Review articles

Clinical application of adenosine and ATP for pain control

Masakazu Hayashida[1], Ken-ichi Fukuda[2], and Atsuo Fukunaga[3]

[1] Surgical Center Research Hospital, The Institute of Medical Science, The University of Tokyo, 4-6-1 Shiroganedai, Minato-ku, Tokyo 108-8639, Japan
[2] Department of Dental Anesthesia, Tokyo Dental College, Suidobashi Hospital, Tokyo, Japan
[3] Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA, USA

Abstract This review summarizes clinical application of adenosine and adenosine 5′-triphosphate (ATP) in pain conditions. Investigations have been performed in patients with acute perioperative pain or chronic neuropathic pain treated with intravenous adenosine or ATP, or intrathecal adenosine. Characteristic central adenosine A1 receptor-mediated pain-relieving effects have been observed after intravenous adenosine infusion in human inflammation/sensitization pain models and in patients with chronic neuropathic pain. Adenosine compounds, in low doses, can reduce allodynia/hyperalgesia more consistently than spontaneous pain, suggesting that these compounds affect neuronal pathophysiological mechanisms involved in central sensitization. Such pain-relieving effects, which are mostly mediated via central adenosine A1 receptor activation, have a slow onset and long duration of action, lasting usually for hours or days and occasionally for months. With acute perioperative pain, treatment with a low-dose infusion of adenosine compounds and the A1 receptor-mediated central antisensitization mechanisms may play only a minor part in the total perioperative pain experience. By administering sufficient doses of adenosine compounds during surgery, however, significant and long-lasting perioperative pain relief can be achieved via central A1 receptor-mediated antinociceptive/analgesic actions as well as via peripheral A2a or A3 receptor-mediated antiinflammatory actions. Thus, adenosine compounds have significant potential for alleviating various types of pain.

Key words Adenosine · Adenosine 5′-triphosphate (ATP) · Human experimental pain · Perioperative pain · Neuropathic pain

Introduction

The pivotal roles that purine compounds play in central and peripheral nociception/pronociception or antinociception/analgesia have been extensively reviewed by a number of investigators [1–6]. Clinical application of purine compounds as pain medicine has been recently reviewed [7–10]. This review summarizes updated knowledge of the clinical application of purine nucleoside (adenosine) and purine nucleotide adenosine 5′-triphosphate (ATP) in patients with acute or chronic pain, with condensed experimental background data to support such application in humans.

Experimental background

Extracellular adenosine and ATP have been proposed as neuromodulators or neurotransmitters. Adenosine is now well recognized to be an important modulator of neurotransmission in many physiological functions, such as regulation of arousal and sleep, anxiety, cognition, and memory [2,4,6]. Under certain pathological conditions (e.g., trauma, ischemia, seizure activity), it can serve a significant protective role. In addition, adenosine regulates pain transmission by its action at spinal, supraspinal, and peripheral sites. Adenosine and ATP act on specific receptors designated P1 (adenosine) and P2 (ATP) receptors, respectively. Adenosine receptors are classified into four subtypes (G protein-coupled A1, A2a, A2b, and A3 receptors), and ATP receptors are classified into two subfamilies (ligand-gated, ionotropic P2X receptors and G protein-coupled, metabotropic P2Y receptors) on the basis of their structures and signal transduction systems [3,4]. Currently, P2X and P2Y receptors expressed in mammalian cells are classified into seven subtypes of P2X receptors ($P2X_{1-7}$) and six subtypes of P2Y receptors ($P2Y_{1,2,4,6,11,12}$), respectively [11,12].

Abundant studies in rodents have demonstrated that spinal or systemic administration of adenosine and adenosine analogues inhibits pain behaviors in response to noxious stimuli in a variety of test systems, including

acute nociceptive pain tests, inflammatory pain tests, and peripheral and central neuropathic pain tests [1,13–15]. At peripheral nerve terminals in rodents, adenosine A1 receptor activation produces antinociception, whereas adenosine A2 receptor activation produces pronociceptive or pain-enhancing properties in the sensory nerve terminal. In the spinal cord, adenosine A1 receptor activation produces antinociceptive properties in a variety of acute nociceptive, inflammatory, and neuropathic pain tests [1]. Antinociception via the A1 receptor activation in the spinal cord results primarily from postsynaptic hyperpolarization of pain-transmitting neurons through an increase in K^+ conductance and secondarily from presynaptic inhibition of the release of substance P and other excitatory neurotransmitters from sensory nerve terminals [1,6].

In contrast to adenosine administration, peripheral and spinal administration of ATP and other P2X receptor agonists elicits nociceptive behaviors and increases sensitivity to noxious stimuli in both humans and animals [5]. Physiologically, ATP is released in the periphery from neuronal and nonneuronal sources as a result of tissue injury and inflammation, and it excites nociceptive primary afferents by activating homometric P2X3 receptors or heterometric P2X2/3 receptors. Centrally, ATP (released from central afferent terminals or second-order neurons) can modulate neurotransmitter release, or it can postsynaptically activate neurons involved in central nociceptive transmission, with P2X2, P2X4, P2X6, and some other receptors being potentially involved [3]. Although P2Y receptor activation may inhibit pain behaviors in animals, intrathecal administration of ATP leads to pronociception via P2X receptors rather than antinociception via P2Y receptors [16]. Thus, endogenous and exogenous ATP acts basically as an algogenic or pronociceptive substance. When administered intravenously, however, ATP inhibits pain behaviors in response to various noxious stimuli in animal acute nociceptive pain models [8,17]. Because ATP is rapidly broken down into adenosine in the bloodstream by ectonucleotidases, with its plasma half-life less than seconds [18,19], an intravenous dose of ATP may reach a site of action as adenosine and thus may exert antinociceptive rather than pronociceptive effects in both experimental and clinical pain conditions [7,8,20,21].

Human experimental studies on pain-relieving effects of adenosine

Intravenous administration

Continuous intravenous infusion of adenosine at doses of up to 140 μg·kg⁻¹·min⁻¹ does not decrease the mean arterial blood pressure or heart rate in conscious humans [22]. Doses up to 200 μg·kg⁻¹·min⁻¹ were given in conscious subjects [23]. However, adenosine administration at doses above 70 μg·kg⁻¹·min⁻¹ causes pain/discomfort in various parts of the body, most commonly the chest, via direct activation/sensitization of peripheral sensory nociceptive afferents [24,25]. Given as an intravenous bolus to healthy volunteers or to patients with ischemic heart disease, high-dose adenosine provokes angina pectoris-like chest pain [without electrocardiographic (ECG) signs of myocardial ischemia], which is similar to habitual angina pectoris with regard to quality and location [26]. A patient with a gastric ulcer may experience gastric pain during adenosine infusion at 50 μg·kg⁻¹·min⁻¹, although the symptom immediately disappears following a dose reduction or discontinuation of the infusion [10], reflecting the extremely short plasma half-life of adenosine in the blood (less than seconds) [23,27]. For treatment of neuropathic pain in conscious humans, intravenous infusion of adenosine is usually given in a nonhypotensive, nonalgogenic low-dose range of 50–70 μg·kg⁻¹·min⁻¹ [24,25], although some awake subjects may experience innocuous chest discomfort/pain, skin flushing, or both even at this dose [10]. In anesthetized patients, a relatively low dose of adenosine infusion (80 μg·kg⁻¹·min⁻¹) has been used [28–30]. However, much higher doses (up to 290–500 μg·kg⁻¹·min⁻¹) also have been successfully administered using a variable rate of titration protocol (Table 1) [31,32].

