J Anesth (2007) 21:24–30
DOI 10.1007/s00540-006-0444-3

Journal of
Anesthesia

Pain-relieving effects of intravenous ATP in chronic intractable orofacial pain: an open-label study

Ken-ichi Fukuda[1], Masakazu Hayashida[2], Atsuo Fukunaga[3], Masataka Kasahara[1], Yoshihiko Koukita[1], Tatsuya Ichinohe[4], and Yuzuru Kaneko[4]

[1] Department of Dental Anesthesia and Orofacial Pain Center, Tokyo Dental College, Suidoubashi Hospital, 2-9-18 Misaki-cho, Chiyoda-ku, Tokyo 101-0061, Japan
[2] Surgical Center Research Hospital, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan
[3] Professor Emeritus, Department of Anesthesiology, UCLA, Los Angeles, California, USA
[4] Department of Dental Anesthesiology, Tokyo Dental College, Tokyo, Japan

Abstract
Purpose. Chronic orofacial pain is often refractory to conventional pain therapies. We conducted an open-label study to determine whether adenosine 5′-triphosphate (ATP) could alleviate chronic intractable orofacial pain, and if so, which type of pain could respond to ATP.
Methods. In 8 and 16 patients with non-neuropathic and neuropathic intractable orofacial pain, respectively, ATP was intravenously infused at a rate of 100 μg·kg^{-1}·min^{-1} over 120 min. The magnitudes of spontaneous pain and brush-evoked allodynia were graded with a visual analog scale (VAS). When a VAS score for spontaneous pain was decreased by 50% or more by ATP, the patient was classified as a responder.
Results. The patients could be clearly divided into 10 responders and 14 non-responders. Ten of the 16 patients (62.5%) with neuropathic pain, but none of the 8 patients with non-neuropathic pain, responded to ATP. In particular, all of 8 patients with neuropathic pain following pulpectomy, with or without subsequent tooth extraction, responded to ATP. In the 10 responders, VAS scores for spontaneous pain decreased slowly but progressively during the infusion period, and eventually, ATP reduced the VAS scores for spontaneous pain and allodynia by 82 ± 15% and 74 ± 9%, respectively. In these responders, the analgesic and anti-allodynic effects of ATP outlasted the infusion period for medians of 7 and 12 h, respectively.
Conclusion. Intravenous ATP did not relieve non-neuropathic orofacial pain. However, it exerted slowly expressed but long-lasting analgesic and anti-allodynic effects in patients with neuropathic orofacial pain, especially in those suffering from neuropathic pain following pulpectomy and/or tooth extraction.

Key words Adenosine triphosphate (ATP) · Neuropathic pain · Postherpetic neuralgia · Pulpectomy · Tooth extraction

Address correspondence to: K. Fukuda
Received: April 27, 2006 / Accepted: August 24, 2006

Introduction

Chronic intractable pain affecting the orofacial area, specifically termed "atypical odontalgia", "phantom tooth pain", "the syndrome of oral complaint", and "atypical facial neuralgia", still remains as a major problem for both patients and clinicians, as the efficacies of various conventional pain therapies, including systemic analgesics and nerve blocks, have often been inadequate and inconsistent [1]. Therefore, new treatment modalities need to be explored.

Intravenous (i.v.) infusion of adenosine 5'-triphosphate (ATP) has been used for a variety of clinical indications [2]. There have been a few case reports or studies suggesting that intravenous ATP can alleviate neuropathic pain [3–5], as well as chronic intractable pain of non-neuropathic origin [6].

The aims of the present open-label study were to determine whether ATP could alleviate chronic intractable orofacial pain of both neuropathic and non-neuropathic origins, and if so, what type of orofacial pain could respond to ATP.

