Palliative Care Rounds

An Unusual Case of Chronic Neuropathic Pain Responds to an Optimum Frequency of Intravenous Ketamine Infusions

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Abstract

The effective treatment of patients suffering from a variety of difficult pain syndromes, including phantom pain and other neuropathic pains, remains a clinical challenge. Neuropathic pain has been shown to respond to drugs that block the N-methyl-D-aspartate (NMDA) receptor, such as ketamine and amantidine. A 44-year-old woman with a previous right-sided forequarter amputation presented to the Palliative Medicine Team complaining of neuropathic pain in her left arm, which was neurologically intact. The pain was treated with repeated infusions of intravenous ketamine. Twenty-one infusions were given over a period of four months. The pain intensity experienced by the patient lessened as the frequency of the ketamine infusions increased. This finding has not been described previously and supports the theory that there may be an optimum frequency of ketamine infusions to achieve adequate pain control.

Key Words
NMDA-receptor antagonist, ketamine, chronic pain, phantom pain

Introduction

The effective treatment of patients suffering from a variety of difficult pain syndromes, including phantom limb pain and other types of neuropathic pain, remains a clinical challenge. Neuropathic pains, like phantom limb pain, can be poorly responsive to opioid analgesia.1 Patients will, therefore, not always be completely relieved by a standard pharmacological approach such as the stepwise escalation of the World Health Organization analgesic ladder.2

Neuropathic pain syndromes can include the clinical components of allodynia, hyperalgesia, and hyperpathia. Evidence from the basic sciences suggests that hyperalgesia and allodynia following peripheral nerve damage is due not only to an increased sensitivity of peripheral nociceptors in the affected area, but also to N-methyl-D-aspartate (NMDA) receptor mediated changes in synaptic excitability in the dorsal horn of the spinal cord.3–5

Phantom limb pain, and other types of neuropathic pain, have been shown to respond to drugs which block the NMDA receptor, such as ketamine and amantidine.6,7 We describe a patient suffering from prolonged phantom limb pain, who developed neuropathic pain in the contralateral uninjured limb. Frequent infusions of intravenous ketamine were required to achieve and maintain a reasonable level of pain control.
Case Report

A 44-year-old woman was referred to the Palliative Medicine Team for pain control in June 1998. Two and a half years prior to this, she had undergone a right-sided forequarter amputation for fibrohistiocytoma. She had suffered severe phantom pain on the right side immediately postoperatively, for which she was prescribed immediate release morphine 10 mg every 4 hours. This had little effect and was discontinued 3 weeks postoperatively. The phantom pain was predominantly felt in the patient’s missing right hand.

Within a few weeks of the amputation, she developed pain in her left upper arm. Initially her left elbow was injected with steroids and then she underwent a left carpal tunnel decompression. Neither of these interventions had any effect on the pain.

The pain continued to increase in the left arm until her referral to the palliative medicine team 30 months after her original operation. At that time, the pain radiated from her axilla to her forearm, and she described the pain as excruciating. In contrast, the phantom pain on the right side was gradually lessening, and the predominant feeling on referral was of persistent ‘tightness’. An MRI scan of the entire spine was performed to try to account for the persistent and severe left arm pain. There was no sign of disease recurrence and the MRI was reported as entirely normal. Electrodiagnostic studies were not performed.

On examination at referral, she was found to have generalized allodynia and hyperalgesia throughout her left arm, in the distribution of all the cervical nerve roots and T1 dermatome. The hyperalgesia was accompanied by hyperpathia. The pain was provoked by normal use of her left arm. On referral, her only analgesic medication was a combination product containing dextropropoxyphene 32.5 mg and paracetamol 325 mg, 2 tablets as required. She took these infrequently for severe pain.

There was no clinical or radiological evidence of recurrence to account for the clinical changes in the left arm. It was therefore felt that severe and prolonged right-sided phantom limb pain had initiated sensitization and ‘wind-up’, which had resulted in neuropathic pain being experienced following normal use of the left arm. At referral, she complained of phantom sensations but no longer had phantom pain on her right side. The severe neuropathic pain she complained of and was subsequently treated for, was in her neurologically intact left arm.

The patient could not tolerate codeine, and was very resistant to starting morphine. She was therefore commenced on regular dextropropoxyphene/paracetamol 2 tablets four times daily and amitriptyline 25 mg at night. This had very little impact on her pain, and a trial of the NMDA receptor antagonist ketamine was commenced. A continuous subcutaneous infusion was started at a dose of 200mg/24 hours. The pain responded very well to the ketamine infusion, but the infusion has to be discontinued after one week because of the problems with sterile abscesses at the syringe driver sites. Oral ketamine 40 mg twice daily was then tried, but was not particularly effective.

