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Analgesic effect of intravenous ATP on postherpetic neuralgia in comparison with responses to intravenous ketamine and lidocaine

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Abstract
Purpose. No study has been performed on the analgesic effect of adenosine 5′-triphosphate (ATP) on postherpetic neuralgia (PHN). We conducted an open-label trial of ATP in patients with PHN, and compared ATP with ketamine and lidocaine.
Methods. Twelve patients with PHN were studied. On separate days, ketamine ($0.3\,mg\cdot kg^{-1}$), lidocaine ($2\,mg\cdot kg^{-1}$), and ATP ($100\,\mu g\cdot kg^{-1}\cdot min^{-1}$ or less for 120 min) were administrated intravenously. The intensity of spontaneous pain as well as tactile allodynia was assessed using a visual analog scale (VAS). When the VAS score for spontaneous pain was decreased by more than 50%, the patient was classified as a responder.
Results. Five, 6, and 6 patients responded to ketamine, lidocaine, and ATP, respectively. In 6 ATP responders, pain relief developed slowly and lasted for 9 (median) h (range: 3–72 h). All 5 ketamine responders and only 1 of 7 ketamine nonresponders responded to ATP (5/5 vs 1/7, $P < 0.05$, χ^2 test) whereas 2 of 6 responders to lidocaine and 4 of 6 nonresponders to lidocaine responded to ATP (2/6 vs 4/6, $P > 0.05$). The ketamine responders responded to ATP more often than did the lidocaine responders (5/5 vs 2/6, $P < 0.05$).
Conclusion. Intravenous ATP exerted slowly developing and long-lasting analgesic effects in half of patients with PHN. Patients with ketamine-responsive PHN were likely to respond to ATP.

Key words Postherpetic neuralgia · Neuropathic pain · Adenosine 5′-triphosphate · Ketamine · Lidocaine

Introduction

Postherpetic neuralgia (PHN), a subtype of neuropathic pain, is a common and often devastatingly painful condition. Responses of this type of pain to conventional pharmacotherapy are generally inhomogeneous; some patients may experience pain control with some treatments while others may not respond to any measures [1]. Such inconsistency may result from different pathophysiological mechanisms underlying the pain of the PHN patients [2,3]. To differentiate the pain mechanisms for each subject, drug tests with lidocacine, ketamine, and other drugs may be helpful [4].

Because conventional treatments usually can provide less than satisfactory pain relief for PHN, new treatment modalities have been explored extensively. Among them, intravenous infusion of adenosine (ADO) seems to be promising [5–9]. A number of studies have demonstrated that intravenous ADO alleviates neuropathic pain, including PHN. However, ADO is not approved for clinical use in Japan, and some clinicians may use adenosine 5′-triphosphate (ATP) instead of ADO. When administrated intravenously, ATP is rapidly metabolized to ADO in the blood [10], and one case report has suggested effectiveness of ATP in chronic intractable pain [11]. We, therefore, applied ATP to a patient with devastatingly painful PHN and observed its remarkable pain-relieving effect [12]. Encouraged by this initial experience, we herein conducted an open-label study to assess the analgesic efficacy of intravenous infusion of ATP in patients with intractable PHN. We also compared ATP with ketamine or lidocaine in an attempt to identify the subtype of PHN that would respond to ATP.

Methods

After approval by the local ethical committee at each institute and informed consent, we enrolled 12 patients with PHN who were under treatment at the pain clinic at The University of Tokyo Hospital or Tokyo Dental

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College Suidobashi Hospital. Their pain was resistant to conventional treatments, including stellate ganglion block, local anesthetic infiltration, epidural block, peripheral nerve block, phototherapy, acupuncture, and/or systemic administration of nonsteroidal antiinflammatory drugs, anticonvulsants, antidepressants, and/or opioid analgesics. All the patients had spontaneous pain rated 30 mm or more on the 100-mm visual analog scale (VAS) that lasted for 3 months or more. Eleven patients also had tactile allodynia. Exclusion criteria included patients with known pregnancy, asthma, gout, or heart block, or those who were taking methylxanthine medications.

Patients were instructed not to take caffeine-containing beverages for at least 24 h before and after the trial of ATP. 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 a drug trial. However, if patients suffered intolerable pain 1 h after finishing a drug administration, these maneuvers were carried out.

