Clinical Note

Long-Term Ketamine Subcutaneous Continuous Infusion in Neuropathic Cancer Pain

Sebastiano Mercadante, MD, Franco Lodi, MD, Monica Sapio, MD, Marina Calligara, MD, and Roberto Serretta, MD

Department of Anesthesia and Intensive Care (S.M., M.S., R.S.), Buccheri La Ferla Hospital, Fatebenefratelli, Palermo; Pain Relief and Palliative Care Unit (S.M.), SAMOT, Palermo; and Department of Toxicology (F.L., M.C.), Forensic Medicine, University of Milan, Milan, Italy

Abstract

Neuropathic cancer pain may be less responsive to opioids than other pain. Several studies suggest that N-methyl-D-aspartate (NMDA)-receptor antagonists could play a role in the treatment of neuropathic pain. Ketamine is an NMDA-receptor antagonist that is used as an anesthetic and has been suggested as a useful drug for neuropathic pain. Subanesthetic doses of ketamine can yield analgesia without hypnosis. We describe a patient who developed neuropathic cancer pain unresponsive to opioid escalation and spinal administration of a combination of bupivacaine-morphine and was subsequently treated by subcutaneous continuous ketamine infusion. A starting dose of 150 mg/day provided good pain relief and a dramatic reduction of the oral morphine dose (from 5 g to 200 mg). A slow and progressive increase of ketamine and morphine dosage (400 mg and 200 mg by the subcutaneous route, respectively) continued to provide adequate pain relief after 13 months of therapy despite signs of progressive disease. J Pain Symptom Manage *1995;10:564–568.*

Key Words

Ketamine, opioids, bupivacaine, neuropathic cancer pain, opioid unresponsiveness, subcutaneous route, spinal route

Introduction

Cancer pain that is inferred to have neuropathic mechanism can be clinically challenging. Although pain mechanism should not be used as a criterion to determine opioid responsiveness,[1,2] and neuropathic pain does not show any particular disadvantage in the overall prognosis of the pain,[3] some patients with neuropathic pain are extremely difficult to manage.[4]

Ketamine, an N-methyl-D-aspartate (NMDA)-receptor noncompetitive antagonist, may be an alternative solution for the treatment of neuropathic pain unresponsive to opioid escalation. Ketamine has been recognized for many years as an anesthetic.[5] Subanesthetic doses can yield analgesia without hypnosis.[6] Recent reports have described pro-

Address reprint requests to: Dr. Sebastiano Mercadante, Pain Relief and Palliative Care, SAMOT, via Liberta 191, 90125, Palermo, Italy.

Accepted for publication: January 13, 1995.

0885-3924/95/$9.50
SSDI 0885-3924(95)00102-5

longed analgesic effects from ketamine in patients with neuropathic pain[5,7,8] We now report the first case in which a long-term subcutaneous infusion of ketamine was used in the home setting to manage advanced cancer pain that was not responsive to either oral morphine or combined morphine-bupivacaine spinal infusion.

Patient History

A 67-year-old man presented with a 3-month history of bilateral lumbosacral pain. The pain interfered with his sleep and was described as lancinating, burning, shooting, or aching in character. On physical examination, there was weakness in the right leg, and decreased sensation along the posterior aspect of the right thigh, leg, and foot, with areas of allodynia and paresthesia. Computerized tomography revealed a tumor infiltrating the lumbosacral plexus. The nature of the primary tumor remained unknown. Palliative radiotherapy and buprenorphine administration were unsuccessfull in controlling the pain and oral morphine in escalating doses, diclofenac 75 mg twice daily parenterally, and amitriptyline, from 25 mg to 75 mg a day, were prescribed. A new course of radiotherapy was proposed again, but refused by the patient. Every increase in opioid dosage was associated with adverse effects, such as drowsiness, hallucinations, confusion, nausea, agitation, and episodes of myoclonus. The administration of haloperidol in increasing doses up to 10 mg daily and promazine 100 mg was not helpful. During the following weeks the morphine dosage was gradually increased to 4 g per day without achieving an acceptable balance between pain relief and side effects. The dose would "plateau" (400 mg daily and 2 g daily, respectively) for a few weeks, after which acceptable pain control was lost. Increasing amitriptyline dosage yielded more sedation and confusion, without additional relief.

