Role of Spinal Cyclooxygenase in Human Postoperative and Chronic Pain

James C. Eisenach, M.D.,* Regina Curry, R.N.,† Richard Rauck, M.D.,‡ Peter Pan, M.D.,§
Tony L. Yaksh, Ph.D.‖

ABSTRACT

Background: Nonsteroidal antiinflammatory drugs are commonly used to treat postoperative and chronic pain. Animal studies suggest that these drugs act, in part, by blocking prostaglandin production in the spinal cord. The authors tested intrathecal ketorolac in patients with chronic or postoperative pain.

Methods: After approval of the institutional review board and the Food and Drug Administration, three clinical studies were performed. First, 15 patients receiving chronic intrathecal morphine received 0.5–2.0 mg of intrathecal ketorolac. Second, 12 patients receiving chronic intrathecal morphine received, in a double-blinded, randomized, cross-over design, intrathecal saline or 2.0 mg of ketorolac, with pain intensity as the primary outcome measure. Third, 30 patients undergoing total vaginal hysterectomy received, in a double-blinded, randomized, controlled design, intrathecal saline or 2.0 mg of ketorolac, with bupivacaine with time to first morphine dose after surgery as the primary outcome measure.

Results: Patients with chronic pain had many symptoms before intrathecal injection, without worsening of these symptoms from ketorolac. Pain intensity was reduced by intrathecal ketorolac, but this did not differ from placebo. In the first study, pain was reduced by intrathecal ketorolac in patients with high cerebrospinal fluid prostaglandin E2 concentrations but not in those with normal concentrations. Intrathecal ketorolac did not alter time to first morphine after surgery.

Conclusions: Intrathecal ketorolac did not relieve chronic pain or extend anesthesia or analgesia from intrathecal bupivacaine administered at the beginning of surgery. Under the conditions of these studies, it seems that spinal cylcooxygenase activity does not contribute to chronic or postoperative pain.

What We Already Know about This Topic

❖ Spinal cyclooxygenase is activated in animal models of acute and chronic pain, but the relevance of this to human clinical pain conditions is uncertain

What This Article Tells Us That Is New

❖ In three studies including 27 chronic pain and 30 postoperative patients, intrathecal injection of the cyclooxygenase inhibitor, ketorolac, failed to reduce pain more than placebo

❖ A subset of chronic pain patients had higher than normal cerebrospinal fluid concentrations of prostaglandins, and ketorolac reduced pain in this subset

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THE goal of this research was to translate laboratory studies on the spinal sites of action of nonsteroidal antiinflammatory drugs (NSAIDs) to humans with acute and chronic pain. These drugs are commonly administered to treat postoperative pain, either alone after procedures including dental extractions or, more commonly, with opioids. In addition, NSAIDs are the primary constituents of the first step in the three-step treatment approach to cancer pain advocated by the World Health Organization,[1] now commonly applied to chronic pain.

It is usually assumed that NSAIDs produce pain relief by blocking cyclooxygenase at the sites of inflammation causing the pain. More recently, a spinal site of cyclooxygenase activity relevant to pain has been proposed. In animals, prostaglandins are synthesized in the spinal cord. This synthesis is increased by peripheral nerve stimulation,[2] and the spinal

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⊕ Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

injection of cyclooxygenase inhibitors reduces nocifensive behaviors from excitatory input into the spinal cord.[3] In humans, epidural injection of an aspirin derivative produced long-lasting analgesia in patients with chronic cancer pain,[4] consistent with these observations in animals. Although cyclooxygenase inhibitors have not been previously administered intrathecally or epidurally in humans after surgery, the concentrations of the prostaglandin, PGE2, increase postoperatively, and these concentrations correlate with the intensity of postoperative pain.[5]

To test the role of spinal cyclooxygenase in human postoperative and chronic pain, we performed a series of studies with intrathecal injection of the NSAID ketorolac. This followed animal testing for safety[6] of a commercially available, preservative-free formulation of ketorolac (Acular PF®; Allergan, Irvine, CA) and the approval of regulatory agency to test this drug in humans by intrathecal injection. We previously showed that intrathecal ketorolac not only failed to produce side effects in healthy volunteers but also failed to reduce pain to acute noxious heat stimuli applied to the skin.[7] In a series of studies on experimental pain in humans, intrathecal ketorolac failed to reduce hypersensitivity from topical capsaicin, a model of acute sensitization thought to be relevant to chronic pain states, although it did reduce the area of hypersensitivity from ultraviolet-B burn alone or combined with local heat to a small degree.[8] These studies suggest that intrathecal ketorolac may have limited analgesic effects in humans, but it could be active in states of central sensitization, including postoperative and chronic pain.

Materials and Methods

Three independent clinical studies were performed in a total of 57 adult patients between August 2002 and November 2005. In each study, Institutional Review Board (Wake Forest University and Forsyth Medical Center, Winston-Salem, North Carolina) approval was obtained; all patients gave written informed consent, and an independent Data Safety Monitoring Board regularly reviewed all adverse events. All three studies were performed with Food and Drug Administration regulatory oversight under Investigational New Drug approval 62,179. Before the studies began, stability testing of preservative-free ketorolac mixed with bupivacaine or with morphine was performed and submitted to the Food and Drug Administration.