In healthy volunteers with normal skin, intravenous infusion of adenosine at 50–80 μg·kg⁻¹·min⁻¹ increased a heat pain threshold but did not affect warm and cold perception thresholds [33]. Other investigators also showed the ability of adenosine to elevate the heat pain threshold of normal skin in human volunteers [34]. These studies suggested a selective influence of adenosine on thermal C fiber-mediated nociceptive transmission in the normal nonsensitized state but without influence on thermal nonnoxious threshold perception. A study using a blink reflex electrode specifically stimulating nociception-specific fibers showed that a slow intravenous injection of a potent adenosine A1 receptor agonist (GR79236 10 μg·kg⁻¹) inhibited the nociceptive stimulus-evoked blink reflex presumably by inhibiting trigeminal nociceptive pathways in human volunteers with normal nonsensitized skin [35].

Ischemic pain models have also been tested. Infusion of adenosine at 70 μg·kg⁻¹·min⁻¹ reduced C fiber-mediated ischemic pain induced in the arm by the submaximum effort tourniquet technique, which resembled clinical postoperative deep somatic pain [36]. Another group of investigators also showed measurable analgesic effects of adenosine infusion at 100 μg·kg⁻¹·min⁻¹ for 10 min on pain during tourniquet-induced

Table 1. Effect of intravenous adenosine infusion during surgery on postoperative pain[a]

Type of surgery	Infusion rate of adenosine (μg·kg^{-1}·min^{-1})		Total dose of adenosine (mg·kg^{-1})	% Reduction in 24-h opioid consumption compared to control group	Reduction in pain scale compared to control group	Reference
	Intraoperative	Postoperative				
Breast surgery	80	—	4.4	27	NSR	28
Shoulder joint surgery	80	—	5.6	NSR	NSR	29
Abdominal hysterectomy	80	40 (for 3 h)	14.2	18	NSR	30
Abdominal hysterectomy or myomectomy	72–290 (variable) 166 ± 17 (mean ± SEM)	—	18.7	28	46%, 33%, NSR: at 2 h, 12 h, 24 h	31
Abdominal hysterectomy or knee or hip joint surgery	50–500 (variable) 292 ± 82 (mean ± SEM)	—	35.7	50	57%, 48%, 62%, 68%: at 2 h, 12 h, 24 h, 48 h	32

NSR, no significant reduction

[a]Terms of the percentile reduction in 24-h opioid consumption and the percent reduction in pain scales at the times indicated compared to control groups

ischemia in an exercising arm [37]. In a study on patients with known effort-induced ischemic heart disease, low-dose adenosine ($35\,\mu$g·kg^{-1}·min^{-1}) reduced effort-induced angina by 45%, although it did not affect the heart rate/blood pressure product or ECG signs of myocardial ischemia, suggesting an antinociceptive effect on visceral pain as well [34].

Skin inflammation/sensitization models also have been used. Adenosine infusion at $50\,\mu$g·kg^{-1}·min^{-1} over 70 min reduced the area of secondary allodynia/hyperalgesia by 50% in volunteers with a chemical burn experimentally induced by topical application of mustard oil [38]. In the following study, cutaneous inflammatory pain was induced by a 4-min topical application of mustard oil or by heat (47°C for 7 min) in healthy subjects, which would result in a chemical or heat burn strong enough to activate nociceptive afferent C-fibers and induce a surrounding area of secondary allodynia/hyperalgesia as an expression of central sensitization [39]. In these models, adenosine infused at 50–$60\,\mu$g·kg^{-1}·min^{-1} during the 60-min test period attenuated development of the areas of allodynia by 39% for the chemical burn and by 58% for the heat burn compared with placebo, suggesting that adenosine infusion primarily counteracts pain mechanisms involved in central sensitization. On the other hand, one study reported that intravenous infusion of adenosine at $60\,\mu$g·kg^{-1}·min^{-1} for 85 min had no analgesic or antiallodynic/antihyperalgesic effects in a human heat/capsaicin model, where sensitization was induced by heating the skin to 45°C for 5 min followed by a 30-min application of 0.075% capsaicin cream and maintained by periodically reheating the sensitized skin to 40°C for 5 min at 40-min intervals [40]. Stimuli applied to induce skin inflammation/sensitization appeared to be less intense in the heat/capsaicin model [41] than in previous models [39]. Such methodological differences might have contributed to the different results.

Intrathecal administration

After confirming in the preclinical studies that chronic intrathecal administration of high-dose adenosine or its analogue causes no spinal neurotoxicity in rats or dogs [42–44], safety and dose escalation studies of intrathecal injection of adenosine at the lower lumbar level have been performed by two groups of investigators in human volunteers; they used a Swedish mannitol-containing formulation of adenosine (500, 1000, or $2000\,\mu$g) [45] and an American mannitol-free formulation (250, 500, 1000, or $2000\,\mu$g) [46]. These authors found that intrathecal adenosine did not produce any systemic, neurological, or cardiovascular adverse effects, although a substantial number of subjects after spinal injection experienced backache, headache, or both lasting as long as several hours, especially at the

highest dose [45,46]. Intrathecal adenosine caused a 1000- to 2000-fold elevation of the cerebrospinal fluid (CSF) adenosine concentration, with a half-life of approximately 10–20 min [45].

Various pain models have been tested. Analogous to previous studies with intravenous adenosine, intrathecal adenosine reduced the ischemic pain ratings as well as the area of secondary allodynia surrounding a chemical burn induced by topical mustard oil; and it prevented mustard oil-induced reductions in tactile pain thresholds, whereas the cold immersion pain was unaffected [45]. In another study, human volunteers were subjected to acute heat stimulation and chemical stimulation with intradermal capsaicin injection [47]. Intrathecal adenosine produced no effect on pain resulting from acute noxious thermal or chemical stimulation but reduced mechanical hyperalgesia/allodynia from intradermal capsaicin injection for at least 24 h despite the fact that adenosine was found in CSF for only a short time (<4 h). Similarly, antiallodynic and antihyperalgesic effects of intrathecal adenosine (500 and 2000 µg) were observed also using a human heat/capsaicin sensitization model [48]. The results of these studies imply that intrathecal adenosine primarily counteracts pain symptoms related to central sensitization, and the long-lasting antiallodynic or antihyperalgesic effect is not due to prolonged residence of adenosine in the CSF.

