Intrathecal Adenosine Administration

A Phase 1 Clinical Safety Study in Healthy Volunteers, with Additional Evaluation of Its Influence on Sensory Thresholds and Experimental Pain

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Background: Several animal studies show antinociceptive effects of intrathecally administered adenosine and its analogs. However, there is no clinical experience regarding the effects of intrathecal adenosine in humans.

Methods: The side effects and analgesic effects of intrathecal adenosine (500–2,000 µg) on experimental pain were studied in 12 healthy volunteers. Before and after adenosine was given, the authors evaluated the cold pain rating of the foot (submersion in ice water for 1 min), the forearm ischemic pain rating during a 30-min tourniquet test, and the thermal and tactile pain thresholds on healthy and inflamed skin after application of mustard oil (4 min) to the calf. The areas of secondary allodynia surrounding the inflammation were also determined. The cerebrospinal fluid level of adenosine was determined before and after injection.

Results: Intrathecal adenosine caused a 1,000- to 2,000-fold elevation of the cerebrospinal fluid concentration. One volunteer experienced transient (30 min) lumbar pain after injection at a dose of 2,000 µg. There were no other complications in any other volunteers. Adenosine reduced, in a non–dose-dependent manner, the areas of secondary allodynia after skin inflammation (brush, $P < 0.06$; and von Frey hair, $P < 0.03$) and reduced the forearm tourniquet ischemic pain rating ($P = 0.01$). Tactile pain thresholds were significantly reduced by mustard oil inflammation during control, whereas adenosine treatment prevented this reduction. The ice water–induced cold pain rating was not influenced by adenosine.

Conclusions: An intrathecal adenosine injection of 1,000 µg lacked side effects in healthy volunteers. The compound attenuated different types of experimental pain. (Key words: Antinociception; mustard oil; nucleosides; spinal pharmacology; tourniquet test.)

ADENOSINE is an endogenous compound with various modulatory effects in the peripheral and central nervous system. Its actions are mediated through specific cell-surface–associated receptors.[1,2] Several studies have shown the antinociceptive effects of adenosine and adenosine agonists (analogs) when administered intrathecally to rodents, in models of acute and chronic pain.[3–8] In rats with mononeuropathy induced by a chronic sciatic nerve injury, the adenosine A_1 receptor agonist R-phenyl-isopropyl adenosine effectively reduces pain behavior, as assessed by skin tactile hypersensitivity and scratching behavior,[7,8] probably by a spinal site of action. This effect of A_1 receptor stimulation can be abolished by adenosine receptor antagonistic drugs, such as methylxanthines.[4,8] Furthermore, chronic (2 weeks) intrathecal adenosine administration to rats, at the maximal deliverable dose of the commercially available (in Sweden) clinical solution (5 mg/ml adenosine in isotonic mannitol) resulted in no morphologic signs of spinal cord damage (K Rane *et al.*, unpublished observations, 1997).

Recent placebo-controlled clinical studies in healthy volunteers, in patients during surgery, and in patients with chronic neurogenic pain showed that continuous intravenous adenosine administration (50–80 $\mu g \cdot kg^{-1} \cdot min^{-1}$)

has antinociceptive effects.[9-14] In addition, case reports have documented pain relief by intrathecal adenosine and R-phenyl-isopropyl adenosine in patients with severe neuropathic pain and allodynia.[15,16] However, there have been no systematic studies regarding the tolerability or efficacy of intrathecally administered adenosine in humans.

This study evaluates the tolerability to escalating doses of intrathecal adenosine. In addition, we examined its influence on some experimental pain modalities and the level of adenosine in the cerebrospinal fluid (CSF).

Volunteers and Methods

The study protocol was approved by the Karolinska Hospital Human Research Ethics Committee and the Medical Products Agency of Sweden. Twelve healthy volunteers (aged, 18-52 yr; seven women) were enrolled. Written and signed informed consent was obtained before participation. No volunteer was taking any concomitant medication. Neither caffeinated beverages nor smoking were allowed for 12 h before the experiment, which was performed in the morning after a light breakfast. Another group of nine volunteers was studied as a control group for the cold immersion provocation, and they did not receive adenosine (explained in detail below).

