Effects of Intrathecal Ketorolac on Human Experimental Pain

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ABSTRACT

Background: Nonsteroidal antiinflammatory drugs, the most commonly used analgesics, reduce pain not only by inhibiting cyclooxygenase at peripheral sites of inflammation but also by potentially inhibiting cyclooxygenase in the central nervous system, especially the spinal cord. Animal studies suggest that products of cyclooxygenase in the spinal cord do not alter pain responses to acute noxious stimuli but reduce pain and sensitization after peripheral inflammation. We used a spinal injection of small doses of the cyclooxygenase inhibitor ketorolac to survey the role of spinal cyclooxygenase in human experimental pain and hypersensitivity states.

Methods: After regulatory agency approval and informed consent, we examined the effect of 2.0 mg intrathecal ketorolac in 41 healthy volunteers to acute noxious thermal stimuli in normal skin and to mechanical stimuli in skin sensitized by topical capsaicin or ultraviolet burn. We also examined the effect of intravenous ketorolac.

Results: Intrathecal ketorolac reduced hypersensitivity when it was induced by a combination of ultraviolet burn plus intermittent heat and, according to one of the two analytical strategies, when it was induced by ultraviolet burn alone.

Conclusions: These data suggest a more limited role for spinal cord cyclooxygenase in human pain states than predicted by studies in animals.

NONSTEROIDAL antiinflammatory drugs (NSAIDs), the most widely used pharmacologic treatment for pain, are believed to act by primarily inhibiting cyclooxygenase and thereby reducing prostaglandin production at peripheral sites of inflammation. However, more than 40 yr ago prostaglandin were shown to be synthesized in the spinal cord, with increased synthesis in response to high threshold afferent input. This led Yaksh and co-workers to postulate and demonstrate that intrathecal injection of NSAIDs produces analgesia after excitatory input into the spinal cord, and it led Pellerin et al. to inject an aspirin derivative epidurally in patients with cancer pain, resulting in prolonged analgesia. Numerous studies have been performed in animals showing the importance of spinal cord cyclooxygenase expression and activity in pain states and inhibition of pain behaviors by spinally administered NSAIDs. Understanding the relevance of these observations to pain in humans has been hampered by lack of regulatory approval for intrathecal injection of these products.

To address the gap in our knowledge regarding the relevance of spinal cord cyclooxygenase in human pain, we performed a series of neurotoxicity studies in dogs and rats with a preservative-free formulation of the NSAID ketorolac and received approval under Investigational New Drug regulations from the Food and Drug Administration to test this agent via intrathecal injection in humans. In an open label,

What We Already Know about This Topic

❖ Studies in animals suggest that the spinal cord may be a site for analgesia from nonsteroidal antiinflammatory drugs (NSAIDs), suggesting that intrathecal NSAIDs could be analgesic.

What This Article Tells Us That Is New

❖ In three models of experimental pain and hypersensitivity intrathecal injection of the NSAID, 2 mg ketorolac exerted no or minor effects.

❖ Spinal cyclooxygenase activity plays a minor role in hypersensitivity in these human models of pain.

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Received from Department of Anesthesiology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, and the Department of Anesthesiology, University of California, San Diego, San Diego, California. Submitted for publication August 22, 2009. Accepted for publication November 23, 2009. Supported in part by grants GM48905 and M01-RR07122 from the National Institute of Health, Bethesda, Maryland.

Steven L. Shafer, M.D., served as Acting Editor-in-Chief for this article.

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This article is accompanied by an Editorial View. Please see: Angst MS: Intrathecal cyclooxygenase inhibitors in humans: Don’t throw in the towel ANESTHESIOLOGY 2010; 112:1082-3.

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).
dose-escalating safety study, 0.25–2.0 mg intrathecal ketorolac was well tolerated, with the only adverse effect being a mild reduction in heart rate 15–60 min after injection. Ketorolac had no effect on verbal pain rating of heat stimuli applied to the leg. One purpose of this study was to confirm, under randomized and double-blinded conditions, the effect of ketorolac on heart rate and the lack of its analgesic effects to acute noxious heat stimuli.