All patients were of American Society of Anesthesiologists physical status 1, 2, or 3 and had no history of allergy to ketorolac, morphine, or bupivacaine. Women of childbearing potential had a negative pregnancy test just before study.

Open-Label Chronic Pain Study

To assess tolerability in the first study of intrathecal ketorolac in patients, 15 subjects with chronic pain who were receiving intrathecal morphine *via* an implanted pump for at least 3 months were recruited. This study was performed at the

Center for Clinical Research, an active research arm of Piedmont Anesthesia and Pain Associates, Winston-Salem, North Carolina.

By using a standard open-label, dose escalation study design, the first five subjects received 0.5 mg of preservative-free ketorolac (Acular PF®; Allergan) in a 1-ml volume diluted with normal saline, the next five subjects received 1.0 mg of ketorolac, and the last five subjects received 2.0 mg of ketorolac. These doses were chosen based on the anticipated therapeutic dose range and did not exceed the maximum dose of 2.0 mg under our regulatory approval. The study focused on safety, with analysis of adverse events at the end of each fifth patient and with predetermined stopping conditions before escalating to the next dose.

On the day of study, a neurologic examination was performed, testing for gross motor strength and sensory deficits and deep tendon reflexes in all extremities. Any subjective neurologic symptoms were noted. Blood pressure and heart rate were measured using a noninvasive automated blood pressure cuff. A needle was then inserted into the side port of the pump, the deadspace of the catheter (calculated from the known length of catheter in each subject) was aspirated, and 2 ml of cerebrospinal fluid (CSF) was aspirated and frozen for PGE2 analysis. Ketorolac was then injected after preservative-free saline to flush the deadspace of the catheter system, and the pump was programmed to stop the infusion of morphine. One hour after injection, a needle was inserted into the side port of the pump, the deadspace was aspirated, and 2 ml of CSF was aspirated and frozen for PGE2 and ketorolac analysis. The pump was then programmed to provide a loading infusion of the deadspace of the catheter (which required 6–8 h), followed by return to normal infusion rate.

Blood pressure and heart rate were measured noninvasively before and at 15-min intervals for 1 h, then hourly until 4 h after administering spinal ketorolac. Patients reported pain using a standard 10-cm visual analog scale (VAS) before injection and at the times of blood pressure monitoring. At these same times, patients were queried for the presence of headache, anxiety, dizziness, lower extremity weakness, nausea, sedation, or abdominal or bladder discomfort, and if present, they were asked to rate each as mild, moderate, or severe. They were also asked to report any other side effects. Subjects were discharged and contacted daily for 2 days, then 1week after the study and questioned about neurologic symptoms, symptoms of postdural puncture headache, or other complaints. Patients were paid $100 for their participation in this research study.

Randomized, Controlled Chronic Pain Study

The aforementioned open-label study showed that ketorolac was well tolerated to the maximum dose studied (2.0 mg). Therefore, we designed a double-blinded, randomized, controlled, cross-over study comparing 2.0 mg of intrathecal ketorolac with normal saline placebo. Twelve patients with chronic pain and receiving intrathecal morphine *via* an im-

planted pump for at least 6 weeks were included. This study was also performed at the Center for Clinical Research, Winston-Salem, North Carolina.

Patients were studied twice. Patients were randomized, using a computer-generated series of random numbers, to receive either preservative-free ketorolac (2 mg) or saline on their first visit, with the alternative treatment on their second visit. The intrathecal injection solution was prepared by an individual not involved in the patient's care or research evaluation.

On the day of each study, before drug administration, patients underwent a baseline neurologic examination, testing for gross motor strength and sensory deficits and deep tendon reflexes in all extremities. Any subjective neurologic symptoms were noted. Blood pressure and heart rate were measured using a noninvasive automated blood pressure cuff. Ongoing pain was recorded using a sliding mechanical VAS device separately for pain intensity and unpleasantness. In addition, VAS pain assessments to heat stimuli applied to the skin on a lower extremity at a site without spontaneous pain were obtained using a commercially available Peltier-controlled thermode (Medoc, Durham, NC). The thermode temperature was increased from baseline (35°C) to 43°, 44°, 45°, 46°, 47°, 48°, or 49°C in random order with 25-s interstimulus intervals between stimuli.

After baseline measures, a needle was inserted into the side port of the pump, the deadspace was aspirated, and study drug was injected in a 1-ml volume after preservative-free saline to flush the deadspace of the catheter system. Patients were randomized, using a computer-generated series of random numbers, to receive either preservative-free ketorolac (2 mg) or saline on their first visit, with the alternative treatment on their second visit. Ongoing pain intensity and unpleasantness were assessed using a mechanical VAS at 15 and 30 min, then at 1, 2, and 4 h after intrathecal injection. The responses to thermal nociceptive testing as performed at baseline were determined at 30 min and 2 h after injection on the skin of a lower extremity at a site without spontaneous pain. Patients were queried regarding the same side effects listed in the open-label study at 30, 60, 120, 180, and 240 min after injection, and if side effects were present, they were asked to rate them as mild, moderate, or severe. They were also asked to report any other side effects. Subjects were discharged and contacted daily for 2 days, then 1 week after the study and questioned about neurologic symptoms, symptoms of postdural puncture headache, or other complaints.

