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Preliminary Efficacy Assessment of Intrathecal Injection of an American Formulation of Adenosine in Humans

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Background: **Preclinical studies of intrathecal adenosine suggest it may be effective in the treatment of acute and chronic pain in humans, and preliminary studies in volunteers and patients with a Swedish formulation of adenosine suggests it may be effective in hypersensitivity states but not with acute noxious stimulation. The purpose of this study was to screen for efficacy of a different formulation of adenosine marketed in the US, using both acute noxious stimulation and capsaicin-evoked mechanical hypersensitivity.**

Methods: **Following Food and Drug Administration and institutional review board approval and written informed consent, 65 volunteers were studied in two trials: an open-label, dose-escalating trial with intrathecal adenosine doses of 0.25–2.0 mg and a double-blind, placebo-controlled trial of adenosine, 2 mg. Cerebrospinal fluid was obtained for pharmacokinetic analysis, and pain ratings in response to acute heat stimuli and areas of mechanical hyperalgesia and allodynia after intradermal capsaicin injection were determined.**

Results: **Adenosine produced no effect on pain report to acute noxious thermal or chemical stimulation but reduced mechanical hyperalgesia and allodynia from intradermal capsaicin injection for at least 24 h. In contrast, residence time of adenosine in cerebrospinal fluid was short (< 4 h).**

Conclusions: **These results show selective inhibition by intrathecal adenosine of hypersensitivity, presumed to reflect central sensitization in humans after peripheral capsaicin injection. The long-lasting effect is consistent with that observed in preliminary reports of patients with chronic neuropathic pain and is not due to prolonged residence of adenosine in cerebrospinal fluid.**

ADENOSINE receptors represent a logical target for treatment of pain. Administration of adenosine agonists to normal animals results in blockade of responses to acute nociception[1] and reduces hypersensitivity to thermal or mechanical stimuli in animals with sensitization after peripheral inflammation[2] or nerve injury.[3] Adenosine agonists probably produce these effects by actions on extracellular G protein–coupled receptors, primarily of the A_1 subtype, as defined pharmacologically, and such inhibitory receptors are present both in the periphery and the central nervous system, primarily in the spinal cord.[4] For these reasons, there has been some commercial development of new molecules acting as adenosine agonists, modulators, or inhibitors of metabolism for clinical analgesia.[5,6]

There has been relatively little study of adenosine receptor activation in humans for the treatment of pain. Dipyridamole, an agent used primarily for its cardiovascular indications, is a potent inhibitor of adenosine reuptake and has been suggested in open-label trials to exhibit efficacy in the treatment of chronic pain.[7] Intravenous administration of adenosine itself increases heat pain thresholds[8] and provides analgesia to acute postoperative pain,[9] presumably by an action in the periphery. In addition, uncontrolled trials in Sweden of intrathecal injection of adenosine in mannitol suggest that it may reduce hypersensitivity from topical administration of mustard oil to the skin in normal volunteers[10] and may provide long-lasting reduction in pain in patients with chronic neuropathic pain,[11] but it exhibits little or no effect in reduction of responses to acute noxious stimuli in normal volunteers[10] or reduction of pain scores in patients after abdominal hysterectomy.[12]

The purpose of the current study is to report our experience with two clinical trials in normal human volunteers with the preservative-free, non–mannitol-containing formulation of adenosine available in the United States (Adenoscan; Fujisawa Pharmaceutical Co., Deerfield, IL). The results come from the first two human trials with this agent, and the study design of these trials focused primarily on safety assessment. Safety aspects of these trials are reported in our companion article.[13] However, we also screened for efficacy to acute noxious thermal nociception in the first, open-label, phase I clinical trial and for efficacy to hypersensitivity induced by intradermal injection of capsaicin in the second, double-blind, phase I clinical trial. Intradermal capsaicin injection results in areas of mechanical allodynia and hyperalgesia reflecting spinal cord sensitization[14] and has been used to probe for activity of compounds that may provide analgesia in patients with presumed sensitization, including chronic neuropathic pain.[15–17]

Materials and Methods

After approval by the Wake Forest University School of Medicine Institutional Review Board (Winston-Salem, NC), two clinical trials were performed. The first trial, an open-label, dose escalation study investigating the safety and tolerability of intrathecal adenosine, examined the effect of this treatment (0.25–2 mg) against acute noxious heat stimulation. The second trial, a double-blind,

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placebo-controlled study, examined efficacy and time course of intrathecal adenosine, 2 mg, against mechanical hyperalgesia and allodynia elicited by intradermal injection of capsaicin. In both studies, healthy volunteers were recruited, and written informed consent was obtained. Volunteers were trained on a day before the study to reliably rate pain intensity from thermal stimulation on the arm and leg. For the second study, they also were trained to report sensation of hyperalgesia and allodynia after intradermal injection of 100 μg capsaicin in the forearm.

