Case Report

Improved Opioid Analgesic Effect Following Opioid Dose Reduction

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ABSTRACT

Introduction. Traditionally, opioids have been the cornerstone of therapy for patients suffering from cancer pain, regardless of the potential to develop opioid tolerance. In chronic pain patients who experience worsening pain despite increasing doses of opioids, the clinical role of opioid-induced hyperalgesia is gaining more recognition.

Case. Presented here is the case of a 56-year-old man with recurrent squamous cell lung carcinoma and spinal metastases, suffering with intractable 8/10 pain on the visual analog scale in his chest, lower thoracic spine, and upper lumbar spine. He was admitted five times for pain control. In spite of escalating doses of oxycodone, morphine, and hydromorphone, the patient continued to experience severe pain. Also, he endured undesirable sedation, fatigue, and generalized weakness. The clinical picture suggested the possibility of opioid-induced hyperalgesia. We decreased the hydromorphone dose by 40–50% and started methadone. The patient's pain level dropped to a more acceptable 3/10. He was more alert, and his pain was tolerable until his death.

Discussion. Opioid-induced hyperalgesia might be considered in a patient who has no evidence of disease progression, who is on clinically reasonable doses of opioids, and whose pain escalates as opioid doses are increased. A reduction of opioids and the addition of a low-dose N-methyl-D-aspartate receptor antagonist may provide a favorable clinical outcome in those patients who have failed to benefit from opioid rotation and other adjunctive pain treatments.

Key Words. Opioid-Induced Hyperalgesia; Cancer Pain; Methadone; Chronic Pain; NMDA Receptor Antagonist

Introduction

Opioid medications have a long history as the principal therapy for intractable cancer-related pain. Despite some undesirable side effects, many terminal patients are able to improve their quality of life because of the pain control provided by opioids. The notion that opioids may have no “ceiling effect” has contributed to the use of large doses of opioids in oncology patients. However, an increasing body of evidence demonstrates some exceptions to this clinical practice [1]. Even when disease progression is ruled out, some patients do not get pain relief despite high doses of opioids. There are multiple possibilities for such clinical situations. A minority of patients may be suffering from neuropathic pain, for which opioid analgesics might be less effective [2]. Other patients may have a reduced response to opioids because of pharmacodynamic desensitization induced by opioids (i.e., opioid tolerance) and may benefit from...
opioid rotation [3,4]. Decreased response to opioids may also be due to pharmacokinetic and drug delivery factors [5].

Recently, the role of opioid-induced hyperalgesia in clinical situations of reduced opioid responsiveness has been increasingly recognized in chronic pain patients who experience increased pain despite escalating doses of opioids. A considerable number of studies have investigated the cellular mechanisms of opioid-induced hyperalgesia. There is evidence of neuroplasticity occurring in the rostral ventromedial medulla of the brain as well as the dorsolateral funiculus of the spinal cord [6–11]. Among the neural mechanisms of opioid pronociceptive activity, there is substantial evidence describing the downregulation of glutamate transporters in the spinal cord and the activation of N-methyl-D-aspartate (NMDA) receptors [12–15]. Several clinical case reports have shown improvement in cancer patients with neuropathic pain when high doses of oral morphine are successfully converted to methadone, an opioid that may also function as an NMDA receptor antagonist [16]. In addition, ketamine, another NMDA antagonist, has been well described for preventing and treating opioid-induced analgesia [17–19].

Presented here is a clinical case of a patient with intractable cancer-related pain despite receiving very high doses of hydromorphone and undergoing repeated trials of opioid rotation during the course of his pain management. Opioid-induced hyperalgesia was considered a possible cause of his intractable pain, and a substantial opioid dose reduction resulted in significant pain relief.

**Case Report**

A 56-year-old man with a history of squamous cell carcinoma of the lung, status post left lower lobectomy and four cycles of chemotherapy, was initially admitted to the hospital because of a new onset of severe sharp, aching, lower thoracic and upper lumbar pain, rated as 8/10 on the visual analog scale. Before this admission, his moderate pain in the left chest area around the surgical scar had been well controlled for a year by a combination of sustained-release morphine 120 mg three times daily (TID) and immediate-release morphine 60 mg every 4 hours as needed for breakthrough pain. On this admission, a stat magnetic resonance image (MRI) revealed mass lesions in the T12 and L1 vertebrae with paraspinal extension, and a subsequent computed tomography (CT)-guided biopsy verified the recurrence of squamous cell carcinoma. The patient received dexamethasone 10 mg intravenously (IV), and was continued on 4 mg dexamethasone every 6 hours. He was prescribed a morphine PCA (patient-controlled analgesia) for pain control. Radiation therapy was also started on the same admission. The pain intensity decreased to 4–5/10, and the patient was discharged home on controlled-release oxycodone 140 mg every 12 hours, oxycodone 15 mg every 4 hours as needed, and ibuprofen 800 mg three times a day.