Patients returned at least 1 week, but no more than 3 months later, for the crossover treatment. Patients were paid $50 for completion of the first study day and an additional $100 for completion of the second study day.

The primary outcome measure was mechanical VAS pain intensity after intrathecal injection, with groups compared by repeated measures two-way ANOVA. Based on our previous studies in patients with chronic pain,[9–11] a study of 12 individuals was planned to distinguish an average difference

in pain scores over the time of testing between placebo and ketorolac of 2.2 with an α of 0.05 and $1 - \beta$ of 0.8, assuming a mean pain score of 5 in the control condition and a group SD of 2.5.

Postoperative Pain Study

The postoperative pain study was performed at the Sarah Lee Center for Women's Health, Winston-Salem, North Carolina. Women scheduled for total vaginal hysterectomy with estimated surgical duration less than 2 h under spinal anesthesia were recruited. Women taking more than 60 mg of codeine or equivalent per day for pain were excluded.

Intraoperative anesthesia was provided with a combined spinal–epidural technique, using an initial intrathecal injection of bupivacaine (15 mg) with either preservative-free ketorolac (2 mg) or an equal volume (0.4 ml) of saline. The study was double-blinded and randomized, using a computer-generated table of random numbers. The intrathecal injection solution was prepared by an individual not involved in the patient's care or research evaluation. Intraoperative sedation was provided with intravenous (IV) midazolam (up to 4 mg), fentanyl (up to 100 μg), and propofol titrated according to the patient request and response. The sensory level to pinprick and verbal pain score (0–10) were determined at 20 and 40 min after injection, then at 40-min intervals until the sensory level was resolved caudad to S1 or until morphine was self-administered by the patient. We recorded blood pressure every 5 min for 60 min, then every 30 min for 3 more hours, and the timing and dose of ephedrine was administered to treat hypotension associated with spinal anesthesia.

Patients received analgesia in the postanesthesia recovery unit via IV patient-controlled analgesia (PCA) with morphine (2 mg per dose, 5 min lockout, and 20 mg/h maximum). Additional boluses of 2–5 mg of morphine or 50 μg of fentanyl were administered by the investigator if necessary. On leaving the postanesthesia recovery unit, the patient received IV PCA morphine (1 mg per dose, 10 min lockout, and 6 mg/h maximum). Oral analgesics were allowed within the first 24 h if PCA was discontinued before that time. PCA and total morphine (morphine equivalents including oral medication) use for the previous 24 h were obtained on the first postoperative day.

The primary outcome measure was time to first IV PCA morphine dose. Based on the survey of time to first analgesic use in the postanesthesia recovery unit, a study of 30 individuals was planned to distinguish an average difference in time to first IV PCA morphine between placebo and ketorolac of 29 min with an α of 0.5 and $1 - \beta$ of 0.8, assuming a mean time of 95 min in the control condition and a group SD of 55 min. Secondary measures included verbal pain score in the postanesthesia care unit and 24 h PCA and total morphine use. Patients were excluded from data analysis if their epidural catheter was dosed. Indication for epidural dosing intraoperatively was patient discomfort despite intravenous fentanyl or sensory level to pinprick more caudad

than T10. Two milliliters of epidural lidocaine, 2%, followed by 5 ml was administered to exclude intrathecal or IV catheter placement, followed by 0.5% bupivacaine in 5-ml increments as necessary to achieve analgesia and a sensory level of T8 or more cephalad. The number of patients requiring epidural dosing intraoperatively and its timing and the time course of sensory block resolution were compared between groups. Patients were given a compensation of $100 for completion of the study.

Assays

CSF samples were frozen in a −80°C freezer until assay. Ketorolac was measured in undiluted CSF using high-pressure liquid chromatography as described previously.[7] In brief, the samples were extracted by C-18 reverse phase cartridge chromatography, eluted with acetonitrile, and chromatography was performed using a Phenomex Prodigy (Phenomex, Torrance, CA) C-18 reverse phase column with ultraviolet detection at 313 nm. The absolute sensitivity was 5 ng/ml, and the coefficient of variation was less than 10% within the concentration range of 5–500 ng/ml. PGE2 was measured using an enzyme immunoassay kit from Cayman Chemicals (Ann Arbor, MI) according to the manufacturer's directions, with the final endpoint measured as absorbance at 405 nm. Standard curves revealed linear response to 10 pg/ml.

Statistics

Data are presented as mean ± SEM unless otherwise indicated. The effects of intrathecal injections over time were determined by two-way ANOVA for repeated measures with factors time and dose (open-label chronic pain study) or injection drug (randomized, controlled chronic pain study, and postoperative pain study). Incidence of side effects was compared across doses or treatments by Chi-Square or Fisher exact test. Exploratory analyses were performed using Pearson correlation and linear regression. A value of $P < 0.05$ was considered significant.

Results

Open-Label Chronic Pain Study

The 15 subjects recruited to this study (10 women and 5 men) were 53 ± 11-yr old, 170 ± 11 cm tall, and weighed 88 ± 11 kg (mean ± SD). Duration of pain was 13 ± 3 yr (range, 2.5–26 yr). Five patients had primarily lower back pain, four had lower extremity pain, three had both lower back and lower extremity pain, two had coccydynia, and one had abdominal and flank pain. The cause of pain was secondary to the postlaminectomy (failed back) syndrome in five patients, degenerative disc disease with radiculopathy in three patients, complex regional pain syndrome type I in two patients, painful diabetic neuropathy in two patients, and one patient each with metastatic cancer, spinal stenosis or peripheral polyneuropathy. In all patients, the catheter tip was in the low thoracic intrathecal space. Patients received 192 ± 33 mg of intrathecal morphine per day.

