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Research Overview

Adenosine and Pain Relief: A Clinical Overview

Märta Segerdahl and Alf Sollevi*

Department of Anaesthesiology and Intensive Care, Huddinge University Hospital, Huddinge, Sweden

Strategy, Management and Health Policy				
Venture Capital Enabling Technology	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT This overview summarizes the current clinical state of knowledge in the field of adenosine-mediated pain reduction, also including a condensed experimental background of relevance for clinical implementation. Clinical investigations have been systematically performed and include experimental pain models in volunteers, as well as studies in acute perioperative pain and in chronic neuropathic pain. Adenosine has been administered as a low-dose intravenous infusion and as an intrathecal injection. Effects on pain and on signs of hyperexcitability in the nervous system have been investigated, both after administration of adenosine alone and in combination with well-known analgesic agents. The different modes of adenosine administration demonstrate reduced pain, primarily in modalities that involve mechanisms of hyperexcitability of the central nervous system, i.e., central sensitization. Because this phenomenon is an important factor in chronic pain conditions, the promising results of pain relief in patients with neuropathic pain suggest that this is especially relevant for future development and research. In addition, the potential use of adenosine in combination with other pain-modulating agents deserves further evaluation. Drug Dev. Res. 45:151–158, 1998.

Key words: analgesic; antinociception; chronic pain; experimental pain; postoperative pain

EXPERIMENTAL BACKGROUND

The animal data suggesting adenosine receptor–mediated antinociception are being reviewed elsewhere in this issue. In brief, abundant studies in rodents have demonstrated a delay in withdrawal tests for noxious stimuli [Sawynok and Sweeney, 1989; Sawynok, 1998], in normal tissue and in tissues compromised by peripheral inflammation [Karlsten et al., 1992a], peripheral and central nerve injury [Lee and Yaksh, 1996; Sjölund et al., 1996, 1997, 1998; Cui et al., 1997, 1998], or during anesthesia [Birch et al., 1988; Seitz et al., 1990]. However, there are difficulties in translating these experimental data into the clinic. This may partly be due to species differences, but mainly to difficulties in interpreting the reaction as antinociceptive or related to motor impairment or sedation. It is also not evident that antinociception (neurophysiologic or behavioral) in rodents should be interpreted as the equivalent to pain reduction in humans. Furthermore, animal studies mainly involve adenosine analogs, whereas adenosine is used in human studies. Importantly, each animal model should be considered with its corresponding clinical situation or experimental model, and direct comparison should be performed with caution.

In addition to behavioral studies, there are indications that adenosine receptor stimulation can depress levels of substance P (SP) in cerebrospinal fluid (CSF) in parallel with reduction in presumed pain behavior [Sjölund et al., 1997]. In the experimental model of peripheral nerve injury (Bennett and Xie model), treatment with intrathecal (i.t.) R-PIA reduced pain behavior [Lee and Yaksh, 1996; Sjölund et al., 1996; Cui et al., 1997], with an effect duration of approximately 1 h. Furthermore, in photochemically induced chronic spinal cord lesion in rats, tactile and thermal hypersensitivity has been reduced by R-PIA [Sjölund et al., 1998], with a

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*Correspondence to: Alf Sollevi, Department of Anaesthesiology and Intensive Care, K32, Huddinge University Hospital, S-141 86 Huddinge, Sweden.

markedly longer duration (5–7 h) than seen in the peripheral nerve injury model. Thus, there is abundant experimental evidence to support investigations of potential adenosine-mediated pain relief in humans.

Safety Perspectives

A dose-dependent and reversible motor impairment has been demonstrated by various adenosine analogs [Holmgren et al., 1986]. However, motor impairment has not been reported after adenosine administration in mice [DeLander and Hopkins, 1986]. Toxicity by chronic i.t. administration of R-PIA has also been investigated, and no change was seen in spinal cord vascularisation, morphology, or quantitative morphometry [Karlsten et al., 1992a, 1994]. With respect to adenosine, potential toxic effects of chronic (2 weeks) of two times daily intrathecal administration (100 μg) in rats has been evaluated regarding behavior, spinal cord morphology, and quantitative morphometry. Long-term administration was not associated with any detectable neurotoxicity or behavioral adverse effects [Rane et al., unpublished data].