He was admitted to the outpatient pain clinic for a continuous lumbar spinal infusion of bupivacaine and morphine. A nylon catheter was introduced at L2-3 and advanced into the subarachnoid space. The catheter was tunneled and anchored to the flank. There was free flow of cerebrospinal fluid. A syringe driver was connected to the catheter and morphine 80 mg and bupivacaine15 mg a day were started continuously. A supplemental bolus dose of 1 mg of bupivacaine and 5.3 mg of morphine was also offered "as needed." Oral morphine was reduced to 2 g a day according to a schedule already used for oral–spinal conversion,[9] and he was discharged home.

The patient did not tolerate this treatment. He described an excruciating sensation (like "a vice in the legs") and myoclonus, without reporting any advantage in terms of pain relief. He refused to continue the treatment preferring the previous unfavorable treatment with oral opioids. The catheter was removed and oral morphine was again increased to 5 g daily. The pain was not well controlled. The patient was not able to walk or eat because of pain and the periods of confusion and hallucinations lengthened. Episodes of vomiting appeared. His daughter, a general practitioner, was in a hopeless state, exhausted by her father's poor quality of life.

A subcutaneous "butterfly" cannula was placed in the anterior thoracic wall, and a continuous subcutaneous infusion of ketamine 150 mg a day (2 mg/kg) was given using a portable syringe driver. Excellent pain relief was rapidly achieved, permitting the gradual reduction of the morphine dose to 200 mg daily over the next 2 weeks.

The neurological side effects dramatically decreased. Haloperidol 5 mg a day was mixed with ketamine in the same syringe, yielding good control of vomiting. A sensation of nausea remained. The patient was able to walk, although with some difficulty due to right leg weakness, and began eating again. Karnofsky performance status score was 50–60. The patient continued this treatment for 2 months achieving acceptable pain relief throughout this period. He then required an increase in ketamine dosage to 200 mg/day (about 10 mg/hr). Only rare, minor, self-limited episodes of neurological impairment, including confusion and drowsiness, were evidenced.

After 3 months, the pain relief continued to be acceptable. The patient was receiving subcutaneous ketamine 200 mg daily mixed with haloperidol 5 mg daily, oral morphine 200 mg daily, and oral prednisone 50 mg daily. Ketamine was temporarily discontinued due to inadequate availability, and the symptomatology worsened.

Table 1
Blood Concentrations, Route of Administration, and Dosage of Ketamine (KE) and Morphine After 5 Months (T1), 6 Months and 3 Weeks (T2), and 8 Months (T3)

	T1	T2	T3
KE dose mg	200	240	300
KE route	s.c.	s.c.	s.c.
KE concentration (ng/mL)	240	996	528
MO dose mg	200	300	150(450)*
MO route	o.s.	o.s.	s.c.
FREE MOconcentration (ng/mL)	66	36	105
TOT MO concentration (ng/mL)	4884	6050	2094

s.c., subcutaneous; os, oral; FREE MO, free morphine; TOT MO, total morphine after acid hydrolysis.
* Oral equivalent using a ratio 1/3. See text.

Morphine and ketamine plasma concentration during 5 months of therapy are shown in Table 1. These values were obtained using a gas chromatography method (HP 5890, series II), with mass spectrometry (HP 5972) for ketamine and radioimmunoassay (Coat-a count serum morphine, DPC, Los Angeles) for morphine.

When a large neck mass developed, pain level worsened. Oral morphine dosage was increased to 300 mg daily, and ketamine was increased to 240 mg daily (Table 1). Drowsiness and confusion appeared again. Laboratory findings showed a plasma creatinine concentration of 2.7 mg%. The patient's oral intake declined due to dysphagia, and Karnofsky performance status score was 40.

Morphine was administered as a continuous subcutaneous infusion (150 mg daily), and the ketamine dosage was increased to 300 mg daily (Table 1). The patient agreed to radiotherapy to the neck mass but it was suspended due to the appearance of intolerable side effects (vomiting). The dosages of morphine and ketamine were progressively increased to 200 mg and 450 mg daily, respectively, which again provided acceptable pain relief until the patient's death. The total duration of ketamine therapy was 13 months. The progressive neurological impairment observed in the last stage of illness was attributed to progression of disease and the limited intake of food and fluids, rather than to the effects of the drugs administered.