Experimental pain paradigms have been used to mimic sensitization that occurs in acute and chronic pain conditions and may be of benefit in guiding early assessment of new analgesics. Herein, we tested intrathecal ketorolac in two such models—hypersensitivity from topical capsaicin, a model of neuropathic sensitization and previously shown to respond to drugs approved in the treatment of neuropathic pain, and hypersensitivity from ultraviolet radiation, a model of acute peripheral inflammation and central sensitization. Studies in rodents, although not always consistent, predict that intrathecal ketorolac in humans would have no effect on pain from acute noxious heat but would reduce hypersensitivity after high-intensity C-fiber input from topical capsaicin and inflammation from ultraviolet radiation.

Materials and Methods

After Institutional Review Board (Wake Forest University School of Medicine, Winston-Salem, North Carolina) approval and, for intrathecal studies, Food and Drug Administration Approval under Investigational New Drug regulation (IND 62,179), 52 healthy volunteers were recruited and studied in the General Clinical Research Center (GCRC) of Wake Forest University School of Medicine. The written informed consent document was approved by the Institutional Review Board, the Food and Drug Administration, and the GCRC, and an independent Data Safety Monitoring Board regularly reviewed the progress of the studies and any adverse events. Volunteers of American Society of Anesthesiologists physical status 1, age 18–55 years, weighing less than 220 pounds, and without a history of skin cancer or allergy to lidocaine, ketorolac, or capsaicin were recruited and consistent areas of hypersensitivity. This concluded the training session.

On the second day, the volunteer came to the GCRC in the morning, having had nothing to eat or drink since midnight. A peripheral intravenous catheter was inserted into a forearm vein and lactated Ringer’s solution was infused at 1.5 ml/kg/h for the duration of the study. Subjects were maintained in all four studies at 30°C with a heating lamp in the areas of hypersensitivity. Heat-sensitivity was then induced on the lateral calf contralateral to this retraining by heat followed by capsaicin as described for the training session. Rekindling by application of a thermode maintained at 40°C for 5 min, and areas of hyperalgesia and allodynia were determined after removing the thermode. This rekindling by intermittent heat results in sustained and consistent areas of hypersensitivity. This concluded the training session.

After the first rekindling, a #27 Whitacre spinal needle was inserted at a lower lumbar interspace, 5 ml cerebrospinal fluid (CSF) sampled, and 2 ml of either normal saline or preservative-free ketorolac, 2 mg (Acular PF®, Allergan, Irvine, CA) in a 2-ml volume was injected over 60 s. Randomization was performed using a computer-generated table of numbers, and the study was double blinded. A second CSF sample was obtained at the same interspace as the original injection by insertion of a #27 Whitacre spinal needle 30 min or 1, 2, or 4 h after injection. The timing of the second used this UV-B burn plus heat model to reexamine the efficacy of intrathecal ketorolac.

Study 1: Intrathecal Ketorolac in Capsaicin + Heat-induced Hypersensitivity

Fourteen subjects came to the GCRC on two occasions separated by at least 2 days. On the first day, subjects were trained to consistently rate pain intensity on a 10-cm mechanical visual analog scale, bounded on one end with no pain and on the other most intense pain, in response to 5-s pulses of heat using a 1-cm² Peltier thermode (Medoc, USA, Durham, NC) applied to the skin of the arm. Thermode temperature was increased from baseline (35°C) to 39°, 41°, 43°, 45°, 47°, 49°, or 51°C in random order with 25-s interstimulus intervals for training. Next, they were trained to report changes in sensation to tactile stimuli after capsaicin treatment. For this, the thermode was placed on the volar forearm and heated to 45°C for 5 min. Areas surrounding the thermode placement of mechanical hyperalgesia to a 225 mN von Frey filament application and of mechanical allosthenia to cotton wisp stroking were determined as previously described. Capsaicin cream (0.075%; Bioglan Pharma Inc., Malvern, PA) was applied and covered with an occlusive dressing to the area previously contacted by the thermode for 30 min and then removed. Every 40 min for 160 min the thermode was reapplied to the same area and maintained at 40°C for 5 min, and areas of hyperalgesia and allodynia were determined after removing the thermode. This rekindling by intermittent heat results in sustained and consistent areas of hypersensitivity. This concluded the training session.
sample was randomized using a computer-generated table of numbers.