Clinical application of adenosine to chronic neuropathic pain

It has been suggested that with neuropathic pain conditions there are disturbances in the endogenous adenosine system that lead to blood and CSF adenosine deficiency, which may explain the potential therapeutic effects of adenosine or its analogues on this disease entity [49]. In the first case report, two patients suffering from neuropathic pain were treated with low-dose adenosine infusion (50–70 µg·kg^{-1}·min^{-1} for 45–60 min), resulting in analgesic or antiallodynic effects (or both) lasting several hours to 48 h after termination of the infusion [24]. Subsequently, in a randomized double-blind placebo-controlled crossover study, seven patients with neuropathic pain received intravenous adenosine 50 µg·kg^{-1}·min^{-1} for 45–60 min [25]. In six of the seven patients, pain ratings of the spontaneous pain were reduced by 50%, and tactile allodynia was relieved significantly. The duration of the perceived pain relief extended from 6 h to 4 days. In a randomized multicenter double-blind placebo-controlled crossover study, 26 patients with neuropathic pain received intravenous adenosine 50 µg·kg^{-1}·min^{-1} for 60 min [50]. In this study, spontaneous pain ratings and the areas of allodynia were significantly reduced by adenosine treatment but not by placebo. Two patients experienced complete pain relief that lasted more than 6 months, and improvement after adenosine in the other patients had a duration of about 10 h. Patients received repeated intravenous adenosine infusions if the duration of pain relief was longer than 1 week [10]. In such cases, repeated intravenous administration may provide progressive pain relief without causing tolerance development [51]. In another double-blind placebo-controlled crossover study, 23 patients received an intravenous infusion of adenosine 50 µg·kg^{-1}·min^{-1} over 60 min [52]. It led to a significant reduction in spontaneous pain as well as pinprick hyperalgesia. Of 66 patients who participated in an open trial prior to this double-blind study, 3 experienced long-term resolution of their pain (5, 16, and 25 months, respectively) following a single intravenous adenosine infusion [52].

In the first clinical case report on intrathecal adenosine analogue administration to a patient with neuropathic pain, abolition of tactile allodynia induced by a single spinal injection of an A1 receptor agonist (R-PIA) lasted at least several months [53]. In an open-label study in 14 patients suffering neuropathic pain, 500 or 1000 µg of adenosine was injected intrathecally at the lumbar level [54]. Intrathecal adenosine reduced spontaneous pain as well as allodynia/hyperalgesia and areas of tactile allodynia. Twelve patients experienced pain relief for a median duration of 24 h. In a double-blind, crossover study of seven patients with neuropathic pain, the patients were assessed on two occasions: once with intrathecal adenosine 2000 µg and once with intravenous adenosine 2000 µg [55]. Intrathecal but not intravenous adenosine reduced the intensity and area of allodynia, (which lasted 2–24 h) without affecting the spontaneous pain.

Thus, in patients with neuropathic pain, intravenous and intrathecal adenosine reduce spontaneous pain, allodynia/hyperalgesia, or both. The antiallodynic and antihyperalgesic effects seem to be more consistent than the analgesic effect on spontaneous pain, suggesting the ability of adenosine and its analogues to affect neuronal pathophysiological mechanisms involved in central hyperexcitability (sensitization). Such beneficial effects can last longer than the period of direct exposure to these compounds, usually remaining for hours or days. It should be noted that a single session of therapy with adenosine and its analogues provides permanent (>6 months) pain relief in a limited number of patients with neuropathic pain [50,52,53].

Clinical applications of adenosine to acute perioperative pain

Continuous intravenous adenosine administration

After several pilot studies suggesting that continuous infusion of ATP (100–130 μg·kg^{-1}·min^{-1}) and adenosine (70–130 μg·kg^{-1}·min^{-1}) during inhalation anesthesia may replace opioids and reduce inhalational anesthetic requirements [7,56], three clinical randomized placebo-controlled double-blind studies were conducted to assess the effect of intraoperative adenosine infusion on inhalation anesthetic requirements and postoperative analgesic requirements in patients undergoing various (breast, shoulder, abdominal hysterectomy) surgical procedures (Table 1) [28–30]. Adenosine infusion at a nonhypotensive low dose (80 μg·kg^{-1}·min^{-1}) during surgery reduced the inhalational anesthetic requirements by 20%–50% and kept intraoperative systolic blood pressure levels more stable and less responsive to painful surgical stimuli in the adenosine group than in the placebo group. After breast surgery and hysterectomy, postoperative opioid requirements during the first 24 h were reduced by 27% and 18%, respectively, at a similar degree of pain relief, suggesting an extended antinociceptive/analgesic effect of the adenosine treatment [28,30].

Two additional double-blinded, comparative studies with adenosine or remifentanil infusions have been performed in patients undergoing abdominal hysterectomy [31] and in another report abdominal hysterectomy and orthopedic hip or knee joint surgery [32], comparing the effects of intravenous infusions of adenosine and remifentanil given as an adjunct to low, constant concentrations of desflurane (2% and 3%, respectively) with 65% nitrous oxide in oxygen (Table 1). In these two studies, sufficiently high doses of adenosine or remifentanil infusions were carefully titrated (with variable-rate intravenous infusion) to the varying intensity of painful surgical stimulation to achieve and maintain hemodynamic stability with either adenosine (72–290 and 50–500 μg·kg^{-1}·min^{-1}) or remifentanil (0.02–0.38 and 0.05–0.50 μg·kg^{-1}·min^{-1}) in the respective studies. In both studies, adenosine and remifentanil infusions were equally effective anesthetic adjuvants for inhibiting cardiovascular responses to surgical stimulation; thus, excellent hemodynamic stability could be maintained during the operations by both drugs [31,32]. In addition, intraoperative levels of consciousness/hypnosis assessed by the bispectral index were similar for adenosine and remifentanil [31]. These results clearly demonstrated that adenosine infusion could safely replace the opioid analgesic as an anesthetic adjuvant to inhaled anesthetics. In addition, both studies revealed rapid, smooth emergence from anesthesia and improved postopera-
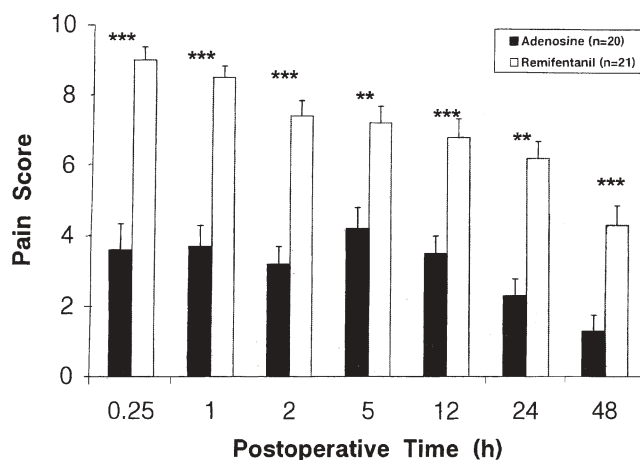

Fig. 1. Postoperative pain scores for the adenosine group (*solid bars*) and the remifentanil group (*open bars*). A variable-rate intravenous infusion of adenosine (50–500 μg·kg^{-1}·min^{-1}) or remifentanil (0.05–0.50 μg·kg^{-1}·min^{-1}) as an adjunct to inhaled anesthetics (3% desflurane and 65% nitrous oxide) was initiated 5 min before the skin incision and was titrated to maintain the systolic blood pressure and heart rate within 20% of baseline values during surgery. Postoperative pain scales: 0 and 10 indicate no pain and the worst imaginable pain, respectively. Results are expressed as the mean ± SEM. Differences between groups at the time indicated: **$P < 0.01$; ***$P < 0.001$ (From [32], with permission)

tive recovery profiles associated with significant reductions in postoperative pain and opioid consumption lasting 12 h [31] and 48 h [32] in the adenosine group compared to the remifentanil group, again confirming that persistent analgesic effects of adenosine by far outlasted the period of adenosine infusion (Figs. 1, 2).

