with ROX-888 compared to placebo (83.3 vs. 37.2, *P*<0.007). PID was significantly greater in the ROX-888 group by 30min (Figure). In the multidose arm, a significantly greater proportion of pts in the ROX-888 group reported excellent pain control compared with placebo on day 3 (27% vs. 10%, *P*< 0.002). MS use was significantly lower in the ROX-888 group (29%) compared to placebo for all time intervals. Incidence of treatment emergent adverse events (98%) was similar in the ROX-888 and placebo groups reflecting the large number of events typical of pts with major surgical procedures and receiving opioid analgesics. Common adverse events (*P*<0.001) were nausea, vomiting, fever and constipation. There was a trend in the ROX-888 group for lower incidence of opioid-related side effects (e.g., constipation, intermittent pyrexia), but statistical significance was not reached. Local nasal irritation occurred more frequently in the ROX-888 group vs. placebo (24% vs. 2%), and most events were mild. Incidence of serious adverse events was similar in the 2 groups: 2.5% (n=5) in the ketorolac group and 2.0% (n=2) in the placebo group.

Conclusion: IN ketorolac 30 mg was well tolerated and provided fast and effective pain relief with reduced opioid analgesia use.

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 has been shown to result in rapid absorption of ketorolac across the nasal mucous membrane.

Evaluation of 15- 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 a shorter Tmax than IM injection (3). The efficacy of IN ketorolac 30 mg was established in a Phase 2 trial in patients undergoing major orthopedic or abdominal surgery. In that trial, patients receiving IN ketorolac 30 mg experienced significantly better analgesia while consuming significantly less morphine compared to placebo.

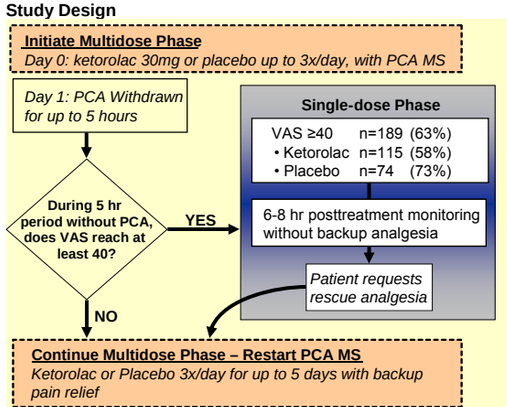
RESULTS

Patients

Major Inclusion Criteria: men or women age 18 years or older; body weight ≥ 100 pounds and ≤ 300 pounds; negative serum pregnancy test; able to provide written informed consent; PI score of ≥ 40 mm on a 100-mm VAS; expected to remain in the hospital for at least 48 hours with the possibility of remaining for 5 days

Major Exclusion Criteria: current respiratory tract infection; active ulcer disease or recent history of peptic ulcer disease or GI bleeding; advanced renal impairment or risk of renal failure due to volume depletion; allergy to NSAIDS or opioids.

Study Design



Results

Single-dose Analysis: statistically significant superiority for ketorolac was demonstrated for:

- The primary endpoint SPID-6, as well as SPID-4 and Peak Relief (Table 1)
- PID scores at all timepoints through 4 hours (Figure 1)
- Quality of Analgesia at all timepoints through 5 hours
- Time to restart of rescue analgesia (PCA morphine)
- % of subjects who experienced meaningful analgesia in ≤1.0 and ≤1.5 hours

Multidose Analysis: statistically significant superiority for ketorolac was demonstrated for:

- Morphine consumption over all intervals analyzed (Table 3), including 29.8% less morphine in the ketorolac group during the first 24 hours after surgery
- Quality of Analgesia 8 hours after the first dose on Day 0 (Figure 2)
- Global evaluations on Days 3 and 4 (Figure 3)

Safety

The overall rates of treatment-emergent AEs were similar in the 2 treatment groups. No deaths occurred. The rates of SAEs were also similar, with 5 (2.5%) in the ketorolac group and 2 (2.0%) in the placebo group, one of which was considered possibly related to study treatment. One subject in the ketorolac group experienced a moderate wound complication that was considered to be possibly related to study drug by the investigator.

The AEs that occurred more frequently in the ketorolac group were most often related to nasal irritation. The majority of nasal irritation events were typically transient and rated as mild. There was a trend for reduction in opioid-related side effects in the ketorolac group compared to the placebo group. The lower rates of pruritus, constipation and tachycardia in the ketorolac group (Table 4) likely reflected the decreased morphine use by patients in that group.