On the day of the study, the volunteers came to the General Clinical Research Center, having had nothing to eat or drink since the night before. A peripheral intravenous catheter was inserted into a vein in an upper extremity, and lactated Ringer's solution was infused at 1.5 ml $\cdot$ kg^{-1} $\cdot$ h^{-1} for the duration of each study. Adenosine (Adenoscan) was diluted in normal saline to a volume of 2 ml for intrathecal injection. All but six injections were performed with the volunteer in the lateral position; then the volunteers were positioned supine, with the head of the bed elevated for their comfort. Injections were performed using a No. 27 Whitacre spinal needle. Cerebrospinal fluid (CSF), 2 ml, was sampled before spinal injection and stored for later adenosine analysis. The studies were performed under Investigational New Drug approval from the Food and Drug Administration, with a maximum allowable single dose under this approval of 2 mg.

Clinical Trial A: Acute Thermal Nociception

Twenty-five volunteers were studied in an open-label, dose-escalating, single-blind design. There were five volunteers at each of five dose levels of intrathecal adenosine (0.25, 0.5, 1, 1.5, and 2 mg). Volunteers were tested as previously described[16] with a 1-cm^2 Peltier-controlled thermode maintained at 30°C and increased to between 39 and 51°C in 2°C increments, in random order, for 5 s every 25 s, until each of the seven temperatures had been tested. Volunteers rated their pain on a numerical scale of their choosing, with 0 indicating no pain, and rated the magnitude of the pain for any stimulus above 0 using their own scale. These pain magnitudes were normalized to the response to the 51°C stimulus on the first testing session of the study day. Normalization was done by dividing their response to all pain stimuli below 51°C by the number the individual assigned to the 51°C stimulus, which was the most noxious of the stimuli. Volunteers were not instructed to use any arbitrary numerical scale other than that 0 represented no pain. These noxious heat stimulus–response curves were obtained on the ventral surface of the thigh (L3 dermatome) and the volar surface of the forearm (C8 dermatome). Thermal testing was performed before adenosine injection, at 15 and 30 min, and 1, 2, 3, 4, and 24 h after adenosine administration. A second sample of CSF was obtained in all volunteers 1 h after adenosine administration *via* a No. 27 Whitacre needle. Safety assessment was the primary focus of this investigation, and is described elsewhere.[13]

Clinical Trial B: Capsaicin-induced Hypersensitivity

The effect and time course of intrathecal adenosine on mechanical hypersensitivity induced by intradermal capsaicin was studied in an additional 40 volunteers. On the day of the study, each volunteer first received an intradermal injection of capsaicin, 100 μg, on the lateral calf. Areas of flare, allodynia to a cotton wisp, and hyperalgesia to punctate stimulation with von Frey filaments were determined as previously described, using a 225-mN von Frey filament,[18] and pain magnitude estimates to 225-mN von Frey filament testing in the hyperalgesic area 1 cm from the site of injection were determined at 5-min intervals until 15 min after injection and then at 15 min intervals until 60 min.

Each volunteer then received an intrathecal injection of adenosine, 2 mg, or an equal volume of saline. To determine the time course of adenosine effect, a second 100-μg intradermal capsaicin injection into the other lateral calf was performed at one of the following times: 30 min, 60 min, 2 h, 4 h, or 24 h after adenosine. Just before this capsaicin injection, lumbar CSF (2 ml) was obtained *via* a No. 27 Whitacre needle to assess the time course of adenosine residence in CSF. Assignment to drug group and time was randomized and double blind. For each of the times, there was an unequal randomization, with six volunteers having received adenosine and two having received saline. Thus, for the five times, a total of 30 volunteers received adenosine and 10 received saline. Safety assessment in comparison with placebo was the primary focus of this investigation and is described elsewhere.[13] CSF was collected in a syringe, immediately cooled to 4°C, and centrifuged at this temperature at 4,000*g* for 10 min, and the supernatant was stored to −70°C until analysis. Adenosine was determined using a Rainin Dynamax Model UV-D II absorbance detector (Phenomenex, Torrance, CA) at 254 nm, with limit of sensitivity of 10 pmol per injection and a coefficient of variation at 50 pmol of 7%.