An intravenous catheter was introduced. Each volunteer was studied in a standardized manner. After sequential control assessments of sensory function, each volunteer received a single intrathecal injection of adenosine in one of three doses (500, 1,000, or 2,000 μg). The lowest dose (500 μg) was given to the first two volunteers. The next five received 1,000 μg, whereas the last five received 2,000 μg. After injection, additional sensory testing was performed sequentially.

Drugs
Adenosine Administration and Determination. The commercially available adenosine solution (Adenosine Item, 5,000 μg/ml in isotonic mannitol; Item Development AB, Stocksund, Sweden) was dissolved to its final concentrations (250, 500, and 1,000 μg/ml) with isotonic saline. The drug was injected in a volume of 2 ml, giving final doses of 500 to 2,000 μg.

The volunteers received topical local anesthesia (1-2 ml EMLA, ASTRA, Södertälje, Sweden) over the L3-L4 lumbar interstitium 1 h before spinal puncture. The dura mater was punctured with the volunteers in a lateral position, using a pencil-point spinal needle (27-gauge

Whitacre) between the L3 and L4 vertebrae. One milliliter CSF was collected 10 min before (n = 9) and at 10 min after (n = 8) intrathecal injection of adenosine to analyze adenosine concentration. During that period, the needle was locked with a mandrin and left in place. After the adenosine injection, the first 1 ml CSF spillover at 10 min was discarded before sampling. In the two volunteers who received 500 μg, the spinal needle was left in place for 2 h, and intermittent CSF samples were collected to determine the elimination half-life of adenosine. The CSF was immediately stored at $-20°$C until analysis.

Adenosine, inosine, and hypoxanthine were determined by high-pressure liquid chromatography using ultraviolet detection, in a volume of 10 μl, with duplicate injections. The detection limit for adenosine and inosine was 0.2 μM. When used to assess basal CSF adenosine levels, aliquots of CSF samples were freeze dried and redissolved in 10% of its original volume. The detection limit was then 0.02 μM.

Bedside Examinations
Blood pressure and heart rate were measured before and at 45, 120, and 240 min after adenosine administration. Reflex testing of the extremities (biceps and triceps brachii tendons, patellar and Achilles tendons) and testing of gross muscle force (bending and stretching forces of both legs and arms) was performed before and 60 and 240 min after adenosine was given. Romberg's test for balance was also conducted at these intervals (the first two volunteers were only tested at 240 min). Subjective symptoms were assessed at 15-min intervals throughout the entire procedure. The volunteers were interviewed for fatigue, nausea, malaise, and dizziness. The volunteers were instructed to note any side effects (such as fatigue, nausea, malaise, dizziness, balance disturbances, headache, weakness, voiding or intestinal function problems, puncture site or other pain) during the week after the injection.

Sensory Skin Testing
Healthy Skin (Lateral Part of the Calf). Pain thresholds to tactile stimulation was obtained by using calibrated (in grams) von Frey filaments (0.01 to 279 g). The filaments are applied to the skin in alternating ascending and descending series. The threshold is calculated from the average of the first stimulus of four ascending series to be felt as painful and the first stimulus in each of four descending series not to be felt as painful. This was done before and 90 min after adenosine was given.

The detection thresholds for cold, warmth, and heat pain detection were assessed using thermal pulses with a constant rise time of 1°C/s, using a standard Peltier element (Thermotest; Somedic Sales AB, Farsta, Sweden). The volunteers were instructed to press a hand-held button as soon as he or she experienced the intended sensory threshold. The means of five values of cold and warmth, respectively, were calculated and constituted the perception thresholds. The heat pain threshold was determined by increasing the probe temperature until the volunteer perceived the thermal stimulus as being just barely painful. The mean of three values was calculated. This was done before and 95–100 min after adenosine was given.

Inflamed Skin (Medial Part of the Calf). Mustard oil application to hairy skin is associated with a burning pain followed by a painful inflammatory reaction of the applied skin and secondary allodynia in the surrounding area. A compress (2 × 3 cm) soaked with mustard oil (allylisoyhiocyanate, Merck, KGaA, Darmstadt, Germany) stained with ink (Märkbläck, ACO, Stockholm, Sweden) was applied to the skin for 4 min. The application site was gently dried with a clean compress immediately after the applicator was removed. Mustard oil was applied to the left leg 45 min before adenosine and to the right leg 100 min after spinal injection. Development of secondary allodynia around the mustard oil–stimulated area (brush stimulus and normally nonpainful von Frey filament stimulus [20 g]) were assessed by radially striking a soft brush and intermittently applying the von Frey filaments hair from eight different directions. The margins of the brush- and von Frey–induced allodynic areas were marked on the skin with colored felt-tipped pens. Sensory testing of the area where mustard oil was applied (primary area) was conducted 20–30 min after application, with tactile pain thresholds determined as described earlier. The tactile pain threshold was also assessed in the area of secondary allodynia. After completion of the experiment, area markings were transferred to plastic film, and the areas were measured planimetrically by an independent, blinded observer. The application area, represented by the ink-marked skin area, was subtracted from the total planimetric area, thereby providing the area of secondary allodynia (given in square centimeters).

