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Analgesic Effect of a Single Dose of Adenosine for Neuropathic Pain Reduction in a Patient with Primitive Neuroechtodermal Tumor

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Abstract

Background: We report the analgesic efficacy of lumbar epidural adenosine injection in reducing the chronic neuropathic pain in a patient with primitive neuroectodermal tumor.

Report of the Case: In this case report a 13-year-old male with primary neuroectodermal tumor (PNET) was administered in epidural space with adenosine to reduce his pain. The patient received 10ml of 0.25% ropivacaine and 2mg adenosine in the epidural space using the L4-L5 interspinous approach. The neuropathic characteristics were assessed using Douleur Neuropathic 4 (DN4) neuropathic pain diagnostic questionnaire. We also evaluated the pain intensity using the visual analogue scale (VAS). The sedation score, patient's satisfaction, nausea and vomiting and the use of additional analgesia at 1, 3, 7, 15 and 21 days after the procedure were recorded.

Result: The DN4 neuropathic questionnaire and VAS pain intensity scores before intervention were 8/10 and 9/10 respectively. After 3 and 7 days, they both decreased to 3/10. Level of sedation as well as nausea and vomiting were satisfactory. Conclusion: The bolus epidural administration of adenosine might improve the cancer related chronic neuropathic pain.

Keywords: Adenosine, primitive neuroectodermal tumor, cancer, pain.

Introduction

Adenosine analogs show analgesic properties in nociceptive models and have been reported to alleviate manifestations of neuropathic pain in nerve injury models in rodents [1]. In humans, previous work indicates an analgesic effect for adenosine administered intravenously in postoperative and neuropathic pain [1]. Adenosine is an endogenous purine nucleoside that modulates many physiological processes. Cellular signaling by adenosine occurs through four known adenosine receptor subtypes (A_1, A_{2A}, A_{2B}, and A_3) [2]. Adenosine is believed to be an anti-inflammatory agent at the A_{2A} receptor [3,4]. Adenosine receptors of the A_1 subtype are associated with a modulatory effect on pain transmission at spinal cord level[5]. The endogenous compound adenosine has various modulatory effects in the peripheral and central nervous system, mediated through specific cell-surface associated receptors [5]. Loram et al., showed that a single intrathecal injection of adenosine A_2 receptor agonists has a therapeutic effect in treatment of neuropathic pain by increasing IL-10 in the immunocompetent cells of the CNS [6]. A_1 agonists are clinical candidates to treat atrial arrhythmias, angina, type 2 diabetes and also chronic pain [7]. Gong et al., showed that N6-cyclopentyladenosine (CPA) is a selective adenosine A_1 receptor agonist and this compound in rats with neuropathic pain induced by spinal nerve ligation could reduce thermal hyperalgesia and mechanical allodynia, which could last 6 hours and 10 hours, respectively [8]. Spinal application of CPA also depresses long-term potentiation (LTP) of A- and C-fiber evoked field potentials; mechanisms thought to play an important role in neuropathic pain 8. Activation of A(2A) receptors thus may be a novel, therapeutic approach for the treatment of neuropathic pain by increasing IL-10 in the immunocompetent cells of the CNS 9. Some studies have indicated that there are reduced

levels of blood and CSF adenosine in patients with neuropathic pain. This adenosine deficiency could explain the potential therapeutic effects of administering adenosine or its analogs [10]. As we know, neuropathic pain is a heterogeneous entity that can be produced by multiple etiologies[11]. In the setting of malignancy, neuropathic pain can be generated by nerve compression, deafferentation, nerve injury, and sympathetically induced pain [12,13]. Stute et al., found nerve compression to be the most common cause of neuropathic pain in cancer patients (79%), followed by nerve injury (16%) and sympathetically mediated pain (5%) [14].

Epidural or intrathecal administrations of analgesics directly target the receptors or pain transmission pathways in the spinal cord. The use of these techniques is mainly proposed in situations were oral or transdermal analgesics have insufficient effect or produce unacceptable side effects. Central administration of the analgesics is then expected to increase the analgesic effect and reduce the risk of side effects. In addition, this administration route allows simultaneous administration of other analgesics, such as ropivacaine and clonidine [15].

In the present case we report the analgesic efficacy of lumbar epidural adenosine injection in reducing the chronic neuropathic pain in a patient with primitive neuroectodermal tumor.

Report of the Case

Patient was a 13 years old male who was referred to our pain clinic by respected oncologist. His chief complaint was leg pain (VAS= 9/10), and DN4 score of 8/10 in the dermatomes of L4, L5 and S1 and claudication for more than 3 months, which usually resolved using conservative therapy by oral and PCIA routes. His family history indicated that he is the first child delivered by cesarean section and his past medical history was unremarkable. The physical exam showed a 55*60*30mm mass in the right pelvic area, bone marrow aspiration and lung CT scan with and without contrast were normal. MRI of the pelvic and abdomen regions reported an destructive lesion within sacrum involving S2 to S3 particularly on the right side, intermediate signal intensity on T1W1, destruction of anterior and posterior sacral cortex particularly at S2 level with presacral and intraspinal extension of the lesion, involvement of the right sacral neural foramina and encasement of exiting nerve root by the mass. Brain CT scan was normal and biopsy reported monotonous small round cells with scant cytoplasm and high N/C ratio, occasionally forming rosette-like structures and fibrillary background. The final diagnosis was small round cell tumor. Immunohistochemistry reported; negative NSE, negative Desmin, negative LCA, positive CD99 and was compatible with Primitive Neuroectodermal Tumor (PNET). A primary lumbar epidural corticoste¬roid and local anesthetic injection relieved pain for only four days.

Assessment

After informing the patient's parents about the experimental nature of the study and receiving an informed consent, the patient entered the study. In addition to epidural injection of adenosine, other methods of analgesia were also used for the patient.