Before the ATP trial, analgesic effects of intravenous ketamine hydrochloride (Ketalar; Sankyo, Tokyo, Japan) and intravenous lidocaine hydrochloride (Xylocaine; Astra-Zeneca, Osaka, Japan) were tested in random orders on separate days according to the protocols described by other investigators [13]. Briefly, the ketamine test consisted of two bolus injections of normal saline (NS) as a placebo and subsequent three bolus injections of ketamine 0.1 $mg \cdot kg^{-1}$, given via a venous line at intervals of 5 min. The lidocaine test consisted of two bolus injections of placebo NS and a subsequent bolus injection of lidocaine hydrochloride 1 $mg \cdot kg^{-1}$ given at intervals of 5 min, immediately followed by intravenous infusion of lidocaine hydrochloride 1 $mg \cdot kg^{-1}$ over 30 min.

An open-label trial of ATP infusion was performed on a separate day, only when patients felt that the pain had returned to the "baseline" after a previous drug test. A venous line was established in the forearm and lactated Ringer's solution was infused at a rate of 30 $ml \cdot h^{-1}$. Infusion of ATP (Adephos L; Kowa, Nagoya, Japan) was started using a syringe infusion pump. Beginning from 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$, the infusion rate was increased in increments of 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every 5 min until a maximum dose of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$, or a maximum tolerable dose, if lower, had been reached. Thereafter, the infusion rate of ATP was kept constant. The infusion period was 120 min. If any adverse effects occurred, the dose was reduced in decrements of 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ every 5 min until the side effects disappeared. The adverse effect usually disappeared within a few minutes of lowering the infusion rate.

During these drug trials, electrocardiogram (ECG), heart rate (HR), noninvasive blood pressure (BP), and pulse oximeter (Sp_{O_2}) were monitored. During ketamine and lidocaine tests, the VAS score for spontaneous pain was measured before the start of the drug test, after each of placebo and test drug injections/infusion, and 60 min after the end of the test drug administration. During the ATP trial, the VAS score for spontaneous pain was measured before starting ATP (0 min), then every 60 min until the end of ATP infusion (120 min), and 60 min after stopping ATP (180 min). In 11 patients presenting with tactile allodynia, allodynia was evoked by light stroking of a soft brush on the most painful skin area. The VAS score for tactile allodynia was measured immediately before and after administration of drugs. The assessment of pain intensity was done by the same investigator at each institute. Subsequent changes in intensity of spontaneous pain as well as touch-evoked allodynia were self-assessed, and duration of subjective pain relief was reported later by patients. When the VAS score for spontaneous pain in a patient was reduced by more than 50% with a test drug, the patient was classified as a responder to the drug. Otherwise, the patient was classified as a nonresponder [4].

Data are presented as mean ± SD or median, percentiles, and range. Changes in HR, AP, and Sp_{O_2} during ATP infusion were tested with repeated measures analysis of variance (ANOVA). Changes in VAS scores for spontaneous pain and allodynia were tested with Friedman test followed by Wilcoxon test and Wilcoxon test alone, respectively. Frequency variables were compared using the χ^2 test. $P < 0.05$ was considered to be statistically significant.

Results

The patients' characteristics are listed in Table 1. Intravenous infusion of ATP over 120 min was completed in all 12 patients. No significant change in HR, BP, or Sp_{O_2} was observed during ATP infusion (data not shown). The maximum tolerable infusion rates were 100, 80, and 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in 9, 2, and 1 patients, respectively. The dose-limiting adverse effects were nausea in 1 patient and chest discomfort in 2 patients, which did not accompany clinically relevant changes in ECG, HR, BP, or Sp_{O_2}. Although 2 other patients also felt mild chest discomfort, they could tolerate the maximum dose (100 $\mu g \cdot kg^{-1} \cdot min^{-1}$) until the end of infusion.

No patient responded to NS whereas zero, five, six, and six patients responded to ketamine, lidocaine, and ATP, respectively (Table 1). All five responders to ketamine responded also to ATP although only one of seven nonresponders to ketamine responded to ATP (5/5 vs 1/7, $P < 0.01$). On the other hand, two of six responders to lidocaine and four of six nonresponders

Table 1. Patient demographic data, response to placebo, ketamine, lidocaine, and adenosine 5′-triphosphate, and duration of pain relief in responders