In another study, the combined use of regional brachial plexus block with intravenous adenosine infusion at 80 μg·kg^{-1}·min^{-1} over 60 min in patients undergoing upper extremity surgery prolonged the duration of postoperative analgesia [57], whereas addition of adenosine (10 mg) to local anesthetics for a brachial plexus block did not significantly extend the duration of analgesia [58], suggesting that peripheral nerve trunks may not be the site of action for adenosine analgesia.

On the other hand, intrathecal (spinal) adenosine (500 μg) used in patients undergoing hysterectomy or in women in labor did not attenuate acute perioperative pain or labor pain significantly [59,60], although an antinociceptive action of adenosine is probably exerted primarily at the spinal level via A1 receptor activation [1,6]. These results are in contrast to the significant perioperative analgesia induced by intravenous adenosine shown in patients undergoing various types of surgery [28–32].

Possible explanations for the difference in results between intravenous and intrathecal adenosine for acute perioperative pain are as follows. First, intravenous/
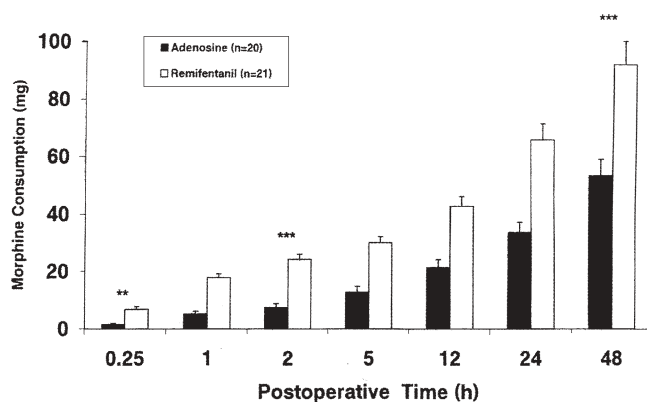
Fig. 2. Postoperative morphine consumption in the adenosine (*solid bars*) and remifentanil (*open bars*) groups. Patients were given intravenous boluses of morphine on demand in the postanethesia care unit (PACU) (<2h), followed by patient-controlled analgesia (PCA) infusion pump administration. Each histogram represents the mean ± SEM at each designated time. Because the morphine effect is longitudinally cumulative, differences between groups were compared at a specific time point [upon arrival in the PACU (<0.25h), at discharge from the PACU (2h), and on the following 2 days (48h)] to minimize statistical bias. **$P < 0.01$; ***$P < 0.001$ (From [32], with permission)

systemic adenosine may attenuate perioperative pain primarily through its antiinflammatory actions mediated by peripheral adenosine A2a or A3 receptors [61,62]. Such an antiinflammatory effect may reduce the ongoing stimulation of peripheral nociceptors by suppressing inflammation following tissue damage [10,59,60]. This assumption is supported by the result of a study showing that an antiinflammatory drug, ibuprofen, but not a long-acting selective A1-adenosine receptor agonist, SDZ WAG994, provided significant postoperative analgesia after third-molar surgery [63].

Second, intrathecal adenosine at a dose larger than 500μg might be required to attenuate perioperative nociceptive pain. Reportedly, intrathecal adenosine at 500–2000μg·kg^{-1} consistently attenuates allodynia, hyperalgesia, or both (an expression of central sensitization) in experimental human allodynic/hyperalgesic pain [45,47,48] or clinical neuropathic pain [54,55], but it does not affect nociceptive pain in humans [45,47]. Therefore, the dose requirement may be greater for acute nociceptive pain with massive ongoing afferent nociceptive barrages than for experimental allodynic or neuropathic pain due to central sensitization, where there may be little or no continuous nociceptive input [59]. Another explanation for the lack of efficacy by intrathecal adenosine for nociceptive pain might be due to the diffusion factor, where penetration of adenosine into the spinal cord is poor in an intact nervous system [60]. Because the spinal A1 receptor-mediated

antinociception has been demonstrated in a variety of animal nociceptive pain models using adenosine analogues and not adenosine itself [1,13], it would be relevant to study adenosine analogues with better tissue penetration in the future to increase drug concentration at the potential site of action [60].

In contrast, it does not seem clinically relevant to evaluate whether an increased intrathecal adenosine dose leads to significant antinociception in the clinical setting because intrathecal injection should, in principle, be performed in conscious subjects to avoid nerve damage, in whom intrathecal adenosine at 2000μg is associated with frequent occurrence of headache or backache lasting as long as several hours [45,46]. In this regard, clinical trials to determine if an increased intravenous dose leads to increased antinociception can be much more easily performed in anesthetized patients [31,32]. Our animal study using a rabbit acute nociceptive pain model [64] suggested that intravenous infusion of adenosine at a high dose (200, 400, or 800μg·kg^{-1}·min^{-1}) but not at a low dose (100μg·kg^{-1}·min^{-1}) can significantly inhibit escape movement in response to noxious stimuli (antinociception/analgesia) in a dose-dependent manner [65]. The antinociceptive effect of adenosine, probably mediated via A1 receptor, was slow in onset and long-lasting, outlasting the infusion period by several hours, in contrast to immediate on–off profiles of its A2 receptor-mediated hypotensive effects [65]. Comparisons of data from five clinical studies on the perioperative use of intravenous adenosine [28–32] suggest that adenosine-induced postoperative analgesia is also dose-dependent in terms of the potency (peak effect) and duration of analgesia (Table 1). Clinically, intraoperative adenosine infusion, titrated at a dose of up to 500μg·kg^{-1}·min^{-1}, has been safely used in anesthetized patients [32]. It is conceivable that, when given at high doses, its central A1 receptor-mediated antinociceptive action and its peripheral A2a or A3 receptor-mediated antiinflammatory actions might have contributed preemptively to the long-lasting postoperative analgesia by intraoperative administration of adenosine [31,32].

Clinical application of ATP to acute and chronic pain

As described earlier, endogenous and exogenous ATP acts basically as an algogenic/pronociceptive substance. When administered intravenously, however, ATP may act as adenosine at sites of action in both the peripheral and central nervous systems. Therefore, we have applied ATP to acute and chronic pain [7,8,21,66,67].