All quantitative testing of skin sensory modalities was hidden to the volunteers by a screen.

Cold Immersion Test. To test pain ratings by cold challenge, the volunteers placed one foot (up to the ankle) in ice water (2–4°C) for 60 s. Pain ratings were assessed at 60 s, using a visual analog scale (VAS, 0–100 mm, where 0 is no pain at all and 100 is worst imaginable pain). The test was conducted 1 h before adenosine was given and 1, 2, 3, and 4 h after the injection. Nine separate volunteers were used as controls, with the hourly cold challenge protocol applied without any adenosine to assess the reproducibility of VAS-reported pain by repeated cold stimuli.

Tourniquet Ischemic Test

Ischemic pain of the forearm was obtained by a tourniquet applied to the upper arm on the nondominant side, according to the method previously described.[17] Briefly, the arm was raised for 5 min before occlusion to drain the venous system. A tourniquet was inflated to a pressure exceeding systolic blood pressure by 100 mmHg or a minimum of 250 mmHg was applied. A weight of 3 kg was then slowly and steadily lifted from the surface (15 times for the women, 20 times for the men) as a submaximal effort during 90 s. After these muscle contractions, representing time zero, pain was assessed every minute until VAS 100 was reached, or for a maximum duration of 30 min. The tourniquet was then deflated. If deflated before 30 min of occlusion, a VAS score of 100 was used for the remaining period. The sum of pain VAS rating scores over the 30-min test was determined and represents the "sum of pain score," which was used to compare the control occasion and adenosine administration.

The tourniquet tests were only performed in those volunteers who received 1,000 and 2,000 μg. A training occasion was undertaken about 1 week before the adenosine experiment to demonstrate the procedure of the tourniquet test. The tests (n = 9) were performed at 60–90 min after intrathecal administration of adenosine. Because repeated tourniquet testing cannot be performed in the same person at one occasion, separate follow-up controls were performed 7–10 days after the main experiment.

Statistics

Data are presented as mean (± SD), with the exception of the tactile pain threshold data given in median (quartiles). Statistical analyses were performed by Wilcoxon's signed rank test, two-tailed analysis. A probability value < 5% was considered significant.

Table 1. Skin Sensory Testing

	Before Adenosine	After Adenosine	Significance
Normal skin			
Cold detection threshold (°C)	25.8 ± 4.8	24.8 ± 2.2	NS
Warmth detection threshold (°C)	40.0 ± 3.7	39.9 ± 3.8	NS
Heat pain threshold (°C)	45.8 ± 2.2	44.7 ± 1.3	NS
Tactile pain threshold (g)	212 (107/279)	155 (79/236)	NS
Inflamed skin (20–30 min after mustard oil)			
Cold detection threshold (°C)	21.3 ± 5.9*	20.9 ± 5.2*	NS
Warmth detection threshold (°C)	35.7 ± 2.3*	36.9 ± 4.1	NS
Heat pain threshold (°C)	38.8 ± 2.9†	40.2 ± 4.2*	NS
Tactile pain threshold (g), primary area	47 (11/184)†	113 (50/279)	$P < 0.05$
Tactile pain threshold (g), secondary area	33 (12/158)*	144 (26/279)	$P < 0.05$

NS = not significant.

* Difference from "normal skin", $P < 0.05$.

† Difference from "normal skin", $P < 0.01$.