One month after discontinuing the subcutaneous ketamine, the patient was again complaining of excruciating pain in her left arm. The phantom pain on her right side was also escalating. She was therefore given intravenous ketamine, 30 mg in 500 ml saline over 4 hours (Figure 1, infusion 1). The analgesic medication was changed to morphine 10 mg every 4 hours. The patient had five days of complete pain relief before the left-sided upper arm pain returned. When the pain did return, it was severe and did not respond to morphine 10 mg orally.

Two weeks after the initial intravenous infusion of ketamine, the infusion was repeated at an identical dose. The analgesic medication was changed from 4 hourly morphine to 4 hourly hydromorphone 1.3 mg with the same dose for breakthrough pain, as the patient was very reluctant to remain on morphine. Good analgesia was again obtained but only for 3 days. When the pain returned, it was again very severe and not opioid responsive. A third infusion, this time of 50 mg of intravenous ketamine in 500 ml saline was given four weeks after the initial dose (Figure 1, infusion 3). Good analgesia was obtained for only 2 days, and when the pain returned it was severe and not responsive to hydromorphone.

It was, therefore, decided to increase the frequency with which the ketamine was being administered. The frequency was increased firstly to weekly infusions (Figure 1, infusions 4, 5), but these did not result in any pain-free peri-
ods at all. The frequency was then increased to three infusions per week (Figure 1, infusions 6–11). The dose of ketamine administered was increased to 60 mg in 500 ml saline over 3 hours. The dose of hydromorphone was also increased to 2.6 mg every 4 hours, with 2.6 mg for breakthrough analgesia.

The patient’s analgesia improved markedly with the increase in frequency of the ketamine infusions (Figure 1, infusions 6–11). When the pain did return it was of lesser severity than previously, and was more responsive to hydromorphone 1.3 mg.

After two weeks of 3 weekly infusions, the frequency of infusions was reduced to twice a week. The dose of ketamine was also reduced to 40 mg as the patient had become transiently hypertensive towards the end of infusion no. 11. Three further infusions were given over 10 days, with good effect (Figure 1, infusions 12–14). The patient was either pain-free or had only mild pain which responded to hydromorphone.

The frequency of infusion was then reduced to weekly (Figure 1, infusion 15). The patient obtained 10 completely pain-free days, but following the second weekly infusion (Figure 1, infusion 16), the pain returned again. It was rated as very severe, and did not respond to hydromorphone, or a further infusion of ketamine (Figure 1, infusion 17). The frequency of infusion was increased again (Figure 1, infusions 18, 19) with good effect—the patient became pain-free, and opioid responsiveness returned.

Since then the patient has been receiving weekly infusions of intravenous ketamine, with recurrence of pain approximately 24–48 hours prior to the next infusion. When the pain returns, it does not respond to breakthrough doses of hydromorphone.

**Discussion**

This case report presents two interesting points. First, the apparent initiation of neuropathic pain in a neurologically intact limb following severe prolonged phantom pain on the contralateral side is a highly unusual occurrence.

Second, for this patient there appeared to be an optimum frequency for the administration of intravenous ketamine infusions to maintain adequate analgesia.

Following amputation, phantom and stump pain is a common, almost universal experience. Although for some patients, phantom pain decreases with time, for others this is not the case and the pain remains static over a considerable period of time.\(^8\)

Hyperexcitability of the NMDA receptors
has been postulated as one of the factors in the maintenance of ongoing phantom limb pain and the NMDA receptor antagonist ketamine has been used effectively to treat phantom limb pain. There is increasing evidence in the literature of the efficacy of NMDA receptor antagonists to treat a variety of neuropathic pain conditions, including post herpetic neuralgia, painful diabetic neuropathy and cancer pain, as well as phantom limb pain. Studies using animal models have shown that NMDA receptor antagonists can delay and even block the development of hyperalgesia and allodynia following peripheral nerve injury.

There is evidence from the literature that the NMDA receptor is likely to be involved in the maintenance of post-amputation pain. This may have initially been the case in this patient in whom postoperative phantom limb pain seems to have led to central sensitization, which in turn appears to have led to normal use of the intact arm being perceived as painful. The neuropathic nature of the left arm pain was suggested by the triad of allodynia, hyperpathia, and hyperalgesia.

The mechanisms by which this unusual situation arose can only be speculated upon, as the nerve supply to the intact arm was anatomically normal and not disrupted.

For this patient, there appeared to be an optimum frequency of administration of intravenous ketamine in order to obtain both good analgesia and reasonable opioid responsiveness. Presumably 30 months of poorly controlled pain had given rise to a state of chronic central hypersensitivity which required frequent regular administration of the NMDA antagonist ketamine to control. Weekly infusions appear to give reasonable pain control in this patient, but experience with other patients suggests that the optimum frequency of infusion is very variable.

In summary, this case presents two fascinating points. First, the patient underwent apparent initiation of neuropathic pain in a neurologically intact limb following prolonged phantom pain on the contralateral side. Second, there appeared to be an optimum frequency of administration of intravenous ketamine to achieve adequate analgesia and opioid responsiveness.

References
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