Discussion

Spinal NMDA receptors play a role in nociceptive processing.[10] Several experimental studies have shown that repetitive C-fiber activation produces central changes that may be relevant to neuropathic pain and are attenuated by NMDA receptor antagonists.[11-16] These experimental observations suggest that ketamine and other NMDA antagonists may be useful in neuropathic cancer pain. Ketamine has many properties that may be advantageous in advanced cancer patients, including rapid onset of effect and low incidence of respiratory depression. However, so-called emergence reactions, excessive salivation, and prolonged recovery time limit its routine use. Side effects of excess salivation, purposeless movements, and behavior changes have been reported after both intravenously and intramuscular use.[17]

Administration of subdissociative doses of ketamine provide balanced sedation with limited respiratory depression, emergence phenomena, and significant changes in blood pressure or heart rate.[6] The dosage that leads to side effects is not clear, especially in advanced cancer patients, who are often predisposed to confusion and delirium due to tumor effects, metabolic disturbances, or the use of other drugs.

The daily dose of ketamine initially used in our patient was very low compared to previous experience in chronic pain and cancer pain patients (ranging from 0.2 mg/kg/hr to 1.5 mg/kg/hr).[5,18,19] In a previous report, 13 of 18 patients achieved good pain relief with infusion rates of 60–360 mg/day (2–15 mg/hr).[19] Several routes of administration were used by Luczak et al. (cited in Twycross[18]), mostly to relieve pain on movement (e.g., turning and washing bedridden patients) in 26 cancer patients with different pain syndromes (dosage ranging from 40 to 180 mg/day). Some patients described in these reports received ketamine for 4–6 months. In other experiences with ketamine in neuropathic cancer pain, the dosage could be reduced during the course of the therapy without a return of pain.[18]

Our patient was administered ketamine for over 1 year. Although a placebo effect might be considered, the duration of good effect in

a cancer patient unresponsive to opioids makes this possibility unlikely. The dose of ketamine was gradually increased to 450 mg a day. Although tolerance and enzyme induction have been reported following chronic administration, the slow escalation seems more attributable to an increase of the pain from the progression of the cancer than the appearance of ketamine tolerance.

Although the side effects of ketamine often outweight the benefits, in this patient the neurologic symptoms were attributable to the previous high opioid dosage and were reduced after starting ketamine. Important adverse effects, such as injection site inflammation, salivation, and insomnia, were not observed in spite of the long period of administration and the dosage used in time. The ketamine blood concentration was related to dose increases during the treatment. Norketamine, an active metabolite with one-third the potency of ketamine, can account for part of the analgesic effect observed with a constant infusion. The influence of this metabolite possibly reduced the need for higher opioid and ketamine doses. Norketamine concentrations are higher following oral administration than parenteral administration, probably from first-pass metabolism.[20] Ketamine metabolites were not determined in this case.

Free morphine blood concentration decreased while total morphine blood concentration (including morphine-6-glucuronide and morphine-3-glucuronide) increased when the dosage of oral morphine was increased from 200 mg up to 300 mg after about 7 weeks. The free morphine/total morphine ratio changed (about 1/20) when morphine 150 mg was continuously administered by subcutaneous route. The response in this case suggests that ketamine may have a positive effect on opioid responsiveness, reversing a rightward shift of the dose-response curve that may be typical of some pain syndromes. Ketamine infusion may represent an alternative pharmacological method to control neuropathic cancer pain.

The influence of ketamine on opioid analgesia could also result from a reversal of opioid tolerance. Mu-opioid tolerance involves the mediation of NMDA receptors and the nitric oxide system.[21] Mu-opioid-NMDA receptor interaction results in an increase of intracellular free calcium.[22] NMDA receptor antagonists would be expected to inhibit tolerance to the analgesic effect of repeated morphine administration, interfering with the cellular and molecular changes thought to be involved in pain tolerance mechanisms.[23–25] Regarding the myoclonus induced by spinal morphine, this effect is well recognized, although the mechanism is not clear. It was refractory to local anesthetic addition at the concentration used in this patient. This observation has been already reported with other opioids.[26] We found that a low-dose continuous subcutaneous infusion of ketamine was reliable and well accepted. By changing the skin site every 2 days, we did not observe adverse reactions at the subcutaneous site. The use of continuous subcutaneous ketamine may be useful in neuropathic cancer pain unresponsive to opioids. Other studies should be performed to confirm the role and the optimal dosage of this drug in cancer pain.

Acknowledgment

I wish to thank Dr. Robert Twycross for the materials kindly supplied and Prof. Geoffrey W. Hanks for his comment. We would like to thank Mrs. Josephine Muscat for her help in translating the manuscript.

References

1. McQuay HJ, Jadad AR, Carroll D, et al. Opioid sensitivity of chronic pain: a patient-controlled analgesia method. Anesthesia 1992;47:757–767.