HUMAN EXPERIMENTAL STUDIES

Intravenous Administration

To facilitate the understanding of the terminology related to pain physiology/pathophysiology, we have included Table 1, with some definitions of relevance.

TABLE 1. Definitions of Pain-Related Terminology

Allodynia	Pain due to a stimulus that does not normally provoke pain.
Antinociception	The attenuation of the neural response to noxious stimulation.
Dynamic allodynia	Allodynia provoked by a continuous movement, i.e., stroking a soft brush along the skin.
Static allodynia	Allodynia provoked by a single touch, i.e., pressing a graded von Frey filament to the skin.
Analgesia	Absence of pain in response to stimulation that would normally be painful.
Central sensitization	The increased excitability of the nociceptive system after repetitive or continuous noxious stimulation, leading to reactions such as increased level and extension of pain. These are most likely mediated by means of increased excitability in the wide dynamic range neurons in the dorsal horn of the spinal cord.
Dysesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked.
Hyperalgesia	An increased response to a stimulus that is normally painful.
Nociceptor	A receptor preferentially sensitive to a noxious stimulus or to a stimulus that could be noxious if prolonged.
Noxious stimulus	A noxious stimulus is one that is damaging to normal tissues.
Pain	An unpleasant sensory and emotional experience associated with actual or potential damage, or described in terms of such damage.
Pain threshold	The least experience of pain that a subject can recognize.
Pain tolerance level	The greatest level of pain that a subject is prepared to tolerate.
Tactile perception threshold	The threshold for touch perception as assessed with graded von Frey filaments, using the method of limits.
Tactile pain threshold	The pain threshold as detected by graded von Frey filaments, using the method of limits.

In normal hairy skin of healthy volunteers, an i.v. infusion of adenosine 50–70 $\mu g \cdot kg^{-1}$ per min increases the heat pain threshold (C-fiber mediated), with no effect on a suprathreshold pain provocation [Ekblom et al., 1995]. Similar results on elevated heat pain threshold was recently reported by Sylvén et al. [1996]. We have not seen any effect on cold (Aδ-fiber mediated) or warmth (C-fiber mediated) perception. Also, there was no augmentative effect of the combination of adenosine with morphine (in a clinical dose) nor any effect by morphine alone on thermal perception. These studies lend support to a selective influence of adenosine on thermal C-fiber–mediated nociceptive transmission in the normal nonsensitized state, but without influence on thermal non-noxious threshold perception.

An ischemic pain model has also been used. A well documented tourniquet method [Woolf, 1979; Pertovaara et al., 1982], was applied to induce a continuous nociceptive type pain, mainly C-fiber mediated [Crews et al., 1994]. This experimental model may resemble clinical postoperative deep somatic pain. The subjects rated pain every minute, while the tourniquet was inflated on their upper arm, for up to 30 min. Pain (VAS 0-100) was assessed every minute during the test, and the VAS scores were then added to a sum of pain scores (SPS). Adenosine infusion (70 $\mu g \cdot kg^{-1}$ per min) reduced the SPS by 30% compared with placebo, i.e., to the same extent as a clinical dose of morphine [Segerdahl et al., 1994] (Fig. 1). In addition, it was found that the combined administration of a clinical dose of morphine (0.1 mg/kg) or a low dose of the *N*-methyl-D-aspartate–blocker ketamine (0.1 mg/kg) increased pain tolerance, expressed as the number of subjects not reaching VAS 100 within the 30 min of provocation time. This finding is interpreted as exogenous adenosine exerting an inhibitory effect on some pain processing at a level proximal to the occluded arm, and that this action has a positive interaction with clinical doses of morphine or ketamine.