Methods

Subjects

After receiving approval from the institutional clinical research ethics committee and informed consent, we enrolled 24 patients with chronic intractable orofacial pain under treatment at the Orofacial Pain Center, Tokyo Dental College Suidoubashi Hospital. Patients eligible to take part in the study were those who suffered from chronic intractable orofacial pain, which had been present for 6 months or longer; rated 30 mm or more on a 100-mm visual analog scale (VAS); was unresponsive or only temporarily responsive to conventional pain therapies; and was attributable to one of the five typical

orofacial pain syndromes, i.e., (1) temporomandibular muscular pain (TMP) following repeated corrective procedures for malocclusion, (2) idiopathic burning pain of the tongue (BPT), (3) neuropathic pain, with widespread dysesthesia, due to inferior alveolar nerve damage (NP post-IAND) occurring during extraction of the third molar (wisdom) tooth, (4) postherpetic neuralgia (PHN) involving the mandibular and/or maxillary nerves, and (5) neuropathic pain following dental pulp extirpation (pulpectomy), with or without subsequent tooth extraction (NP post-PE, or NP post-PE,TE) (Table 1). At least 4 consecutive patients were recruited for each of the five typical orofacial pain syndromes. The demographic data of the patients are presented in Table 1. Patients with known pregnancy, asthma, gout, or heart block, or those who were taking methylxanthine medications, were excluded.

At some time during the course of ambulatory treatment at our institute and by the time of the ATP trial, all the patients had received a ketamine test, which consisted of two intravenous bolus injections of normal saline as a placebo and three subsequent intravenous bolus injections of ketamine 0.1 mg·kg^{-1}, given at intervals of 5 min; and the lidocaine test, which consisted of two intravenous bolus injections of normal saline and a subsequent intravenous bolus injection of lidocaine 1 mg·kg^{-1}, given at intervals of 5 min, immediately followed by the intravenous infusion of lidocaine 1 mg·kg^{-1} over 30 min [3,4]. Pain relief in a patient in response to the test drug (ketamine or lidocaine) was indicated by a 50% or more reduction in a VAS score for spontaneous pain induced by the drug [4].

Patients were instructed not to take caffeine-containing beverages for 24 h before and after the trial. Otherwise, there was no restriction on diet or daily medications, including analgesics. Local anesthetic infiltration and nerve blocks were not allowed on the day of the ATP trial. However, if patients suffered intolerable pain 1 h after the ATP infusion ended, these maneuvers could be performed.

A venous line was established in the forearm and lactated Ringer's solution was infused at a rate of 30 ml·h^{-1}. Infusion of ATP (Adephos L; Kowa, Nagoya, Japan) was started, using a syringe infusion pump. Beginning from 40 μg·kg^{-1}·min^{-1}, the infusion rate was increased in increments of 20 μg·kg^{-1}·min^{-1} every 5 min to a maximum of 100 μg·kg^{-1}·min^{-1}, or until a maximum tolerated dose, if lower, had been reached. Thereafter, the infusion of ATP was continued, in principle, at a constant rate for 120 min. Throughout the infusion period, 5-lead electrocardiogram (ECG), heart rate (HR), noninvasive blood pressure (BP), and pulse oximetry (S_{PO_2}) were continuously monitored. If any adverse effects occurred, the dose was reduced to the last given dose, or further, until the adverse effects disappeared. When patients experienced chest pain/discomfort of mild grade, however, the infusion rate was not reduced, as far as patients could tolerate the symptom.

Prior to the ATP infusion, the quality and nature of the spontaneous pain was described by each patient as "tingling", "piercing", "shooting", "pressing", "dull", "sharp", "aching", "throbbing", or "burning" (Table 1). The intensity of spontaneous pain was assessed with a 100-mm VAS immediately before the start of the ATP infusion (baseline, 0 min), and then every 15 min until 180 min after the start (i.e., 60 min after the end) of the infusion. Allodynia to soft brush-stroking on the most painful area was assessed with a VAS at 0 min and 180 min. The assessment of pain intensity was done by the same investigator in all patients. Subsequent changes in the intensity of spontaneous pain, as well as finger-touch-evoked allodynia were self-assessed, and the duration of subjective pain relief was reported by patients. Patients were classified as responders if their VAS score for spontaneous pain was decreased by 50% or more at 180 min, compared with the baseline. Otherwise, the patient was classified as a non-responder.