Table 1. Adverse Events Reported by Subjects in the Open Label Chronic Pain Study

Subject/ Dose (mg)	Adverse Event	Onset after Injection (h)	Comments
1/0.5	Headache	5.5	
2/0.5	Headache, nausea	12	Nausea was preexisting
3/0.5	Headache	24	
4/0.5	Multiple*	24–96	—*
8/1.0	Sleepiness	6	
11/2.0	Dizziness, nausea	6	
12/2.0	Nausea	48	
13/2.0	Multiple†	6	—†

* Jitteriness in the hands and feet 13 h after injection, nausea 16 h after injection, chills 21 h after injection, and fever 33 h after injection, with subsequent diagnosis of bronchitis and resolution of symptoms with antibiotic treatment. † Headache, metallic taste, nausea, and blurred vision lasting 15 min, occurring 10 min after injection. Patient reported that this had occurred with previous manipulations of the intrathecal pump.

The focus of this study was safety and tolerability. On systematic questioning before injection, there was a high incidence of symptoms in this population. Eight patients reported lower extremity weakness before injection, five reported sedation, four reported anxiety, one reported dizziness, one reported nausea, and four reported other forms of gastrointestinal distress. In no case was the severity of these preexisting symptoms worsened during the 4 h after intrathecal ketorolac injection. Overall, the proportion of subjects reporting any adverse event within 24 h of injection was 80% with the 0.5 mg dose, 20% with the 1.0 mg dose, and 40% with the 2.0 mg dose. The median onset time for adverse events was 9 h after injection (range, 5.5–48 h). The most common adverse events were headache and nausea, although there was no dose dependency to these adverse events (table 1), and in all cases, they were rated as mild or moderate. Ketorolac did not affect blood pressure or heart rate, as shown in Supplemental Digital Content 1, http://links.lww.com/ALN/A582.

Pain scores declined after intrathecal injection in a dose independent manner, with an onset of significant analgesia 45–60 min after injection, a peak reduction occurring 1–3 h after injection, and a duration of 2 h or greater (fig. 1). At the 0.5- and 2.0-mg dose levels, pain scores were still lower than baseline at the end of the observation period, 4 h after injection.

For technical reasons, we were unable to obtain CSF after injection in three patients who received the 2.0-mg ketorolac dose. In the remaining subjects, CSF was sampled before ketorolac injection and 72 ± 2 min after injection. Pain scores and CSF PGE2 concentrations before and after injection and ketorolac and morphine concentrations after injection are listed in Supplemental Digital Content 2, http://links.lww.com/ALN/A583. Ketorolac concentrations were statistically similar at all dose levels, ranging from 2.2 to 7.7
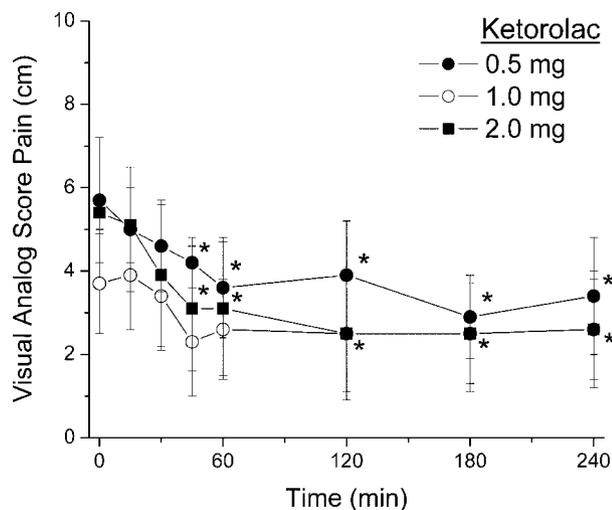
Fig. 1. Spontaneous pain intensity ratings before and after intrathecal injection of ketorolac (just after time 0) in patients in the open-label chronic pain study. Each symbol represents the mean ± SEM of five subjects. * $P < 0.05$ compared with time 0 value.

μg/ml. There were no significant correlations between CSF drug or PGE2 concentrations and pain scores, either before or after injection.

In exploratory analysis, we noted a significant inverse relationship between CSF PGE2 concentrations before ketorolac injection and the change in CSF PGE2 after ketorolac injection (fig. 2). Because ketorolac failed to reduce CSF PGE2 concentrations in healthy volunteers,[7,8] this relationship suggests that ketorolac may be active only in subjects in whom the spinal cyclooxygenase is activated above normal, as measured by CSF PGE2.