In another experimental model, inflammatory pain was induced by mustard oil (MuO), topically applied to the forearm or the shin. This application will result in a chemical burn, strong enough to activate antinociceptive afferent C-fibers and induce a sur-

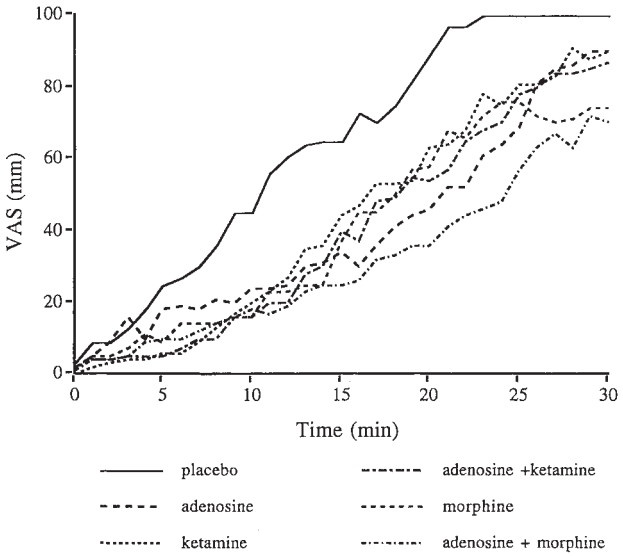

Fig. 1. The median values for each drug or combination of drugs during 30 min of experimentally induced pain. All drugs treatments reduced the ongoing ischemic pain, compared with placebo.

rounding area of secondary allodynia/hyperalgesia, as an expression of central sensitization [Koltzenburg et al., 1992]. Another validated method of inducing skin burn is by applying a Peltier thermode firmly to the skin, keeping it at a temperature of 47°C for 7 min [Dahl et al., 1993]. Around this superficial burn, an area of secondary hyperalgesia/allodynia will develop. In these models, double-blind placebo controlled crossover studies in healthy subjects have been performed, which revealed that adenosine infused at 50–60 $\mu g \cdot kg^{-1}$ per min during the 60-min test period attenuated development of the areas of dynamic and static allodynia by 30–50% (Table 2) [Segerdahl et al., 1995a; Sjölund et al., unpublished data]. Although adenosine infusion clearly reduces areas of hypersensitive skin, the reduction in tactile pain threshold within the allodynic area occurring after inflammation was not attenuated. Thus, all experimental studies in healthy volunteers suggest that adenosine infusion primarily counteracts pain mechanisms involved in central sensitization.

Intrathecal Administration

A safety and dose escalation study has been performed in healthy volunteers, injecting 500, 1,000, or 2,000 μg of adenosine at the lower lumbar level. The occurrence of adverse effects is addressed in its separate section below. Different models of pain were tested; tactile and thermal thresholds for perception and pain, cold immersion pain, ischemic tourniquet test, and sensory changes induced by skin inflammation [Rane et al., 1998]. In analogy with previous studies during iv adenosine administration, it adenosine reduced the area of secondary allodynia as well as ischemic pain rating, without influencing tactile pain thresholds in the remaining secondary allodynic area. The cold immersion pain was unaffected. Again, this implies that it adenosine primarily counteracts pain symptoms related to central sensitization.

Adenosine levels in CSF were also determined. In all 12 subjects, concentrations of adenosine were analyzed at preinjection and at 10 min after injection. Preinjection values were detectable at normal CSF levels of 50 nM. Peak concentrations showed marked increase, up to 200 μM, corresponding to more than three orders of magnitude. In two of the subjects, elimination half-life was determined by serial samples. There was good semilogarithmic correction, with half-lives of approximately 10 and 20 min. Thus, pharmacologically elevated adenosine levels in human CSF can remain for a considerable time.

CLINICAL APPLICATIONS: ACUTE PAIN

Intravenous administration

Perioperative pain.

