

Ultra-Low Dose Ketamine and Memantine Treatment for Pain in an Opioid-Tolerant Oncology Patient

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Patients taking high-dose opioids chronically for tumor-related or neuropathic pain may develop pain that is refractory to opioids. One option for control of such pain is the use of the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine. We describe a case of opioid-refractory pain that responded to a low-dose IV infusion of ketamine in the inpatient setting. The patient was then successfully transitioned to oral memantine for long-term outpatient management, in a novel use of this oral NMDA receptor antagonist. We present recent findings from basic research on pain mechanisms to explain why opioid tolerance, as in this patient, may contribute to the analgesic benefit of NMDA receptor antagonists.

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The development of opioid tolerance poses a significant therapeutic challenge in both chronic and postoperative pain management. Long-term use of opioids may result in opioid escalation to achieve adequate pain relief. The occurrence of side effects such as sedation can become problematic.¹ Opioid escalation can sometimes appear futile, with inadequate pain control despite very high doses. In addition, some types of pain, particularly central neuropathic pain, can be refractory to opioid therapy.²

Use of the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine for pain refractory to high-dose opioids is well described in a number of clinical trials.^{3,4} Such use is supported by preclinical data demonstrating an important role for the NMDA receptor in opioid-induced hyperalgesia^{5,6} and in persistent pain from inflammation,⁷ nerve injury,⁸ and cancer.⁹

Widespread use of ketamine has been limited by clinicians' concerns about adverse effects such as dysphoria, hallucinations, and dissociative symptoms. Furthermore, the dosing of ketamine is inconvenient in chronic pain patients as it is relatively short acting and is unavailable as oral tablets. Analgesic use of dextromethorphan, an oral NMDA receptor antagonist with preclinical effectiveness,¹⁰ has been largely disappointing clinically.¹¹

Memantine is a long-acting oral NMDA receptor antagonist with a high therapeutic index.¹² Its demonstrated analgesic effectiveness for neuropathic pain in

case series,^{13,14} but not placebo-controlled trials,¹⁵⁻¹⁸ indicates a need to elucidate characteristics of the pain that best responds to its use.

We describe the use of ketamine and, subsequently, memantine in managing intractable pain in a setting of severe opioid tolerance.

CASE DESCRIPTION

A 43-yr-old man with known metastatic liposarcoma of the thigh presented acutely with progressive bilateral lower extremity weakness and paresthesias and with worsening of his chronic back pain. The liposarcoma had progressed over 4 yr despite multiple surgical excisions, chemotherapy, and radiation, and he had known vertebral, epidural, and pulmonary metastases. His back pain was not controlled at home despite oral methadone (120 mg/d), gabapentin (1800 mg/d), and IV hydromorphone patient-controlled analgesia (demand dose 1.2 mg, lockout period 6 min, basal rate 1.2 mg/h, total use approximately 7 mg/h).

The patient was admitted for pain management and further workup. Magnetic resonance imaging of the spine showed extension of epidural metastases with circumferential compression of the spinal cord at the T9-10 level (Fig. 1). An urgent palliative decompressive laminectomy was performed, with partial tumor resection at levels T8-L1. Improved motor function was observed in the immediate postoperative period.

Postoperatively, he reported severe burning low back and bilateral lower extremity pain of intensity rating 8-9 of 10, and a less severe stabbing upper back pain exacerbated by movement. Pain was uncontrolled despite continuation of oral methadone and gabapentin, initiation of IV lorazepam and ketorolac (90 mg/d) and escalating doses of IV hydromorphone. Hydromorphone was titrated to an average use of 63 mg/h on postoperative day (POD) 0 and reached a peak of 333 mg/h in the afternoon of POD 1 (Fig. 2), including bolus doses of up to 50 mg which had little impact on pain severity.

Because of unsatisfactory pain relief, a continuous infusion of ketamine at $55 \mu\text{g kg}^{-1} \text{h}^{-1}$ (5 mg/h) was begun on the afternoon of POD 1. After 5 h, the constant burning low back and lower extremity pains were essentially resolved and, although upper back pain continued, its intensity was tolerable at 2 of 10. During this time, his patient-controlled analgesia use decreased to about one demand dose per hour,

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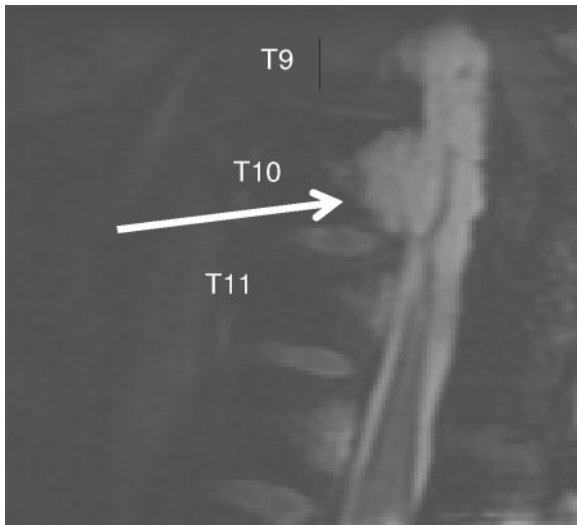