Peripheral oxyhemoglobin saturation, blood pressure, and heart rate were measured noninvasively before and every 30 min after capsaicin application. At these same times, subjects were queried for presence of sedation, anxiety, nausea, dizziness, leg weakness to movement in the bed and, if present, to rate these effects on a 0- to 10-point verbal scale from not present to most severe. They were also asked at these times to report any other sensations. Volunteers were contacted by telephone daily for 5 days, weekly for 1 month, and at 6 months after study and questioned regarding any side effects.

**Study 2: Intrathecal Ketorolac in UV-B Burn-induced Hypersensitivity**

Fourteen subjects came to the GCRC on four separate occasions. On the first occasion, subjects were trained to consistently rate pain from heat stimuli as described in the training session to study 1 (Capsaicin study). UV light was administered to 3-cm² diameter circles of skin on the calf using a controlled system that meets specifications for Food and Drug Administration sunscreen testing (Solar Light Co., Inc., Glenside, PA). This solar simulator consists of a 150-W xenon bulb that produces the full range of solar UV energy (290–400 nm) without exposing subjects to thermal energy and provides simultaneous calculation of energy focused on the skin. Depending on skin pigmentation and history of response to sunlight, subjects received three exposures on separate areas of skin for 30, 60, and 90 s or 60, 90, and 120 s. Subjects returned for a second time to the GCRC the following day, and the minimum erythematous dose (MED) of UV energy was determined by visual inspection of the three areas of exposure as the skin area with the lowest energy required to cause a complete reddening of the exposed skin (none-spotty reddening).

On the third visit, at least 4 days after the second, subjects came to the GCRC and skin on the lateral calf was exposed to twice their MED using the solar simulator. They then returned for a fourth time to the GCRC on the following day, having had nothing to eat or drink since overnight. An intravenous catheter was inserted into the forearm and lactated Ringer’s solution was infused as in study 1 (capsaicin study). Subjects were retrained to consistently rate pain from heat stimuli as in the training session and to report changes in sensation to tactile stimuli, and using the same methods as in study 1 (capsaicin study) the surrounding area of UV-B burn were determined.

We reasoned that intermittent heat would rekindle and expand areas of hypersensitivity in this model as it does after topical capsaicin, and we used a similar protocol. Thus, we placed the thermode over the area of UV-B burn at 40-min intervals and maintained it at 40°C for 5 min, measuring areas of hypersensitivity after each rekindling. After the second heat application, subjects received a 10-ml infusion of saline and after the third heat application they received a 10-ml infusion of ketorolac, 30 mg (Toradol; Hoffman-LaRoche Ltd., Nutley, NJ). The subject and the nurse who obtained all experimental measures were blinded to the order of infusions. The study ended after the fourth rekindling.

**Study 3: UV-B Burn + Heat-induced Hypersensitivity: Effect of Intravenous Ketorolac**

Ten subjects came to the GCRC on four separate occasions. During the first, they were trained to rate pain from heat pulses as described in study 1 (capsaicin study) and were exposed to three doses of UV energy as described in study 2 (UV-B burn alone study). They returned for a second time on the following day and the MED was determined as in study 2.

On the third visit, at least 4 days after the second, subjects came to the GCRC and skin on the lateral calf was exposed to twice their MED using the solar simulator. They then returned for a fourth time to the GCRC on the following day, having had nothing to eat or drink since midnight. An intravenous catheter was inserted into the forearm and lactated Ringer’s solution was infused as in study 1 (capsaicin study). Subjects were retrained to consistently rate pain from heat stimuli as in the training session and to report changes in sensation to tactile stimuli, and using the same methods as in study 1 (capsaicin study) the surrounding area of UV-B burn were determined.

