J Anesth (2004) 18:36–38
DOI 10.1007/s00540-003-0212-6

Journal of
Anesthesia

Clinical reports

Intravenous infusion of adenosine 5′-triphosphate alleviated a disabling postherpetic neuralgia

Masakazu Hayashida[1], Kanako Sato[1], Atsuo Fukunaga[2], Ken-ichi Fukuda[3], Hiroshi Sekiyama[1], Shigehito Sawamura[1], Hideko Arita[1], and Kazuo Hanaoka[1]

[1]Department of Anesthesiology and Pain Relief Center, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[2]Department of Anesthesiology, Harbor-UCLA Medical Center, Torrance, CA, USA
[3]Department of Dental Anesthesiology, Tokyo Dental College Suidobashi Hospital, Tokyo, Japan

Key words Adenosine · Adenosine triphosphate · Neuropathic pain · Postherpetic neuralgia

Introduction

Intravenous infusion of adenosine (ADO) at a high rate has been reported to exert algogenic effects via the peripheral activation/sensitization of nociceptive afferents [1]. On the other hand, ADO infused at a low rate exerts long-lasting antinociceptive effects via central mechanisms of action [1]. Such pain-relieving effects of ADO have been clinically applied, successfully, for the treatment of inflammatory, perioperative, and neuropathic pain [1–6]. Adenosine 5′-triphosphate (ATP), a phosphorylated adenosine, has been used intravenously for various clinical indications [7,8], but it has not been used for the treatment of pain, probably because of its algogenic rather than analgesic property [9,10].

When ATP is infused intravenously, however, it is rapidly broken down into ADO by ectoenzymes [7,11] and may act as ADO at effector sites in the central nervous system. Thus, we hypothesized that ATP would act in a similar fashion to ADO after intravenous infusion. Here, we report a case of successful treatment of neuropathic pain with intravenous ATP, which resulted in the complete alleviation of intractable and disabling neuralgia.

Case report

A 74-year-old woman (weight, 50 kg) had been suffering from herpes zoster infection and inflammatory pain on the lateral site of the right leg as well as the dorsal and plantar sites of the right foot. The patient was initially treated at a dermatology clinic with oral valaciclovir (an antiviral agent) and diclofenac (an anti-inflammatory agent), and subsequently, with diclofenac alone for several weeks. Within a month of its onset, the pain in the leg and the dorsum of the foot subsided concomitantly with the skin rash healing. However, severe pain in the plantar site of the foot persisted.

Three months after the initial onset, the patient presented at our pain clinic, in a wheelchair, because of intractable pain with severe tactile allodynia on the sole and on the heel of the right foot, which was so severe that it prevented her from walking normally. Resting spontaneous pain was moderate, being rated at 50 mm/100 mm on the visual analog scale (VAS). However, marked tactile allodynia was observed on the right heel, which was rated at 91/100 mm. Because of the severe touch-evoked allodynia, she could not stand on the right foot, nor could she wear a sock or shoe on the right foot. She could hardly walk, limping and relying mostly on the left foot, stepping on the right tiptoe, and she wore beach sandals. She was treated initially with oral amitriptyline and repeated (caudal) epidural blocks, which resulted in only a slight improvement in her pain status.

Five months after the onset of pain, she was admitted to our hospital to study the mechanisms underlying her pain condition, and to seek potentially effective therapeutic measures. After obtaining institutional review board approval and written informed consent from the patient, we assessed various intravenous (IV) drugs for analgesic efficacy. Because the severe tactile allodynia was elicited most prominently when she was trying to walk, she was asked to rate her pain using VAS both at rest (for spontaneous pain) and when standing/stepping (for evoked tactile allodynia) before, during, and after administration of each test drug.

Address correspondence to: M. Hayashida
Received: August 28, 2003 / Accepted: November 4, 2003

Drug testing

The following IV drugs was administered on a separate day for each drug; after two bolus injections of normal saline (NS) as a placebo control: morphine (15 mg), lidocaine (100 mg), thiopental (150 mg), phentolamine (15 mg), and ketamine (15 mg), given by bolus injection in three to five divided doses at intervals of 5 min. Neither resting spontaneous pain nor tactile allodynia was affected by morphine, lidocaine, thiopental, or phentolamine. With ketamine, however, both spontaneous pain and tactile allodynia were significantly reduced, from 49 and 76 mm/100 mm before ketamine injection to 26 and 22 mm/100 mm after the injection, respectively, but the pain-relieving effect was short-lived (less than 24 h). Three days after the last test drug, she received a continuous IV infusion of ATP for 3 h (after 1 h of placebo NS infusion). A pharmaceutical formulation of ATP (Adephos L; Kowa, Nagoya, Japan) was IV infused continuously, using a syringe pump. The infusion rate was increased in three steps, from 50 to 75, and to 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at 5-min intervals, under continuous hemodynamic monitoring. The patient reported chest discomfort at the highest dose (100 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Therefore, the infusion rate was decreased back to 75 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The chest symptom disappeared immediately and the infusion rate was kept at 75 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until the end of the 3-h infusion period.

