Neuromodulation: Technology at the Neural Interface

Received: April 17, 2022 Accepted: May 3, 2022

https://doi.org/10.1016/j.neurom.2022.05.003

CLINICAL LETTER

Ketamine Infusion After Abrupt Cessation of High-Dose Intrathecal Hydromorphone: A Case Report

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To the Editor:

We report the successful use of intravenous ketamine infusion for preventing opioid withdrawal in a patient who was receiving long-term, high-dose intrathecal (IT) hydromorphone therapy. The four-day ketamine infusion helped facilitate weaning from approximately 25,000 mg oral daily morphine equivalent (MME) to 48 MME in a matter of six days. Our case report endorses the hypothesis that *N*-methyl D-aspartate (NMDA) antagonists may inhibit the expression of opioid withdrawal. The patient did not experience significant withdrawal symptoms. Intravenous ketamine can be used as a bridge to successfully wean a patient from high-opioid doses, including IT administration, while providing adequate analgesia during the transition period and limiting or mitigating opioid withdrawal effects.

We report a case of successful use of a ketamine infusion in preventing opioid withdrawal in a patient with an IT drug delivery (IDD) system (IDDS) delivering high-dose hydromorphone, who was emergently explanted secondary to infection.

CASE DESCRIPTION

A woman aged 57 years was transferred from an outside facility because of concern over an infected pump reservoir site that required immediate explant. Her medical history included hypertension, diabetes mellitus, anterior cervical discectomy, and fusion at C4–C6, cervical spinal cord stimulator, thoracic and lumbar laminectomies with IDDS implant in 2003 by an outside neurosurgeon. The patient's medication was titrated by her implanting physician, and she reported adequate relief of pain with her latest IT medication regimen. The patient's IT medication consisted of hydromorphone 70 mg/ml, bupivacaine 20 mg/ml, and clonidine 120 mcg/ml, with a daily dose of 17-mg IT hydromorphone, 4.8-mg bupivacaine, and 29-mcg clonidine. Eight weeks before her presentation to our hospital, the patient had her pump reservoir replaced, owing to end of battery life, by a pain medicine specialist because her implanting neurosurgeon had recently retired. Approximately three weeks after the replacement, the patient began to complain of redness and drainage around the pump site. She underwent surgical site revision and washout by her physician the next day; intraoperative cultures revealed *Pseudomonas aeruginosa*. Despite four weeks of management with ciprofloxacin, symptoms persisted, and Infectious Disease recommended IDDS explant. The patient presented to our hospital Emergency Department and within hours underwent IDDS explant by the neurosurgical team. Given the patient's high-dose opioids, the chronic pain team was consulted for recommendations immediately after the explant.

Based on the patient's previous opioid requirements of up to ~25,000 MME and abrupt discontinuation, we recommended admission to a monitored intensive care unit (ICU) setting. Her initial numerical rating scale (NRS) pain score was 3 of 10, baseline back pain, yet she denied any incisional pain. In addition to clonidine patch 0.2 mg, around-the-clock acetaminophen, and her home analgesic regimen of gabapentin, a hydromorphone intravenous patient-controlled analgesia pump was started with the following settings: 0.2 mg per bolus, 4-minute lockout time, with no basal infusion, and 0.6- to 2-mg intravenous bolus per bedside nurse was available every 3 hours as needed. To help manage both the opioid taper and withdrawal, a ketamine infusion was started at 25 mg/h. Intravenous midazolam 2 mg every one hour also was available when necessary for agitation or hallucinations during the ketamine infusion. The patient was monitored closely for withdrawal using the Clinical Opiate Withdrawal Scale (COWS), with titration of ketamine and opioids as needed (Table 1; Fig. 1). She had transient nausea on postoperative day (POD) 1 and three episodes of loose stools, nausea, and increased pain on POD 2. There were no hemodynamic changes. She had no adverse effects from the ketamine infusion and was remarkably lucid at her maximal infusion rate of ketamine 100 mg/h. The patient was able to tolerate oral intake throughout her stay. The ketamine infusion was discontinued on POD 4. As expected, the patient required a larger number of opioids on this day than any previous day. Her opioid requirements and pain scores dwindled the next day, and

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Conflict of Interest: The authors reported no conflict of interest.

Source(s) of financial support: The authors reported no financial support.

Table 1. Hospital Course.

Hospital day	−1	0	1	2	3	4	5	6
Pain score (NRS)	3–4/10	0–3/10	0–8/10	3–10/10	3–8/10	3–9/10	3–9/10	6/10
MME	25,500	80	100	265	400	730	152	48
Ketamine infusion rate (mg/h)	0	25	25→50	50→100	100	100→0	0	0
COWS	0	2	5	5	3	2	0	0
Heart rate (bpm)	79–92	63–91	57–78	48–71	50–64	51–68	54–68	55–67

5- 12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal.
NRS, numeric rating scale; MME, oral daily milligram morphine equivalents; COWS, clinical opiate withdrawal scale.

the patient was transferred out of the ICU and monitored on the floor. While there, the patient had a COWS score of 0 and pain score of 6 of 10; vital signs were stable and she met the discharge criteria. She was provided with an opioid taper, which consisted of hydromorphone 2-mg tablets, gradually decreasing by 2 mg every third day from 12 mg/d to discontinuing all oral opioids over 15 days. The patient was recommended to continue the clonidine patch until she had been off all opioids for at least three days. On discharge, the patient elected to return to her previous pain physician for outpatient management. Ethical approval was not required for this single case report.