Statistics

Data are presented as mean ± SE or median ± quartiles, as indicated. Pain scores, normalized to the response to 51°C, were compared between arm and leg before drug injection by two-way analysis of variance and were compared over time within treatment groups by two-way repeated-measures analysis of variance. Threshold to pain was analyzed by the Friedman two-way analysis of variance. Areas of hyperalgesia and allodynia were averaged over the 30- to 60-min period after intradermal capsaicin injection, and effect of intrathecal drug treatment was assessed using the percent change in

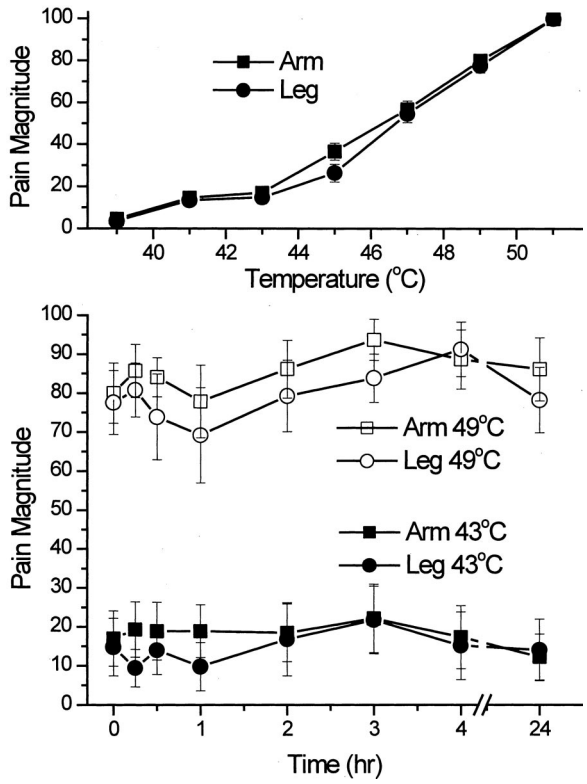

Fig. 1. (*Top*) Pain report to thermal testing of the arm (solid squares) or leg (solid circles) in the population of 25 individuals in clinical study A before drug injection. In both panels, pain is normalized to each individual's rating of the pain of a 51°C stimulus as 100. No significant differences. (*Bottom*) Pain report over time to a high-intensity heat stimulus (49°C, open symbols) or a low-intensity heat stimulus (43°C, closed symbols) in 25 individuals receiving, after time 0, intrathecal injection of adenosine in various doses between 0.25 and 2.0 mg. Results are shown to testing in the arm (squares) and leg (circles). No significant difference at each temperature of testing between groups or of time within each group.

these areas after the second capsaicin injection compared with the first. Effect of adenosine over time was analyzed by two-way repeated-measures analysis of variance. $P < 0.05$ was considered significant.

Results

Clinical Trial A: Acute Thermal Nociception

Ten women and 15 men were studied, including 1 African-American, 1 Hispanic, 1 Asian, and 22 white subjects. Their average age was 33 ± 1.4 yr, average height was 180 ± 6.2 cm, and average weight was 69 ± 0.9 kg. There was no difference in pain report to heat stimulation between the arm and leg before drug treatment (fig. 1, top). Similarly, the threshold to first report of pain before drug treatment did not differ between the arm (median: 41°C [39, 43°C; 25th, 75th percentiles]) and the leg (41°C [39, 43°C]). When all adenosine doses were combined, there was no effect of treatment on pain report to a mildly noxious (43°C) or an intensely noxious (49°C) stimulus (fig. 1, bottom). In addition, there was no effect of adenosine within each dose group of pain report in the arm or the leg over time (data not shown). Threshold to first report of pain after drug treatment did not differ overall or within any group over time. The median threshold in both arm and leg was 41°C for all times before and after adenosine except the leg at 24 h after intrathecal injection of 2 mg adenosine, when the median was 43°C (not significant). CSF adenosine concentration before injection was 0.57 ± 0.11 μM. Adenosine administration resulted in a dose-dependent increase in CSF adenosine concentration 1 h later (0.25 mg, 1.8 ± 0.5 μM; 0.5 mg, 2.8 ± 0.9 μM; 1.0 mg, 9.8 ± 3.9 μM; 1.5 mg, 21 ± 6.2 μM; 2.0 mg, 26 ± 3.2 μM).

