Use of Ketamine in a Multimodal Analgesia Setting for Rapid Opioid Tapering in a Profoundly Opioid-Tolerant Patient: A Case Report

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Opioids are frequently used for the treatment of chronic pain, and patients taking high doses are at increased risk of complications and adverse opioid-related events. Ketamine is appealing as an opioid adjunct because of its lack of respiratory depression and potential prevention of hyperalgesia and central sensitization. We present a case in which a ketamine infusion was utilized over a 7-day period to provide rapid taper of a daily dose of 400 mg of morphine equivalents to less than one-third of that dose on discharge with unchanged pain levels and no symptoms of opioid withdrawal. (A&A Practice. 2018;10:179–81.)

Opioids are commonly used for the management of chronic pain. As tolerance develops, the dose is often escalated. Not infrequently, opioids may be escalated in the absence of a clear analgesic benefit. Although higher doses may occasionally be warranted, they increase the risk of adverse effects. Some, such as pruritus, are more of a nuisance, while others negatively impact quality of life and become ongoing concerns, like opioid-induced constipation or respiratory depression.[1] Opioid tapering may be considered to reduce hyperalgesia or to decrease adverse events but can be challenging because of potential withdrawal, increased pain, dropout, relapse, and medicolegal issues.[2] Opioid tapering recommendations are surprisingly scarce,[2] leaving physicians with little guidance. Slow tapers may occur in the outpatient setting while rapid tapers typically require inpatient admission. We present the case of a patient who was tapered from almost 400 mg of oral morphine equivalents daily to less than one-third of that dose on discharge 7 days later utilizing a subanesthetic ketamine infusion without experiencing significant opioid withdrawal or worsening pain.

The patient provided written consent for the publication of this case report.

CASE DESCRIPTION

A 74-year-old opioid-tolerant man with chronic low-back pain presented to the emergency room after several days of severe pain, tremors, nausea, and diarrhea. He stated that he ran out of his pain medications 2 weeks prior. He had a history of multiple lumbar spine surgeries with minimal pain relief and over 20 years of oral opioid therapy. While opioids provided some relief of his pain, he complained of excessive sedation, difficulty concentrating, and other opioid-related adverse effects. On admission, his regimen included extended-release morphine sulfate (Kadian Actavis, Parsippany, NJ) 100 mg every 8 hours, immediate-release morphine sulfate 30 mg every 8 hours as needed, pregabalin 100 mg every 12 hours and 50 mg with lunch, and diclofenac 1% gel as needed applied to the buttocks. His outpatient pain physician (M.J.C), the acute pain management service director (E.R.V.), and the admitting internal medicine team decided to admit him for treatment of opioid withdrawal and opioid tapering.

In addition to a clonidine patch, around-the-clock acetaminophen, and his home analgesic regimen of pregabalin, a hydromorphone patient-controlled analgesia pump was started with the following settings: 0.4 mg per push, 6-minute lockout time, no basal infusion, and a maximum of 4 mg/h with additional intravenous boluses of 0.8 mg being permitted by nursing every 2 hours. To help manage both the opioid taper and withdrawal, a ketamine infusion was started at 10 mg/h.

Over the next 7 days, the patient's opioids were gradually tapered with close monitoring of pain levels and adverse effects (Table). All pain ratings reported were measured on an 11-point Numerical Rating Scale with 0 being no pain and 10 being the worst pain imaginable. The tremors, nausea, and diarrhea all resolved the first day of ketamine treatment and with the addition of clonidine. All assessments were performed each morning by the acute pain management service team. Although pain ratings waxed and waned, on discharge, his pain was the same (5/10) as on admission. On day 2, the patient experienced hallucinations that were attributed to the ketamine infusion, requiring temporary stoppage and restarting at a lower rate. His maximum pain (10/10) on day 4 coincided with the temporary withholding of ketamine and clonidine patch the night before because of sedation. In the previous 24 hours, he had consumed 27 mg of oral morphine equivalents. The morning of day 4 he was more alert; ketamine was restarted at a lower dose along with a buprenorphine patch at 20 μg/h for improved analgesia. In total, the patient received 441 mg oral morphine equivalents during his hospitalization. All opioids were converted to morphine equivalents using a standard conversion table.[3]

The hydromorphone patient-controlled analgesia pump was discontinued on day 2 and an oral regimen of oxycodone

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Accepted for publication September 12, 2017.

Funding: None.

Conflicts of Interest: See Disclosures at the end of the article.

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DOI: 10.1213/XAA.0000000000000653

Table. Hospital Course

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Discharge
Pain rating (NRS)	5/10	6/10	7/10	10/10	7/10	7/10	5/10
Ketamine infusion rate (mg/h)	10	20→0	10→0	0→10	10	5	Off
Oral morphine equivalents (mg)[a]	333	0	27	27	27	27	0
Adverse effects	None	Hallucinations	Sedation	None	None	None	None
Intervention	…	Brief stoppage of infusion	Brief stoppage of infusion	…	…	…	…

Abbreviation: NRS, Numerical Rating Scale.
[a]Calculated using a conversion table from Sinatra.[3]

10 mg every 4–6 hours as needed was recommended. The patient was discharged on the following: acetaminophen 1000 mg every 6 hours, pregabalin 150 mg every 12 hours, buprenorphine patch 20 µg/h every week, and immediate-release oxycodone 10 mg every 6 hours as needed.

