

## Perioperative dilemma: Challenges of the management of a patient on mega doses of morphine and methadone

Alan David Kaye, MD, PhD, DABA, DABPM, DABIPP; Aymen A. Alian, MD; Nalini Vadivelu, MD; Keun Sam Chung, MD

### ARTICLE INFO

*Keywords:*

opioids  
methadone  
NMDA receptors  
ketamine  
opioid-induced hyperalgesia  
cancer pain

*Article history:*

Received 24 March 2013  
Received in revised form 28 May 2013;  
11 September 2013; 5 November 2013  
Accepted 7 November 2013  
DOI:10.5055/jom.2014.0194

© 2014 Journal of Opioid Management,  
All Rights Reserved.

### ABSTRACT

*High doses of opioids are often needed in the management of cancer-related pain. A discussion of a patient's perioperative opioid management and mechanisms contributing to opioid-induced hyperalgesia (OIH) are presented. In the present case report, a patient on high doses of opioids, including morphine and methadone, with severe worsening back pain and a history of increasing opioid requirements for the last 2 months due to metastatic leiomyosarcoma to the femur, spine, and neck is described. Use of high dose opioids is associated with numerous challenges, including tolerance. The successful management of this patient was multimodal and included the use of potent analgesics, N-methyl-D-aspartate-receptor antagonists, and the  $\alpha$ -2 agonist clonidine.*

### INTRODUCTION

Tolerance is a normal expected physiologic response that can occur with exposure to not only opioids but also certain class of drugs or substance such as alcohol, benzodiazepines, antidepressants, corticosteroids, alcohol, cardiac medications, antidiabetics, and many other medications used in clinical medicine. Mechanisms of tolerance include either pharmacokinetic tolerance, which involves decreased quantity of a drug reaching the site it effects through an induction of the enzymes involved in the degradation of the drug, or pharmacodynamic tolerance, which is a reduced responsiveness to a drug through downregulation of a receptor. High doses of opioids are often required to treat cancer-related pain and therefore, tolerance to these agents is frequently observed. We present a patient with cancer pain who required large doses of methadone for preoperative pain management and large doses of intraoperative sufentanil, who eventually achieved successful

postoperative pain control with small doses of ketamine, clonidine, and moderate doses of methadone.

### CASE REPORT

The patient was a 67-year-old female, 61 in tall, weighing 165 lb (75 kg). She was admitted to the emergency department with severe worsening back pain and a history of increasing opioid requirements for the last 2 months due to metastatic leiomyosarcoma to the femur, spine, and neck. Her magnetic resonance imaging showed a left-sided intradural sheet-like mass extending from L3 to T12, compressing the distal spinal cord at the levels of the eleventh and twelfth thoracic vertebrae. Her chronic back pain had been controlled with intravenous (IV) morphine and oral methadone. The patient was receiving on average 44 mg/h of morphine IV as a continuous infusion rate and 10 mg of morphine IV bolus every 30 minutes as needed. The patient had received approximately 1,400 mg of morphine per

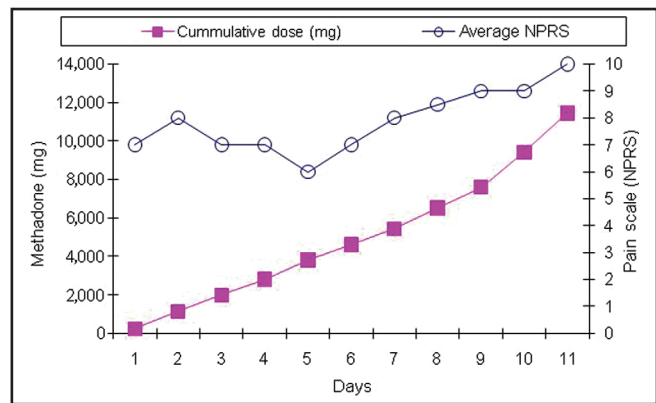
day over the 24 hours prior to admission with a numeric pain rating scale (NPRS) of 8-9. Additional daily medications included oral delivery of each of the following agents: methadone 10 mg TID, clonazepam 0.5 mg BID, clonidine 0.1 mg, amitriptyline 50 mg QD, gabapentin 300 mg five times daily (1,500 mg/d), phenytoin 100 mg TID, and dexamethasone 4 mg QID.