Clinical Trial B: Capsaicin-induced Hypersensitivity

Nineteen women and 21 men were studied, including 5 African-American, 3 Asian, and 32 white subjects. Their average age was 31 ± 1.1 yr, average height was 163 ± 5.1 cm, and average weight was 68 ± 0.6 kg. Capsaicin injection resulted in acute, burning pain, which rapidly resolved over 3–5 min. When all data were combined, saline- and adenosine-treated volunteers did not differ in their magnitude rating of capsaicin before intrathecal drug injection, nor did they differ afterward (fig. 2). In addition, there was no effect of intrathecal injection of adenosine on the pain response to the second injection of capsaicin.

Capsaicin injection resulted in areas of hyperalgesia and allodynia that were stable between 30–60 min (fig. 3, top), and these areas were statistically similar before intrathecal injection between volunteers randomized to saline and adenosine groups (data not shown). Pain from

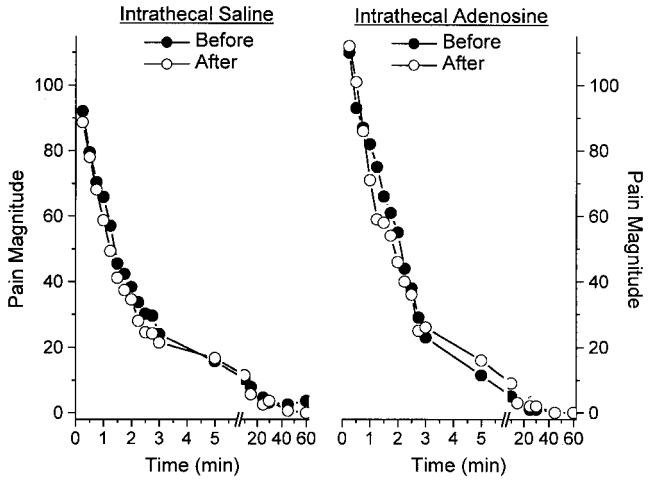

Fig. 2. Pain magnitude estimates after intradermal injection of 100 μg capsaicin into the lateral calf of volunteers receiving intrathecal saline (*left*) or adenosine, 2 mg (*right*). Pain estimates are the mean of 10 volunteers in the saline group and 30 volunteers in the adenosine group, obtained on the first capsaicin administration, before intrathecal injection (closed circles), or after intrathecal injection (open circles). No significant difference in either drug treatment group or between groups.

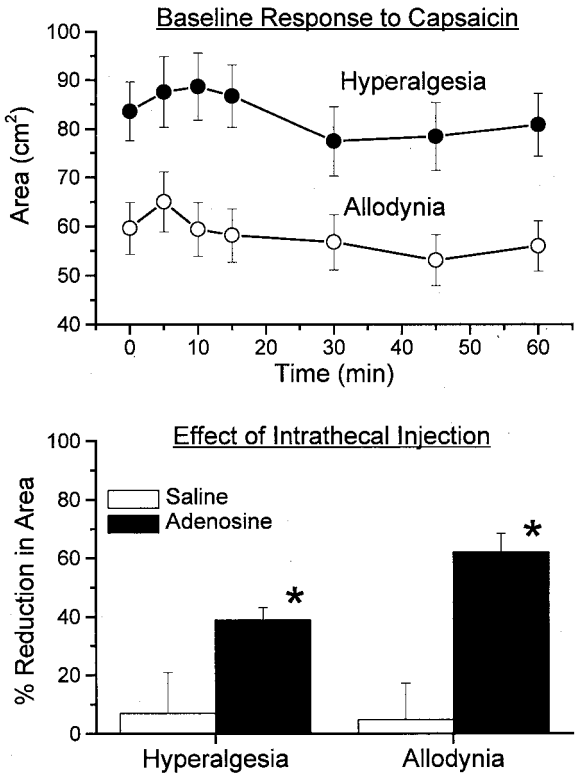

Fig. 3. (*Top*) Area of hyperalgesia to punctate mechanical stimulation (closed circles) and area of allodynia to light brush (open circles) after the first capsaicin injection, before intrathecal drug injection. Each symbol represents the mean ± SE of 40 volunteers. (*Bottom*) Percent reduction in area of hyperalgesia and allodynia to capsaicin injection after intrathecal drug treatment with saline (open bars) or adenosine, 2 mg (filled bars). *$P < 0.05$ compared with saline.