Data values are presented as means ± SD, or medians (ranges). Changes in HR, BP, and S_{PO_2} during ATP infusion were examined with repeated-measures analysis of variance (ANOVA). Changes in the VAS score for spontaneous pain were analyzed with the Friedman test, followed by the Dunn test for multiple comparisons of nonparametric data. Changes in the VAS score for allodynia were tested with the Wilcoxon test. Pairwise comparisons of other nonparametric data were also analyzed with the Wilcoxon test. Frequency variables were compared using Fisher's exact probability test. $P < 0.05$ was considered statistically significant, except where adjusted for multiple comparisons.

Results

Twenty-four patients, clinically diagnosed as having TMP ($n = 4$), BPT ($n = 4$), NP post-IAND ($n = 4$), PHN ($n = 4$), and NP post-PE or post-PE,TE ($n = 8$) participated in the study. The demographic data, characteristics of the pain, therapeutic modalities (including ketamine and lidocaine) that had provided temporary pain relief, changes in spontaneous pain VAS scores in response to ATP, and the duration of pain relief in ATP-responders are summarized in Table 1. By the time of the ATP trial, 5 of the 8 patients with NP post-PE had undergone tooth extraction (i.e., NP post-PE,TE) because of persisting "odontalgia" despite repeated root canal treatments, but the tooth extraction did not induce pain relief. All of the 4 patients with NP post-IAND, and 5 with NP post-PE,TE exhibited brush-evoked as well as finger-touch-evoked allodynia

Table 1. Demographic data and effects of ATP infusion

Patient no.	Age (years)/ Sex	Weight (kg)	Diagnosis and Etiology	Pain				Spontaneous pain		Duration of pain relief	
				Type	Characteristics	Duration	Temporary pain relief	Before/After (VAS [mm])	% Change	Spontaneous pain	Touch-evoked pain
Non-responders to ATP											
1	68/F	42	TMP	Spon	Pressing, dull	9 Years	SG, LA, ns	63/73	+16		
2	33/F	43	TMP	Spon	Pressing, dull	6 Years	SG, TG, LA, ad, ns	72/68	−6		
3	39/M	75	TMP	Spon	Pressing, dull	3 Years	TG, LA	53/54	+2		
4	31/F	68	TMP	Spon	Pressing, dull	1 Years	SG, LA, ad, ns	49/50	+2		
5	42/F	49	BPT	Spon	Burning	2 Years		58/56	−3		
6	48/F	54	BPT	Spon	Burning	3 Years	ac	47/51	+9		
7	52/M	65	BPT	Spon	Burning	9 Years	ac	42/41	−2		
8	66/F	41	BPT	Spon	Burning	3 Years	SG, ac	82/76	−7		
9	47/F	55	NP post-IAND	Spon, touch	Tingling, piercing	3.5 Years	SG, K, ac	66/62	−6		
10	49/F	49	NP post-IAND	Spon, touch	Tingling, shooting	6 Months	SG, K	57/48	−16		
11	59/M	65	NP post-IAND	Spon, touch	Tingling, piercing	2.5 Years	SG, L, ad	53/44	−17		
12	42/M	74	NP post-IAND	Spon, touch	Tingling	11 Months	ad, ac	46/42	−9		
13	80/M	62	PHN	Spon, touch	Tingling	1 Years	SG, LA, L, ad	36/36	0		
14	81/F	44	PHN	Spon, touch	Burning, throbbing	6 Months	SG, L, ad	40/39	−3		
Responders to ATP											
15	41/M	69	PHN	Spon, touch	Tingling, throbbing	6 Months	SG, L	45/21	−53	4 h	4 h
16	75/F	48	PHN	Spon, touch	Throbbing	6 Months	SG, K, ad	70/13	−81	8 h	8 h
17	48/F	56	NP post-PE	Spon	Aching	9 Months	SG, K, ad	60/10	−83	5 h	
18	25/F	45	NP post-PE	Spon	Aching, throbbing	6 Months	K, ad	82/11	−88	5 h	
19	32/F	54	NP post-PE	Spon	Aching	8 Months	K, ad	77/3	−96	9 h	
20	20/F	52	NP post-PE and TE	Spon, touch	Aching, throbbing	2 Years	K, ad	81/2	−98	10 h	26 h
21	32/F	53	NP post-PE and TE	Spon, touch	Aching, throbbing	8 Months	K	60/24	−60	5 h	24 h
22	21/F	48	NP post-PE and TE	Spon, touch	Aching	7 Months	K, ad	69/12	−83	8 h	13 h
23	38/F	47	NP post-PE and TE	Spon, touch	Aching, burning	2 Years 4 Months	SG, K	56/5	−91	6 h	9 h
24	65/F	58	NP post-PE and TE	Spon, touch	Aching, dull	1 Years 6 Months	SG, LA	40/5	−88	8 h	12 h