To further explore this possibility, we compared the five subjects (four who received 1 mg and one who received 2 mg of ketorolac) whose CSF PGE2 concentrations were more than the 90th percentile (173 pg/ml) from the 66 normal volunteers previously studied in our research unit[7,8] to those
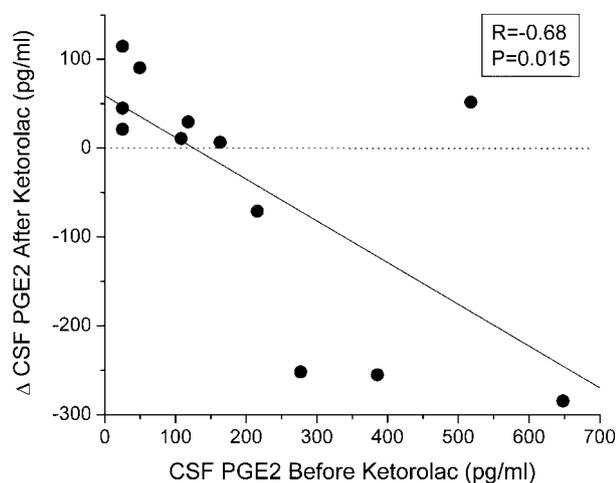

Fig. 2. The relationship between the cerebrospinal fluid (CSF) concentration of prostaglandin E2 (PGE2) before intrathecal ketorolac injection and the change (Δ) in CSF PGE2 concentration 1 h after ketorolac injection in subjects in the open-label chronic pain study. Each symbol represents one subject.

lesser than this value. The change in CSF PGE2 after ketorolac administration in the high resting CSF PGE2 concentration subgroup (from 409 ± 88 pg/ml before ketorolac to 247 ± 109 pg/ml after) differed significantly ($P = 0.005$) from the change in those with normal resting CSF PGE2 concentrations (from 74 ± 23 pg/ml before ketorolac to 119 ± 18 pg/ml after). Pain report was significantly reduced after ketorolac in the high resting CSF PGE2 concentration subgroup (from 4.7 ± 0.9 cm before to 2.1 ± 1.1 cm after ketorolac; $P = 0.02$) but not in the normal resting CSF PGE2 concentration group (from 4.0 ± 1.2 cm before to 3.5 ± 1.0 cm after ketorolac). These subgroups differing in CSF PGE2 concentration did not differ in demographic variables or side effects but did differ in CSF concentrations of morphine, with higher morphine concentrations in the high resting CSF PGE2 concentration group (200 ± 39 μg/ml compared with 96 ± 28 μg/ml; $P = 0.03$). Similarly, the group with high resting CSF PGE2 concentrations received more morphine per day than those with normal resting CSF PGE2 concentrations (257 ± 45 mg/day compared with 107 ± 41 mg/day; $P = 0.03$).

Randomized, Controlled Chronic Pain Study

The 12 subjects recruited into the randomized, controlled, chronic pain study (five women and seven men) were 51 ± 9-yr old, 174 ± 10 cm tall, and weighed 91 ± 9 kg. Duration of pain was 12 ± 2 yr (range, 5–23 yr; mean ± SD). In addition to these 12, one subject was studied on only one occasion and experienced a numb left leg for less than 2 h after injection. Further review of the medical record showed that this subject was receiving bupivacaine in addition to morphine in the intrathecal pump. This subject was replaced, and the data of the subject were not included in analysis. All subjects had back or leg pain, three were associated with degenerative disc disease, one was associated with chronic regional pain syndrome of the lower extremities, and one was associated with phantom leg pain. In all patients, the catheter tip was in the low thoracic intrathecal space.

The focus of this study was efficacy, with primary outcome variable mechanical VAS intensity of ongoing pain. Both pain intensity ($P = 0.01$) and unpleasantness ($P = 0.02$) decreased with time after intrathecal injections, but there was no difference between ketorolac and saline (fig. 3), and there was no significant interaction between treatment and time. Similarly, the proportion of subjects who experienced at least 30 or 50% pain relief after intrathecal injection did not differ between the ketorolac and saline groups. Neither ketorolac nor saline altered pain intensity or unpleasantness reports to thermal testing, as shown graphically in Supplemental Digital Content 3, http://links.lww.com/ALN/A584.

We did not sample CSF in this study. Given the greater reduction in pain score after ketorolac administration in subjects with high CSF concentrations of morphine in the open-label study, we explored the relationship between intrathecal morphine dose and response to ketorolac in the randomized,
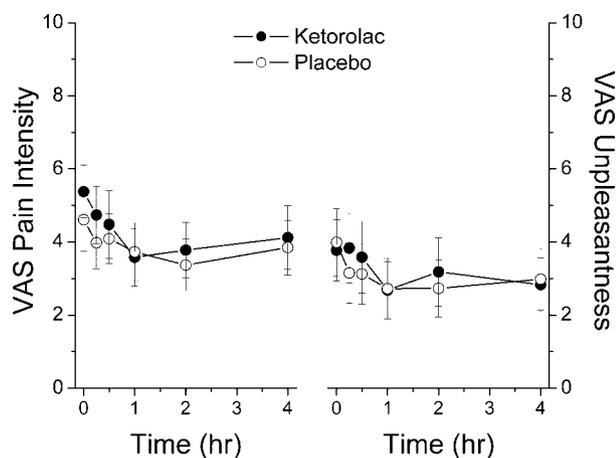
Fig. 3. Visual Analog Scale (VAS, in cm) pain intensity and unpleasantness before and after intrathecal ketorolac or saline injection, just after time 0, in patients in the randomized, controlled chronic pain study. Each symbol represents the mean ± SEM of 12 subjects. Groups do not differ by two-way repeated measures analysis of variance.

