Clinical Note

Systemic adenosine infusion: a new treatment modality to alleviate neuropathic pain

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Summary Adenosine, an endogenous antinociceptive compound acting in the central nervous system, was infused intravenously (50–70 μg/kg/min) to 2 patients with peripheral neuropathic pain. In 1 subject, spontaneous pain was alleviated, and tactile allodynia was essentially relieved during 40 min of infusion. Allodynia to warmth and touch were abolished in the other subject. In addition, hyperalgesia to pinprick was markedly attenuated as was pressure-induced allodynia. The reported effects lasted for hours after termination of the infusion. Our preliminary encouraging data call for further controlled studies of the potentially relieving effect of adenosine in painful neuropathic conditions.

Key words: Neuropathic pain; Sensory dysfunction; Adenosine; (Human)

Introduction

Adenosine is an endogenous compound with various modulatory effects in the central nervous system (CNS) and in the periphery, mediated through specific cell-surface associated receptors (cf., Daly 1985; Sollevi 1986). Animal studies have demonstrated an adenosine- and an adenosine analogue-mediated inhibitory influence on presumed nociceptive reflex responses (cf., Sawynok and Sweeney 1989). Most studies relate to intrathecal (i.t.) drug treatment. No animal studies have demonstrated antinociception during systemic administration of the endogenous receptor ligand adenosine. On the other hand, clinical studies have revealed adenosine to be a pain-inducing compound (Bleehen and Keele 1977; Sylvén et al. 1986). Intravenous (i.v.) adenosine dose-dependently induced discomfort/pain in humans at infusion doses above approximately 70 μg/kg/min or by bolus injections (Biaggioni et al. 1987; Sylvén et al. 1988; Verani et al. 1990). Pain was reported from the chest, neck, head, abdomen or extremities (Biaggioni et al. 1987; Sylvén et al. 1988; Verani et al. 1990). It is possible that earlier clinical studies, using i.v. adenosine infusions, have shown discomfort/pain at higher doses than that required for antinociceptive effects.

In the current report we present evidence showing that low infusion doses of adenosine alleviate ongoing neuropathic pain, hyperalgesia and allodynia without inducing other pain symptoms.

Methods

Treatment trials with adenosine, as a pilot-evaluation in patients with painful neuropathic conditions, were approved by the local Human Research Ethics Committee at the Karolinska Hospital and were conducted after obtaining informed consent. During each trial the patients were subjected to repeated neurological examination with emphasis on somatosensory function. A camel-hair brush, cold (20°C) and warm (40°C) metallic rollers as well as disposable pins were used for bedside examination of sensibility (Hansson and Lindblom 1993). Modality-specific quantitative sensory testing (QST) using a modified Marstock technique (Hansson et al. 1988) (Thermotest®, Somedic Sales, Farsta, Sweden) was employed for assessment of perception thresholds for cold, warmth, painful heat and cold. In addition, von Frey hairs were used to assess tactile perception thresholds and, when applicable, thresholds for painful tactile perception (the threshold is the average of the first stimulus of an
ascending series (n = 4) of strengths to be felt ('yes' values) and the first stimulus of a descending (n = 4) series not to be felt ('no' values)). Before introducing an i.v. route, subjective pain intensity was assessed using a 100 mm visual analogue scale (VAS). Bedside sensory examination and QST were then performed before the start of a 30-min placebo infusion period with saline. Bedside testing was repeated at the end of the placebo period and at 25 min after start of infusion of adenosine (Adenosine Item™, 5 mg/ml in isotone mannitol, Item Development, Stocksund, Sweden) infusion which lasted for 40 min. Thermal QST and von Frey hair examination were repeated after bedside examination shortly before the end of adenosine infusion. Rating of spontaneous pain was performed every 5 min throughout the test period using the VAS. At equal intervals, treatment side effects were requested.

Case reports

Case 1

A 50-year-old man, with a prosthesis in the right distal femur due to a sarcoma, reported burning, radiating pain and numbness in the lateral aspect of the lower leg and foot as a result of surgical damage (3 months previously) to the distal part of the sciatic nerve. The patient was not on any medication. Bedside examination of sensibility as well as QST revealed undissociated hypoesthesia/hypoalgesia in the innervation territory of the sural nerve. In the peroneal territory on the dorsum of the foot, a marked brush-evoked allodynia was demonstrated which prevented us from evaluating other somatosensory modalities since all bedside tools induce a certain amount of activity in mechanoreceptive afferents. Von Frey hair testing in the region of the foot innervated by the peroneal nerve revealed allodynia at the detection threshold level (1.0 g). In the contralateral homologous region the patient reported a normal tactile sensation at detection threshold (0.1 g). Thermal QST demonstrated significantly elevated perception thresholds to cold and warmth. The distribution of pain and signs of sensory aberrations supported a postsurgical neuropathic pain diagnosis. Before start of infusion the ongoing pain intensity was rated at 40/100 mm using the VAS.