TMP, temporomandibular pain; BPT, burning pain of tongue; NP, neuropathic pain; IAND, inferior alveolar nerve damage; PHN, postherpetic neuralgia; PE, pulpectomy; TE, tooth extraction; Spon, spontaneous pain; touch, touch-evoked pain; SG, stellate ganglion block; TG, trigger point block; LA, local anesthetic infiltration or block; K, IV ketamine; L, IV lidocaine; ad, antidepressants; ac, anticonvulsants; ns, nonsteroidal antiinflammatory drugs; VAS, visual analog scale

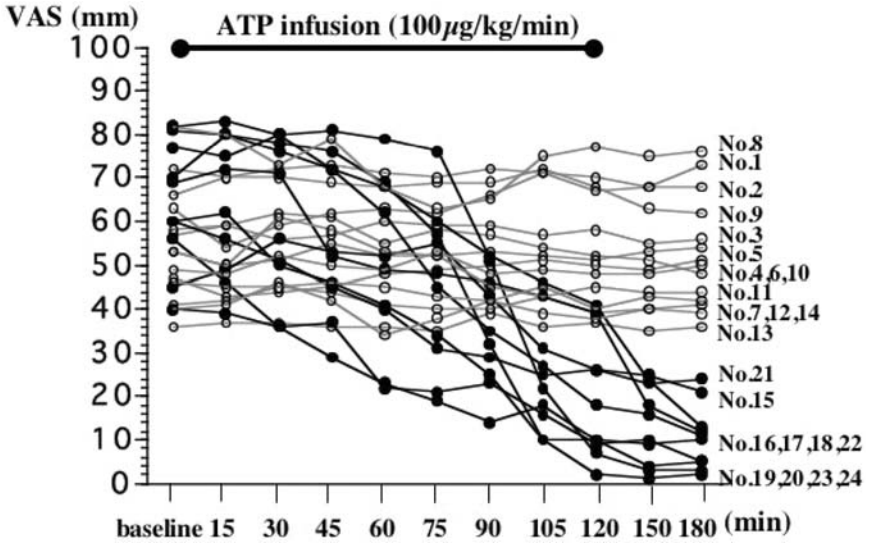

Fig. 1. Changes in visual analog scale (*VAS*) scores for spontaneous pain during and after intravenous infusion of ATP in individual patients. Changes in VAS scores in individual responders and non-responders are shown in *black lines* and *gray lines*, respectively

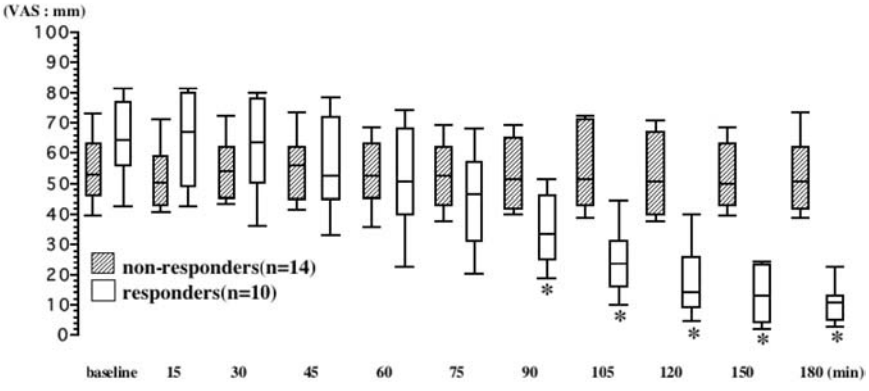

Fig. 2. Changes in visual analog scale (*VAS*) scores for spontaneous pain during and after intravenous infusion of ATP in the 10 responders and 14 non-responders. Data values are shown as medians (*bars*), 25th and 75th percentiles (*boxes*), and 10th and 90th percentiles (*whiskers*). *$P <$ 0.05 vs baseline at 0 min