Results

Tolerability and Safety

After adenosine injection, there were no nonspecific subjective symptoms such as fatigue, nausea, dizziness, or malaise. Basal blood pressure (115 ± 10 mmHg and 70 ± 5 mmHg) and heart rate (66 ± 5 beats/min) were unchanged at 45 min and at 2 and 4 h after adenosine. We found no change in the reflex testings of the arms and legs. The bedside assessments of motor function and gross muscle strength of arms and legs were not in any way affected. Results of the Romberg test were normal before and on the two occasions tested after adenosine was given. No disturbance in the voiding reflex was reported. However, one volunteer who received the adenosine dose of 2,000 μg experienced a pain sensa-

tion with a maximum pain intensity VAS of 70, starting approximately 5 min after injection, tapering off, and vanishing within 30 min. This pain was located in a circular area around the lower part of the trunk (below T12), both inguinal regions, and the lumbar part of the back. This transient side effect terminated further dose-escalation.

All volunteers returned after approximately 1 week to perform the tourniquet test control, and there were no reports of any late side effects. None of the volunteers experienced postspinal headache.

Sensory Testing

Before Adenosine Administration. Table 1 shows the basal thermal detection thresholds and tactile pain thresholds. After mustard oil was applied, heat pain

Fig. 1. Pain (visual analog scale [VAS] range, 0–100) induced by 60 s of ice-water immersion of the foot, tested hourly in control participants who did not receive drug (n = 9) and in volunteers receiving an intrathecal dose of adenosine (n = 10), 1 h before and hourly after adenosine administration (mean ± SD).

RANE *ET AL.*

A

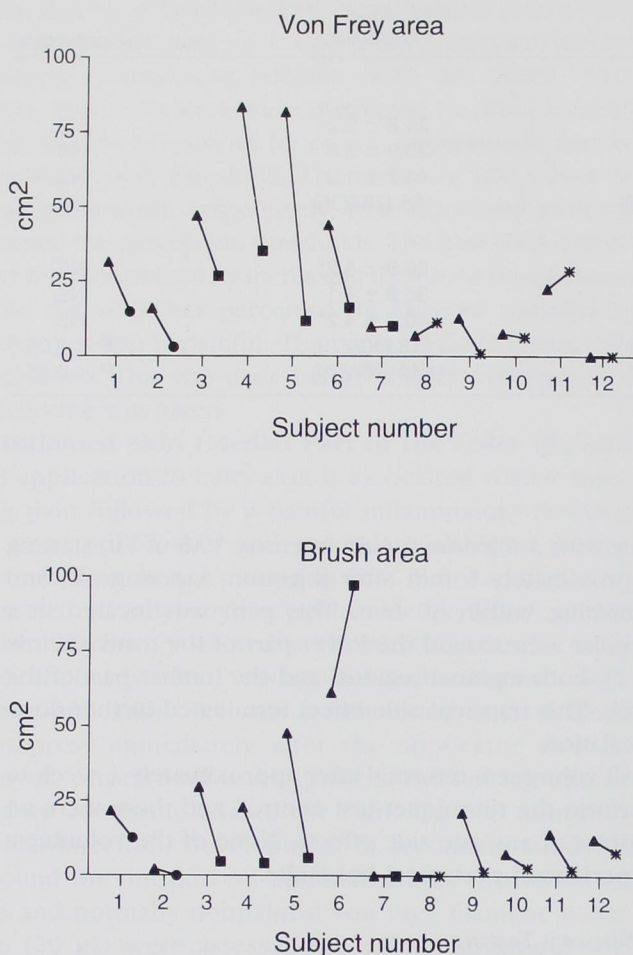### Von Frey area

B

Brush area
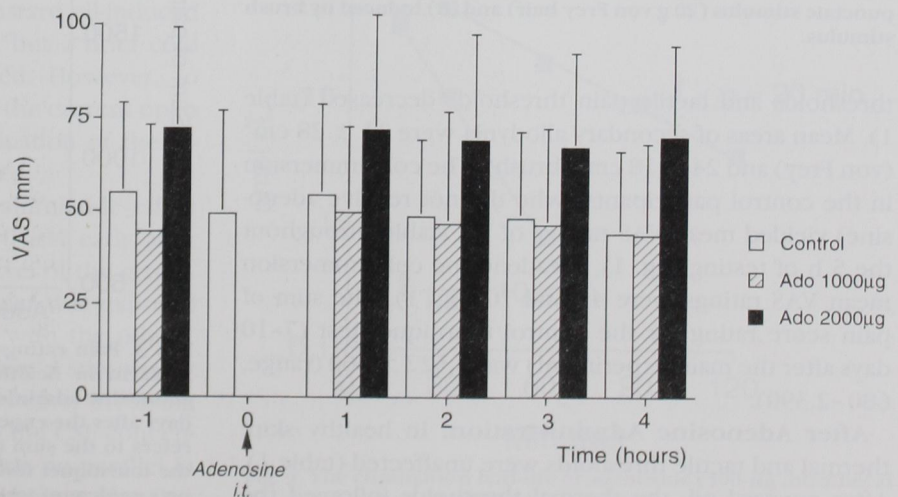
Fig. 2. Individual areas (in square centimeters) of allodynia–dysesthesia 20–30 min after mustard oil application to the calf, before (▲) and 120–130 min after intrathecal adenosine at three dose levels (●500 μg, ■1,000 μg, *2,000 μg), (*A*) induced by punctate stimulus (20 g von Frey hair) and (*B*) induced by brush stimulus.

