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Systemic ATP infusion improves spontaneous pain and tactile allodynia, but not tactile hypesthesia, in patients with postherpetic neuralgia

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Abstract
Purpose. Activation of purinoceptors may improve neuropathic pain. Accordingly, the effects of systemic ATP infusion were assessed in patients with postherpetic neuralgia (PHN).
Methods. Eight patients with PHN lasting over 3 months were enrolled. Initially, patients received the vehicle (20% dextrose) or ATP (at a dose of 1 mg·kg^{-1} in 20% dextrose) infused intravenously for 60 min on two separate occasions in a single-blinded manner. The levels of spontaneous continuous pain, paroxysmal pain, and tactile allodynia were assessed by a visual analogue scale (VAS), and tactile hypesthesia was assessed by Semmes-Weinstein monofilament before and after infusion. Subsequently, the eight patients received an ATP infusion (1 mg·kg^{-1} in 20% dextrose) once a week for 5–12 weeks in an open-label manner, and changes in the above parameters were assessed.
Results. In the initial study, VAS for spontaneous continuous pain and tactile allodynia decreased significantly with ATP infusion but not with placebo infusion. After repeated ATP infusions for 5–12 weeks, the median VAS for spontaneous continuous pain, paroxysmal pain, and tactile allodynia decreased significantly from 32.1 to 13.0, from 46.9 to 17.5, and from 49.5 to 15.6 respectively. However tactile hypesthesia did not improve significantly.
Conclusion. This study demonstrated that repetitive intravenous ATP infusion could improve spontaneous continuous pain and paroxysmal pain, as well as improving tactile allodynia, but did not influence tactile hypesthesia.

Key words Postherpetic neuralgia · Adenosine 5′-triphosphate · Spontaneous pain · Tactile allodynia · Tactile hypesthesia

Introduction

Varicella-zoster virus causes chickenpox and latent infection of somatic nerve roots, after which reactivation leads to herpes zoster associated with skin rash and spontaneous pain. Most cases of herpes zoster resolve without complications after less than one month. However, severe pain persists after the skin rash resolves in 10% to 50% of patients, especially in the elderly [1,2]. This is considered to be a form of neuropathic pain and is occasionally resistant to treatment with topical and oral medications or nerve block [3].

Adenosine 5′-triphosphate (ATP) is a member of the purine family that is found in all cells, being synthesized by oxidative phosphorylation within the inner mitochondrial membrane. It is well known that purines are involved in the transmission of sensory stimuli in both the peripheral and the central nervous systems [4,5]. ATP is metabolized rapidly to adenosine 5′-diphosphate or adenosine by ecto-ATPases [6], and adenosine has been suggested to be effective for neuropathic pain [7–10]. Some studies have shown improvement in neuropathic pain after administration of adenosine via an action on A1 receptors in both animals and humans [10–14].

However, there have been few reports on the usefulness of ATP for patients with painful conditions caused by postherpetic neuralgia (PHN). In the present study, we investigated the effect of intravenous ATP on pain in patients with PHN.

Materials and methods

The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from each patient. Eight patients receiving nerve block therapy and/or medication for the treatment of PHN at the outpatient pain clinic of Nippon

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Medical School Hospital were enrolled. Nerve block therapy consisted of stellate ganglion block for PHN affecting the face, head, neck, or upper arm, and epidural block for PHN of the trunk or lower extremities. Topical and oral medications consisted of nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, and selective serotonin reuptake inhibitors. These therapies were continued without change throughout the study period.

The inclusion criteria were spontaneous continuous pain and paroxysmal pain associated with tactile allodynia or impaired tactile sensory sensation that had lasted for at least 3 months since the onset of herpes zoster. In all patients, the pain symptoms had been stable for at least 2 weeks. Patients who could not clearly describe or judge their pain were excluded.