**Study 4: Intrathecal Ketorolac in UV-B Burn + Heat-induced Hypersensitivity**

Fourteen subjects came to the GCRC on six separate occasions. The first involved training in rating pain from acute heat stimuli and exposure to UV-B light, the second involved determining the MED by visual inspection the following day, and the third involved administering twice their MED as described in study 2 (UV-B burn alone study). On the fourth visit, the day following their exposure to twice the MED, an intravenous catheter was inserted, and heat was applied every 40 min to rekindle areas of hyperalgesia and allodynia as described in study 3 (UV-B burn + heat Study). Following the second rekindling, a #27 Whitacre needle was placed over the area of UV-B burn at 40-min intervals and maintained it at 40°C for 5 min, measuring areas of hypersensitivity after each rekindling. After the second heat application, subjects received a 10-ml infusion of saline and after the third heat application they received a 10-ml infusion of ketorolac, 30 mg (Toradol; Hoffman-LaRoche Ltd., Nutley, NJ). The subject and the nurse who obtained all experimental measures were blinded to the order of infusions. The study ended after the fourth rekindling.
inserted into a lower lumbar interspace and 2 ml of saline or an equal volume containing preservative-free ketorolac, 2 mg, was injected over 60 s. The study was double blinded. Areas of hypersensitivity were measured for three more cycles of rekindling, and side effects were assessed with long-term telephone follow-up as described in study 1 (capsaicin study).

Subjects returned twice more using a crossover design. On the fifth visit, at least 2 weeks after the fourth, they were exposed to twice their MED and on the sixth visit, 1 day later, the experimental procedures of the fourth visit were repeated, including an intrathecal injection of the solution not used during the fourth visit. The order of intrathecal drug solutions was randomized using a computer-generated table of numbers, and the study was double blinded.

**Intrathecal Ketorolac Dose**
It should be noted that before the spinal delivery of ketorolac in humans, preclinical evaluations were undertaken with a continuous spinal delivery of ketorolac in a concentration of 0.5 and 5 mg/ml at a rate of 50 µl/h (1.2 ml/day) in dogs for 28 days.5 In rats, four repeated daily bolus injections of ketorolac (5 mg/ml/10 microl) were carried out. Systematic histopathology revealed no spinal effects distinct from observations made in vehicle-treated animals. In the human study, we limited drug dosing to a single exposure of 2 mg in 2 ml. This was chosen to provide a conservative drug exposure in man relative to those concentrations to which the animals were exposed either repeatedly (rats) or continuously (dog) without deleterious spinal effects. Importantly, these doses in dogs led to steady-state CSF concentrations of around 50 µg/ml at the level of the catheter and a significant reduction in CSF prostaglandins. Kinetic studies revealed half-lives of 10 and 53 min, indicating a relatively short residence time. Comments on the importance of the parameters of robust preclinical drug safety assessment and elements constituting a robust safety assessment are made elsewhere.10–12

**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.6 In brief, samples were extracted by C-18 reverse-phase cartridge chromatography, eluted with acetonitrile, and chromatography performed using a Phenomex Prodigy (Phenomex, Torrance, CA) C-18 reverse phase column with UV 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. Prostaglandin E2 (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 a linear response from 10 to 500 pg/ml.

**Statistics**
Primary outcome measures in all the four studies were areas of hyperalgesia and of allodynia and, for study 2, pain intensity and unpleasantness. A priori power analysis, using our previous experience with capsaicin, published experience with UV-B burn, or results from study 3 of UV-B burn + heat, supported the study of 14, 14, 10, and 14 subjects in studies 1–4, respectively, to see a difference between saline and ketorolac of at least 45% in area of hyperalgesia and 35% in area of allodynia.

All analyses were conducted with SPSS 15.0 (Chicago, IL) or SAS 9.1 (Cary, NC). Sample characteristics are presented using mean ± SD or frequency counts, as appropriate. Because the areas of hyperalgesia and allodynia were positively skewed, differences in the two treatment conditions were analyzed using a 2 (saline, ketorolac) × 4–6 (times of measurements) ANOVA. Treatment and time were initially specified as fixed effects and the area was examined using a log-link function in a generalized linear model. In response to reviewer concerns about the planned model, we respecified a mixed effects model in which a drug effect was added to a simple model that only considered time. This model more aptly considered intersubject variability for its treated subjects as a random effect. The added benefit of ketorolac was assessed using a χ² evaluation of a likelihood ratio test of the difference in model fit between the two models. Pain and unpleasantness scores are presented as mean and were compared using repeated measures two-way ANOVA. PGE2 concentrations before and after intrathecal injection were compared using paired t tests. Wherever relevant, all analyses are two-tailed with P less than 0.05 considered statistically significant.