At his first follow-up appointment 2 days after discharge with his pain physician (M.J.C.), he rated his pain at 6–7 on a 0–10 Numerical Rating Scale and stated it to be little different from his pain level before hospitalization. He was able to travel with his family but otherwise had returned to his sedentary baseline without any continued withdrawal symptoms.

DISCUSSION

The use of opioids for chronic noncancer pain has grown exponentially over the past few decades and remains controversial with questionable evidence.[4] Despite this commonly encountered clinical scenario, standardized recommendations for rapid tapering of opioids are scarce, likely because of the difficulty in outpatient settings. We have described here the potential of ketamine to play a role in this often complex and frustrating process.

High-dose opioids pose many risks including potentially life-threatening respiratory and cardiovascular events and increased overall all-cause mortality.[5] Long-acting opioids, frequently prescribed for chronic pain, may exacerbate this risk because of the presence of µ-receptor agonism even in the absence of pain.[5] In addition to safety risks, tolerance, hyperalgesia, and allodynia are often associated with long-term, high-dose opioids and contribute to poor quality of life.[6]

Ketamine modulates pain signals through a variety of mechanisms, primarily *N*-methyl-D-aspartate (NMDA) receptor antagonism.[7] The NMDA receptor is an excitatory glutamatergic receptor present in spinal and supraspinal sites and is involved in afferent transmission of nociceptive signals. In chronic pain states, prolonged nociceptive signal transmission causes upregulation and activation of the NMDA receptor at dorsal horn synapses. This results in amplified pain signals (central sensitization).[7] At subanesthetic doses, NMDA receptor antagonism is thought to prevent central sensitization and reduce opioid-induced hyperalgesia.[6,8] Ketamine binds to activated, open NMDA channels and resets neuronal hyperexcitability.[7]

This hyperexcitability present in hyperalgesic patients makes ketamine ideal for a high-dose opioid taper. The process of tapering opioids is often limited by opioid withdrawal symptoms. Ketamine holds potential to facilitate tapering by resetting neuronal hyperexcitability through a potent analgesic effect, demonstrated in multiple studies.[9] These properties also make it favorable for attenuating withdrawal symptoms.

Indeed, ketamine may abolish withdrawal symptoms via mechanisms distinct from simply attenuating hyperalgesia. Freye et al[10] reported that ketamine reduced opioid withdrawal symptoms in patients given naltrexone while under general anesthesia. Unlike our patient, however, these patients were administered general anesthesia and opioid antagonists to precipitate opioid withdrawal. Our case is unique because the patient's withdrawal symptoms were adequately managed without general anesthesia.

As increasing efforts are being made to reduce opioid use in light of the current epidemic, therapeutic agents that can potentially assist in these efforts are needed. Long-term opioid therapy has not been shown to improve quality of life.[2] In addition, the burden of opioid tapering falls largely on community pain practices that have fewer resources than tertiary care centers.[2] One author made a Grade C recommendation (based on studies with methodologic limitations) that a fast or ultrafast taper can be considered "when inpatient taper is needed because of significant coexisting psychiatric or medical illness."[2] Our patient clearly fits that description. Quinlan[11] described a series of 15 opioid-tolerant patients who were tapered off of all opioids in 5 days using subanesthetic ketamine. Eight of the 11 who responded to follow-up at 2 months had sustained improvement; however, no information about ketamine or opioid doses was provided. Ketamine, as both an opioid-sparing and antihyperalgesic agent, clearly has the potential to allow physicians to rapidly taper opioids while minimizing unpleasant withdrawal symptoms.

Widespread adoption of subanesthetic ketamine infusions remains elusive, possibly because of concerns about ketamine's neuropsychiatric adverse effects. While some studies suggest that subanesthetic ketamine increases the incidence of neuropsychiatric effects,[9] others have found no difference compared to placebo.[12] In addition, concerns remain about the possibility of hepatic toxicity,[13] although most cases have occurred in ketamine abusers.[14] These risks must be weighed against the potential benefit that ketamine may offer in providing assistance with tapering. Although this patient experienced an episode of hallucinations and mild sedation, both resolved promptly after ketamine discontinuation and did not return at lower rates. Similarly, Schwenk et al[15] reported that >95% of adverse effects resolved after discontinuation of ketamine infusions.

In conclusion, rapid tapering of opioids remains challenging. Ketamine reduces tolerance, hyperalgesia, and attenuates opioid withdrawal, in addition to providing potent analgesia. We believe that this case demonstrates an important role ketamine could play in high-dose rapid opioid tapering while significantly reducing unwanted opioid withdrawal effects. Additional studies are needed.

DISCLOSURES

Name: Elise M. Strickler, DO.
Contribution: This author helped write the manuscript, manage the patient, and approve the final manuscript.
Conflicts of Interest: None.
Name: Eric S. Schwenk, MD.
Contribution: This author helped write the manuscript, manage the patient, and approve the final manuscript.
Conflicts of Interest: None.
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Contribution: This author helped write the manuscript, manage the patient, and approve the final manuscript.
Conflicts of Interest: None.
Name: Eugene R. Viscusi, MD.
Contribution: This author helped write the manuscript, manage the patient, and approve the final manuscript.
Conflicts of Interest: Eugene R. Viscusi has received research grants from Pacira and Durect; he has received consulting fees from AcelRx, AstraZeneca, Cara, Egalet, Mallinckrodt, Medicines Company, Merck, Pacira, Pfizer, Salix, and Trevena.
This manuscript was handled by: Hans-Joachim Priebe, MD, FRCA, FCAI.

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