at or around the site of tooth extraction. All 4 of the patients with PHN presented with brush-evoked and finger touch-evoked allodynia in the lesions (Table 1).

During the ATP infusion, three patients experienced transient or continuous chest pain/discomfort, which did not accompany clinically relevant changes in ECG, HR, BP, or Sp_{O_2}. However, the intravenous infusion of ATP at a dose of 100 μg·kg^{-1}·min^{-1} over 120 min was completed in all participants without problematic adverse effects. Significant changes in HR, BP, or Sp_{O_2} were not observed during and after ATP infusion (data not shown).

The patients could be clearly divided into 10 responders and 14 non-responders (Table 1, Figs. 1 and 2). In the 14 non-responders, the VAS score for spontaneous pain did not change with ATP ($P > 0.05$). In the 10 responders, the VAS score for spontaneous pain decreased significantly, by 82 ± 15% (mean ± SD) at 180 min, compared with the baseline at 0 min ($P < 0.0001$). During the infusion period, the decrease in VAS scores progressed only slowly and reached statistical significance only at 90 min and later (Fig. 2). In the 10 responders, the subjective relief of spontaneous pain lasted for a median of 7 h (range, 4–10 h) after the infusion ended (Table 1). The VAS score for brush-evoked allodynia decreased by 50% or more in none of 6 non-responders presenting with allodynia, and in these patients the VAS score for allodynia did not decrease significantly with ATP ($P > 0.05$). In contrast, the VAS score for allodynia decreased by more than 50% in 7 responders in whom allodynia was present, and in these patients the VAS score for allodynia decreased significantly, by 74 ± 9% (mean ± SD) at 180 min, compared with the baseline ($P < 0.0001$). The anti-allodynic effect of ATP lasted for a median of 12 h (range, 4–26 h). The anti-allodynic effect lasted significantly longer than the analgesic effect on spontaneous pain ($P = 0.043$; Table 1).

When the pain syndromes were classified into non-neuropathic pain (TMP and BPT; $n = 8$) and neuropathic pain (NP post-IAND, PHN, and NP post-PE or

post-PE,TE; $n = 16$), 10 of the 16 patients (62.5%) with neuropathic pain, but none of the 8 patients (0%) with non-neuropathic pain, responded to ATP (10/16 vs 0/8; $P = 0.0064$; Table 1). Among those with neuropathic pain, a response to ATP was recorded in all of the 8 patients with NP post-PE or post-PE,TE, but only in 2 of the 4 with PHN, and in none of the 4 with NP post-IAND (Table 1). Eight of the 10 patients with ketamine-responsive pain responded to ATP, whereas only 2 of 14 patients with ketamine-unresponsive pain responded to ATP (8/10 vs 2/14; $P = 0.001$; Table 1). Ten of 11 patients presenting with spontaneous pain of aching or throbbing nature responded to ATP, whereas none of the 13 patients having pain of another nature responded to ATP (10/11 vs 0/13; $P < 0.0001$; Table 1).

Discussion

In the present study, responders and non-responders to ATP could be clearly identified among patients with chronic intractable orofacial pain. A substantial number of patients with neuropathic pain responded to ATP, whereas none of patients with chronic non-neuropathic pain responded to ATP. More specifically, intravenous ATP infusion showed clear signs of pain relief in patients suffering NP post-PE or post-PE,TE, which would correspond to so-called "atypical odontalgia" and "phantom tooth pain" [1]. In the ten responders, VAS scores for spontaneous pain and allodynia decreased consistently and remarkably with ATP, by more than 70%, indicating that ATP produced profound analgesic and anti-allodynic effects in a subgroup of patients with orofacial neuropathic pain. The pain-relieving effect of intravenous ATP was slow in onset and long in duration, outlasting the infusion period for at least several hours. These results were in agreement with those of previous studies in patients with PHN [3,4].