controlled study. Intrathecal morphine dose averaged 9.8 mg/day in this study, with a wide range (1.3–50 mg/day). There was no correlation, however, between intrathecal morphine daily dose and resting pain score, minimum pain score after ketorolac, average pain score after ketorolac, or summed pain intensity difference scores after ketorolac administration, as shown in Supplemental Digital Content 4, http://links.lww.com/ALN/A585. Similarly, there was no correlation between intrathecal morphine daily dose and pain scores after intrathecal saline, or between intrathecal morphine daily dose and the difference in pain score after ketorolac and saline (data available in Supplemental Digital Content 4, http://links.lww.com/ALN/A585).

The incidence of adverse events did not differ between ketorolac or saline injection. There was a high incidence of symptoms in these subjects before intrathecal injection, with six patients reporting lower extremity weakness before both injections, five reporting headache before saline injection, four reporting headache before ketorolac injection, two reporting anxiety before both injections, one reporting nausea before both injections, and one reporting sedation before both injections. The incidence and intensity of the symptoms present before intrathecal injection did not change after the administration of either ketorolac or saline (data not shown). Four subjects reported new symptoms after ketorolac injection and five after saline. After ketorolac injection two subjects described mild sedation lasting less than 2 h, one reported mild dizziness lasting less than 30 min, and one experienced a hot sensation in the back, headache, urinary retention, and hives beginning 4 days after injection and lasting less than 4 h. After saline injection, two subjects described mild sedation lasting less than 1 h, two had mild nausea lasting less than 1 h, and one had a mild headache lasting less than 2 h. Two serious adverse events occurred. One patient experienced a numb left leg for less than 2 h after intrathecal injection of saline, and, as noted, this subject's

pump contained bupivacaine. One patient committed suicide 6 months after study. Both cases were reported to the Institutional Review Board, the Data Safety Monitoring Board, and the Food and Drug Administration and were not considered related to study drug. Neither ketorolac nor saline affected blood pressure or heart rate, as shown in Supplemental Digital Content 5, http://links.lww.com/ALN/A586.

Postoperative Pain Study

Forty subjects were recruited for the postoperative pain study. Of these, 10 were excluded from efficacy data analysis. In one case (randomized to ketorolac), surgery was canceled. In two other cases, both randomized to saline, the surgical procedure was changed to abdominal hysterectomy. In seven other cases (four randomized to ketorolac and three to saline), the epidural catheter was dosed. Epidural dosing occurred on average 69 min after intrathecal ketorolac plus bupivacaine injection (range, 16–142 min) and 44 min after intrathecal saline plus bupivacaine injection (range, 10–106 min).

Of the remaining 30 subjects, 14 were randomized to intrathecal ketorolac and 16 to saline. Groups did not differ in age (44 ± 5 yr in ketorolac group, 41 ± 7 yr in saline), height (163 ± 7 cm in ketorolac group, 163 ± 6 cm in saline), or weight (69 ± 10 kg in ketorolac group, 68 ± 15 kg in saline). There was one protocol violation in the ketorolac group, the data of a woman who received 200 μg of fentanyl during surgery were included in the reported analyses, but the exclusion of her data did not alter the results of statistical testing. All patients underwent total vaginal hysterectomy. In the ketorolac group, two patients also underwent bilateral oophorectomy, one underwent bilateral oophorectomy and culdoplasty, and two underwent anterior vaginal repair, whereas in the saline group, one also underwent culdoplasty and one underwent anterior vaginal repair. Groups did not differ in the duration of surgery (58 ± 4 min in ketorolac group, 58 ± 7 min in saline) or in the amounts of intraoperative midazolam (3.6 ± 0.2 mg in ketorolac group, 3.4 ± 0.2 mg in saline), fentanyl (98 ± 10 μg in ketorolac group, 91 ± 7 μg in saline), or propofol (99 ± 24 mg in ketorolac group, 80 ± 22 mg in saline).

The primary outcome measure, time to first IV PCA morphine dose, did not differ between those receiving intrathecal ketorolac nor did the amount of morphine received in the postanesthesia care unit or during the first 24 h (table 2). Groups differed neither in regression of sensory blockade after intrathecal injection of bupivacaine nor in pain scores after injection (fig. 4). Similarly, groups did not differ in blood pressure or heart rate, as shown in Supplemental Digital Content 6, http://links.lww.com/ALN/A587, or in the proportion of subjects receiving ephedrine or phenylephrine to treat hypotension after intrathecal bupivacaine injection.