Figure 1. Preoperative magnetic resonance imaging (STIR) of the thoracic spine in the region of tumor resection for spinal cord decompression. Vertebral metastases are seen, with epidural extension causing circumferential compression of the spinal cord at T9 and T10.

so a downward titration of the hydromorphone infusion was begun. Over the following days, pain intensity remained at 1–3 of 10 despite a decrease in average hydromorphone use to 63 mg/h on POD 2 and 21 mg/h on POD 4 (Fig. 2). Mild somnolence which had begun with the ketamine infusion subsequently resolved with the decrease in hydromorphone use. The patient denied significant side effects such as dysphoria, hallucinations, or memory issues.

Oral memantine was started at 5 mg bid on POD 5 and ketamine was titrated downward to $27.5 \mu\text{g kg}^{-1} \text{h}^{-1}$, and then to $13.8 \mu\text{g kg}^{-1} \text{h}^{-1}$ on POD 6. This attempted ketamine taper was unsuccessful, resulting in an increase in pain intensity and hydromorphone use, both of which returned to baseline with resumption of ketamine to $55 \mu\text{g kg}^{-1} \text{h}^{-1}$ on POD 7 (Fig. 2). Also on POD 7, the memantine dose was doubled to 10 mg bid and gabapentin was increased from 1500 to 2100 mg/d.

A successful slower ketamine taper was initiated on POD 8 with a dose decrease to $36.8 \mu\text{g kg}^{-1} \text{h}^{-1}$ and discontinuation finally on POD 11. The patient reported satisfactory pain control (average intensity 1–3 of 10), and IV hydromorphone was tapered and finally discontinued on POD 13. Oxycodone 30 mg was then provided as needed, about once daily. Memantine (10 mg bid), methadone (120 mg/d), and gabapentin (2100 mg/d) were continued unchanged, and ketorolac was replaced with naproxen (1000 mg/d).

The patient's pain remained well controlled despite a medically complicated course and progressive development of paraplegia. He was discharged to a nursing home on POD 49. On discharge, the memantine was inadvertently discontinued. During the following 2 wk he complained of a return of his burning low back pain and lower extremity pain, which proved refractory to IV morphine even when administered to the point of over sedation.

After readmission on POD 65 for pain control, he was restarted on memantine at 10 mg bid. In addition, methadone was increased in stages from 120 to 200 mg/d, and naproxen was increased from 1000 to 1500 mg/d. Over 3–4 days the pain resolved, and IV morphine was replaced with as-needed oxycodone (about 20 mg/d). After a week, he was discharged to the nursing home. He remained comfortable, alert, and lucid without further changes in analgesic regimen until his death 2 mo later from complications of pulmonary metastases (POD 112).

DISCUSSION

At least four factors contributed to this patient's severe back and leg pain after surgery: 1) tumor, 2) spinal cord injury, 3) opioid tolerance with associated hyperalgesia, and 4) surgical trauma. The rapid and almost complete resolution of pain with an extremely low dose infusion of IV ketamine and the absence of side effects indicate a highly sensitive response to this drug. Continued pain relief with transition to memantine, loss of pain relief with its discontinuation, and return of pain relief after its resumption (and after an increase in methadone, also with NMDA receptor antagonist effects¹⁹) demonstrated that his pain was responsive to diverse NMDA receptor antagonists. The patient's continued sharp upper back pain with movement suggests a fifth (perhaps acute musculoskeletal) pain less responsive to NMDA receptor antagonists.

Although ketamine reduces postoperative opioid requirements,^{20,21} its benefits have been modest in most studies. Why was this patient's pain so opioid-resistant, yet so sensitive to NMDA receptor antagonists? We propose that sensitization of central pain pathways due to spinal cord injury, tumor, and chronic high-dose opioid use contributed to the patient's pain, and also predisposed him to the extreme opioid tolerance evident after surgical trauma. NMDA receptor antagonists, we hypothesize, dampened central sensitization from all of these causes and this modified the mechanisms primarily responsible for his intractable pain.

Activation of the NMDA-type ionotropic glutamate receptor occurs after an intense or repeated stimulus, and results in a long-term increase in cell excitability because of second messenger effects initiated by calcium influx.²² NMDA receptors are densely expressed at nociceptive synapses in the spinal cord dorsal horn.²³ A NMDA receptor-mediated increase in dorsal horn synaptic efficacy is an important contributor to the sensitization of central pain pathways seen in both chronic pain syndromes and opioid tolerance.^{7–9,22,24}

Our patient's spinal cord injury likely contributed to a central neuropathic pain responsive to NMDA receptor antagonists. For example, in a rat model of spinal cord injury pain, enhanced responsiveness was found in spinal sensory neurons adjacent to the lesion.²⁵ Pain behaviors were reversed in this model by administration of an NMDA receptor antagonist.²⁶