Among patients with neuropathic pain, all of the eight patients with NP post-PE or post-PE,TE responded dramatically to ATP. In contrast, none of the four patients with NP post-IAND exhibiting regional dysesthesia and only two of the four patients with PHN responded to ATP. It is conceivable that the nerve damage might have occurred only at a terminal nerve branch in patients with NP post-PE or post-PE,TE, while it might have been more serious and extensive, occurring at the more proximal nerve trunk in those with NP post-IAND and those with PHN. Such differences in the sites and grades of nerve damage may have contributed to the different responses to ATP. Among the four patients with PHN, only two patients experienced pain relief with ATP. Reportedly, both peripheral and central pathophysiological mechanisms can contribute to neuropathic pain including PHN, and the relative contributions of peripheral and central mechanisms to the pathophysiology of neuropathic pain may vary between neuropathic patients [7–9], as may be suggested by interindividual variability in the responses of neuropathic pain to ketamine and lidocaine [8]. In previous studies, patients with ketamine-responsive PHN pain were much more likely to respond to ATP, compared to those with ketamine-unresponsive, lidocaine-responsive PHN pain, suggesting that PHN pain involving N-methyl-D-aspartic acid (NMDA) receptor activation and central sensitization is much more likely to respond to ATP, compared to PHN pain due to hyperexcitability or ectopic firing of damaged peripheral nerves [3,4]. As a result of such inter-individual differences in pain mechanisms, response to ATP may vary even between PHN patients. The response of neuropathic pain to ATP may thus vary between patients, being affected by various factors such as the type, stage, site, and grade of nerve damage and subsequent pathophysiological neuronal changes.

The analgesic property of intravenous ATP demonstrated in the present and previous clinical studies [3–6] appeared to be in contrast to the algogenic or pronociceptive property of peripherally or spinally administered ATP, shown in experimental studies [10]. It is quite conceivable that the analgesic effects of intravenous ATP observed in the present study are those of adenosine via A1 receptor activation, because ATP is extremely rapidly converted to adenosine by ectoenzymes when given intravenously [2,11,12]. Therefore, the present analgesic activities of intravenous ATP appear to be consistent and in agreement with the alleviation of neuropathic pain with intravenous adenosine [13–18].

It has been reported that ATP infusion, at $160\,\mu g \cdot kg^{-1} \cdot min^{-1}$, causes angina-like chest pain in most conscious subjects [19]. It is known, however, that such chest symptoms result not from actual myocardial ischemia, but from the direct activation/sensitization of nociceptive afferents by adenosine compounds, and these symptoms resolve spontaneously, or immediately after stopping the infusion or reducing infusion rates [13–15,19], reflecting the extremely short plasma half-life of ATP and adenosine (less than seconds) [2,11,12]. Therefore, intravenous infusions of ATP can be performed quite safely [19]. In the present study, the infusion of ATP, at $100\,\mu g \cdot kg^{-1} \cdot min^{-1}$ over 120 min, was well tolerated by all 24 participants, although some patients experienced chest pain/discomfort during the infusion.

In the present study, we used ATP at $100\,\mu g \cdot kg^{-1} \cdot min^{-1}$, which could produce chest pain/discomfort in some subjects, for several reasons. First, data from four

clinical studies on the intraoperative use of adenosine suggest that the potency and duration of adenosine-induced postoperative analgesia are dependent on the adenosine dose, ranging from 80 to 292 ± 82 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [20–23], suggesting that adenosine compounds at higher doses would provide greater pain relief. Second, in our initial experience with ATP therapy in two patients with ATP-responsive NP post-PE,TE, ATP at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or more provided more profound and more prolonged pain relief, compared with ATP at 80 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or less (unpublished data). Third, in a series of previous studies in healthy volunteers, ATP at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ produced significant analgesia to tooth pulp electrical stimulation and potentiated the sedative effect of midazolam, without producing any noticeable adverse effects [24]. Fourth, studies on the analgesic effects of adenosine have most commonly employed adenosine doses of 50–80 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [13–17,20,21,25,26], which would correspond to ATP doses of 75–120 $\mu g \cdot kg^{-1} \cdot min^{-1}$, given the 1.5 times greater molecular weight of ATP than adenosine, suggesting that ATP at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ would be appropriate for pain therapy.