### Preoperative course

On the day of admission, the patient reported a pain intensity of 10. She was administered fentanyl 100 µg IV, her methadone was increased to 20 mg PO TID, and her morphine dose was increased with a 125 mg/h continuous infusion rate. Over the first 36 hours, the patient received a total dose of 5,000 mg of morphine IV, yet her reported pain intensity was 10. The morphine infusion was discontinued and substituted with methadone IV (10 mg/ml) by the Primary Care team (PCT), at 20 mg as an IV bolus dose every 15 minutes with a continuous infusion of 10 mg/h. The total dose of IV methadone received over the first 24 hours was 242 mg. The next day, her NPRS score was 8, which required an increase in the IV methadone to 25 mg every 15 minutes; the continuous infusion dose of methadone was increased by the PCT to 20 mg/h. Although her pain was described as slightly improved after the increased dose of methadone, by day 5 her pain level began to climb again, and did not respond to increased methadone doses. There were no other drug changes over the next 11 days. Figure 1 shows the cumulative IV dose of methadone and NPRS of each preoperative day. The total cumulative IV dose of methadone delivered preoperatively to the patient was 11,444 mg over 11 days.

### Intraoperative course

After 10 days of crescendo pain despite the IV methadone infusion, the patient underwent a T11-L3 laminectomy, with anterior and posterior decompression of the spinal cord, and a posterior spinal fusion from T10 to L4. The patient was premedicated with 100 µg clonidine TTS and 2 mg of midazolam intravenously. General anesthesia was induced with 170 mg propofol, 500 µg sufentanil, 200 µg clonidine, and 50 mg rocuronium. Anesthesia was maintained with isoflurane (<1 MAC), intermittent IV fentanyl boluses, a sufentanil infusion (which ranged from 3.5 to 9 mg/h), a propofol



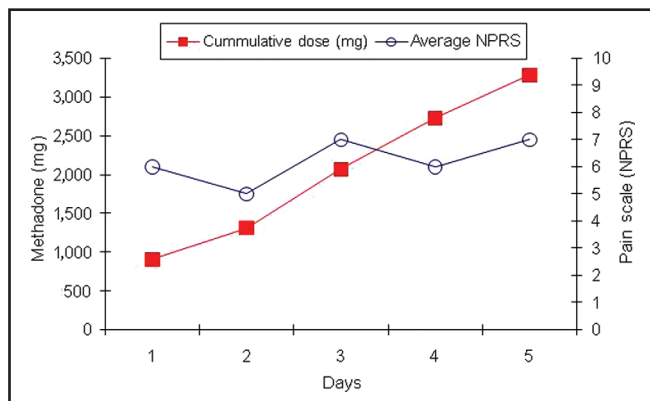
**Figure 1. Preoperative cumulative IV dose of methadone and average NPRS.**

infusion (which ranged from 60 to 90 µg/(kg min)), and a ketamine infusion for the first 2 hours of the surgery with a total dose of 1,200 mg.

Monitoring consisted of American Society of Anesthesiologists standard monitors, arterial line, and somatosensory evoked potentials (SSEP). The doses of the intraoperative opioids were titrated according to the vital signs response of the patient. The primary anesthesia team initially used fentanyl 200 µg, with clonidine TTS, and switched to the more potent opioid (sufentanil) in the light of the high preoperative utilization use of opioids to provide better pain control. The total intraoperative opioid requirement was 19 mg of sufentanil (253 µg/kg) and the initial 200 µg of fentanyl. During the 8-hour procedure, the patient received 6 L of lactated Ringer's solution plus 1 L of hetastarch; her urine output was 2,500 ml and estimated blood loss was 1,700 ml. At the end of the procedure, the patient was awake, following commands and moving her lower extremities. The patient was transferred to surgical intensive care unit, where she remained intubated overnight, sedated with a propofol infusion.

### Postoperative course

Postoperatively, the patient received a propofol infusion for 14 hours, as well as IV methadone at 25 mg every 15 minutes with a continuous infusion rate of 15 mg/h. A ketamine infusion was started at a rate of 15 mg/h to supplement the IV methadone after the propofol was turned off. Figure 2 shows the postoperative cumulative IV dose of methadone together with NPRS each postoperative day. The ketamine infusion was stopped on the fourth postoperative day as ketamine is not allowed to be



**Figure 2. Postoperative cumulative IV dose of methadone and average NPRS.**

given on the general wards per our hospital policy. On sixth postoperative day, all IV opioids were stopped and oral administration of 80 mg methadone TID was started with good pain control.