For other clinical indications, ATP could be safely infused at rates of up to 350μg·kg^{-1}·min^{-1} to produce

hypotension in anesthetized patients deliberately and up to $100\mu g\cdot kg^{-1}\cdot min^{-1}$ to control pulmonary hypertension in conscious subjects [19]. Some investigators have infused ATP in cancer patients over extended periods of 30 and 96h at rates of up to 75 and $100\mu g\cdot kg^{-1}\cdot min^{-1}$, respectively; they found that at the higher doses patients may experience chest pain/discomfort, analogous to that seen with adenosine [68,69]. Other authors have reported that ATP infusion at $160\mu g\cdot kg^{-1}\cdot min^{-1}$ causes angina-like chest pain in most conscious subjects but with no ECG evidence of myocardial ischemia [70]. Because such pain symptoms resolve spontaneously or immediately after reducing/discontinuing the infusion without any evidence of deleterious sequelae, intravenous infusion of ATP can be performed safely [69,70]. In conscious subjects, intravenous infusion of adenosine at more than $70\mu g\cdot kg^{-1}\cdot min^{-1}$ may cause chest pain/discomfort [24,25]. Because ATP has a molecular weight 1.5 times greater than that of adenosine, adenosine at $70\mu g\cdot kg^{-1}\cdot min^{-1}$ may correspond to ATP at $105\mu g\cdot kg^{-1}\cdot min^{-1}$. Based on these data, we infused ATP at a rate of $100\mu g\cdot kg^{-1}\cdot min^{-1}$ (or at a maximally tolerated dose if lower) in patients suffering from intractable chronic pain [21,66,67]. Similar to adenosine, ATP at $100\mu g\cdot kg^{-1}\cdot min^{-1}$ caused chest pain/discomfort in some patients without noticeable changes in the ECG. The symptoms disappeared within a minute of dose reduction or discontinuation [21,66,67], reflecting the extremely short plasma half-life of ATP and adenosine (less than seconds) [18,19,23]. In our experience, co-administration of small doses of midazolam for light sedation can safely attenuate the chest pain/discomfort to a tolerable level in most patients.

ATP as an anesthetic adjuvant

In most anesthetic practices, combinations of multiple drugs are used to achieve various endpoints of general anesthesia. Often a combination of inhalation anesthetics and several intravenous (sedative, analgesic, and vasoactive) drugs are used as a balanced anesthetic technique to avoid or minimize the adverse side effects of using a large dose of any single agent. The combined use of ATP during clinical anesthesia is not new, and the safety of ATP for inducing and maintaining deliberate hypotension for considerably long periods of time has been clinically proven. An analgesic drug with rapid-acting sympatholytic, antiadrenergic, and powerful vasodilator properties that is capable of reducing the requirement of inhaled anesthetics, opioids, or both and is easily titratable intraoperatively without cardiorespiratory depression appears to have potential advantages as an anesthetic adjuvant. Clinically, we first observed the surprisingly effective vasodilator and sympatholytic, antiadrenergic, and long-lasting antinociceptive/analge-

sic properties after intravenous ATP infusion in surgical patients during the early 1980s. Subsequent laboratory studies and clinical investigations confirmed these findings in patients undergoing various surgical procedures [7,8]. Indeed, intravenous infusion of ATP (100–$130\mu g\cdot kg^{-1}\cdot min^{-1}$) could effectively inhibit surgical stress responses and safely reduce the anesthetic requirement up to 50%–60% for inhaled agents (halothane, enflurane, isoflurane, sevoflurane, nitrous oxide) in patients undergoing various surgical procedures, such as maxillofacial, orthognathic, superficial extremity, and intraabdominal operations.

ATP for chronic pain patients

There were few reports on the application of ATP to chronic pain patients until recently. Two case reports have now suggested that ATP may be effective in attenuating not only neuropathic pain [21] but also nonneuropathic chronic intractable pain [20]. Therefore, we applied intravenous ATP ($100\mu g\cdot kg^{-1}\cdot min^{-1}$ or less for 120 or 180min) to patients having chronic intractable orofacial pain of neuropathic ($n = 43$) or nonneuropathic ($n = 16$) origin [67]. Two-thirds of the patients with neuropathic orofacial pain but none of the patients with nonneuropathic orofacial pain responded to ATP; the response was defined as more than 50% reduction in the spontaneous pain VAS scores. Neuropathic pain following pulpectomy with or without subsequent tooth extraction was most likely to respond to ATP. In responders, the analgesic and antiallodynic effect of ATP was slow in onset and prolonged, outlasting the infusion period by at least several hours. Antiallodynic effects tended to last longer than analgesic effects on spontaneous pain. In two patients, permanent abolition of spontaneous pain or tactile allodynia (or both) was achieved with a single ATP infusion therapy.

To clarify which type of neuropathic pain is likely to respond to ATP, 15 patients suffering intractable postherpetic neuralgia (PHN) received intravenous ATP ($100\mu g\cdot kg^{-1}\cdot min^{-1}$ or less for 120 or 180min), ketamine ($0.3mg\cdot kg^{-1}$), and lidocaine ($2mg\cdot kg^{-1}$) on separate days [21,66]. Seven, six, and eight patients responded to ketamine, lidocaine, and ATP, respectively. In eight ATP responders, pain relief progressed slowly during the infusion period (Fig. 3) and outlasted it for several hours; the median duration of pain relief after ATP was 9h (range 3h to 18 months) (Table 2). One patient experienced permanent abolition of spontaneous pain and mechanical allodynia after a single session of ATP therapy [21]. The response to ATP correlated significantly with the response to ketamine but not with the response to lidocaine (Table 2). Because ATP exerted pain-relieving effects in ketamine-responsive

Table 2. Results of drug test with intravenous ketamine, lidocaine, or ATP in 15 patients with intractable postherpetic neuralgia

Case	Age (years)	Sex	Site[a]	Pain and allodynia			Positive drug response to treatment[b]	Duration of pain relief after treatment		
				Duration (months)	Spontaneous	Allodynia		K	L	ATP
1	51	M	V2	10	+	+	K, ATP	1 h	—	4 h
2	81	F	V2	3	+	+	L	—	<1 h	—
3	79	M	V2–3	12	+	+	L	—	<1 h	—
4	49	M	V2–3	12	+	+	L	—	3 days	—
5	44	F	V3	3	+	+	L	—	<1 h	—
6	75	F	V3	4	+	+	K, ATP	1 h	—	10 h
7	60	F	V3	18	+	+	K, ATP	5 h	—	4 h
8	41	M	C4	6	+	+	L, ATP	—	<1 h	8 h
9	76	M	T1–2	72	+	+	K, ATP	4 h	—	3 days
10	74	M	T5–6	7	+	+	K, ATP	48 h	—	2 days
11	74	M	T10–12	47	+	+	—	—	—	—
12	64	F	L2	52	+	+	K, L, ATP	<1 h	1 h	3 h
13	71	F	L4–5	6	+	+	K, ATP	3 days	—	18 months
14	65	M	L4–5	4	+	−	—	—	—	—
15	69	M	S1–2	22	+	+	—	—	—	—
Median duration of pain relief in responders								4 h	<1 h	9 h