Initially, we performed a placebo-controlled, single-blind study. The patients received an intravenous infusion of 20 ml of dextrose containing ATP at a dose of 1 mg·kg^{-1} or 20 ml of 20% dextrose alone (placebo). Infusion was given for 50 to 60 min with monitoring of the blood pressure and heart rate. One week later, the patients received in a blinded manner the second treatment of ATP or placebo. We compared the effects of the infusion of ATP or placebo on spontaneous continuous pain, spontaneous paroxysmal pain, tactile allodynia, and impaired tactile sensation. Each assessment was done before starting the infusion, and within 3 min after the infusion. Subsequently, the same patients received repeated infusions of ATP (1 mg·kg^{-1} in 20 ml of 20% dextrose) once a week for up to 12 weeks in an open-label manner, and the above-mentioned parameters were tested again. If a patient was satisfied with the improvement of PHN, treatment was finished before 12 weeks. All the assessments were performed by the same pain clinician.

Subjective pain and allodynia were assessed by a 100-mm visual analogue scale (VAS) before administering the usual treatment and establishing intravenous access, and assessment was repeated at the completion of infusion. The VAS was a 100-mm-long horizontal line with the words "no pain" at the left end and "worst imaginable pain" at the right end. The patients were instructed to slide a plastic marker along the scale to the point representing the intensity of their pain. Prior to each assessment, the marker was placed at the center of the scale.

Allodynia was tested by stimulation of the skin lesions caused by herpes zoster with a soft brush, and the intensity of the pain elicited was determined by using the VAS. Tactile sensation was assessed with a Semmes-Weinstein monofilament (Prenova touch test foot-kit, Arkray, Kyoto, Japan) on the code of Japanese clinical trial of capsaicin ointment, and was classified into three grades: grade 0, "normal" (sensation was noted at a force of 0.4 g); grade 1, "impaired" (sensation was noted at a force of 2.0 g); and grade 3, "deficit" (no sensation was detected at 2.0 g). Each assessment was repeated on the same lesion after the infusion.

Statistical analysis was performed by Stat-View 4.5 software (Abacus Concepts, Berkeley, CA, USA). Numerical data were represented as the median (range). For the initial placebo-controlled study, the differences between "before" and "after" values were tested by Wilcoxon's rank sum test. To assess the effect of repeated ATP infusions, the differences between baseline and post-treatment values were also tested by Wilcoxon's rank sum test. A P value <0.05 was defined as indicating statistical significance.

Results

The clinical profile of the patients enrolled in this study is shown in Table 1. The age of the patients ranged from 57 to 83 years, with a median of 70.6 years. There were five men and three women.

The VAS values obtained in the initial placebo-controlled study are shown in Tables 2 and 3. There was a significant reduction of the VAS values for spontaneous continuous pain at the end of ATP infusion (Table

Table 1. Demographic data from eight patients with postherpetic neuralgia

Patient no.	Sex	Age (yr)	Duration of illness (m)	Location	Spontaneous pain	Allodynia	Tactile hypesthesia	No. of ATP infusions
1	F	76	31.4	Rt.V1	Yes	Yes	Yes	12
2	M	79	7.5	Rt.V1–2	Yes	Yes	Yes	12
3	F	66	6.1	Lt.L5	Yes	No	Yes	12
4	M	69	4.8	Rt.Th6–7	Yes	Yes	Yes	12
5	M	65	4.8	Rt.C7-Th2	Yes	Yes	Yes	12
6	F	83	14.7	Lt.V1	Yes	Yes	Yes	7
7	M	70	33.3	Rt.Th9/10	Yes	Yes	No	6
8	M	57	4.0	Lt.Th2–3	Yes	Yes	Yes	5

F, Female; M, male; Rt., right; Lt., left; V, trigeminal nerve area; C, cervical nerve area; Th, thoracic nerve area; L, lumbar nerve area

Table 2. Changes in continuous pain and paroxysmal pain in the initial placebo-controlled study of ATP infusion[a]

Treatment	Before	After
Dextrose		
Continuous pain VAS (mm)	28.4 (0–46)	27.9 (0–40)
Paroxysmal pain VAS (mm)	29.5 (0–71)	19.4 (0–53)
ATP		
Continuous pain VAS (mm)	32.1 (0–59)	19.1 (0–60)*
Paroxysmal pain VAS (mm)	27.1 (0–60)	11.2 (0–50)