During the next month, the patient’s pain became increasingly intolerable, despite increasing the dose of controlled-release oxycodone to 120 mg TID, and immediate-release oxycodone to 50 mg every 8 hours as needed. After several visits to the emergency room, the patient was readmitted for pain control. At that time, the radiation oncology service did not feel he would benefit from radiation therapy, and our neurosurgeons determined that there was no indication for surgical procedures. The patient was then started on a fentanyl patch 200 mcg, controlled-release oxycodone 60 mg twice daily (BID), and a morphine PCA with a 3 mg demand dose every 6 minutes and a 6 mg/h basal rate. As the pain continued to be excruciating, the patient’s palliative care physician increased the PCA settings to a 4 mg demand dose and 10 mg/h basal rate. After a 2-week hospital stay, the patient was discharged on sustained-release morphine 230 mg TID, immediate-release morphine 120 mg every 3 hours for breakthrough pain, and ibuprofen 800 mg TID. The patient was hospitalized again 3 weeks later with agonizing lower back pain in spite of a recent increase of immediate-release morphine dose to 200 mg every 3 hours. A hydromorphone PCA with very liberal settings was started. The patient’s pain was somewhat mitigated, and he went to home hospice with a hydromorphone PCA, programmed for a 4.5 mg demand dose every 12 minutes with a 9 mg/h basal rate.

Over the next several weeks, the patient’s pain continued to be very severe, 7–10/10 in intensity. The palliative care team had been constantly increasing the dose of the hydromorphone PCA until it reached a demand dose of 13 mg every 10 minutes with a 27 mg/h basal rate, a daily dose equivalent to more than 50,000 mg of oral morphine. Ibuprofen 400 mg TID, lorazepam 0.25 mg TID, and lidocaine 5% patch were also used as adjuvant medications. Because of continuous relentless back pain, the patient was hospitalized again. It was his fourth admission within 5 months. A preadmission CT scan demonstrated a slight
interval progression of metastatic lesions at T12 and L1, but a positron emission tomography scan did not identify any additional metastasis. A stat pain management consult was requested, and the patient was seen on the day of admission. He appeared weak, fatigued, and very sedated. Most of the time, he kept his eyes closed. The back pain was rated as 8/10 in intensity, and was described as sharp, stabbing, and aching. Nausea and vomiting, along with somnolence, were also among the patient’s major complaints. The spinous processes of the T12 and L1 vertebrae were painful to pressure, reproducing and exacerbating the patient’s usual pain. No areas of allodynia, hypo- or hyperesthesia, or hyperpathia were identified.

Based on the history of excruciating recalcitrant pain unresponsive to progressively increased mega doses of opioid analgesics, we suspected the development of opioid-induced hyperalgesia in this patient. We recommended decreasing the hydromorphone dose by 40–50% and starting methadone 10 mg BID. A trial of neuroaxial opioids was not recommended at the time because of the short life expectancy of this patient (fewer than 6 months) and his lack of response to intravenous opioid administration. A neurosurgical consultation was also requested to determine the possibility of palliative surgery such as cordotomy. The patient tolerated the decrease of the hydromorphone dose very well. By the fourth day of his hospital stay, the pain intensity decreased to 3/10, he became more alert, did not complain of nausea, and declined any surgical interventions. He was discharged to the hospice on the ninth day after the admission with a hydromorphone PCA (10 mg demand dose every 15 minutes with 20 mg/h basal rate) and methadone 10 mg BID. His pain remained tolerable until his death a month after the last discharge from the hospital.

Discussion

While several factors may possibly contribute to this patient’s pain exacerbation despite a high-dose opioid regimen, opioid-induced hyperalgesia may have contributed to his clinical pain condition for several reasons. First, both radiological and clinical examinations did not reveal significant progression of his cancer with minimal metastatic changes. Second, he had a history of pain exacerbation when his opioid dose was relatively in line with most clinical practice. During that episode of pain exacerbation, his clinical condition was substantially improved with adjunctive therapies without substantially increasing his opioid dose. Third, there appeared to be a temporal correlation between the increase of his pain intensity and the escalating doses of opioid analgesics in which his pain became increasingly intolerable while his daily opioid doses were dramatically increased in a rather short period of time. Of interest, his neurological examination did not reveal overt allodynia and hyperalgesia although spine pain was exacerbated by deep palpation. Fourth, his pain condition was dramatically improved with a substantial decrease in his daily opioid doses without additional surgical or palliative interventions.

The successful management of this patient’s pain with a substantial opioid dose reduction lends some support to the notion that better pain control could be achieved by reducing opioid doses in certain cases [15]. A possible reason of an unsuccessful outcome with opioid rotations in this patient is that a more or less equipotent opioid analgesic dose was continued during each rotation such that the overall opioid dose remained unchanged after each rotation. In addition, methadone, albeit at a low dose, was added into the opioid regimen in combination with a nearly 50% reduction of his daily opioid doses. As pharmacological opioid tolerance would have been present before the dose reduction, methadone may have acted primarily as an NMDA receptor antagonist (without much mu-agonist effect due to tolerance) and reduced the hyperalgesic response [16], which is consistent with the literature on the effect of NMDA receptor antagonists (e.g., ketamine) on hyperalgesia. Therefore, it seems that the combination of opioid dose reduction with a low dose of a clinically available NMDA receptor antagonist (such as methadone) may attenuate opioid-induced hyperalgesia while restoring the opioid analgesic effect through reduced opioid tolerance [15].

In summary, the present case report suggests that 1) opioid-induced hyperalgesia should be considered particularly in patients on high doses of opioid analgesics, and 2) opioid dose reduction in combination with a low dose of NMDA receptor antagonist may provide a beneficial clinical outcome in those patients who have failed to benefit from opioid rotation and other adjunctive pain treatments.

References