K, ketamine; L, lidocaine; ATP, adenosine triphosphate
Positive response to a drug was defined as more than 50% reduction in the Visual Analogue Scale for spontaneous pain
[a] V, C, T, L, and S indicate trigeminal, cervical, thoracic, lumbar, and sacral regions, respectively
[b] The response to ATP was correlated with the response to ketamine but not with the response to lidocaine
Modified from [66], with permission, by adding data from three cases including one in [21]
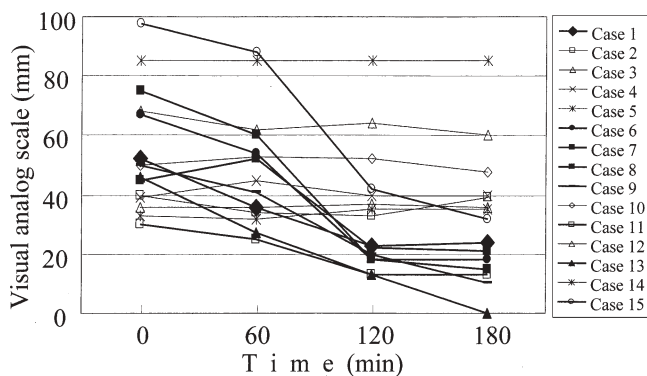

Fig. 3. Changes in the Visual Analogue Scale (VAS) for pain during infusion of ATP at $100\,\mu g\cdot kg^{-1}\cdot min^{-1}$ or less over 120 or 180 min in 15 patients with intractable postherpetic neuralgia. In eight patients VAS scores decreased slowly but progressively by more than 50% by the end of the infusion period, whereas in the remaining seven patients the VAS scores did not decrease. Thus eight patients responded to ATP, whereas seven did not (Modified from [66], with permission, by adding data from three cases including one in [21])

PHN, irrespective of the responsiveness to lidocaine, PHN pain associated with central sensitization via activation of NMDA receptors is likely to respond to ATP, whereas pain due to hyperexcitability of damaged peripheral nerves is not [21,66]. Both peripheral and central pathophysiological mechanisms contribute to PHN [71], and the relative contributions of peripheral and central mechanisms to the pathophysiology of PHN pain differ among subjects [72]. Therefore, the response to adenosine and ATP may vary among patients because of differences in pathophysiological mechanisms underlying the PHN pain. In recent report of eight PHN patients, spontaneous pain and tactile allodynia were significantly reduced by intravenous ATP infusion at a much lower dose ($16.7\,\mu g\cdot kg^{-1}\cdot min^{-1}$ over 60 min) [73] than the dose we used ($100\,\mu g\cdot kg^{-1}\cdot min^{-1}$ or less over 120–180 min) [21,66,67]. Therefore, dose-response studies may be required to determine an optimal ATP infusion dose for each of the various pain conditions.

The above-described studies regarding application of ATP to painful conditions have suggested that in conscious patients intravenous ATP infusion in the currently used low-dose regimens can alleviate pain or allodynia in a substantial proportion of (though not all) patients with neuropathic pain. Similar to adenosine, the pain-relieving effect of ATP is slow in onset and long-lasting. Therefore, sufficiently high doses of ATP infusion over a long period of time (e.g., 2–3 h) may provide better pain relief than shorter infusions (e.g., 1 h or less). It is noteworthy that in a limited number of cases, permanent abolition of spontaneous pain and allodynia can be achieved with a single adenosine or ATP infusion [10,21,50,52,53,67], and that repeated adenosine or ATP infusions provide progressively improved pain relief in some responders [51,73].

Conclusions

Adenosine and ATP have been shown to have a wide spectrum of unique pain-relieving effects in various clinical situations. In patients with chronic neuropathic pain, the main effect of adenosine compounds in pain modulation seems to be mediated through A1 receptor-related modulation of central sensitization at a spinal or supraspinal level. Probably for this reason low-dose intravenous adenosine and ATP as well as intrathecal adenosine administration can reduce allodynia/hyperalgesia more consistently than it can reduce spontaneous pain. Such pain-relieving effects are slow in onset and can last longer than the period of direct exposure to these compounds, usually by hours or days. Adenosine, its analogues, and ATP may provide permanent pain relief (>6 months) in a selected group of patients with neuropathic pain. For acute perioperative pain, however, treatment with low-dose adenosine or ATP infusion and adenosine A1 receptor-mediated antisensitization mechanisms may play only a minor role in the total perioperative pain experience. Effective, long-lasting perioperative pain relief was achieved safely by administering optimal doses of adenosine compounds to individual patients using titration to achieve and maintain perioperative hemodynamic stability. Both combined central A1 receptor-mediated analgesic/antinociceptive/antisensitizing actions and peripheral A2a or A3 receptor-mediated antiinflammatory actions may make these agents particularly suitable and efficacious against acute perioperative pain, where a variety of noxious stimuli may be present. Thus, intravenous adenosine and ATP as well as intrathecal adenosine seem to be useful pharmaceuticals as a novel modality of pain treatment and therapeutic advances. Adenosine compounds appear to have potential therapeutic properties, particularly for acute perioperative pain as well as chronic neuropathic pain, where currently available pain medications have limited effect or therapeutic utility.