Case no.	Age (years)/ sex	Site of PHN lesion	Duration of pain (months)	Spontaneous pain	Brush-evoke allodynia	VAS for spontaneous pain before/after			VAS for tactile allodynia before/after			Positive response to P, K, L, ATP	Duration of pain relief after		
						K	L	ATP	K	L	ATP		K	L	ATP
1	51/M	V2	10	Yes	Yes	48/10	50/42	52/23	56/11	55/45	64/30	K, ATP	1 h		4 h
2	81/F	V2	3	Yes	Yes	36/33	32/15	40/33	47/48	41/15	53/39	L		<1 h	
3	79/M	V2–V3	12	Yes	Yes	40/40	38/15	36/37	44/41	42/28	40/38	L		<1 h	
4	49/M	V2–V3	12	Yes	Yes	34/35	34/6	39/40	45/44	40/23	40/40	L		72 h	
5	44/F	V3	3	Yes	Yes	33/34	33/14	33/35	35/37	36/23	35/38	L		<1 h	
6	75/F	V3	4	Yes	Yes	68/19	71/39	67/18	75/20	80/54	68/18	K, ATP	1 h		10 h
7	41/M	C4	6	Yes	Yes	40/36	41/17	45/22	46/31	46/20	45/23	L, ATP		<1 h	8 h
8	76/M	T1–T2	72	Yes	Yes	76/33	80/88	75/18	92/40	100/100	90/25	K, ATP	4 h		72 h
9	74/M	T5–T6	7	Yes	Yes	50/0	40/45	50/10	75/20	71/68	78/15	K, ATP	48 h		48 h
10	74/M	T10–T12	47	Yes	Yes	60/48	55/60	50/52	75/60	73/70	72/52				
11	64/F	L2	52	Yes	Yes	45/17	42/19	30/13	62/29	55/30	52/18	K, L, ATP	<1 h	1 h	3 h
12	65/M	L4–L5	4	Yes	No	75/70	68/72	68/64							

ATP, adenosine 5′-triphosphate; PHN, postherpetic neuralgia; VAS, visual analog scale; P, placebo; K, ketamine; L, lidocaine; V, trigeminal nerve; C, cervical spinal nerve; T, thoracic spinal nerve; L, lumbar spinal nerve

to lidocaine responded to ATP (2/6 vs 4/6, $P > 0.05$). Ketamine responders more often responded to ATP than did lidocaine responders (5/5 vs 2/6, $P < 0.05$) (Table 1).

During ATP infusion, the VAS score for spontaneous pain decreased slowly but progressively in six ATP responders (Fig. 1), although it did not decrease in six nonresponders (Table 1). The pain relief in the six responders lasted for 9 (median) h (range, 3–72 h) after stopping ATP (Table 1). In contrast, only two ketamine responders and one lidocaine-responder experienced such prolonged pain relief lasting for hours or more (Table 1).

Discussion

In the treatment of neuropathic pain with intravenous ADO, the infusion rates of 50–70 $\mu g \cdot kg^{-1} \cdot min^{-1}$ have been advocated because ADO at a dose of more than 70 $\mu g \cdot kg^{-1} \cdot min^{-1}$ causes chest pain/discomfort through direct activation/sensitization of the peripheral nociceptive afferents [5–9]. Because ATP has a molecular weight 1.5 times greater than that of ADO, ADO at 50–70 $\mu g \cdot kg^{-1} \cdot min^{-1}$ would correspond to ATP at 75–105 $\mu g \cdot kg^{-1} \cdot min^{-1}$. We, therefore, decided to infuse ATP at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Reportedly, ATP infusion at doses of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or more has been safely used for clinical indications other than the pain treatment [10], although some patients may experience chest pain at these higher doses [14]. In the current study, ATP at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ caused chest discomfort in some patients without noticeable ECG changes, which disappeared within a few minutes of a dose reduction, exactly reflecting the extremely short plasma half-life of ATP and ADO in the blood (less than seconds) [10,15]. The ATP infusion over 120 min thus could be completed in all participants with maintenance infusion rates of 60–100 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

In our study, responses to three drugs were nonhomogeneous, and only about half of the patients responded to each of the drugs. When responses to different drugs were compared, response to ATP was significantly correlated with response to ketamine, but not with that to lidocaine. Both peripheral and central pathophysiological mechanisms contribute to PHN, and the relative contributions of peripheral and central mechanisms to development of PHN differ among subjects [2,3]. The *N*-methyl-D-aspartate (NMDA) receptor mechanisms are involved in the development of sensitization, windup, expansion of receptive fields, and neuroplastic changes in the central nervous system, and ketamine may reduce neuropathic pain via an antagonistic action on the NMDA receptor [2,4]. Lidocaine also may reduce some neuropathic pain through sup-