During placebo (NS) infusion for 1 h, neither spontaneous pain nor tactile allodynia was affected. During ATP infusion, all the vital signs, including blood pressure, heart rate, electrocardiogram, and oxygen saturation remained unchanged. However, the intensity of the spontaneous pain gradually declined from 46 prior to ATP infusion to 27, 15, and 0/100 mm at 1, 2, and 3 h, respectively, and the tactile allodynia declined from 78 to 29, 9, and 0/100 mm, respectively. Both the spontaneous pain and the tactile allodynia were completely abolished by the end of 3-h ATP infusion. The patient could stand up and walk without any claudication or support.

She was discharged from hospital without any medication or prescription for further pain control. Subsequently, neither the resting spontaneous pain nor the tactile allodynia has recurred for at least 18 months (observation by telephone conversation). Currently, she even enjoys occasional dancing.

Discussion

Multiple peripheral as well as central mechanisms can contribute to the pathogenesis of neuropathic pain, including postherpetic neuralgia [12], and drug testing has been carried out to clarify the pathophysiological mechanisms underlying such chronic pain [13,14]. Morphine is effective in relieving nociceptive pain by acting on the μ-opioid receptor in the spinal cord and brain [13,15]. Barbiturates, including thiopental, may exert analgesic effects by depressing nociceptive transmission at the spinal level, presumably via γ-amino butyric acid (GABA) receptor activation [16]. Barbiturates may be also useful in differentiating pain of psychological origin from that with a pathological basis [17,18]. An α-adrenoreceptor antagonist, phentolamine, allows for the differentiation of sympathetically maintained pain that may respond to interventional or pharmacological sympathetic blockade [12,19,20]. Lidocaine can inhibit neuronal hyperexcitability of damaged peripheral primary afferents characterized by spontaneous (ectopic) impulses and repetitive firing [12,14,21]. Excitatory amino acids acting on the N-methyl-D-aspartic acid (NMDA) receptor may contribute to central sensitization, and the NMDA receptor antagonist ketamine is often effective in relieving neuropathic pain in which such central mechanisms are involved [12–14,22].

ADO also may allow for the alleviation of neuropathic pain through its neuromodulatory effects, mediated primarily by the spinal adenosine A1 receptor [1,5,6,23,24]. In Japan, not ADO but ATP is available as a pharmaceutical formulation. Intravenous infusion of ATP may exert pain-relieving effects, contrary to its pronounced algogenic effects mediated by the P2X purinoceptors [9,10], because of its extremely rapid conversion to ADO in the blood stream [7,11]. The side-effect profile of ATP infusion appears to be almost identical to that of ADO infusion; ATP infusion at a rate of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [7] and ADO infusion at a rate of more than 70 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [1] both cause chest pain/discomfort in conscious humans. In agreement with the above reports, ATP infusion at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$, but not at 75 $\mu g \cdot kg^{-1} \cdot min^{-1}$ caused chest discomfort in our patient.

In the present patient with severe postherpetic neuralgia, gradual-onset but remarkable and extremely longlasting analgesic as well as antiallodynic effects were observed with ATP; complete abolition of resting pain and tactile allodynia, lasting for over 18 months, was achieved after a single treatment with ATP. In previous studies, analgesic and/or antiallodynic effects of ADO or its analog lasting for months have been reported in some, albeit not all, patients with neuropathic pain, though the mechanisms underlying such longlasting effects have not been elucidated [5,6,23]. Our patient had suffered not only from spontaneous pain but also from pronounced tactile allodynia, and both the pain and the allodynia had been transiently but effectively reduced with ketamine. These observations suggest that central mechanisms might have primarily contributed to her postherpetic neuralgic pain [12–14,22]. Although the mechanisms underlying ATP's

extremely longlasting analgesic action are not clearly understood, intravenous ATP may have acted, at least in part, as ADO on the central adenosine A1 receptor to modulate and affect the pathophysiological changes responsible for neuropathic pain [1,5,6,23,24]. Furthermore, although ATP facilitates pain transmission by activating the P2X purinoceptor [9,10], a recent report suggests that the P2Y purinoceptor (another ATP receptor subtype) activation results in both analgesic and antiallodynic effects in an animal model of neuropathic pain [25]. Moreover, in human peripheral nerves, ATP activates both adenosine receptors and P2Y, but not P2X, purinoceptors [26]. These observations highlight the possibility that ATP itself may exert antinociceptive effects in humans.