Table 1. Subject Disposition & Baseline Characteristics

	Placebo	IN Ketorolac 30 mg	Total
Number of Patients	40	40	80
Age - Mean (SE)	51.0 (1.2)	51.7 (0.9)	51.5 (0.7)
Sex			
Male	37 (37%)	55 (28%)	92 (31%)
Female	64 (63%)	144 (72%)	208 (69%)
Weight (kg) - Mean (SE)	86.8 (1.82)	82.2 (1.26)	83.7 (1.04)
Height (cm) – Mean (SE)	169.2 (0.99)	167.1 (0.70)	167.8 (0.58)
Type of Surgery			
Abdominal	54 (53.5%)	102 (51.3%)	156 (52.0%)
Orthopedic	43 (42.6%)	96 (48.2%)	139 (46.3%)
Other	4 (4.0%)	1 (0.5%)	5 (1.7%)
Baseline Pain Intensity, Day 0 Predose Mean (SE)	51.1 (0.9)	54.7 (0.6)	

Table 2. Single-dose Phase – Pain Intensity Difference

	Placebo *n = 73*	IN Ketorolac 30 mg *n = 115*	*P* Value
4 hour SPID	32.9 (9.20)	71.0 (7.46)	.002
6 hour SPID	37.2 (12.87)	83.3 (10.60)	.007
Peak Relief	19.8 (2.76)	30.9 (1.88)	.001

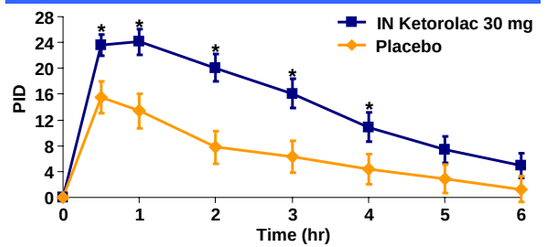
Table 3. Multidose Phase – Morphine Consumption

	Placebo *n = 101*	IN Ketorolac 30 mg *n = 199*	*P* Value
0 – 24 hour	48.4 mg (2.93)	34.0 mg (1.64)	<.001
24 – 48 hour	29.2 mg (2.61)	18.8 mg (1.51)	<.001
0 – 48 hour	77.4 mg (5.28)	51.4 mg (2.75)	<.001

Table 4. Most Commonly Reported (>10%) Adverse Events

	Placebo	IN Ketorolac 30 mg	Total
Number of Patients	101	199	300
Nausea	61 (60%)	115 (58%)	176 (59%)
Pyrexia/intermittent pyrexia	68 (67%)	87 (44%)	155 (52%)
Constipation	36 (36%)	57 (29%)	93 (31%)
Vomiting	29 (29%)	56 (28%)	85 (28%)
Nasal passage irritation	2 (2%)	48 (24%)	50 (17%)
Headache	19 (19%)	47 (24%)	66 (22%)
Flatulence	32 (32%)	46 (23%)	78 (26%)
Anemia	12 (12%)	37 (19%)	49 (16%)
Tachycardia	20 (20%)	28 (14%)	48 (16%)
Wound secretion	9 (9%)	24 (12%)	33 (11%)
Pruritus	19 (19%)	21 (11%)	40 (13%)
Dizziness	11 (11%)	11 (6%)	22 (7%)

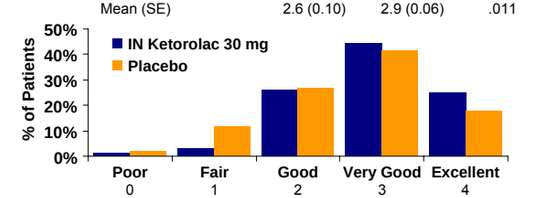
Figure 1. Mean PID (SE) Single Dose Phase (no PCA MS)



** Significantly different from placebo, P<0.05*

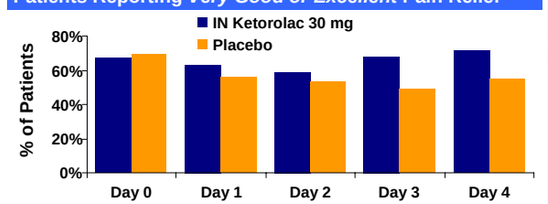
Figure 2. Quality of Analgesia on Day 0 8 hours After First Dose (scale: 0 = poor, 4 = excellent)

Quality of Analgesia *(0 = poor, 4 = excellent)*	Placebo *n = 101*	IN Ketorolac *n = 199*	*P* Value
Mean (SE)	2.6 (0.10)	2.9 (0.06)	.011



Note: all patients had access to PCA MS

Figure 3. Global Assessment of Pain Control Patients Reporting *Very Good or Excellent* Pain Relief



Note: all patients had access to alternative pain relief if required

CONCLUSION

Ketorolac administered as an IN spray provided excellent analgesia in the postoperative period following major surgery, and was generally well tolerated. This new formulation of ketorolac provides a valuable alternative to intravenous and intramuscular administration for use either alone or in "balanced" or "multimodal" analgesic regimens.

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