In three clinical studies in shoulder surgery (30 patients), breast surgery (72 patients), and hysterectomies (41 patients) [Segerdahl et al., 1995b, 1996, 1997], representing deep somatic, cutaneous/subcutaneous, and visceral pain, anesthetic requirements and postoperative analgesics requirements were compared in relation to adenosine/placebo infusion. The studies were randomized and double blind. During surgery, anesthetic requirements were significantly reduced, most prominent

TABLE 2. Effect of Intravenous Adenosine Infusion, 50–60 $\mu g \cdot kg^{-1}$ per min During 60 min, On the Development of Secondary Allodynia (Brush and von Frey Area)

Pain model	Adenosine route	von frey area (%)	Brush area (%)	Reference
MuO[a]	iv	–30–40[c]	–75[c]	Segerdahl et al., 1995a
MuO	iv	–30[c]	–22[c]	Sjölund et al., Anesth Analg, in press
MuO[a]	it	–50[c]	—	Rane et al., Anesthesiology, in press
Thermal burn[b]	iv	–55[c]	—	Sjölund et al., Anesth Analg, in press

[a]Mustard oil.
[b]47°C during 7 min.
[c]Compared with placebo.

during visceral surgery (Fig. 2). An antinociceptive effect of adenosine infusion is a likely explanation for the difference in anesthetic requirement. Intraoperatively, systolic blood pressure was increased in the placebo treatment groups, compared with presurgical values, whereas the adenosine-treated groups, in all studies, showed a stable level of intraoperative systolic blood pressure. The significantly smaller increase in systolic blood pressure at commencement of surgery indicates a significantly weaker response to the surgical painful afference in the adenosine groups. Further support for the theory of a pain-reducing effect of intraoperative adenosine infusion is that fewer patients, 8 of 31 vs. 19 of 32, perceived pain when regaining consciousness after surgery in the adenosine group compared with placebo [Segerdahl et al., 1995b]. However, there was a notable difference between type of surgery and influence of adenosine. Anesthetic requirements were similar during placebo treatment in all studies, but the effect of adenosine was less pronounced during superficial and most pronounced during visceral surgery. A differential susceptibility to the action of agents with presumed analgesic activity is also a clinical knowledge [Arnér and Arnér, 1985]. Nociceptive activity from different tissues may activate different mechanisms. It may be speculated that a more marked effect of exogenous adenosine is achieved in deeper tissues and that this is due to a larger extent of central sensitization in this type of surgical pain [McMahon, 1994]. Another factor, which could contribute to the marked reduction in anesthetic requirement by adenosine in hysterectomies, is the possibility of a positive pharmacologic interaction between opioid premedication and adenosine infusion, as is also demonstrated in the human ischemic pain model [Segerdahl et al., 1994]. A low dose of adenosine infusion (35 $\mu g \cdot kg^{-1}$ per min) to patients with known coronary heart disease has been shown to reduce exercise induced pain rating, in a double-blind placebo-controlled study [Sylvén et al., 1996]. Thus, that study in fact illustrates that i.v. adenosine reduces visceral pain in nonanesthetized patients.

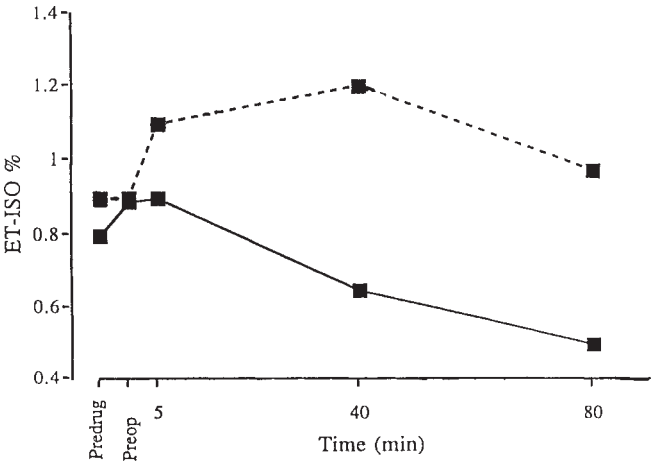

Fig. 2. Anesthetic requirements in end-tidal isoflurane concentration (ET-ISO, in percentage) during hysterectomies. ET-ISO was increased in the placebo group at 5 and 40 min of surgery. In the adenosine group, ET-ISO remained stable at 5 min of surgery and was then further reduced during surgery.