**Results**
Patient characteristics and UV-B energy applied on the day before drug treatment are given in table 1. For parallel studies (studies 1 and 2), demographic variables did not differ between drug assignments. For study 4, a crossover study, UV-B exposure did not differ between study days or between drug assignments. The solar simulator provided a near-linear energy as a function of time, with measured energy during determination of the MED across studies being 26 ± 3, 53 ± 6, 82 ± 10, and 111 ± 7 J/cm² with 30, 60, 90, and 120 s of exposure, respectively. The average and SD of MED across studies was 52 ± 19 J/cm². Although studies were presented in order of performance in the Materials and Methods section, we provide results according to the categories of pain and other effects for clarity.

**Effect of Ketorolac in Hypersensitivity States (All Studies)**
Areas of hyperalgesia and allodynia were stable after topical capsaicin application and intermittent heating and were unaffected by intrathecal saline or ketorolac (fig. 1A). Areas of hyperalgesia after UV-B burn alone were present in all vol-
untreated, although quite small and unaffected by intrathecal saline or ketorolac (fig. 1B). In this model, areas of allodynia were not present in all subjects, were generally limited to the area of UV-B burn itself, and were unaffected by intrathecal saline or ketorolac (fig. 1B). Areas of hyperalgesia and allodynia after UV-B burn plus intermittent heat were stable and considerably larger than with UV-B burn alone (fig. 1C).

Groups differed after intrathecal injection regarding allodynia, but not hyperalgesia, in this crossover study, with reduced areas on days that subjects received intrathecal ketorolac compared with saline (fig. 1C). This effect of ketorolac was significantly present beginning 80 min after injection. In contrast, intravenous ketorolac reduced areas of both allodynia and hyperalgesia and did so within 40 min (fig. 2).

Reviewers of the original version of this article believed that the hypothesis-testing analysis plan may have missed a considerable effect of ketorolac in the UV-B burn alone study and suggested a model-based statistical plan. In response to this concern we respecified, as indicated in the Statistical section of the Materials and Methods section, a mixed effects model in which a drug effect was added to a simple model that only considered time. This analysis yielded a significant effect of ketorolac on UV-B burn alone on hyperalgesia ($\chi^2 [1] = 8.3, P = 0.004$; average 74% reduction in modeled area) and allodynia ($\chi^2 [1] = 6.9, P = 0.009$; average 56% in modeled area). Examination of individual plots, Supplemental Digital Content 1, http://links.lww.com/ALN/A588, suggested that this difference reflected in part a large increase in areas of hyper-sensitivity in a few subjects assigned to intrathecal saline control. The mixed effects model found no effect of intrathecal ketorolac in the capsaicin plus heat model (for hy-

### Table 1. Characteristics and Ultraviolet-B Radiation to Subjects

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age (yr)</th>
<th>Sex (Male/Female)</th>
<th>Race (White/Black)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>UV-B Energy (J/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Capsaicin</td>
<td>14</td>
<td>30 ± 9.4</td>
<td>6/8</td>
<td>10/4</td>
<td>68 ± 4.3</td>
<td>74 ± 13</td>
<td></td>
</tr>
<tr>
<td>2. UV-B burn</td>
<td>14</td>
<td>34 ± 9.5</td>
<td>4/10</td>
<td>14/0</td>
<td>67 ± 4.2</td>
<td>76 ± 17</td>
<td>111 ± 22</td>
</tr>
<tr>
<td>3. UV-B burn + heat (IV injection)</td>
<td>10</td>
<td>33 ± 9.0</td>
<td>4/6</td>
<td>10/0</td>
<td>68 ± 5.5</td>
<td>81 ± 16</td>
<td>94 ± 30</td>
</tr>
<tr>
<td>4. UV-B burn + heat (Intrathecal injection)</td>
<td>14</td>
<td>34 ± 10</td>
<td>4/10</td>
<td>13/1</td>
<td>67 ± 4.7</td>
<td>77 ± 15</td>
<td>93 ± 41*</td>
</tr>
<tr>
<td>All subjects</td>
<td>52</td>
<td>33 ± 9.5</td>
<td>18/34</td>
<td>47/5</td>
<td>67 ± 4.5</td>
<td>77 ± 15</td>
<td>98 ± 48†</td>
</tr>
</tbody>
</table>

* First exposure in crossover study design. † Second exposure in crossover study design. UV-B = ultraviolet-B.
peralgesia $\chi^2 [1] = 0.04, P = 0.84$ and for alldynia $\chi^2 [1] = 0.03, P = 0.86$) and modest effects of intrathecal ketorolac in the UV-B burn plus heat model (for hyperalgesia $\chi^2 [1] = 9.6, P = 0.002$; 17% average reduction in modeled area and for alldynia $\chi^2 [1] = 14.4, P = 0.0001$; average 31% reduction in modeled area).