2. Portenoy RK, Foley KM, Inturrisi CE. The nature of opioid responsiveness and its implications for neuropathic pain: new hypotheses derived from studies of opioid infusion. Pain 1990;43:273–286.

3. Mercadante S, Maddaloni S, Roccella S, Salvaggio L. Predictive factors in advanced cancer pain treated only by analgesics. Pain 1992;50:151–155.

4. Bruera E, MacMillian K, Hanson J, MacDonald RN. The Edmonton staging system for cancer pain: preliminary report. Pain 1989;37:203–209.

5. Sosnowski M, Lossignol D, Fodderie L. Reversibility of opioid insensitive pain. Seventh World Congress on Pain in Paris, August 22–27, 1993:16.

6. Slogoff S, Allen GW, Wessels LV, Cheney DH. Clinical experience with subanaesthetic ketamine. Anesth Analg 1974;53:354–358.

7. Backonja M, Arndt G, Gombar KA, Check B, Zimmermann M. Response of chronic neuropathic

pain syndromes to ketamine: a preliminary study. Pain 1994;56:51–57.

8. Oye I, Mathisen L, Skjelbred P. Studies on effect of ketamine analgesia in neuropathic pain. Seventh World Congress on Pain in Paris; August 22–27, 1993:195.

9. Mercadante S. Intrathecal morphine and bupivacaine inadvanced cancer pain patients implanted at home. J Pain Symptom Manage 1994;9:201–207.

10. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. Pain 1993;52:259–285.

11. Dickenson AH, Sullivan AF. Differential effects of excitatory amino acid antagonist on dorsal horn nociceptive neurons in the rat. Brain Res 1990;506: 31–39.

12. White PF. Clinical uses of intravenous anesthetic and analgesic infusions. Anesth Analg 1989; 68:171–177.

13. Yamamoto T, Yaksh TL. Comparison of the antinociceptive effects of the pre and post treatment with intrathecal morphine and MK801, an NMDA antagonist on the formalin test in the rat. Anesthesiology 1992;77:757–763.

14. Malberg AB, Yaksh TL. Spinal nitric oxide synthesis inhibition blocks NMDA-induced thermal hyperalgesia and produces antinociception in the formalin test in rats. Pain 1993;54:291–300.

15. Davar G, Hama A, Deykin A, Vos B, Maciewicz R. MK801 blocks the development of thermal induced hyperalgesia in a rat model of experimental painful neuropathy. Brain Res 1991;553:327–330.

16. Mao J, Price DD, Mayer DJ, Lu J, Hayes RL. Intrathecal MK801 and local nerve anesthesia synergistically reduce nociceptive behaviors in rats with experimental peripheral mononeuropathy. Brain Res 1992;576:254–262.

17. Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. Can J Anaesth 1989;36:186–197.

18. Twycross R. Pain relief in advanced cancer. Oxford, 1994:476–479.

19. Oshima E. Continuous subcutaneous injection of ketamine for cancer pain. Can J Anaesth 1990; 37:385–392.

20. Grant IS, Nimmo WS, McNicol LR, Clements JA. Ketamine disposition in children and adults. Br J Anestl 1981;53:27–30.

21. Elliot K, Minami N, Kolesnikov YA, Paternak GW, Inturrisi CE. The NMDA receptor antagonists, LY274614 and MK-801, and the nitric oxide synthase inhibitor, NG-nitro-L-arginine, attenuate analgesic tolerance to the mu-opioid morphine but not to kappa opioids. Pain 1994;56:69–75.

22. Mayer L, Miller RJ. Excitatory amino acid receptors, second messengers and regulation of intracellular Ca++ in mammalian neurons. In: Lodge D, Collingridge G, eds. The pharmacology of excitatory amino acids. Cambridge: Elsevier Trends, 1990:36–42.

23. Marek P, Ben-Eliyahu S, Gold M, Iebeskind JC, Excitatory amino acid antagonists (kynurenic acid and MK-801) attenuate the development of morphine tolerance in rat. Brain Res 1991;547:177–181.

24. Trujillo KA, Akil H. Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK 801. Science 1991;51:85–87.

25. Foley KM. Changing concepts of tolerance to opioids: what the cancer patient taught us. IASP Refresher Course Syllabus, Seventh World Congress on Pain in Paris; August 22–27, 1993:221–235.

26. Cartwright PD, Hess C, Jackson AO. Myoclonus spasms following intrathecal diamorphine. J Pain Symptom Manage 1993;8:492–495.