In a patient with severe postherpetic neuralgia, a single session of ATP infusion therapy exerted a remarkable and longlasting analgesic as well as antiallodynic effect. The results suggest that a low-dose ATP infusion may provide safe and effective analgesia in some intractable neuropathic pain conditions, including some postherpetic neuralgias.

References

1. 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
2. Sjolund K, Segerdahl M, Sollevi A (1999) Adenosine reduces secondary hyperalgesia in two human models of cutaneous inflammatory pain. Anesth Analg 88:605–610
3. 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
4. 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
5. Sjolund 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
6. 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
7. 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
8. Agteresch HJ, Dagnelie PC, van den Berg JW, Wilson JH (1999) Adenosine triphosphate: established and potential clinical applications. Drugs 58:211–232
9. Chizh BA, Illes P (2001) P2X receptors and nociception. Pharmacol Rev 53:553–568
10. Tsuda M, Koizumi S, Inoue K (2001) Role of endogenous ATP at the incision area in a rat model of postoperative pain. Neuroreport 12:1701–1704
11. Shapiro MJ, Jellinek M, Pyrros D, Sundine M, Baue AE (1992) Clearance and maintenance of blood nucleotide levels with adenosine triphosphate-magnesium chloride injection. Circ Shock 36:62–67
12. Fields HL, Rowbotham M, Baron R (1998) Postherpetic neuralgia: irritable nociceptors and deafferentiation. Neurobiol Dis 5:209–227
13. Eide PK, Jorum E, Stubhaug A, Bremnes J, Breivik H (1994) Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. Pain 58:347–354
14. Kvarnstrom A, Karlsten R, Quiding H, Emanuelsson BM, Gordth T (2003) The effectiveness of intravenous ketamine and lidocaine on peripheral neuropathic pain. Acta Anaesthesiol Scand 47:868–877
15. Minami M, Satoh M (1995) Molecular biology of the opioid receptors: structures, functions and distributions. Neurosci Res 23:121–145
16. Sudo M, Sudo S, Chen XG, Piercy M, Carstens E, Antognini JF (2001) Thopental directly depresses lumbar dorsal horn neuronal responses to noxious mechanical stimulation in goats. Acta Anaesthesiol Scand 45:823–829
17. Thomas D, Aidinis S (1989) Objective documentation of musculoskeltal pain syndrome by pressure algometry during thiopentone sodium (Pentothal) anesthesia. Clin J Pain 5:343–350
18. Cornell MS, Ahktar T, Slater RN, Walker CJ (1996) The pentothal test in the management of orthopaedic patients with hysterical illness. J R Soc Med 89:37P–38P
19. Raja SN, Treede RD, Davis KD, Campbell JN (1991) Systemic alpha-adrenergic blockade with phentolamine: a diagnostic test for sympathetically maintained pain. Anesthesiology 74:691–698
20. Arner S (1991) Intravenous phentolamine test: diagnostic and prognostic use in reflex sympathetic dystrophy. Pain 46:17–22
21. Strichartz GR, Zhou Z, Sinnott C, Khodorova A (2002) Thrapeutic concentrations of local anaesthetics unveil the potential role of sodium channels in neuropathic pain. Novartis Found Symp 241:189–201
22. Dickenson AH, Chapman V, Green GM (1997) The pharmacology of excitatory and inhibitory amino acid-mediated events in the transmission and modulation of pain in the spinal cord. Gen Pharmac 28:633–638
23. Karlsten R, Gordh, Jr. T (1995) An A1-selective adenosine agonist abolishes allodynia elicited by vibration and touch after intrathecal injection. Anesth Analg 80:844–847
24. Sawynok J, Liu XJ (2003) Adenosine in the spinal cord and periphery: release and regulation of pain. Prog Neurobiol 69: 313–340
25. 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
26. Lang PM, Tracey DJ, Irnich D, Sippel W, Grafe P (2002) Activation of adenosine and P2Y receptors by ATP in human peripheral nerve. Naunyn Schmiedebergs Arch Pharmacol 366:449–457