**Effect of Intrathecal Ketorolac to Acute Heat Pain (Study 2)**

Neither intrathecal ketorolac nor saline altered report of pain intensity or unpleasantness (fig. 3), and either treatment did not affect the lowest temperature (threshold) at which a non-zero pain intensity rating was achieved (data not shown).

**CSF Ketorolac and PGE2**

Because of technical difficulties, CSF was not sampled precisely at the predetermined intervals after intrathecal injection. CSF ketorolac concentrations were variable over an eightfold range (7–58 μg/ml), with the highest concentrations observed at the 60- and 120-min time periods (fig. 4). A second CSF sample was not obtained after ketorolac in the only study in which a pharmacodynamic effect was observed (study 4: UV-B burn plus heat), and so it was not possible to determine the relationship between CSF ketorolac concentrations and antihypersensitivity.

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**Fig. 2. Areas of hyperalgesia and allodynia in volunteers with ultraviolet-B burn plus intermittent heat. Heat was applied for 5 min before each measurement. Intravenous saline was administered immediately after the measurements at 45 min and 30 mg intravenous ketorolac was administered immediately after the measurements at 85 min. Values are mean ± SEM of 10 subjects. * P < 0.05 compared with time 0. # P < 0.05 compared with time 85 min.**

**Fig. 3. Intensity (upper row) and unpleasantness (lower row) visual analog scale (VAS) measurements after intrathecal injection of ketorolac (left column) or saline (right column) immediately after time 0. Values are mean of 7 subjects. No significant effect at any temperature over time in either group.**

**Fig. 4. Cerebrospinal fluid (CSF) concentrations of 2 mg ketorolac after intrathecal injection, at time 0. CSF was only sampled once in each subject, and each symbol represents the time and CSF concentration of ketorolac in one subject.**

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Because of technical reasons, PGE2 was measured only in CSF from subjects in study 1 (capsaicin study). Neither saline nor ketorolac altered CSF concentration of PGE2 (96 ± 24 and 113 ± 13 pg/ml before and after saline, respectively, and 98 ± 11 and 116 ± 10 pg/ml before and after ketorolac; no difference between groups or within groups). There was no effect of time from intrathecal injection to obtaining the second sample on PGE2 concentration after either saline or ketorolac injection (data not shown).

**Side Effects and Safety Assessments**

Two subjects in study 2 who received ketorolac experienced headache beginning on the day after intrathecal injection that resolved without therapy during the next 24 h. Heart rate before intrathecal ketorolac was 71 ± 9 bpm and was not affected 30 min (68 ± 8 bpm) or 60 min (70 ± 10 bpm) after injection (summary data from Studies 1, 2, and 4). Neither intrathecal saline nor ketorolac affected blood pressure or oxyhemoglobin saturation (data not shown), and no subject reported anxiety, nausea, dizziness, leg weakness, or spontaneously reported other symptoms during the study periods. Mild sedation was present in 11 of the 52 subjects before drug administration. Increased sedation, if present before injection, was not observed in subjects who received intrathecal ketorolac or saline, and no subject developed new sedation after intrathecal injection. There were no long-term sequelae observed in any of the subjects.

**Discussion**

Understanding the role of spinal cord cyclooxygenase activity in experimental human pain is important to validate the predictive utility of studies in animals and to elucidate the pathophysiology of central sensitization. This study predicts an important role for spinal cord cyclooxygenase in central sensitization from peripheral inflammation after UV-B burn but not from a period of high-intensity C fiber input from topical capsaicin. Based on the logic behind these models for clinical pain states, the current results would predict that intrathecal ketorolac would treat hypersensitivity from arthritis and perhaps postoperative pain but not chronic neuropathic pain. Following is a discussion of these results within the context of previous animal and human studies.