Postoperative pain: analgesics requirements.

After breast surgery and hysterectomies, at a similar degree of pain relief, the 24-h opioid requirement after adenosine infusion was reduced by 27 and 18%, respectively [Segerdahl et al., 1995b, 1997]. This indicates an extended antinociceptive effect of the adenosine treatment. It, therefore, has been suggested, that adenosine may affect neuronal mechanisms involved in central hyperexcitability (sensitization), and that such effects persist longer than the period of direct exposure to the compound. However, as adenosine was only given in conjunction with surgery, the possibility of a peripheral antinociceptive effect of adenosine cannot be excluded, because adenosine has well-known antiinflammatory properties [Green et al., 1991; Cronstein, 1994]. Such an effect may reduce the secondary inflammation and, in extension, reduce ongoing nociceptive stimulation.

The idea of infusing adenosine intraoperatively is to reduce perioperative opioid related side-effects, i.e., postoperative nausea and vomiting, respiratory disturbances, sedation, and to improve recovery. Analysis of postoperative adverse effects in the 145 randomized surgical patients [Segerdahl et al., 1995b, 1996, 1997], demonstrated that the incidence of opioid-related side-effects was unaffected. It is, therefore, unlikely that the addition of adenosine infusion during general anesthesia would improve perioperative quality and recovery in unselected cases. Furthermore, the potential risk of cardiovascular complications should be kept in mind in patients with coronary heart disease, because adenosine induces intramyocardial flow redistribution and ischemia in a dose range above 80 $\mu g \cdot kg^{-1}$ per min. However, as indicated in the section below, intraoperative adenosine may be of use for pain relief in selected cases with a known history of chronic neuropathic pain. In these cases, all efforts to reduce central sensitization should be used to counteract further deterioration of the chronic pain condition. This aspect requires clinical trials for elucidation.

Intrathecal Administration

To test whether it adenosine administration in conjunction with surgical trauma could reduce intraoperative anesthetic and postoperative analgesic requirements, a randomized double-blind placebo controlled study in 40 patients undergoing elective hysterectomies was performed. Patients received an it injection of 500 µg of aden-

osine or placebo, prior to induction of anesthesia and surgery. Anesthetic requirements as well as postoperative 24-h opioid requirements were not reduced by the it adenosine injection [Rane et al., unpublished data]. Because it adenosine causes marked elevation of CSF adenosine levels, at least during the period of surgery (approximately 1 h), the study clearly indicates that lumbar spinal mechanisms are not primarily responsible for the antinociceptive effect of intraoperative adenosine administration. It is therefore more likely that the perioperative pain reducing effect of i.v. adenosine infusion is mediated by means of peripheral anti-inflammatory actions, or some supraspinal site of action not accessible by means of it adenosine injection.

CLINICAL APPLICATIONS: CHRONIC PAIN

In chronic neuropathic pain, which is present in approximately 1% of the population [Bowsher, 1991], morphine lacks analgesic effect in most cases [Arnér and Meyerson, 1988]. In approximately 50% of the cases of neuropathic pain, no effective treatment is found. A considerable proportion of the pain in these states is related to factors involved in central sensitization, expressed as hypersensitivity to stimulation of the skin or deep tissue [Jensen, 1996].