Intensity and distribution of ongoing pain as well as sensory alterations (bedside examination only) were unaltered after a 30-min period of saline infusion in the territory of the peroneal nerve. Thirty minutes after initiation of i.v. adenosine infusion (70 µg/kg/min) which did not cause any side effects, the ongoing pain was reduced to 18/100 mm. Brush-evoked pain on the dorsum of the foot was abolished and only a slight dysesthesia to pinprick was reported. It was now also possible to assess thermal hypoesthesia to both warmth and cold. Thermal QST was unaltered and von Frey filament testing revealed a perception threshold at 1.9 g, with a sensation which was now only slightly dysesthetic in character. The patient reported alleviation of ongoing pain for about 4 h after termination of infusion.

Case 2

This 24-year-old woman reported intermittent pain accompanied by persistent dysesthesia to touch and allodynia to pressure in the medial part of the lower leg, following orthopedic repair of the knee 14 months previously. The patient was pain free at the time of examination and was not subjected to ongoing pharmacological treatment. At bedside examination of sensibility the patient reported hyperalgesia to pinprick in the painful region, with after-sensation and radiation, as well as brush-evoked dysesthesia. In addition, the patient reported allodynia to warmth and dysesthesia to cold. Using thermal QST a marked allodynia to warmth was recorded (threshold at 38°C compared to 43°C in the control region, see Fig. 1). Light but firm pressure to the affected area caused severe pain. The tactile perception threshold to von Frey hairs was significantly reduced (0.002 g) compared to the control side (0.1 g). A painful sensation...
Adenosine normalized both tactile and pain thresholds in the neuropathic area.

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<th>Normal leg</th>
<th>Neuropathic leg</th>
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<tr>
<td></td>
<td>Tactile threshold</td>
<td>Pain threshold</td>
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<td>Before adenosine</td>
<td>0.1</td>
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<td>During adenosine</td>
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(adynia) was assessed at 2.2 g in the affected area. Diagnostically, the symptoms and signs were compatible with a postsurgical saphenous neuropathy.

Placebo infusion for about 30 min did not influence sensory parameters assessed at bedside examination. Adenosine was then infused at a rate of 50 μg/kg/min for 40 min, without inducing side effects. Twenty-five minutes after the start of infusion the only abnormality at bedside examination was a slight hyperalgesia to pinprick, markedly attenuated compared to pre-infusion. OST revealed a normalized heat pain threshold (i.e., allodynia to warmth was abolished, see Fig. 1), a significantly increased pain threshold to von Frey hair stimulation (24 g), and a normalized tactile perception threshold (0.2 g) (see Table I). Sensation to manual pressure was almost normal. The patient reported a sustained effect on the touch-evoked dysesthesia and pressure allodynia for 6 h followed by a gradual return to pretreatment level during the next 48 h.

Discussion

The present data on adenosine infusion, at doses below those causing a direct algogenic effect, demonstrates for the first time a beneficial pain-relieving effect in patients with ongoing and stimulus-evoked neuropathic pain.

The mechanism by which adenosine may modify nociception and normalize sensory dysfunction associated with neuropathy is not clear. Animal studies have demonstrated that i.t. administered adenosine analogues counteract experimentally induced presumed painful phenomena (Holmgren et al. 1986; Sosnowski et al. 1989). Experimental data suggest a modulatory role of endogenous adenosine in the spinal cord, mainly at the interneuron level (Choca et al. 1988; Sawynok and Sweeney 1989).

The temporal profile of placebo-induced pain relief has recently been reported to occasionally have a duration of several days in patients with chronic idiopathic low back pain (Fine et al. 1994). Whether this is applicable in patients with neuropathic pain is not known. The protocol used in this pilot study enabled us to control optimally for placebo effects. However, the repeatedly and reproducibly assessed normalized somatosensory functions are not likely achieved solely as a placebo response. Furthermore, placebo infusion preceding adenosine infusion did not affect bedside sensory parameters. Controlled studies are currently performed in our laboratory to further elucidate the pain-relieving potential of adenosine in neuropathic conditions.

Adenosine is subjected to extremely rapid elimination (half-life in seconds) in the blood stream (cf., Sollevi 1991). Thus, it may only be speculation that low doses of adenosine (< 70 μg/kg/min) survive elimination before reaching the CNS. However, since peripheral effects of exogenous adenosine are associated with dose-dependent painful symptoms, it is most likely that the modulatory effects on sensory transmission demonstrated here take place in the CNS.

Since direct effects of adenosine (such as vasodilation and electrophysiological effects) are abolished within 1–2 min after termination of infusion due to extremely rapid cellular uptake (Di Marco et al. 1983; Sollevi 1986), the mechanism for the prolonged effect on spontaneous/evoked pain is not understood. The hyperphenomena in neuropathic conditions are considered to involve central hyperexcitability mechanisms (Bennet 1994). In light of our current results, it may be speculated that the effect of adenosine on neuronal mechanisms responsible for central hyperexcitability persists for a much longer period than the direct action of the compound.

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References