von Frey filament probing in the area of hyperalgesia was mild and not different between saline and adenosine at any time. The average pain magnitude over all time periods was 10 ± 4 for saline and 10 ± 2 for adenosine. In contrast to the lack of effect on capsaicin injection-induced pain, adenosine clearly reduced the areas of both hyperalgesia and allodynia. Thus, with all time groups combined, adenosine, but not saline, reduced the areas of mechanical hypersensitivity during the 30- to 60-min period after capsaicin injection, and adenosine treatment differed from saline (fig. 3, bottom). The effect of adenosine in reducing capsaicin-induced hyperalgesia and allodynia was statistically similar at all times of capsaicin injection after intrathecal adenosine injection, from 30 min after adenosine injection to 24 h after adenosine injection (fig. 4). In volunteers receiving intrathecal saline, there was also no change in response to capsaicin injection as a function of time after intrathecal saline injection (data not shown). Intrathecal adenosine injection increased CSF adenosine concentration for less than 4 h after injection (fig. 5). In contrast, intrathecal saline injection had no effect on CSF adenosine concentration at any time (range, 0.83–1.22 μM), and there was no trend in change of CSF adenosine concentration over time in volunteers who received intrathecal saline.

Discussion

The current study confirms that two unexpected observations in rats and in uncontrolled clinical trials in Sweden regarding intrathecal adenosine administration—selectivity for sensitized states and prolonged duration of action— exist in humans receiving preservative-free adenosine by intrathecal injection. However, both observations should be tempered by limitations of study design.

It could be argued that the observed selectivity for hypersensitivity reflects merely a difference in stimulus intensity because thermal stimulation in normal subjects achieves a greater nociception intensity at high temperatures than that achieved for threshold determinations to von Frey filament probing in those with nerve injury. However, this stimulus intensity explanation was not supported in the current study because intrathecal adenosine had no effect on any acute thermal stimulus, even

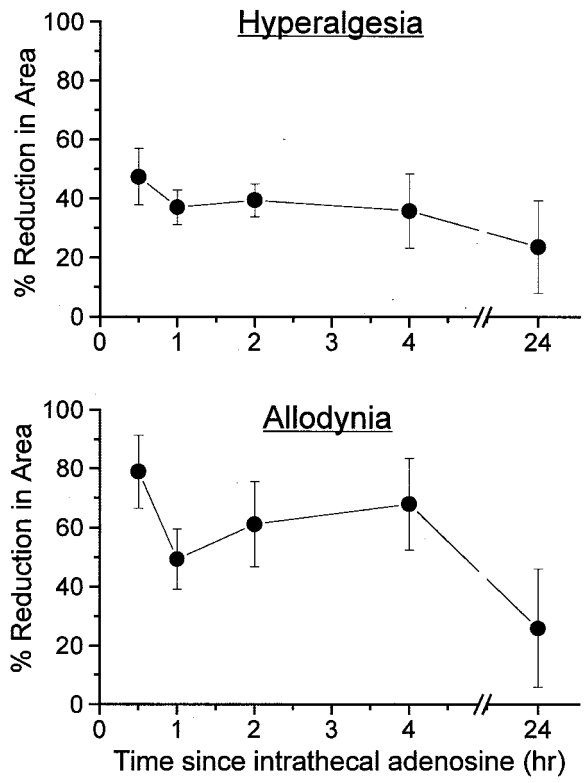

Fig. 4. Percent reduction in hyperalgesia (*top*) and allodynia (*bottom*) from intrathecal injection of adenosine as a function of time of the second capsaicin injection compared with intrathecal adenosine administration. Each symbol represents the mean ± SE of six volunteers. For hyperalgesia and for allodynia, the reduction in area from adenosine was statistically similar when the second capsaicin injection was administered from 30 min to 24 h after adenosine.

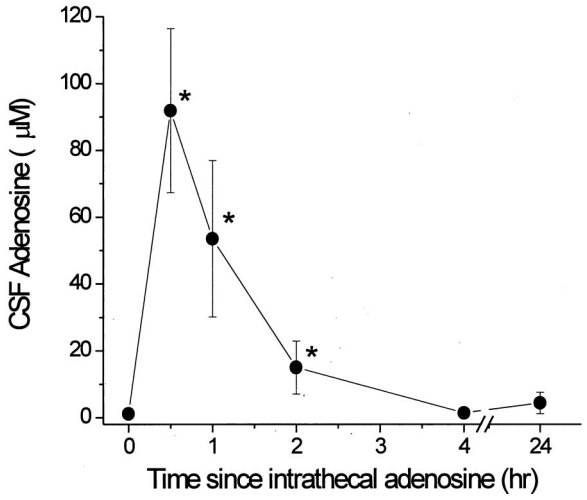

Fig. 5. Cerebrospinal fluid (CSF) concentrations of adenosine after intrathecal injection. Each symbol represents the mean ± SE of six volunteers. *$P < 0.05$ compared with baseline.