In the present study, in agreement with the results of previous studies [3,4], ketamine-responsive pain was more likely to respond to ATP than ketamine-unresponsive pain, suggesting that chronic neuropathic pain involving NMDA receptor mechanisms is more likely to respond to ATP. It is difficult to understand why ATP or adenosine was capable of relieving neuropathic pain, in particular, ketamine-responsive neuropathic pain. However, it is well known that the activation of NMDA receptors by excitatory amino acids (e.g., glutamate) plays a crucial role in central sensitization and the development of neuropathic pain symptoms [27], and therefore, the noncompetitive NMDA receptor antagonist ketamine is effective in relieving neuropathic pain in a substantial number of patients [3,4,8]. In the spinal cord, glutamate is involved in nociceptive transmission by activating α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and in nociceptive facilitation and central sensitization by activating NMDA receptors, while adenosine leads to the suppression of nociception by the activation of pre- and postsynaptic adenosine A1 receptors [27,28]. The spinal application of excitatory neurotransmitters such as NMDA and substance P causes the release of adenosine from the spinal cord [28]. Also, in the brain, excitatory amino acids such as glutamate and NMDA stimulate NMDA as well as non-NMDA glutamate receptors, which, in turn, induce the release of adenosine [29]. Adenosine subsequently inhibits neural activity via A1 receptor activation by presynaptically inhibiting the release of neurotransmitters, including glutamate, and by postsynaptically hyperpolarizing transmission neurons [27,28]. In addition, adenosine postsynaptically inhibits NMDA receptors via A1 or A2A receptor activation [30,31]. Probably by these mechanisms, exogenous adenosine, and ATP given intravenously, can exert a significant inhibitory modulatory effect on neuropathic pain.

The continuous spontaneous pain experienced by patients with neuropathic pain is described as being felt in the skin, and muscles and/or bone, including the teeth [32]. When the pain is felt to lie in muscle or bone, it is generally described with words like “cramping”, “aching”, “throbbing”, and “crushing”. When it is felt to arise from the skin, the reports are usually of “burning”, “cutting”, “pricking”, and “stabbing” [32]. In the present study, patients with pain of an “aching” or “throbbing” nature that mimicked pain arising from deep somatic organs were more likely to respond to ATP than those with pain of another nature, although the reason for this was not clear.

One limitation of the present study was that even in patients with ATP-responsive neuropathic pain, the analgesic and anti-allodynic effects of ATP lasted for only 10 h and 26 h, respectively, at longest. However, a number of studies have shown that even a single treatment with adenosine, ATP, or other adenosine analogs can provide permanent (lasting for more than months) and complete abolition of spontaneous pain and/or allodynia in some patients with neuropathic pain [3,15–17,33]. Actually, in our recent double-blind study with ATP, complete abolition of spontaneous pain and/or allodynia lasting for more than 15 months was achieved with a single session of ATP therapy in 2 out of 12 patients with NP post-PE,TE [34]. In addition, patients experiencing pain relief with adenosine or ATP lasting for days (>48 h) are not rare [4,13–15,17,18], and such patients are considered to be good candidates for repetitive treatment with adenosine or ATP infusion [15], which may provide progressively improving pain relief [5,18]. Further, one study has revealed that a significant reduction in the mean pain scale persisted for at least 2 weeks after a single session of adenosine infusion in 23 patients with adenosine-responsive neuropathic pain [17]. Therefore, ATP or adenosine infusion therapy appears to warrant at least one trial in patients with neuropathic pain in whom currently available pain therapies have only limited effects.