**Acute Thermal Nociception**

Animal data are mixed regarding the effect of intrathecal NSAIDs on acute nociception. In favor of antinociception are reports that intrathecal injection of NSAIDS increases latency to tail flick with noxious heat and reduces sensorimotor reflex responses to acute noxious electrical stimuli in rats. Against antinociception are a lack of effect of intrathecal ketorolac on the first phase of the formalin response, an acute noxious stimulus, and its lack of effect on acute heat-induced skin twitch in the dog. In humans, intravenous ibuprofen and our open-label administration of intrathecal ketorolac failed to produce antinociception from acute heat stimuli to the skin. Although behavioral responses from sustained and intense noxious stimuli, such as direct electrical stimulation or intrathecal injection of the excitatory neurotransmitters glutamate, substance P, or N-methyl-D-aspartate are sensitive to intrathecal NSAIDs, the relative lack of effect of intrathecal NSAIDs in other, more short-lasting stimuli in animals and lack of effect in humans suggest that pain from brief heat stimuli to the skin does not rely on synthesis of prostaglandins in the spinal cord. These data suggest that such acute thermal testing would not be useful in the development of novel drugs in this class.

**Capsaicin-induced Hypersensitivity**

Animal data are not informative regarding the role of spinal cord cyclooxygenase in the response to capsaicin. Perfusion with an NSAID reduces calcitonin gene-related peptide release in the spinal cord from capsaicin, but this experiment was performed *in vitro* with capsaicin applied directly to the spinal cord, and there are no behavioral studies in conscious animals on the effect of intrathecal NSAIDs after topical or intradermal capsaicin. The second phase of nociceptive behavior after intraplantar injection of formalin, such as capsaicin, reflects central sensitization after a barrage of C-fiber activity, and intrathecal ketorolac and other NSAIDs reduce these behaviors. In humans, topical ibuprofen but not systemic aspirin reduces tactile hypersensitivity after topical or intradermal capsaicin. This study adds to this literature by demonstrating a lack of effect of intrathecal ketorolac on areas of hyperalgesia and allodynia from topical capsaicin plus intermittent heat. We recognize that only areas of hypersensitivity were measured in this study, and it is conceivable that subtle effects on degree of hypersensitivity within the areas could have been missed. Other spinal analgesics, clonidine and adenosine, reduce areas of hypersensitivity after capsaicin as they do in patients with neuropathic pain, supporting the use of this outcome measure. Taken together, we find little evidence for a role of central cyclooxygenase in capsaicin-induced hypersensitivity, a model of acute central sensitization sharing some characteristics of neuropathic pain hypersensitivity.

**UV-B Burn**

In animals, intrathecal NSAIDs reduce hypersensitivity to tactile stimuli after acute peripheral inflammation from intraplantar injection of carrageenan or zymosan. This effect may be restricted to the initial period of inflammation, because the NSAID-induced reduction in spinal cord neuronal responses to tactile stimuli after acute inflammation fades within 8 h of onset of knee inflammation. Although no studies are available in animals with intrathecal NSAID administration, systemic and topical NSAIDs reduce thermal and mechanical hypersensitivity at the site of UV-B burn injury. In humans, systemic NSAIDs reduce thermal and mechanical hypersensitivity at the site of UV-B burn injury, although it is controversial whether a wider area of secondary hypersensitivity exists after this injury, perhaps...
due to differences among groups in the strength of the tactile stimulus used to map areas of hypersensitivity.\textsuperscript{30,31} The current study confirms previous observations using a von Frey filament of similar stiffness\textsuperscript{31} that areas of hypersensitivity extend only a small distance from the area of injury itself. Our study suggests that hypersensitivity in the UV-B burn model is primary in nature and likely reflects local injury from the irradiation, previously known to include local prostaglandin production. The secondary analysis proposed by the reviewers of this article better accounted for large inter-individual differences in areas of hypersensitivity before and after intrathecal injection and did predict smaller modeled areas of hypersensitivity from ketorolac treatment. Therefore, we cannot exclude from our study an effect of intrathecal ketorolac in this model.