thresholds and tactile pain thresholds decreased (table 1). Mean areas of secondary allodynia were 33 ± 28 cm² (von Frey) and 24 ± 18 cm² (brush). The cold immersion in the control participants (who did not receive adenosine) yielded mean VAS ratings of 55, stable throughout the 5 h of testing (fig. 1). Preadenosine cold immersion mean VAS ratings were 45 and 70 (fig. 1). The sum of pain score rating for the control tourniquet test (7–10 days after the main experiment) was $1,522 \pm 660$ (range, 680–2,390).

After Adenosine Administration. In healthy skin, thermal and tactile thresholds were unaffected (table 1). After mustard oil, the thermal thresholds followed the

same pattern as before adenosine, whereas no tactile pain threshold reduction was seen after adenosine (table 1). The size of secondary allodynic areas by von Frey hair stimulus was reduced by approximately 50% ($P < 0.03$), whereas a corresponding (but not significant) response pattern was seen by brush stimulation ($P < 0.06$). The individual responses are illustrated in figures 2A and B.

The cold immersion test VAS was not affected by adenosine, as illustrated in figure 1. The sum of pain score during the tourniquet test, including all nine volunteers tested, was $1,270 \pm 560$ (range, 530–2,130). There was no difference in the pattern of the sum of pain score ratings between the two doses of adenosine (fig. 3), and the sum of pain score was 16% less than the control occasion.

Adenosine Determinations

Concentrations of adenosine in CSF are given in table 2. At the highest doses, the levels of adenosine were three orders of magnitude higher than during basal conditions. In the two volunteers in whom the elimination half-life was determined, there was good logarithmic correlation of adenosine levels (fig. 4), and the two

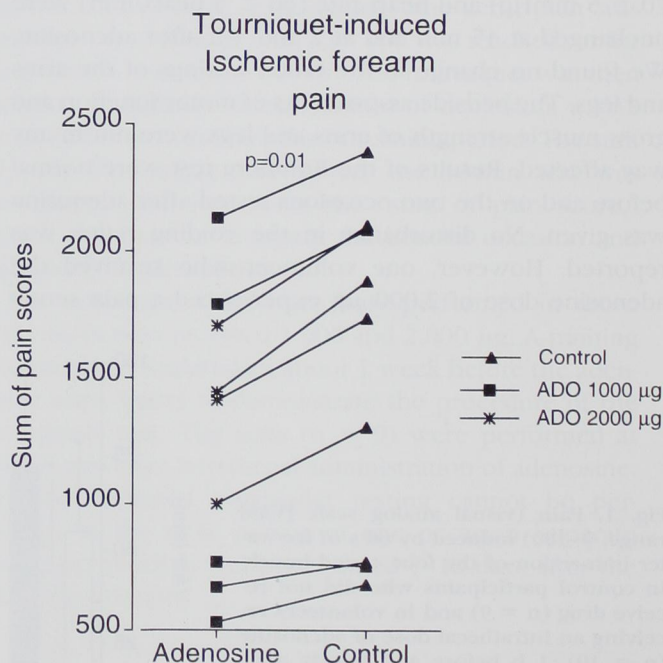### Tourniquet-induced Ischemic forearm pain

Fig. 3. Pain ratings during the ischemic tourniquet test of the forearm in healthy volunteers, 60–90 min after intrathecal adenosine administration, and in control tests performed 7–10 days after the experiment (n = 9). The sum of pain scores (SPS) refers to the sum of visual analog scale ratings over 30 min of the tourniquet test. Statistical analysis was done using Wilcoxon's rank sum test.