References

1. Sawynok J (1998) Adenosine receptor activation and nociception. Eur J Pharmacol 317:1–11
2. Guieu R, Dussol B, Halimi G, Bechis G, Sampier F, Berland Y, Sampol J, Couraud F, Rochat H (1998) Adenosine and the nervous system: pharmacological data and therapeutic perspectives. Gen Pharmacol 31:553–561
3. Chizh BA, Illes P (2001) P2X receptors and nociception. Pharmacol Rev 53:553–568
4. Ribeiro JA, Sebastiao AM, de Mendonca A (2002) Adenosine receptors in the nervous system: pathophysiological implications. Prog Neurobiol 68:377–392
5. Jarvis MF (2003) Contributions of P2X(3) homometric and heterometric channels to acute and chronic pain. Expert Opin Ther Targets 7:513–522
6. Sawynok J, Liu XJ (2003) Adenosine in the spinal cord and periphery: release and regulation of pain. Prog Neurobiol 69: 313–340
7. Fukunaga AF, Miyamoto TA, Kikuta Y, Kaneko Y, Ichinohe T (1995) Role of adenosine and adenosine triphosphate as anesthetic adjuvants. In: Belardinelli L, Pelleg A (eds) Adenosine and adenine nucleotides: from molecular biology to integrative physiology. Kluwer Academic, Boston, pp 511–523
8. Fukunaga AF (1997) Adenosine compounds. In: White PF (ed) Textbook of intravenous anesthesia. Williams & Wilkins, Baltimore, pp 413–432
9. Sollevi A (1997) Adenosine for pain control. Acta Anaesthesiol Scand Suppl 110:135–136
10. Segerdahl M, Sollevi A (1998) Adenosine and pain relief: a clinical overview. Drug Dev Res 45:151–158
11. Khakh BS, Burnstock G, Kennedy C, King BF, North A, Seguela P, Voigh M, Humphrey PPA (2001) International Union of Pharmacology. XXIV. Current status of the nomenclature and properties of P2X receptors and their subunits. Pharmacol Rev 53:107–108
12. Sak K, Webb TE (2002) A retrospective of recombinant P2Y receptor subtypes and their pharmacology. Arch Biochem Biophys 397:131–136
13. Sumida T, Smith MA, Maehara Y, Collins JG, Kitahata LM (1998) Spinal R-phenyl-isopropyl adenosine inhibits spinal dorsal horn neurons responding to noxious heat stimulation in the absence and presence of sensitization. Pain 74:307–313
14. Sjülund KF, von Heijne M, Hao JX, Xu XJ, Sollevi A, Wiesenfeld-Hallin Z (1998) Intrathecal administration of the adenosine A1 receptor agonist R-phenylisopropyl adenosine reduces presumed pain behaviour in a rat model of central pain. Neurosci Lett 243:89–92
15. Lavand'homme PM, Eisenach JC (1999) Exogenous and endogenous adenosine enhance the spinal antiallodynic effects of morphine in a rat model of neuropathic pain. Pain 80:31–36
16. Okada M, Nakagawa T, Minami M, Satoh M (2002) Analgesic effects of intrathecal administration of P2Y nucleotide receptor agonists UTP and UDP in normal and neuropathic pain model rats. Pharmacol Exp Ther 303:66–73
17. Gomaa AA (1987) Characteristics of analgesia induced by adenosine triphosphate. Pharmacol Toxicol 61:199–202
18. Gordon JL (1986) Extracellular ATP: effects, sources and fate. Biochem J 233:309–319
19. Agteresch HJ, Dagnelie PC, van den Berg JW, Wilson JH (1999) Adenosine triphosphate: established and potential clinical applications. Drugs 58:211–232
20. Guieu R, Sampieri F, Pouget J, Guy B, Rochat H (1994) Adenosine in painful legs and moving toes syndrome. Clin Neuropharmacol 17:460–469
21. Hayashida M, Sato K, Fukunaga A, Fukuda K, Sekiyama H, Sawamura S, Arita H, Hanaoka K (2004) Intravenous infusion of adenosine 5′-triphosphate alleviated a disabling postherpetic neuralgia. J Anesth 18:36–38
22. Biaggioni I, Olafsson B, Robertson RM, Hollister AS, Robertson D (1987) Cardiovascular and respiratory effects of adenosine in conscious man; evidence for chemoreceptor activation. Circ Res 61:779–786
23. Sollevi A (1991) Effect of adenosine infusion in the conscious man. In: Phillis JW (ed) Adenosine and adenosine nucleotides as regulators of cellular function. CRC Press, Boca Raton, FL, pp 283–291
24. Sollevi A, Belfrage M, Lundeberg T, Segerdahl M, Hansson P (1995) Systemic adenosine infusion: a new treatment to alleviate spontaneous and evoked neuropathic pain. Pain 61:155–158
25. Belfrage M, Sollevi A, Segerdahl M, Sjölund KF, Hansson P (1995) Systemic adenosine infusion alleviates spontaneous and stimulus evoked pain in patients with peripheral neuropathic pain. Anesth Analg 81:713–717

26. Sylvén C (1993) Mechanisms of pain in angina pectoris: a critical review of the adenosine hypothesis. Cardiovasc Drugs Ther 7:787–791

27. Parker RB, McCollam PL (1990) Adenosine in the episodic treatment of paroxysmal supraventricular tachycardia. Clin Pharm 9:261–271

28. Segerdahl M, Ekblom A, Sandelin K, Wickman M, Sollevi A (1995) Peroperative adenosine infusion reduces the requirements for isoflurane and postoperative analgesics. Anesth Analg 80:1145–1149

29. Segerdahl M, Persson E, Ekblom A, Sollevi A (1996) Perioperative adenosine infusion reduces isoflurane requirements during general anesthesia for shoulder surgery. Acta Anaesthiol Scand 40:792–797

30. Segerdahl M, Irestedt L, Sollevi A (1997) Antinociceptive effect of perioperative adenosine infusion in hysterectomy. Acta Anaesthiol Scand 41:473–479

31. Zarate E, Sa Rego MM, White PF, Duffy L, Shearer VE, Griffin JD, Whitten CW (1999) Comparison of adenosine and remifentanil infusions as adjuvants to desflurane anesthesia. Anesthesiology 90:956–963

32. Fukunaga AF, Alexander GE, Stark CW (2003) Characterization of the analgesic actions of adenosine: comparison of adenosine and remifentanil infusions in patients undergoing major surgical procedures. Pain 101:129–138

33. Ekblom A, Segerdahl M, Sollevi A (1995) Adenosine but not ketamine or morphine increases the cutaneous heat pain threshold in healthy volunteers. Acta Anaesthesiol Scand 39:717–722

34. Sylvén C, Eriksson B, Jensen J, Geigant E, Hallin RG (1996) Analgesic effects of adenosine during exercise-provoked myocardial ischemia. Neuroreport 7:1521–1525

35. Giffin NJ, Kowacs F, Libri V, Williams P, Goadsby PJ, Kaube H (2003) Effect of the adenosine A1 receptor agonist GR79236 on trigeminal nociception with blink reflex recordings in healthy human subjects. Cephalalgia 23:287–292

36. Segerdahl M, Ekblom A, Sollevi A (1994) The influence of adenosine, ketamine and morphine on experimentally induced ischemic pain in healthy volunteers. Anesth Analg 79:787–791

37. Rae CP, Mansfield MD, Dryden C, Kinsella J (1999) Analgesic effect of adenosine on ischaemic pain in human volunteers. Br J Anaesth 82:427–428

38. Segerdahl M, Ekblom A, Sjölund KF, Belfrage M, Forsberg C, Sollevi A (1995) Systemic adenosine attenuates touch evoked allodynia induced by mustard oil in humans. Neuroreport 6:753–756

39. Sjölund KF, Segerdahl M, Sollevi A (1999) Adenosine reduces secondary hyperalgesia in two human models of cutaneous inflammatory pain. Anesth Analg 88:605–610

40. Dirks J, Petersen KL, Rowbotham MC, Dahl JB (2001) Effect of systemic adenosine on pain and secondary hyperalgesia associated with the heat/capsaicin sensitization model in healthy volunteers. Reg Anesth Pain Med 26:414–419

41. Dirks J, Petersen KL, Dahl JB (2003) The heat/capsaicin sensitization model: a methodologic study. J Pain 4:122–128

42. Karlsten R, Gordh T Jr, Svensson BA (1993) A neurotoxicologic evaluation of the spinal cord after chronic intrathecal injection of R-phenylisopropyl adenosine (R-PIA) in the rat. Anesth Analg 77:731–736