[a] Values are median (range); $n = 8$; VAS, visual analogue scale
* $P < 0.05$

Table 3. Changes in allodynia and tactile hypesthesia in the placebo-controlled study of ATP infusion[a]

Treatment	Before	After
Dextrose		
Allodynia VAS (mm)	32.6 (0–76)	32.0 (0–76)
Tactile hypesthesia (grade)	1.0 (0–2)	1.0 (0–2)
ATP		
Allodynia VAS (mm)	26.4 (0–80)	20.0 (0–70)*
Tactile hypesthesia (grade)	1.1 (0–2)	0.8 (0–2)

[a] Values are median (range); $n = 8$. Tactile sensation was classified as grade 0, normal (force = 0.4 g); grade 1, impaired tactile sensation (force = 2.0 g); and grade 2, tactile sensory deficit (no sensation at 2.0 g)
* $P < 0.05$

2). The VAS values for allodynia also decreased significantly with ATP, whereas they did not with placebo (Table 3). However, paroxysmal pain and tactile hypesthesia did not improve.

After multiple infusions of ATP, the VAS values for spontaneous continuous pain, paroxysmal pain, and allodynia decreased significantly (Table 4). In three of seven patients, paroxysmal pain resolved completely after two to six infusions, and the intervals between attacks of pain increased markedly in three other patients. Tactile allodynia also showed significant improvement after multiple infusions, being normalized in four of seven patients. Furthermore, ATP infusion reduced the area of hypersensitivity to mechanical stimulation in two patients. However, tactile hypesthesia did not show significant improvement (Table 4). Additionally, we found that other symptoms improved, including postherpetic muscle cramps in three patients, as well as chronic joint pain due to rheumatoid arthritis in two patients.

As for the side effects of ATP infusion, two patients showed facial flushing and one patient complained of a desire to urinate. None of the patients had nausea, chest discomfort, palpitations, dyspnea, headache, or muscle weakness. ATP infusion also had no influence on blood pressure or pulse rate.

Table 4. Changes in continuous pain, paroxysmal pain, tactile allodynia, and tactile hypesthesia after an open-label trial of repeated ATP infusions[a]

Treatment	Baseline	Post-treatment
Continuous pain VAS (mm)	32.1 (0–59)	13.0 (0–40)*
Paroxysmal pain VAS (mm)	46.9 (0–69)	17.5 (0–60)*
Allodynia VAS (mm)	49.5 (0–80)	15.6 (0–70)*
Tactile hypesthesia (grade)	1.1 (0–2)	0.6 (0–2)

[a] Values are median (range); $n = 8$. Some values were tested for the effect of a single control infusion in terms of multiple infusions actually, so there are differences in baseline VAS
* $P < 0.05$

Discussion

Intravenous ATP appears to produce hemodynamic effects similar to those of adenosine when administered at high doses as an antiarrhythmic drug [4,15,16]. Adenosine is also reported to reduce somatic and neuropathic pain when administered intravenously at low doses [4,11,15]. In this study, we used low-dose ATP as a precursor of adenosine for the treatment of chronic PHN. A randomized, placebo-controlled, double-blind study would have been ideal, but our patients were in a stable condition because they had suffered consistent pain for over three months since the onset of herpes zoster, despite other therapies. In addition, it seemed appropriate to begin with a single-blinded, placebo-controlled study or an open-label study of ATP infusion therapy, as data are lacking regarding the analgesic effects of ATP in patients with neuropathic pain, including PHN.

In the initial placebo-controlled study, ATP infusion caused a significant reduction of spontaneous pain and tactile allodynia after a single dose in patients with established PHN. In the multiple ATP infusion study, the same patients received weekly infusion of ATP for 5 to 12 weeks and showed significant improvement of spontaneous continuous pain, spontaneous paroxysmal pain, and tactile allodynia.