UV-B Burn Plus Heat

We reasoned that a mild heat stimulus at the site of UV-B burn would induce or increase areas of secondary hypersensitivity as it does after topical capsaicin,\textsuperscript{9} presumably by providing low-level C-fiber input into a spinal cord that had been primed for sensitization. This was observed, with areas greatly expanded beyond the area of burn and stable with intermittent rekindling by heat. Intravenous ketorolac, in a clinically recommended dose for analgesia, reduced areas of both hyperalgesia and allodynia, whereas intrathecal ketorolac only reduced allodynia to a statistically significant degree. Although the combination of UV-B burn and intermittent heat is a logical extension of the capsaicin and intermittent heat method, this model has not been validated, and it is possible that areas of hypersensitivity could spontaneously be reduced over time. We did not administer the intrathecal dose of ketorolac intravenously, and it is conceivable that the effect we observed after intrathecal injection was due to systemic absorption, because systemic doses as low as 1 mg have demonstrated minor analgesia in one clinical trial, although it is unclear from that report whether the analgesia from this dose would differ from placebo.\textsuperscript{32} Based on the large majority of dose–response information with intravenous ketorolac, however, we conclude that allodynia in this model is supported in part by cyclooxygenase activity in the spinal cord. We did not test the intensity of hypersensitivity in areas of injury in the UV-B burn model or at the site of capsaicin application, and so we cannot determine whether intrathecal injection of ketorolac alters peripheral hyperalgesia.

Extrapolation of efficacy and dose response from experimental pain to clinical situations is uncertain, but data from this study provide the following predictions. Intrathecal administration of ketorolac or other NSAIDs should have little effect in acute nociceptive pain (heat pain result), in chronic neuropathic pain associated with hypersensitivity (capsaicin result), or in isolated inflammation (localized arthritis) but may show efficacy in pain with an inflammatory component and hypersensitivity (postoperative pain, arthritis with referred pain). We are in the process of testing these hypotheses.

We note that this interpretation assumes that ketorolac was administered in an adequate dose to inhibit cyclooxygenase in the spinal cord. In this study, concentrations of the drug in CSF are nearly two orders of magnitude greater than plasma concentrations (and CSF concentrations) associated with cyclooxygenase inhibition after systemic administration.\textsuperscript{33} We did not observe a decrease in CSF PGE\textsubscript{2} concentrations after ketorolac in this or in our previous study.\textsuperscript{6} This could be consistent with an inadequate dose of ketorolac or inadequate penetration of this compound into the spinal cord, although other reasons for a lack of change would include the large depot of PGE\textsubscript{2} in CSF which could dilute a localized effect in a section of the spinal cord or minimal cyclooxygenase activity at rest or after the mild stimulus of UV-B burn. It is also possible that resting concentrations of PGE\textsubscript{2} in CSF are not affected by NSAIDs or cyclooxygenase inhibitors, because oral rofecoxib fails to alter PGE\textsubscript{2} before surgery, although it reduces the increase in CSF PGE\textsubscript{2} after surgery.\textsuperscript{34}

Finally, we failed to observe an effect of intrathecal ketorolac on heart rate in this study, in contrast to the unexpected and minor (7 bpm) reduction in heart rate at 15–60 min after intrathecal ketorolac injection in our open-label study. Because there is no physiologic or pharmacologic reason to anticipate an effect of intrathecal ketorolac on sympathetic tone or regulation of heart rate, we conclude that the previous finding was likely due to the lack of control for experiment-wide error of secondary variables in that open-label study. Nonetheless, only 48 subjects have now been reported to have received intrathecal ketorolac, and this therapy should remain investigational until more patients have been studied.

In summary, 2 mg intrathecal ketorolac reduced areas of allodynia after UV-B burn but had no effect on hypersensitivity from capsaicin and no effect on pain from acute heat stimuli to the skin. Extrapolation of these results to clinical pain conditions is uncertain, and it is conceivable that intrathecal ketorolac failed to inhibit cyclooxygenase in the spinal cord. Nonetheless, these data suggest that spinnally produced prostaglandins may have a more limited role in pain and hypersensitivity in humans than predicted by studies in rodents and that this experimental therapy may be particularly relevant to states of peripheral inflammation accompanied by hypersensitivity.

References

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