Discussion

For more than 25 yr[3] studies in animals have demonstrated increased activity of cyclooxygenase in the spinal cord from

Table 2. Time and Amount of Opioid Treatment in the Postoperative Pain Study

	Ketorolac (n = 14)	Saline (n = 16)
Time to first opioid, min	101 ± 11	88 ± 8
Morphine use, mg		
In postanesthesia care unit	4.0 ± 1.6	4.4 ± 1.5
24 h *via* intravenous patient controlled analgesia	39 ± 7	44 ± 6
24 h total (including oral)	53 ± 7	56 ± 6

Values are expressed as mean ± SEM. No differences between groups.

acute and, in a less consistent manner, chronic pain states, with reduction in pain-related behavior after intrathecal injection of NSAIDs. A PubMed search on September 12, 2009, yielded 449 articles with the search terms spinal or intrathecal, rat or mouse, NSAID or COX, and pain, reflecting the considerable research activity in laboratory animals in this area. The current study in patients, similar to our previous studies using various experimental pain and hypersensitivity models,[7,8] questions the relevance of these observations in rodents to human pain. These studies with intrathecal ketorolac do not definitively exclude a role of spinal cyclooxygenase in human pain but define circumstances in which this therapy is unlikely to be useful and beg for more clinical trials to validate or invalidate previous work in rodents. Following is our interpretation of the limitations of the clinical trials on intrathecal ketorolac, how to compare these studies in rodents, and some areas that require further exploration.

Is Spinal Cyclooxygenase Activity Important to Chronic Pain?

We failed to observe greater analgesia from intrathecal ketorolac than saline placebo in patients with primarily low
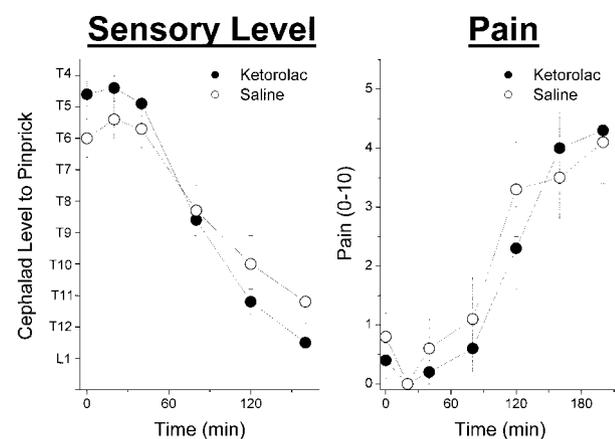

Fig. 4. Sensory level to pin prick testing and verbal pain rating (0–10) after intrathecal injection of bupivacaine with 2 mg of ketorolac or saline, 5 min before time 0, in patients in the postoperative pain study. Each symbol represents the mean ± SEM of 14–16 subjects. Groups do not differ by two-way repeated measures analysis of variance.

back and lower extremity pain and a combination of somatic and neuropathic components. These observations are consistent with clinical studies that demonstrate a small, although significant effect of systemic NSAIDs in patients with back pain, but no effect in those with back pain and sciatica.[12] Although NSAIDs are commonly taken by patients with neuropathic pain, this is not based on strong evidence for efficacy.[13]

The results of studies in rodents are mixed regarding the role for spinal cyclooxygenase activity in chronic pain. Some studies demonstrate the upregulation of spinal cyclooxygenase expression, brush-evoked spinal PGE2 release, and relief of hypersensitivity from intrathecal NSAIDs for only a few days after peripheral nerve injury as a model of neuropathic pain, with no effect later.[14–16] Others show prolonged upregulation of spinal cyclooxygenase expression for weeks after injury and antihypersensitivity effects of intrathecal NSAIDs at this time.[17,18] Importantly, all studies demonstrating the positive effects of intrathecal NSAIDs used reflex withdrawal to mechanical or thermal stimuli. We did not measure areas of hyperalgesia or allodynia in patients in the current study, and it is conceivable that intrathecal ketorolac reduced hypersensitivity in these patients without affecting spontaneous pain. If this were the case, it would be similar to our work with intrathecal adenosine, which demonstrated parallel reduction in hypersensitivity tests in rodents with peripheral nerve injury and areas of allodynia in humans with experimentally induced allodynia or chronic pain, but no relief of spontaneous pain in patients.[19–21] Arguing against an antiallodynic effect of intrathecal ketorolac is its lack of effect in the capsaicin experimental model of hypersensitivity and its minor effect after ultraviolet-B burn peripheral inflammation.[8]

We studied a small number of individuals with complex chronic pain that extended for many years despite chronic intrathecal morphine. In this population, we studied the analgesic efficacy of intrathecal ketorolac for 4 h after a single bolus injection. Intrathecal ketorolac could be effective in other patient populations, in other doses, or after prolonged therapy, but these data are consistent with many studies in animals (reviewed above), and a recent randomized, controlled trial. In that study, a central nervous system penetrating cyclooxygenase inhibitor that reduced hypersensitivity in rats after peripheral nerve injury[22] failed to reduce pain over 3 weeks compared with placebo.[23]

Is Intrathecal Ketorolac Effective in a Subset of Patients with Chronic Pain?

The inverse relationship between CSF PGE2 before ketorolac injection and change in CSF PGE2 afterward (fig. 2) suggests that spinal cyclooxygenase activity may be increased in only some patients with chronic pain. The 40% reduction in CSF PGE2 in this small subgroup, accompanied by significant reduction in pain report, is consistent with this speculation and suggests that the dose of intrathecal ketorolac was adequate to block abnormally high cyclooxygenase activity.

Should this secondary, exploratory analysis be replicated in prospective studies, it would provide rationale for a diagnostic test (CSF PGE2 concentration) to identify the patients who might benefit from this therapy.