Intravenous Administration

In a first report of cases [Sollevi et al., 1995], two patients suffering neuropathic pain were treated with a low dose of adenosine infusion resulting in alleviation of pain. In one of these patients, 45 min of infusion of adenosine 50 $\mu g \cdot kg^{-1}$ per min, but not placebo, abolished the preexisting allodynia to touch and warmth, dysesthesia to cold, increased the tactile pain threshold, and normalized the tactile perception and heat pain threshold. The duration of total pain relief was 6 h, after which time pain gradually returned and reached habitual levels after 48 h. A randomized double-blind placebo controlled cross-over study in seven patients suffering chronic neuropathic pain [Belfrage et al., 1995] also indicated transient pain reduction. These patients had, as part of their pain syndrome, allodynia and hyperalgesia. Quantitative sensory testing was performed before and immediately after completed study treatment. Patients received adenosine 50 $\mu g \cdot kg^{-1}$ per min i.v. for 45–60 min. In all six patients with spontaneous pain, pain ratings were reduced by 50%. Also, tactile pain thresholds in the neuropathic areas were elevated, as an indication of reduced hypersensitivity. Apart from this, the duration of the perceived pain relief extended from 6 h to 4 days, by far outlasting any direct action of the infused compound. Recently, a multicenter randomized cross-over study, in 26 patients with intractable neuropathic pain of postsurgical or posttraumatic origin, confirms the earlier results [Sjölund et al., unpublished data]. In this study, the areas of allodynia were significantly reduced by adenosine treatment. Several patients have, on a clinical basis, received repeated i.v. adenosine infusion, if the duration of pain relief was longer than 1 week. In these cases, repeated i.v. administration provides a method of pain treatment. In the range of 5–10% of adenosine-responsive patients with peripheral neuropathic pain seem to be permanently (>6 months) relieved by a single 60-min infusion. These effects also involve improvement in pathologic tactile hyperphenomena, assessed by quantitative methods.

Intrathecal Administration

The first clinical case report on i.t. adenosine agonist administration to a pain patient relates to R-PIA [Karlsten and Gordh, 1995]. The pain reducing and antiallodynic effects of a single spinal injection (50 μg) of the weak A_1 receptor–selective agonist lasted for several months. In an open tolerability study in 14 patients, suffering intractable chronic neurogenic pain with tactile hyperphenomena and pain duration from 8 months to 27 years, 500 or 1,000 μg of adenosine was injected spinally at the lumbar level [Belfrage et al., unpublished data]. A majority of patients demonstrated a reduction in spontaneous and evoked pain, including an increased tactile pain threshold to von Frey stimulation. Areas of tactile hyperphenomena were also markedly reduced. The median duration of pain reduction was 24 h. Thus, in this patient population, i.t. adenosine administration reduces various aspects of pain, primarily by means of adenosine receptor activation at the spinal level. Patients with good pain relief after i.t. injection and with long duration, are currently receiving spinal injections as clinical treatment. However, randomized placebo-controlled studies are warranted. We have also more closely followed a few patients with disabling syndromes with pain spread over large parts of the body, also including documented motor deficits. Repeated adenosine administrations have resulted in dramatic relief of pain and tactile allodynia as well as reversal of motor deficits during the duration of pain relief.

ADVERSE EFFECTS AND SAFETY ASPECTS

Intravenous Administration

When considering new compounds for pain treatment, knowledge about and minimization of adverse effects are crucial. In the dose range of 50–70 $\mu g \cdot kg^{-1}$ per min i.v., subjects and awake patients may feel a slight chest pressure and cutaneous flushing. In one of our healthy subjects, with an earlier history of gastric ulcer, gastric pain was experienced during infusion of 50 $\mu g \cdot kg^{-1}$ per min. This reaction is previously described at higher doses [Watt et al., 1987]. However, when the infusion rate was reduced by 10%, symptoms immediately disappeared.

Constipation is a common adverse effect of many drugs used for pain relief, especially opioids and tricyclic antidepressants (TCA). There is experimental data suggesting that endogenous adenosine is involved in regulation of lower intestine propulsion [Suzuki et al., 1995]. Exogenously administered adenosine analogs were also shown to inhibit upper gastrointestinal motility [Fargeas et al., 1990; Murthy et al., 1995]. Therefore, the effect on gastric emptying of i.v. adenosine was investigated by using placebo-controlled cross-over study applying the acetaminophen absorption test [Thörn et al., 1992]. An infusion dose of 50 $\mu g \cdot kg^{-1}$ per min (during 2 h) does not affect the rate of gastric emptying [Forsberg et al., 1999]. However, to further elucidate the possibility of constipation as an adverse effect at pain reducing doses of adenosine administration, total oro-cecal transit time should be also investigated.

