CASE STUDY

Using methadone to treat opioid-induced hyperalgesia and refractory pain

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ABSTRACT

A patient was treated for several years with high doses of opioids for malignant pain. During a recent hospitalization, the patient's pain remained uncontrolled despite escalating doses of various opioids. We suspected that this patient suffered from the clinical phenomenon of opioid-induced hyperalgesia (OIH). The patient was then rotated from her other opioids to methadone, and her pain was adequately controlled within several days. Methadone, because of its NMDA antagonist properties, offers an effective treatment for OIH. The use of methadone for analgesia is complex and should be undertaken only by practitioners who have appropriate experience.

Key words: opioid-induced hyperalgesia, methadone, opioid rotation, opioid tolerance

INTRODUCTION

Opioids are well established as effective and safe for treating acute and chronic malignant and nonmalignant pain.[1-7] There is no absolute ceiling on opioid dose. Authorities report prolonged and effective analgesia for up to six years while using as much as 195 mg of morphine or the equivalent.[1] If a patient's pain remains uncontrolled, it is reasonable to increase the opioid dose until adequate analgesia is achieved, as long as the side effects are tolerable. As practitioners grow more comfortable with the use of high doses of opioids for the treatment of pain, an increasing number of patients, such as the patient described in this case report, will undergo such therapy for extended periods of time.

Tolerance and dependence are predictable results of long-term opioid use. However, a growing body of clinical and laboratory evidence demonstrates that the use of opioids may lead to another problem—the clinical phenomenon of opioid-induced hyperalgesia (OIH).[8-13] In OIH, opioids intended to abolish pain paradoxically lead to increased pain, particularly during rapid opioid escalation.[14] The mechanism for this hyperalgesia is poorly understood.

This case report describes a patient with suspected OIH whose pain was eventually controlled through an opioid rotation to methadone.

CASE REPORT

The patient was a 45-year-old Jamaican woman diagnosed with multiple myeloma in 2005 after presenting with back pain. Her treatment included chemotherapy, in both 2005 and 2006, and, most recently, radiation therapy to her lumbar spine. On Day 30 of a recent admission for an autologous stem cell transplantation, the palliative care service was consulted for assistance with pain management, which had been an ongoing problem during the hospitalization. The patient described pain in her lower spine with radiating numbness from her back to both thighs and calves. She also described numbness and "tingling pain" in both feet, with particular pain in the soles. Pain severity was rated as 10/10 most of the time. She described herself as "suffering" with the pain since her diagnosis, with little relief from a variety of pain medicines, including opioids such as morphine and oxycodone at increasing doses and adjuvant medications.

Imaging studies revealed multiple skeletal metastases, most significantly the complete loss of height of the fourth lumbar vertebral body, with left-sided bony retropulsion; mild disc herniation at L3-L4; and numerous lytic metastases along the lumbar spine, right femur, sacrum, and occipital regions. There was no evidence of cord compression. Physical examination was unremarkable.

Analgesic medications included gabapentin 1,200 mg every eight hours, five 100 µg transdermal fentanyl patches every 72 hours, hydromorphone 25 mg/h via IV infusion, and lorazepam 1 to 2 mg orally as needed for muscular discomfort.

We decided to rotate the patient from IV hydromorphone to methadone. After discontinuing the hydromorphone, the patient was started on methadone 60 mg every six hours by mouth. Hydromorphone at a dose of 8 mg IV bolus was available for breakthrough pain as needed.

Within 48 hours, the patient experienced significant improvement, with pain severity scores dropping to 6/10 and no signs of excessive sedation. Some nausea and vomiting were noted, so an oral antiemetic was given 30 minutes prior to methadone administration. At this point, the patient was weaned off of the transdermal fentanyl. After removal of the fentanyl patches, we waited an additional 12 hours before increasing methadone to a dose of 95 mg every six hours. For breakthrough pain, methadone 5 to 10 mg was available in lieu of hydromorphone.

By Day 6 on methadone, the patient felt remarkable improvement and rarely requested medication for breakthrough pain, though a premethadone antiemetic was still required to control nausea. Although there were no signs of sedation, the methadone dose interval was decreased to every eight hours based on the potential for drug accumulation. The patient was followed for an additional 48 hours, and no change was noted in her status. At discharge on Day 8 of methadone treatment, the dose was further tapered to 80 mg every eight hours, and the patient was told to follow up with the pain service within one week. The patient was extremely satisfied and felt adequate pain control for the first time in months.

DISCUSSION

In situations where pain is refractory to high doses of opioids, a common strategy is to rotate to a different opioid.[15] With OIH, methadone may be the optimal medication for opioid rotation. The advantages for methadone in treating OIH include its incomplete cross-tolerance with opioid receptors and its action as an NMDA receptor antagonist.[13]

We believed the patient suffered from chronic malignant pain that was complicated by extreme opioid tolerance, refractory pain, and OIH. The patient had been treated with opioids continuously for two years and continued to experience 10/10 pain despite treatment with escalating doses of transdermal fentanyl and parenteral hydromorphone, as well as adjuvant pain medications. We implemented the rotation to methadone by first calculating the parenteral hydromorphone to an equianalgesic dose of oral morphine. As the oral morphine-equivalent daily dose exceeded 12 g, we used a conversion ratio of 20:1 when converting to methadone.[16]

Converting other opioids to methadone is complex. When converting from high doses of opioids, lower conversion ratios of methadone are advised. In this case, a conversion rate of approximately 20:1 of morphine equivalents to methadone was sufficient to achieve adequate pain control. Methadone should be used cautiously, and only by practitioners who are experienced with the drug. Methadone has a long half-life—up to 190 hours—and therefore oral methadone dosage should not be increased more frequently than every four days.[17]

At high doses, methadone has been associated with Torsades de Pointes syndrome. Therefore, when treating with high doses of methadone an EKG should be obtained at dosing changes to monitor the Q-T interval. Despite these cautions, with the growing recognition of OIH and refractory pain uncontrolled by opioids, methadone may become an increasingly utilized and necessary option for chronic pain.

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