Table 2. Adenosine and Inosine concentrations in human CSF (μM)

	Basal	500 μg	1,000 μg	2,000 μg
Adenosine				
n	9	2	3	3
Individual data		37, 50	65, 187, 200	66, 142, 191
Mean value	0.07 (range 0.02–0.27)	43	151	133
Inosine				
n	8	2	3	3
Individual data	—	11, 19	20, 45, 180	90, 115, 135
Mean value	0.76	15	82	113

values of elimination half-life was 10 and 20 min, respectively. As illustrated in table 2B, inosine levels were elevated already 10 min after adenosine injection. Hypoxanthine levels were not affected by exogenous adenosine acutely or in the two volunteers studied over time (data not shown).

Discussion

The primary finding of this study, which included a limited number of healthy volunteers, is that intrathecal administration of adenosine at a dose of 1,000 μg lacked side effects. In addition, the occurrence of a transient pain symptom in one participant after the highest administered dose (2,000 μg) shows that there is a tolerability limitation with respect to spinal adenosine administration. Adenosine administration was associated with reduced forearm ischemic tourniquet pain and reduced areas of secondary allodynia after mustard oil-induced inflammation, and it counteracted a mustard oil-induced decrease of the tactile pain threshold, but a brief cold pain provocation test was not affected. However, to verify the sensory function results from the current open phase 1 study, placebo-controlled evaluation of the effects of intrathecal adenosine is required.

The volunteer who experienced a painful side effect had an adenosine concentration of 190 μM early after injection, which was not the highest level of the group. Therefore it is unlikely that this volunteer was exposed to a higher adenosine level compared with the others. Consequently adenosine seems to induce a stimulatory effect at the spinal level in some volunteers, involving pain mechanisms not directly related to the CSF concentration. This type of pain provocation has no parallel in animal studies using adenosine or adenosine analog, be-

cause there has been no report of painful behavior (such as vocalization or twitching) with intrathecal administration.[3–8,18] The mechanism for the current pain reaction is not evident. Because it is an effect localized to the lumbar segments close to the site of injection, we could speculate that adenosine locally stimulates the primary afferents of the dorsal root or directly influences the superficial layers of the cord. Because A_2-adenosine receptors have been suggested to be involved in the peripheral algogenic effect of adenosine,[18] adenosine interaction on this receptor might also be involved in the transient pain-inducing effect at the spinal cord level. Another possibility may be that adenosine produces meningeal vasodilatation via A_2 receptor activation, leading to a transient migraine-like pain. In this context, it has been reported that intrathecal adenosine A_1 receptor agonist injection in rats causes vasodilatation of the spinal cord.[19] Furthermore, the pain reaction could also reflect some neurotoxic effect. This is, however, unlikely on the basis of toxicology data from rodents. When adenosine (in isotonic mannitol solution) was injected twice daily for 2 weeks, at a dose corresponding to a human dose of 20,000 μg (when correlated to weight), there were no behavioral or morphologic–morphometric signs of toxicity (K Rane et al., unpublished observations).

The level of adenosine in CSF early after injection ranged from 37 to 200 μM, corresponding to approximately a 1,000- to 2,000-fold elevation compared with

Adenosine concentration in human CSF
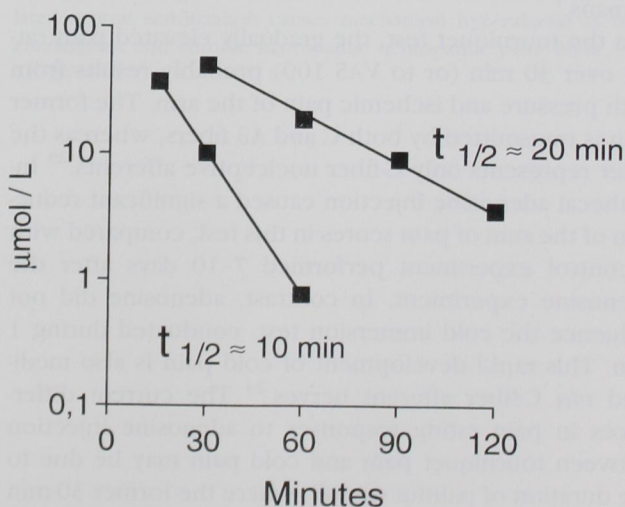
Fig. 4. The elimination half-life of adenosine (500-μg intrathecal dose) in cerebrospinal fluid from two healthy volunteers.