43. Rane K, Karlsten R, Sollevi A, Gordh T Jr, Svensson BA (1999) Spinal cord morphology after chronic intrathecal administration of adenosine in the rat. Acta Anaesthesiol Scand 43:1035–1040

44. Chiari A, Yaksh TL, Myers RR, Provencher J, Moore L, Lee CS, Eisenach JC (1999) Preclinical toxicity screening of intrathecal adenosine in rats and dogs. Anesthesiology 91:824–832

45. Rane K, Segerdahl M, Goiny M, Sollevi A (1998) Intrathecal adenosine administration: a phase I clinical safety study in healthy volunteers, with additional evaluation of its influence on sensory thresholds and experimental pain. Anesthesiology 89:1108–1115

46. Eisenach JC, Hood DD, Curry R (2002) Phase I safety assessment of intrathecal injection of an American formulation of adenosine in humans. Anesthesiology 96:24–28

47. Eisenach JC, Hood DD, Curry R (2002) Preliminary efficacy assessment of intrathecal injection of an American formulation of adenosine in humans. Anesthesiology 96:29–34

48. Eisenach JC, Curry R, Hood DD (2002) Dose response of intrathecal adenosine in experimental pain and allodynia. Anesthesiology 97:938–942

49. Guieu R, Peragut JC, Roussel P, Hassani H, Sampieri F, Bechis G, Gola R, Rochat H (1996) Adenosine and neuropathic pain. Pain 68:271–274

50. Sjölund KF, Belfrage M, Karlsten R, Segerdahl M, Arner S, Gordh T, Solevi A (2001) Systemic adenosine infusion reduces the area of tactile allodynia in neuropathic pain following peripheral nerve injury: a multi-centre, placebo-controlled study. Eur J Pain 5:199–207

51. Gyllenhammar E, Nordfors LO (2001) Systemic adenosine infusions alleviated neuropathic pain. Pain 94:121–122

52. Lynch ME, Clark AJ, Sawynok J (2003) Intravenous adenosine alleviates neuropathic pain: a double blind placebo controlled crossover trial using an enriched enrolment design. Pain 103:111–117

53. Karlsten R, Gordh T Jr (1995) An A1-selective adenosine agonist abolishes allodynia elicited by vibration and touch after intrathecal injection. Anesth Analg 80:844–847

54. Belfrage M, Segerdahl M, Arner S, Sollevi A (1999) The safety and efficacy of intrathecal adenosine in patients with chronic neuropathic pain. Anesth Analg 89:136–142

55. Eisenach JC, Rauck RL, Curry R (2003) Intrathecal, but not intravenous adenosine reduces allodynia in patients with neuropathic pain. Pain 105:65–70

56. Sollevi A (1992) Adenosine infusion during isoflurane-nitrous oxide anaesthesia: indications of perioperative analgesic effect. Acta Anaesthesiol Scand 36: 595–599

57. Apan A, Ozcan S, Buyukkocak U, Anbarci O, Basar H (2003) Perioperative intravenous adenosine infusion to extend postoperative analgesia in brachial plexus block. Eur J Anaesthesiol 20:916–919

58. Apan A, Basar H, Ozcan S, Buyukkocak U (2003) Combination of adenosine with prilocaine and lignocaine for brachial plexus block does not prolong postoperative analgesia. Anaesth Intensive Care 31:648–652

59. Rane K, Sollevi A, Segerdahl M (2000) Intrathecal adenosine administration in abdominal hysterectomy lacks analgesic effect. Acta Anaesthesiol Scand 44:868–872

60. Rane K, Sollevi A, Segerdahl M (2003) A randomised double-blind evaluation of adenosine as adjunct to sufentanil in spinal labour analgesia. Acta Anaesthesiol Scand 47:601–603

61. Cronstein BN (1994) Adenosine, an endogenous anti-inflammatory agent. J Appl Physiol 76:5–13

62. Montesinos MC, Desai A, Delano D, Chen JF, Fink JS, Jacobson MA, Cronstein BN (2003) Adenosine A2A or A3 receptors are required for inhibition of inflammation by methotrexate and its analog MX-68. Arthritis Rheum 48:240–247

63. Seymour RA, Hawkesford JE, Hill CM, Frame J, Andrews C (1999) The efficacy of novel adenosine agonist (WAG 994) in postoperative dental surgery. Br J Clin Pharmacol 47:675–680

64. Hayashida M, Fukunaga A, Hanaoka K (2003) An animal model for surgical anesthesia and analgesia: characterization with isoflurane anesthesia and remifentanil analgesia. Anesth Analg 97:1340–1346

65. Hayashida M, Fukunaga A, Fukuda K, Sakurai S, Hanaoka K (2004) Does intravenous infusion of adenosine really exert an anti-nociceptive effect? In: Proceedings of the 11th International Pain Clinic World Society of Pain Clinicians, Monduzzi Editore, Bologna, pp 475–478

66. Hayashida M, Fukuda K, Fukunaga A, Meno A, Sato K, Tarui K, Arita H, Kaneko Y, Hanaoka K (2005) Analgesic effect of

intravenous ATP on postherpetic neuralgia in comparison with responses to intravenous ketamine and lidocaine. J Anesth 19:31–35

67. Fukuda K, Hayashida M, Fukunaga A, Kasahara M, Koukita Y, Ichinohe T, Kaneko Y (2004) Intravenous ATP in chronic intractable orofacial pain. In: Proceedings of the 11th International Pain Clinic World Society of Pain Clinicians, Monduzzi Editore, Bologna, pp 479–482

68. Agteresch HJ, Dagnelie PC, Rietveld T, van der Berg JWO, Danser AHJ, Wilson JHP (2000) Pharmacokinetics of intravenous ATP in cancer patients. Eur J Clin Pharmacol 56:49–55

69. Haskell CM, Wong M, Williams A, Lee LY (1996) Phase I trial of extracellular adenosine 5′-triphosphate in patients with advanced cancer. Med Pediatr Oncol 27:165–173

70. Komukai K, Hashimoto K, Shibata T, Iwano K, Muto M, Mogi J, Imai K, Horie T, Mochizuki S (2002) Effect of continuous ATP injection on human hemodynamics. Circ J 66:926–929

71. Fields HL, Rowbotham M, Baron R (1998) Postherpetic neuralgia: irritable nociceptors and deafferentation. Neurobiol Dis 5:209–227

72. Pappagallo M, Oaklander AL, Quatrano-Piacentini AL, Clark MR, Raja SN (2000) Heterogenous patterns of sensory dysfunction in postherpetic neuralgia suggest multiple pathophysiologic mechanisms. Anesthesiology 92:691–698

73. Moriyama M, Kitamura A, Ikezaki H, Nakanishi K, Kim C, Sakamoto A, Ogawa R (2004) Systemic ATP infusion improves spontaneous pain and tactile allodynia, but not tactile hypesthesia, in patients with postherpetic neuralgia. J Anesth 18:177–180