on barely suprathreshold heat stimulation at 43°C (fig. 1). Alternatively, one could argue that the selectivity observed in the current study reflects different stimulus modalities (thermal in normal compared with mechanical in hypersensitivity). However, there is no evidence for modality-selective actions of adenosine in the periphery or in the spinal cord.

We used intradermal capsaicin as a model of central sensitization to predict effects in patients with chronic pain. Of course, acute sensitization induced by intradermal capsaicin must be at best an incomplete model of the pathophysiologic processes that occur in chronic neuropathic and inflammatory pain conditions in humans. Nonetheless, several studies support the premise that response to acute central sensitization from intradermal capsaicin might have predictive value in the treatment of chronic inflammatory or neuropathic pain. Intradermal capsaicin does not produce peripheral sensitization at times of hypersensitivity humans,[14] and studies in animals show an exaggerated response of spinothalamic tract neurons to peripheral stimulation after intradermal capsaicin in the receptive field of the spinal cord cell[19] and enhanced sensitivity to excitatory amino acids.[20] Additionally, studies to date suggest that the pharmacology of inhibition of area of hyperalgesia and allodynia in this experimental model in humans predicts efficacy in the treatment of neuropathic pain. Thus, both opioids and N-methyl-D-aspartate antagonists reduce capsaicin-induced hypersensitivity and are effective in neuropathic pain, but only in doses leading to therapy-limiting side effects.[15] The relative potency of epidural compared with intrathecal clonidine to reduce capsaicin-induced hypersensitivity correlates with their relative potencies to treat neuropathic pain, but not to treat postoperative pain,[21] further supporting the relevance of this acute hypersensitivity model to chronic pain conditions in humans associated with hypersensitivity.

Intrathecal adenosine exhibits a remarkably long duration of action to reduce capsaicin-induced hypersensitivity, and there was no statistical difference in the effect of intradermal capsaicin to induce hypersensitivity at 30 min or 24 h after intrathecal adenosine injection. We did not compare the effect of adenosine at each time point with that of saline placebo because ethical considerations prevented us from including an adequate number of intrathecal saline–injected volunteers at each time point. However, there was no overall effect of intrathecal saline on capsaicin-induced hyperalgesia or allodynia (fig. 3) and no trend for any effect of time on capsaicin response in the saline-treated volunteers. This strengthens the assertion that intrathecal adenosine had a prolonged duration of action, as noted in uncontrolled clinical trials in patients with neuropathic pain.[11] This prolonged action, also present in the peripherally nerve-injured rat,[22] does not reflect a pharmacokinetic alteration in either species, as measured by acute sampling of CSF. We note that our baseline concentrations of adenosine in CSF are somewhat greater than those observed in previous reports,[23] perhaps reflecting minor amounts of contamination with blood. However, this should not affect the kinetic observations of the current study. Although residence time of adenosine was considerably longer in CSF in this study than previously demonstrated in plasma,[24] it was nonetheless far too brief to explain the long duration of action. Also, there was no evidence of distribution to lipid-rich stores, such as epidural fat, which would serve as a source of continuous release of the compound, because CSF concentrations returned to basal levels within 4 h. Most likely, adenosine was taken up into tissues, including primarily the neurons and supporting elements of the spinal cord, after intrathecal injection. Our companion article examining the effects of intrathecal adenosine in a rat model of neuropathic pain[25] provides further evidence in support of this hypothesis.

In summary, intrathecal adenosine reduces mechanical allodynia in humans induced acutely by intradermal capsaicin injection, with a remarkably long time course, much longer than its residence time in CSF. In contrast, there is no apparent effect of intrathecal adenosine on acute noxious thermal stimulation. These data are consistent with studies in animals of intrathecal adenosine in acute nociception and chronic nerve injury and with uncontrolled trials in volunteers and patients in Sweden with a different formulation of adenosine. They suggest that further controlled clinical trials of intrathecal adenosine to reduce hypersensitivity phenomena after acute injury, such as surgery, or chronic injury, such as in some patients with neuropathic pain, are warranted.

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