In conclusion, intravenous ATP could provide profound and prolonged pain relief in a subgroup of patients with neuropathic pain affecting the orofacial area. In particular, neuropathic pain following pulpectomy with or without subsequent tooth extraction was highly responsive to ATP. Intravenous ATP infusion may provide improvement in the pain condition and quality of life in a subgroup of patients with chronic intractable neuropathic pain affecting the orofacial area.

References

1. Sharav Y (1994) Orofacial pain. In: Wall PD, Melzack R (eds) Textbook of pain. Churchill-Livingstone, Edinburgh, pp 563–582
2. Agteresch HJ, Dagnelie PC, van den Berg JWO, Wilson JHP (1999) Adenosine triphosphate: established and potential clinical applications. Drugs 58:211–232
3. 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
4. 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
5. 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
6. Guieu R, Sampieri F, Pouget J, Guy B, Rochat H (1994) Adenosine in painful legs and moving toes syndrome. Clin Neuropharmacol 17:460–469
7. Fields HL, Rowbotham M, Baron R (1998) Postherpetic neuralgia: irritable nociceptors and deafferentation. Neurobiol Dis 5:209–227
8. Kvarsnstrom A, Karlsten R, Quiding H, Emanuelsson BM, Gordh T (2003) The effectiveness of intravenous ketamine and lidocaine on peripheral neuropathic pain. Acta Anaesthesiol Scand 47:868–877
9. 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
10. Chizh BA, Illes P (2001) P2X receptors and nociception. Pharmacol Rev 53:553–568
11. Gordon JL (1986) Extracellular ATP: effects, sources and fate. Biochem J 233:309–319
12. Coade SB, Pearson JD (1989) Metabolisim of adenine nucleotides in human blood. Circ Res 65:531–537
13. Sollevi A, Belfrage M, Lundeberg T, Segerdahl M, Hansson P (1995) Systemic adenosine infusion: a new treatment modality to alleviate neuropathic pain. Pain 61:155–158
14. 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
15. Segerdahl M, Sollevi A (1998) Adenosine and pain relief: a clinical overview. Drug Dev Res 45:151–158
16. 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
17. 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
18. Gyllenhammar E, Nordfors LO (2001) Systemic adenosine infusions alleviated neuropathic pain. Pain 94:121–122
19. 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
20. 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
21. Segerdahl M, Irestedt L, Sollevi A (1997) Antinociceptive effect of perioperative adenosine infusion in hysterectomy. Acta Anaesthiol Scand 41:473–479
22. 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
23. 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
24. Fukunaga AF (1997) Adenosine compounds. In: White PF (ed) Textbook of intravenous anesthesia. Williams & Wilkins, Baltimore, pp 413–432
25. 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
26. 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
27. Zeilhofer HU (2005) Synaptic modulation in pain pathways. Rev Physiol Biochem Pharmacol 154:73–100
28. Sawynok J, Liu XJ (2003) Adenosine in the spinal cord and periphery: release and regulation of pain. Prog Neurobiol 69:313–340
29. Latini S, Pedata F (2001) Adenosine in the central nervous system: release mechanisms and extracellular concentrations. J Neurochem 79:463–484
30. de Mendonca A, Sebastiao AM, Ribeiro JA (1995) Inhibition of NMDA receptor-mediated currents in isolated rat hippocampal neurones by adenosine A1 receptor activation. Neuroreport 6:1097–1100
31. Gerevich Z, Wirkner K, Illes P (2002) Adenosine A2A receptors inhibit the M-methyl-D-aspartate component of excitatory synaptic currents in rat striatal neurons. Eur J Pharmacol 13:161–164
32. Bennett GF (1994) Neuropathic pain. In: Wall PD, Melzack R (eds) Textbook of pain. Churchill-Livingstone, Edinburgh, pp 201–224
33. 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
34. Fukuda K, Hayashida M, Fukunaga A, Kasahara M, Ichinohe T, Kaneko Y (2004) Analgesic effects of intravenous ATP infusion on neuropathic pain following pulpectomy and tooth extraction: a double-blind placebo-controlled cross-over study. 11th International Pain Clinic, World Society of Pain Clinicians, Abstract book, p 194