Intrathecal Administration

In a study in healthy volunteers, dose escalation was interrupted due to the appearance of a transient (30-min) dull pain in the lumbar region after administration of a dose of 2,000 μg [Rane et al., 1998]. In the clinical study in chronic neurogenic pain [Belfrage et al., unpublished data], 5 of 14 adenosine injections caused transient lumbar pain. This pain reaction has been dose-dependent, with interindividual differences as to which dose can be given without lumbar pain. All local pain symptoms of i.t. adenosine in patients was abolished upon repeated injection when combined with a low and nonmotorblocking dose of a local anesthetic agent. This lumbar pain adverse effect is possibly mediated by means of direct stimulation of the primary afferents of the dorsal root or by direct influence at superficial layers of the cord. Adenosine A_2 receptors, suggested to be involved in the peripheral algogenic effect of adenosine, may also be involved in this transient pain sensation. Another possibility may be that adenosine induces meningeal vasodilation by means of A_2 receptor stimulation, leading to a migraine-like pain. It has been reported that i.t. injection of an A_1 agonist causes vasodilation in the spinal cord [Karlsten et al., 1992b].

Adenosine (up to 2,000 μg) did not induce sedation or motor deficiencies and neurologic examination revealed no disturbances in extremity reflexes or balance. Voiding reflexes were unaffected. No cardiovascular or other systemic side effects have been observed after intrathecal administration [Rane et al., 1998].

POSSIBLE SITE OF ACTION

Central spinal and supraspinal sites of actions seem probable for a major part of the shown pain-reducing effects involving central sensitization, even though peripheral anti-inflammatory effects may be involved after i.v. infusion. A crucial question is if systemically administered adenosine can reach the CNS and structures modulating nociception and the sensation of pain. First of all, the short elimination time in blood (half-life in seconds) may raise doubt as to the capability of i.v. adenosine to reach the central nervous system in adequate concentrations. The findings of an antinociceptive effect by infusion, resembling data from experimental as well as clinical studies on it administration, nevertheless speaks in favor of a central site of action. This may take place at spinal and/or supraspinal sites. The blood brain barrier is not present in all parts of the central nervous system, and thus, there may be supraspinal regions of penetration, especially at the brain stem level.

FUTURE DEVELOPMENT

What may then be the future regarding adenosine mechanisms and the treatment of clinical pain? The main effect of adenosine in pain modulation seems to be mediated through reduction of central sensitization. In acute postoperative pain, the proportion of tonic nociceptive barrage is large; thus, adenosine-related mechanisms play a minor part of the total pain experience in this clinical setting. There are other clinical situations in which central sensitization is a dominating factor, and here adenosine receptor stimulation may be of greater importance. Probably the most important role for adenosine action will be in neurogenic pain states.

There are five possible applications for adenosine in this aspect. First, its use as a diagnostic tool, with a possibility of reversibility of groups of neurogenic pain cases. Controlled studies are required in well-defined chronic pain conditions, e.g., poststroke pain, pain due to spinal cord lesion, and ritzopathies. Second, to use adenosine as a predictive test, before initializing more complicated treatments, e.g., spinal cord stimulation. Third, as a therapeutic agent, of which repeated administration may be practically feasible when the duration of the effect is several days. Fourth, improvement of long-acting adenosine analogs, or drugs promoting elevation of endogenous adenosine levels. By this approach, there is always the risk of developing tolerance by tonic receptor stimulation by an agonist. Whether tolerance can be avoided by intermittent treatment with adenosine, by means of implantable pumps, still remains to be investigated. Fifth, the potential of drug combination for improved pain relief and less adverse effects by using adenosine-mediated mechanisms along with other pharmacologic principles, such as α_2-agonists, opioids, and *N*-methyl-D-aspartate–receptor antagonists, still remains to be elucidated.

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