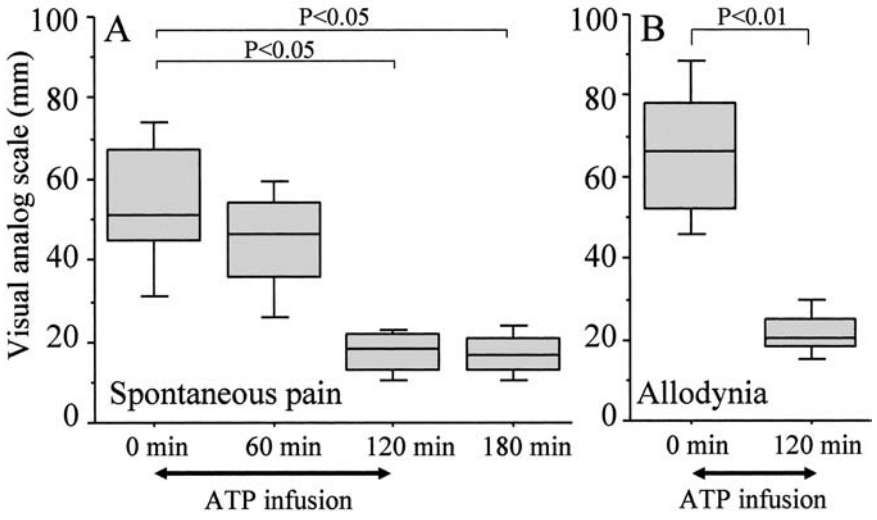

Fig. 1. Change in the visual analog scale for spontaneous pain (**A**) and tactile allodynia (**B**) during and after adenosine 5′-triphosphate (*ATP*) infusion in six ATP responders. Data are presented as median (*bars*), 25 and 75 percentiles (*boxes*), and 10 and 90 percentiles (*whiskers*)

pression of spontaneous ectopic firing of damaged peripheral nerves [2,4]. Ketamine and lidocaine thus may alleviate neuropathic pain originating by distinctive pathophysiological mechanisms. The results of the present study indicate that ATP is more effective in relieving ketamine-responsive PHN than lidocaine-responsive PHN.

Reportedly, ADO can alleviate neuropathic pain mainly by suppressing hyperexcitability of pain-transmitting neurons in the spinal cord [16], primarily through postsynaptic hyperpolarization of transmission neurons and secondarily through presynaptic inhibition of the release of neurotransmitters [17]. Because ATP is extremely rapidly converted to ADO in the blood [10], intravenously administrated ATP also may exert pain-relieving effects by acting centrally as ADO on the adenosine A1 receptors to suppress central hyperexcitability.

In our previous [12] and current reports, analgesic and antiallodynic effects of ATP seems to be slowly developing and long-lasting despite the extremely short plasma half-life of both ATP and ADO [10,15]. Such slow onset–offset profiles of analgesic effects of intravenous infusion of ADO have been shown also in an animal nociceptive pain model [18]. These results may provide clinically important suggestions that a longer-period infusion protocol (e.g., 2–3 h) [12], compared to a shorter-period infusion protocol (e.g., 1 h) [5–9], may provide better analgesia.

Ketamine has been used for treatment of neuropathic pain [2,4,19]. However, widespread clinical use of ketamine is hampered by its frequent side effects such as somnolence, nausea, and dizziness [4,20]. Compared to ketamine, ATP may be more feasible for clinical use because of its much less annoying side-effect profiles and its longer-lasting pain-relieving effects. Furthermore, pain relief lasting for months may occasionally be achieved with a single ATP infusion therapy [12], similarly to ADO or its analog [8,9,16,21]. ATP thus may deserve a trial in patients with devastating neuropathic pain refractory to other treatment modalities. Because ATP may not be effective in all patients, drug tests with lidocaine and especially with ketamine before the ATP trial may be helpful not only to differentiate pathophysiological mechanisms of the pain but also to predict the effectiveness of ATP.

In conclusion, intravenous infusion of ATP exerted slowly developing and long-lasting analgesic and antiallodynic effects in a substantial number of patients with intractable PHN. ATP was much more likely to reduce ketamine-responsive PHN pain than lidocaine-responsive PHN pain.

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