The patient was asked to indicate all painful areas on a pain drawing. The pain intensity (10-point VAS) and the Douleur Neuropathic 4 questionnaire (DN4) were used to access the pain intensity. The contraindications of treatment namely second- or third-degree heart block (without a pacemaker), sick sinus syndrome (without a pacemaker), long QT syndrome, severe hypotension, decompensated heart failure asthma, poison/ drug-induced tachycardia, cauda equina syndrome, anticoagulation, coagulopathy, and suspected local or systemic infection and hypovolemia were ruled out.

Intervention

The procedure was performed in prone position; with a pillow under the abdomen for reducing the lumbar lordosis. Cardiorespiratory monitoring was performed. To access the L4-L5 epidural space AP and lateral views of fluoroscopic guidance and loss of resistance technique were used and after confirmation of correct position of the tip of the needle (18 G Tuohy epidural needle), 2ml of non-ionic water-soluble contrast media (VISIPAQUE 270) was injected slowly and the double line pattern in the lateral view and typical epidurographic pattern in the AP view were observed. After negative aspiration for CSF or blood, patient received 10ml of 0.25% ropivacaine and 2mg adenosine (Gland pharma. INC.) in the epidural space using the L4-L5 midline interspinous approach. After needle

removal, the patient was asked whether any change in pain perception has occurred and was closely observed for any complications. The procedure was done without any early or late technical and pharmacological side effects. The patient's pain was assessed with a visual analogue scale and DN4 neuropathic pain diagnostic questionnaire at time intervals of 1, 2, 3, 5, 7, 10 and 14 days after the procedure.

Results

The DN4 neuropathic questionnaire and VAS pain intensity scores before intervention were 8/10 and 9/10 respectively. After 3 and 7 days, they both decreased to 3/10. Level of sedation as well as nausea and vomiting were satisfactory (Tables 1 and 2).

Discussion

The use of adenosine, by intravenous and intrathecal routes, is known to alleviate various types of pain [16]. However, the role of epidural injection of adenosine in providing chronic neuropathic pain due to cancer has not been confirmed.

Some observations indicate that adenosine mediates the effects of acupuncture and that

Table 1: The evaluation of pain score before and after intervention.

After intervention →				
Days	VAS[1]	DN4[2]	Satisfaction[3]	Nausea & vomiting[4]
1 after	4	4	3	1
2 after	4	3	3	1
3 after	3	3	3	2
5 after	3	3	3	1
7 after	4	3	3	1
10 after	5	4	3	2
14 after	6	6	4	1

1. Pain intensity (10 point VAS) visual analogue scale.
2. Neuropathic Pain Diagnostic Questionnaire (DN4).
3. No=1: excellent, No=2: good, No=3: moderate, No=4: weak, No=5: dissatisfied.
4. No=1: without N& V, No=2: N&V No need for drugs, No=3: N&V need for drugs, No=4: N&V unresponsive to drugs

Table 2: Treatments before and after intervention.

Before intervention	**After intervention**
▪ Fentanyl 2.5 micro/kg/h: 1800 micro/ day(3amp+6ml).	▪ Fentanyl 1micro/kg/h: 720micro(1amp+ 4.5 ml).
▪ Apotel 30mg/kg/day : 450mg/day.	▪ Apotel 30mg/kg/day 2days: 15mg/kg/ day, 2days.
▪ Gabapentin 200 mg /Qhs.	▪ Then 325 (1/2 tab, qid, PO)
▪ Duloxetine (cymbalta)30 mg/day.	▪ Gabapentin 200mg/Qhs.
▪ 25mg PRN, bolus pethidine; 2-4 times a day (without consulting a pain specialist).	▪ Duloxetine (Cymbalta) 30 mg/day.
	▪ pethidine D/C.

interfering with adenosine metabolism may prolong the clinical benefit of acupuncture [17]. Ohtani et al., showed that, epidural adenosine facilitated analgesic effects of neostigmine and improved the postoperative pain status and co-administration of epidural neostigmine and adenosine could be a useful treatment modality to alleviate postoperative pain [18].The antinociceptive actions of adenosine and adenosine analogs in animal models have been known for more than 10 years. Adenosine receptors of the A_1-subtype are associated with a modulatory effect on pain transmission at spinal cord level. Consequently, there is substantial evidence that adenosine can modulate nociceptive input. On the other hand, clinical studies have revealed that adenosine administration by bolus injection or by infusion at doses above 70 micrograms per kg per minute is associated with pain symptoms from different parts of the body [5]. This algogenic effect of higher doses of adenosine is probably related to sensitization/activation of peripheral nociceptive afferents [5].

Gomes et al, showed the usefulness of intrathecal adenosine alone or with clonidine in treatment of chronic pain states that include a component of mechanical hypersensitivity and suggested that, after nerve injury, adenosine acts to reduce hypersensitivity through the release of spinal norepinephrine [19]. In 1995, Belfrage et al. demonstrated that adenosine infusion alleviates spontaneous neuropathic pain, tactile allodynia, and pinprick hyperalgesia in patients with peripheral neuropathic disorders, probably by a central mechanism of action [20]. In another study for evaluation of efficacy and side effects of intrathecal (IT) adenosine administration in 14 patients was performed by Belfrage et al., and they concluded that IT adenosine may reduce various aspects of chronic neuropathic pain. A subset of patients reported transient low back pain as the only side effect. Spontaneous and evoked pain intensity decreased in most patients, an effect lasting for a median of 24 hours [21].

Our preliminary encouraging data call for further controlled studies of the potentially relieving effect of adenosine in painful neuropathic conditions.

Conclusion

The bolus epidural administration of adenosine might improve the cancer related chronic neuropathic pain.

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