DISCUSSION

IDD is often used in the management of refractory pain, especially in the setting of previous spine surgeries. Similar to oral opioids, IDD is plagued with tolerance, and some patients require a gradual IT opioid dose escalation. Abrupt discontinuation of high doses of opioids leads to withdrawal. We describe a case of abrupt discontinuation of high-dose IT opioids with successful prevention of withdrawal symptoms using intravenous ketamine infusion.

Ketamine modulates pain signals through a variety of mechanisms, but primarily through its NMDA receptor antagonism.[1] The NMDA receptor is an excitatory glutamatergic receptor present in the spinal cord and supraspinal sites and is involved in afferent transmission of nociceptive signals and synaptic plasticity. In chronic pain states, prolonged or abnormally intense nociceptive signal transmission has the potential to cause upregulation and activation of the NMDA receptor at dorsal horn synapses.[2] This change in function leads to a phenomenon called central sensitization, wherein the central nervous system amplifies afferent pain signals. At normal resting membrane potentials, the channel is blocked by magnesium and is inactive. When the resting membrane potential is changed during prolonged excitation, the channel is unblocked, and calcium moves into the cell, which leads to neuronal hyperexcitability and results in hyperalgesia and allodynia and a reduction in opioid responsiveness. Importantly, repetitive nociceptive input is blocked by NMDA antagonism.

Ketamine infusions are used to prevent or reduce central sensitization through a "reset" of the mechanism that causes a change in NMDA receptors. In the setting of opioid use, it is believed that there exists an overlap in the mechanism of opioid and NMDA receptors.[3] The activation of the mu opioid receptor increases the activity of the NMDA receptor, which causes a downregulating effect on the mu receptor.[4] This leads to a reduction in opioid responsiveness that arises from crosstalk between opioid receptors and the NMDA receptor. Once activated, the opioid receptor results in phosphorylation and the opening of the NMDA receptors channel, which ultimately downregulates the opioid receptor and its effects.[2] This effect contributes to tolerance and hyperalgesia that are seen in patients who are on chronic opioids.

Although it is debated, the approximate conversion of IT hydromorphone to IT morphine is 5:1. The conversion of IT morphine to oral form also is challenging, with ratios of IT to oral morphine ranging from 300:1 to 12:1. For the sake of simplicity, a commonly accepted conversion factor of 100:1 IT morphine to intravenous morphine is used. Intravenous morphine can then be converted to oral morphine with a ratio of 3:1 (17 mg of IT hydromorphone/d × 5 × 100 × 3). This yields an approximate value of 25,000 mg of oral MME per day.[5]

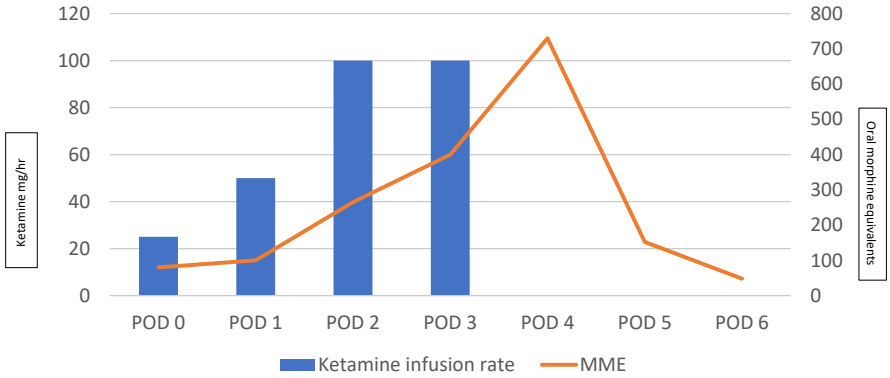

Figure 1. Time course and relative daily doses of intravenous ketamine and oral morphine milligram equivalents (MME). POD, post-operative day. [Color figure can be viewed at www.neuromodulationjournal.org]

In this case, supplementation of systemic opioids with intravenous ketamine facilitated the weaning course, provided an analgesic effect, and prevented withdrawal likely by a decrease in neuronal hyperexcitability. Although further studies are necessary, intravenous ketamine has the potential to allow physicians to taper opioids rapidly while minimizing unpleasant withdrawal symptoms.

CONCLUSIONS

Rapid tapering of opioids can be a challenging process, especially in cases of abrupt discontinuation of high doses. Ketamine appears to reduce tolerance, assist with rapid weaning, and provide analgesia during an emergency sudden weaning process. The case reported herein could provide a blueprint for future similar clinical instances. Further studies are needed to define the efficacy of ketamine as a routine drug of choice for patients who are undergoing rapid opioid taper, its ability to mitigate withdrawal symptoms, and the optimal dose and duration of treatment.

Authorship Statements

Both Brandon G. Stokey and Salim M. Hayek certified that they have participated sufficiently in the work and take public responsibility for the contents, analysis, and writing of the manuscript.

How to Cite This Article

Stokey B.G., Hayek S.M. 2022. Ketamine Infusion After Abrupt Cessation of High-Dose Intrathecal Hydromorphone: A Case Report.
Neuromodulation 2022; ■: 1–3.

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