These results also suggest that ketorolac only reduces CSF PGE2 concentrations in humans when they are abnormally increased. Although the reasons for this are unclear, this hypothesis is consistent with a similar observation with systemic administration of rofecoxib. In that study,[5] patients who received oral rofecoxib for 5 days before surgery had similar CSF PGE2 concentrations at the time of surgery as those who received placebo, but rofecoxib significantly reduced the increase in CSF PGE2 after surgery.

The increased CSF morphine concentrations in patients with high CSF PGE2 concentrations is intriguing for a couple of reasons. In rats with peripheral nerve injury, there is a synergistic antihypersensitivity effect between intrathecal ketorolac and morphine,[14] and such an interaction in the presence of high morphine concentrations is possible. It is possible that a combination of ketorolac with morphine would improve analgesia compared with morphine alone, although all the patients with chronic pain in our studies were receiving morphine, yet we saw no analgesia from addition of ketorolac. Alternatively, higher CSF morphine in those with high CSF PGE2 concentrations could reflect dose escalation and tolerance, and tolerance to intrathecal morphine in animals depends in part on chronic activation of spinal cyclooxygenase.[24] In contrast to this hypothesis, there was no greater effect of intrathecal ketorolac in our randomized, controlled, cross-over study as a function of intrathecal morphine infusion rate. It would be interesting to examine whether there is a correlation between morphine dose escalation and CSF PGE2 concentrations in patients on chronic intrathecal morphine therapy.

Is Spinal Cyclooxygenase Activity Important to Postoperative Pain?

We failed to observe in the current study a prolongation of analgesia beyond the period of spinal anesthesia postoperatively when ketorolac was added to bupivacaine for spinal anesthesia. A short duration of ketorolac effect could explain this, although the half life of ketorolac in CSF after intrathecal injection in humans is approximately 3 h.[8] Alternatively, spinal cyclooxygenase may not be immediately activated during surgery under spinal anesthesia, as supported by a previous observation of a lack of increase in CSF PGE2 until 9 h after surgery.[5] Therefore, we cannot exclude the possibility of analgesic efficacy from intrathecal injection of ketorolac many hours after surgery, although this is impractical to apply clinically.

Most studies in animals support a role for spinal cyclooxygenase activation after surgery, although they differ in the time course of its activation and the isoenzyme involved.

Trial NCT00621530. Available at: www.clinicaltrials.gov. Accessed November 18, 2009.

Some authors observe an increase in cyclooxygenase-2 protein expression,[25] cyclooxygenase-1 protein expression,[18] or both[26] restricted to a few hr after surgery and gone by the first postoperative day. In contrast, we observed a sustained increase in immunohistochemical staining of cyclooxygenase-1 in the spinal cord microglia for several days after incisional surgery of the paw.[27] Intrathecal ketorolac blocks surgery-induced hypersensitivity 1 day after paw incision in rats[27] and also restored exploratory behavior that had been disrupted by hind paw or laparotomy surgery.[28,29] Studies with exploratory behavior and comparing efficacy with intrathecal morphine predict an active intrathecal dose of 2 mg of ketorolac,[28] the dose that failed in the current study. It could be argued that these studies in animals examined ketorolac administered on the first postoperative day, whereas our clinical study injected it just before surgery, explaining the difference in efficacy. Against this argument are observations that intrathecal injection of ketorolac 30 min before paw incision surgery reduces hypersensitivity for up to 3 days after surgery,[30] and that intrathecal injection of ibuprofen before and shortly after spinal nerve ligation permanently prevents hypersensitivity from developing.[31]

We conclude that 2 mg of intrathecal ketorolac injected with bupivacaine fails to sustain analgesia beyond the time course of bupivacaine itself. We do not know whether intrathecal ketorolac reduces areas of hyperalgesia surrounding the surgical wound, and we are currently examining this possibility.# Opioids are commonly administered during spinal anesthesia. Because animal studies suggest the enhancement of spinal opioids by spinal NSAIDs,[32] this combination deserves study.

Safety

As in healthy volunteers,[7,8] side effects after intrathecal ketorolac in patients with chronic pain were mild and did not differ from placebo. Leg weakness after intrathecal ketorolac was not observed in healthy volunteers, and the one patient in this study with this side effect likely received a small bolus of bupivacaine in the catheter. CSF ketorolac concentrations 1 h after injection in chronic pain patients are similar to those observed in healthy volunteers.[7,8] Addition of 2 mg of ketorolac to bupivacaine for spinal anesthesia seems not to alter the distribution of bupivacaine, as sensory block onset, spread, and duration were unaffected by ketorolac. Although these results are reassuring, slightly fewer than 100 humans have received intrathecal ketorolac in published reports, and this therapy should be considered investigational and further studies should be performed under regulatory agency oversight. Investigators interested in accessing our regulatory approval for the study of intrathecal ketorolac should contact the corresponding author.

In summary, 2 mg of intrathecal ketorolac was not associated with serious side effects, failed to reduce ongoing pain in chronic pain patients more than placebo, and failed to prolong analgesia after surgery beyond the duration of bupivacaine given for spinal anesthesia. These observations are

limited by the small number of subjects studied, and patient population, and the amount and timing of ketorolac dosing. They call into doubt the relevance of intrathecal NSAID studies in rodents and suggest that spinal cyclooxygenase is not activated in most patients with these clinical pain conditions.

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