This patient's tumor also likely contributed to his severe pain, not only from tissue destruction from his metastases but perhaps also from tumor-induced sensitization of nociceptive processes through a NMDA receptor-mediated mechanism. In a murine bone cancer model, for example, an increase in dynorphin immunoreactive neurons and massive astrocyte hypertrophy were demonstrated throughout the ipsilateral spinal gray matter at the level innervating the

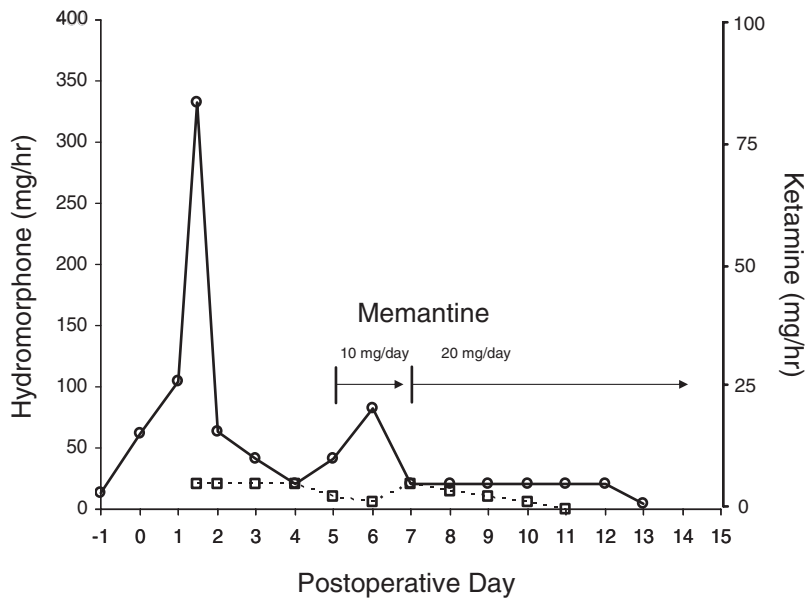


Figure 2. Graph showing the relationship between doses of hydromorphone (solid line) and ketamine (dotted line) in the perioperative period. A nearly inverse relationship can be seen between these drugs through postoperative day (POD) 7. The timing and doses of memantine are indicated. After the memantine dose increase, downward titration of ketamine was possible without an associated increase in hydromorphone use. The preoperative dose of hydromorphone is given as POD-1.

tumor²⁷; both findings have been associated with NMDA receptor-mediated central sensitization.^{28–30}

Finally, the patient's profound opioid tolerance was clearly a major impediment to treating his pain successfully. Although such tolerance is likely due in part to desensitization of the opioid receptors,³¹ hyperalgesia, due to an opioid-induced feedback amplification of the nociceptive signal, likely also contributes.^{22,32} Multiple mechanisms have been reported to explain such amplification including an increase in spinal dynorphin content,³³ increased astrocyte activity,³⁴ and intracellular activation of protein kinase C⁶; all may act directly or indirectly via NMDA receptor activation.^{35–37}

After chronic opioid exposure in rats, nociceptive sensitization mechanisms dependent on the NMDA receptor are in equilibrium⁵ with compensatory endogenous analgesic processes.³⁸ In our patient, such opioid-induced sensitization presumably exacerbated disease-induced sensitization, and balance was maintained only by chronic high-dose opioid use. Balance was lost when tissue damage from disease progression and surgical trauma^{39,40} caused significant new pain. Postoperative opioid escalation appeared futile, although perhaps adequate analgesia would have been achievable with yet higher opioid doses.

However, this opioid escalation may have been truly futile. After chronic opioid exposure, additional opioid exposure leads to increasingly marked and prolonged hyperalgesia.⁵ Eventually, the hyperalgesia which increases over time could exceed the maximum analgesic effect which can be produced by available opiate receptors, making this pain truly refractory to opioids.

Ketamine and memantine, in this patient, may have produced their dramatic analgesic effects both by dampening the central sensitization caused by his multiple spinal pathologies and, at the same time, by diminishing the opioid-induced hyperalgesia which

masked the effects of endogenous and exogenous analgesics.

This case illustrates the potential of a novel use of memantine, an uncompetitive antagonist at the NMDA-type glutamate receptor approved for clinical use in Alzheimer's disease. Memantine's tolerability is due to its low affinity to the receptor-associated ion channel which results in reduced dwell-time in the channel, with preferential blockade of pathologically overactivated channels.¹² It is therefore a promising treatment for disorders in which the pathology includes excessive glutamate release. Examples are neurodegenerative dementias involving excitotoxic cell death¹² and pain involving central sensitization such as neuropathic pain^{13,14} and, we suggest, opioid-induced hyperalgesia. Adverse effects of memantine such as dizziness and restlessness are mild and reversible with discontinuation.

Understanding the mechanisms interfered with by NMDA receptor antagonists may be helpful for clinicians considering the use of these drugs as analgesics. Our experience suggests that pain caused by multiple coexisting dorsal horn pathologies mediated by central sensitization can be extremely responsive to these drugs and, in particular, in the setting of severe opioid tolerance. Memantine is an additional tool for clinicians to consider when treating such complex pains. Additional controlled studies with this drug will be helpful to further guide our management.

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