## DISCUSSION

Opioids are effective broad-spectrum analgesics that are often necessary for treating moderate to severe pain. Use of high dose opioids is associated with the problems of tolerance and opioid-induced hyperalgesia (OIH), which can confound acute perioperative pain management as well as chronic pain states.<sup>1</sup> The etiology of OIH is not fully understood; however, it is well understood that *N*-methyl-D-aspartate (NMDA) activation, “windup” and central sensitization are responsible for clinical hyperalgesia. Tolerance may actually be an early stage in the development of hyperalgesia.<sup>2</sup> This makes the treatment of pain in the opioid-dependent patient very challenging, as increased opioid dosing may actually contribute to increased pain.

Methadone, by virtue of its NMDA-blocking properties, has been thought to be a good choice for preoperative treatment of morphine tolerance and OIH.<sup>3</sup> This patient was not taking any medications that would be expected to alter methadone efficacy. However, in this case report, we had the challenge of treating a patient with very high doses of methadone (11,444 mg in 11 days) in the face of uncontrolled pain.

Our approach to the management of this patient was multimodal and included the use of potent analgesics, NMDA-receptor antagonists, and an  $\alpha$ -2 agonist. The choice of sufentanil as an intraoperative analgesic was made because of its high potency, lack

of active metabolites, and short latency to peak effect after IV injection. It has been shown that sufentanil is approximately 7.5 times as potent as fentanyl during intermediate-term infusion of opioids in patients previously treated with opioids for chronic pain.<sup>4</sup> Ketamine, an NMDA-receptor antagonist, was used intraoperatively and continued postoperatively, and methadone, also an NMDA-receptor antagonist, was used preoperatively and postoperatively. We also used an  $\alpha$ -2 agonist (clonidine) during the hospital stay of the patient, which can cause activation of spinal muscarinic receptors and subsequent inhibition of nociceptive processing.<sup>5</sup>

Joly et al.<sup>6</sup> showed that giving a small dose of ketamine during and after surgery completely prevented the increase in postoperative pain sensitivity and punctate hyperalgesia that otherwise resulted from large-dose remifentanyl administration. Moreover, patients who received a large dose of remifentanyl with ketamine had significantly less postoperative morphine requirements than those receiving only large dose remifentanyl.<sup>6</sup> Ketamine, at subanesthetic doses, is a NMDA-receptor antagonist, a mechanism that likely is related to its analgesic properties.<sup>7,8</sup> It should be noted that the compound with the highest affinity for the NMDA-receptor is MK-801 with a binding affinity of 18 nM. Memantine, dextromethorphan, and ketamine are all very effective NMDA-receptor antagonists; however, none of these compounds shows selectivity and are therefore considered non-competitive antagonists.<sup>9</sup>

Callahan et al.<sup>10</sup> observed in rat NMDA-receptor studies that racemic methadone markedly decreased NMDA-stimulated current activity, but the NMDA concentration producing 50 percent of maximal activation was altered only slightly, indicating that methadone blocks NMDA-receptors in a noncompetitive fashion and binds to the pore of the NMDA-receptor channel. These results in aggregate support the data describing the NMDA-receptor inhibitory actions of methadone. This action appears to be similar to ketamine’s NMDA-receptor antagonism. Thus, methadone acts through both opioid agonist and NMDA-receptor antagonist mediated or modulated mechanisms.<sup>10</sup>

Clonidine (an  $\alpha$ -2 agonist) has been administered preoperatively and intraoperatively by oral, transdermal, IV, and epidural/intrathecal routes to provide sedative, anxiolytic, and analgesic effects and to decrease intraoperative and postoperative opioid requirements.<sup>11</sup>

In opioid-dependent patients, opioid rotation to methadone has been seen to be useful to avoid OIH.<sup>2,3,10,12</sup> It is also known that small doses of ketamine reduce postoperative opioid dosing.<sup>13</sup> Laulin et al. showed that ketamine has a role in preventing fentanyl-induced hyperalgesia.<sup>14</sup> In this case, the amount of methadone needed for adequate pain relief increased again when ketamine was discontinued, which we think showed the beneficial effects of ketamine to treat possible tolerance to methadone. The decreased amount of oral methadone used once the IV methadone and ketamine were discontinued could perhaps be explained by the fact that the patient was recovering from a surgery that addressed the etiology of her pain, and therefore she needed a smaller amount of opioid for pain control. Our case report suggests that ketamine, an agent with NMDA antagonism, may bind the NMDA-receptor differently than methadone, another NMDA pore channel antagonist. The combination of NMDA antagonists may be in actuality a multimodal technique, given that there are various subtype expressions and combinations of NMDA subunits. In addition, hyperalgesia appears to result from the interaction of multiple receptor types, making single modality treatment of OIH less feasible and may be especially relevant when OIH is due to methadone.