RANE *ET AL.*

the basal level. This elevated concentration had an elimination half-life (n = 2) in the range of 10 to 20 min, which is in marked contrast to the half-life in blood (< 10 s).[20] The factors determining the elimination are uptake to tissues and blood and enzymatic degradation to inosine.[20] In contrast to the dominating incorporation of exogenous adenosine to adenine nucleotides in the vasculature after intravenous administration, the current study shows that the elimination of adenosine in CSF involves a much greater proportion of enzymatic degradation to inosine (table 2). Because the elimination of adenosine, resulting from breakdown, uptake, and diffusion, occurs during the course of the pain testing experiments (120-130 min), it is relevant to estimate the duration of elevated levels of adenosine in CSF. With an estimation of approximately 6 or 7 half-life during the first 2 h of the experiment, the adenosine concentration in CSF would be above a 10-fold elevation during the period when pain testing was conducted. However, because the intrathecal adenosine was eliminated rapidly during this early period, information about maximal effects on pain provocation tests after intrathecal administration still remains to be elucidated.

It has been suggested that the antinociceptive effect of intrathecal adenosine receptor stimulation is mediated by the adenosine A_1 receptor subtype.[4,18] This receptor interaction has been shown to modulate potassium and calcium ion channel flux, causing hyperpolarization of neurons and inhibition of nerve transmission.[21,22] Consequently, such a mechanism of action at the spinal or supraspinal levels (or both) may also occur when adenosine is injected into the central nervous system of humans.

In the tourniquet test, the gradually elevated pain rating over 30 min (or to VAS 100) probably results from both pressure and ischemic pain of the arm. The former pain is transmitted by both C and A∂ fibers, whereas the latter represents only C-fiber nociceptive afferents.[23] Intrathecal adenosine injection caused a significant reduction of the sum of pain scores in this test, compared with a control experiment performed 7-10 days after the adenosine experiment. In contrast, adenosine did not influence the cold immersion test, conducted during 1 min. This rapid development of cold pain is also mediated *via* C-fiber afferent nerves.[24] The current differences in pain rating responses to adenosine injection between tourniquet pain and cold pain may be due to the duration of painful stimuli, where the former 30-min pain provocation test probably involves mechanisms of central sensitization.

Mustard oil–induced skin inflammation induces tactile and thermal allodynia–hyperalgesia and blunted cold perception in the primary area. Furthermore, static (von Frey testing) and dynamic (brush testing) allodynia occur in the surrounding secondary area.[25,26] All these expected sensory disturbances by mustard oil were observed during the control situation (table 1, fig. 2). The mustard oil–induced skin inflammation provokes pain by activating C-nociceptive fibers, leading to sensitization of wide-dynamic-range neurons of the spinal cord, after which stimulation of mechanoreceptive Aβ afferents is involved in the phenomenon of tactile allodynia.[25] These changes represent central sensitization as a result of ongoing pain.[27] After intrathecal adenosine, the areas of secondary allodynia–dysesthesia (von Frey and brush) were reduced. In addition, tactile pain thresholds in primary and secondary areas were unaffected, in marked contrast to the clear reduction of tactile pain thresholds in the absence of adenosine treatment. With respect to the primary area, adenosine seems to counteract mustard oil-induced allodynia–hyperalgesia to tactile stimuli, without affecting the mustard oil–induced reduction of heat pain threshold. The heat pain threshold is mediated by C-fiber pain afferents, whereas tactile allodynia is mediated by large-diameter mechanosensitive Aβ fibers.[28] Therefore it is likely that intrathecal adenosine primarily counteracts mechanisms involving central sensitization (reduced secondary allodynic area and unaffected tactile pain thresholds). Thus the current results from different sensory tests suggest that exogenous adenosine administration at the spinal level primarily modulates mechanisms of central sensitization (up-regulation). Intrathecal adenosine administration thus may offer a new treatment modality for different clinical pain states. Randomized clinical trials to elucidate these questions are underway.

In conclusion, a single intrathecal adenosine bolus administration seems to be well tolerated in healthy volunteers at least in doses up to 1,000 μg. The compound attenuates different types of experimental pain, primarily those involving mechanisms of central sensitization.

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