The essential biochemical roles of ATP, adenosine 5′-monophosphate, and free adenosine have long been known, and these compounds have also attracted attention as independent neural signaling molecules. P1 class (A_1, A_{2A}, A_{2B}, A_3) and P2 class (P2X, P2Y) purinergic receptors have been characterized, and it has been reported that A1 and P2Y receptors may contribute to the reduction of neuropathic pain by causing vasodilation, or by presynaptic inhibition or action on the release of excitatory neurotransmitters [8,10,17,18]. ATP and its metabolites are taken up by cells within 1–2 min, so the observation of a long-term effect suggests the existence of a central mechanism [8,15].

We used a much lower dose of ATP than the doses of adenosine used for treatment of neuropathic pain in

previous studies [9,11,15]. However, the analgesic effects of ATP observed in the current study appear to be comparable to those of adenosine in the previous studies. It is possible that more molecules of adenosine may be able to reach the site of action at the central nervous system when it is administered as ATP than when it is administered as adenosine itself, because the plasma half-life of adenosine in the bloodstream is extremely short. Further investigations will be needed to elucidate the mechanism of the antinociceptive effect of ATP and to determine the adequate dose or term of ATP administration.

In conclusion, systemic infusion of ATP ($1\,mg{\cdot}kg^{-1}$) improved spontaneous pain and allodynia, but not impaired tactile sensation, in patients with PHN. The present findings suggest that ATP may be useful for the treatment of neuropathic pain, including PHN.

References

1. Chang CM, Woo E, Yu YL, Huang CY, Chin D (1987) Herpes zoster and its neurological complications. Postgrad Med J 63:85–89
2. Miller LH (1976) Herpes zoster in the elderly. Cutis 18:427–432
3. Bennett GF (1994) Neuropathic pain. In: Wall PD (ed) Textbook of pain, vol 3. Longman, London, pp 201–224
4. Agteresch HJ, Dagnelie PC, van den Berg JW, Wilson JH (1999) Adenosine triphosphate. Drugs 58:211–232
5. Todorov LD, Bjur RA, Westfall DP (1994) Inhibitory and facilitatory effects of purines on transmitter release from sympathetic nerves. J Pharmacol Exp Ther 268:985–989
6. Sawynok J, Sweeney MI (1989) The role of purines in nociceptions. Neuroscience 32:557–569
7. Burnstock G (2002) Potential therapeutic targets in the rapidly expanding field of purinergic signaling. Clin Med 2:45–53
8. Sawynok J (1997) Purines and nociception. In: Jacobson KA, Jarvis MF (ed) Purinergic approachs in experimental therapeutics. Wiley-Liss, New York, pp 495–513
9. 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
10. Gomma AA (1987) Characteristics of analgesia induced by adenosine triphosphate. Pharmacol Toxicol 61:199–202
11. Lynch ME, Clark AJ, Sawnok J (2003) Intravenous adenosine alleviates neuropathic pain: a double blind placebo controlled crossover trial using an enriched enrolment design. Pain 103:111–117
12. Sawynok J (2003) Topical and peripherally acting analgesics. Pharmacol Rev 55:1–20
13. Bantel C, Tobin JR, Li X, Childers SR, Chen SR, Eisenach JC (2002) Intrathecal adenosine following spinal nerve ligation in rat. Anesthesiology 96:103–108
14. Salter MW, Henry JL (1985) Effects of adenosine 5′-monophosphate and adenosine 5′-triphosphate on functionally identified units in the cat spinal dorsal horn. Evidence for a differential effect of adenosine 5′-triphosphate on nociceptive vs non-nociceptive units. Neuroscience 15:815–825
15. Belfrage M, Sollevi A, Segerdahl M, Sjolund KF, Hansson P (1995) Systemic adenosine infusion alleviates spontaneous and stimulus evoked pain in patients with peripheral neuropathic pain. Anesth Analg 81:713–717
16. Lerman BB, Belardinelli L (1991) Cardiac electrophysiology of adenosine: basic and clinical concepts. Circulation 83:1499–1509
17. Hamilton SG, Mcmahon SB (2000) ATP as a peripheral mediator of pain. J Auton Nerv Syst 81:187–194
18. Fredholm BB (1995) Purinoceptors in the nervous system. Pharmacol Toxicol 76:228–239