In summary, although methadone has been recommended as an alternative opioid to address OIH issues, it is apparently capable of causing OIH itself. Additional NMDA inhibitors, such as ketamine, and perhaps  $\alpha$ -2 agonists, such as clonidine, should be considered in cases of poor analgesia despite increasing doses of methadone. Although part of the improvement of this patient is related to her laminectomy procedure, this case report illustrates profound OIH, which was effectively treated with a multimodal approach.

*Alan David Kaye, MD, PhD, DABA, DABPM, DABIPP, Professor and Chairman, Department of Anesthesiology, Louisiana State University Health Science Center, New Orleans, Louisiana; Professor, Department of Pharmacology, Louisiana State University Health Science Center, New Orleans, Louisiana.*

*Aymen A. Alian, MD, Assistant Professor, Department of Anesthesia, Yale University School of Medicine, New Haven, Connecticut.*

*Nalini Vadivelu, MD, Associate Professor, Department of Anesthesia, Yale University School of Medicine, New Haven, Connecticut.*

*Keun Sam Chung, MD, Associate Clinical Professor, Department of Anesthesia, Yale University School of Medicine, New Haven, Connecticut.*

## ACKNOWLEDGMENTS

*The authors thank Dr. Andrea Trescot, MD, for her assistance in the preparation of this manuscript. The authors have no relationships with pharmaceutical companies or products to disclose, nor do they discuss off-label or investigative products.*

## REFERENCES

1. Mao J, Mayer D: Spinal cord neuroplasticity following repeated opioid exposure and its relation to pathological pain. *Ann NY Acad Sci.* 2001; 933: 175-184.
2. Lee M, Silverman SM, Hansen H, et al.: A comprehensive review of opioid-induced hyperalgesia. *Pain Physician.* 2011; 14(2): 145-161.
3. Mercadante S: Switching methadone: A 10-year experience of 345 patients in an acute palliative care unit. *Pain Med.* 2012; 13(3): 399-404.
4. Reynolds L, Rauck R, Webster L, et al.: Relative analgesic potency of fentanyl and sufentanil during intermediate-term infusions in patients after long-term opioid treatment for chronic pain. *Pain.* 2004; 110(1-2): 182-188.
5. De Kock M, Eisenach J, Tong C, et al.: Analgesic doses of intrathecal but not intravenous clonidine increase acetylcholine in cerebrospinal fluid in humans. *Anesth Analg.* 1997; 84(4): 800-803.
6. Joly V, Richebe P, Guignard B, et al.: Remifentanyl-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology.* 2005; 103(1): 147-155.
7. Anis N, Berry S, Burton N, et al.: The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by *N*-methyl-aspartate. *Br J Pharmacol.* 1983; 79(2): 565-575.
8. Woolf C, Thompson S: The induction and maintenance of central sensitization is dependent on *N*-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain.* 1991; 44(3): 293-299.
9. Suzuki M: Role of *N*-methyl-D-aspartate receptor antagonists in postoperative pain management. *Curr Opin Anaesthesiol.* 2009; 22(5): 618-622.
10. Callahan RJ, Au JD, Paul M, et al.: Functional inhibition by methadone of *N*-methyl-D-aspartate receptors expressed in *Xenopus oocytes*: Stereospecific and subunit effects. *Anesth Analg.* 2004; 98(3): 653-659.
11. Park J, Forrest J, Kolesar R, et al.: Oral clonidine reduces postoperative PCA morphine requirements. *Can J Anaesth.* 1996; 43(9): 900-906.
12. Parsons HA, de la Cruz M, El Osta B, et al.: Methadone initiation and rotation in the outpatient setting for patients with cancer pain. *Cancer.* 2010; 116(2): 520-528.
13. Kissin I, Bright C, Bradley EJ: The effect of ketamine on opioid-induced acute tolerance: Can it explain reduction of opioid consumption with ketamine-opioid analgesic combinations? *Anesth Analg.* 2000; 91(6): 1483-1488.
14. Laulin JP, Maurette P, Corcuff JB, et al.: The role of ketamine in preventing fentanyl-induced hyperalgesia and subsequent acute morphine tolerance. *Anesth Analg.* 2002; 94: 1263-1269.