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Opioids including morphine and hydromorphone are widely used for control of moderate to severe pain and dyspnea in hospice and palliative care patients. Accumulation of the active morphine-3-glucuronide (M3G) and hydromorphone-3-glucuronide (H3G) metabolites is one proposed mechanism for the development of neuroexcitatory effects including allodynia and opioid-induced hyperalgesia (OIH). We report the case of a 43-year-old female hospice patient with metastatic non-small cell lung cancer who initially developed allodynia following morphine administration and again following administration of hydromorphone. The allodynia resolved both times following the discontinuation of the opioid and rotation to a different opioid regimen. Potential opioid-induced neuroexcitatory treatment options include opioid rotation to an agent with inactive metabolites, use of adjuvant pain medications for opioid-sparing effects, management of undesired symptoms (e.g., myoclonus), or increasing opioid clearance with intravenous (IV) fluids. Although the incidence is not well defined in the literature, hospice and palliative care clinicians should suspect OIH in patients with allodynia and/or hyperalgesia, especially when repeated dose escalations do not improve analgesia or pain escalates following opioid dose titration.

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Morphine and Hydromorphone-Induced Hyperalgesia in a Hospice Patient

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Abstract

Opioids including morphine and hydromorphone are widely used for control of moderate to severe pain and dyspnea in hospice and palliative care patients. Accumulation of the active morphine-3-glucuronide (M3G) and hydromorphone-3-glucuronide (H3G) metabolites is one proposed mechanism for the development of neuroexcitatory effects including allodynia and opioid-induced hyperalgesia (OIH). We report the case of a 43-year-old female hospice patient with metastatic non-small cell lung cancer who initially developed allodynia following morphine administration and again following administration of hydromorphone. The allodynia resolved both times following the discontinuation of the opioid and rotation to a different opioid regimen. Potential opioid-induced neuroexcitatory treatment options include opioid rotation to an agent with inactive metabolites, use of adjuvant pain medications for opioid-sparing effects, management of undesired symptoms (e.g., myoclonus), or increasing opioid clearance with intravenous (IV) fluids. Although the incidence is not well defined in the literature, hospice and palliative care clinicians should suspect OIH in patients with allodynia and/or hyperalgesia, especially when repeated dose escalations do not improve analgesia or pain escalates following opioid dose titration.

Introduction

MORPHINE AND HYDROMORPHONE are frequently used opioids for moderate to severe pain and dyspnea in hospice and palliative care patients. Morphine and hydromorphone are classified within the phenanthrene opioid class and are metabolized via glucuronidation to active metabolites including morphine-3-glucuronide (M3G) and hydromorphone-3-glucuronide (H3G), respectively, which are renally eliminated.¹⁻⁴ These metabolites do not provide analgesia, but they cross the blood-brain barrier (BBB) and their accumulation may produce neuroexcitatory adverse effects including agitation, myoclonus, seizures, hallucinations, allodynia, and hyperalgesia.²⁻⁵ Allodynia results when non-noxious stimuli are perceived as painful, whereas hyperalgesia occurs when a patient experiences disproportionate responses to painful stimuli.⁶ Pain associated with opioid-induced hyperalgesia (OIH) frequently occurs in a different area of the body, has a dissimilar quality compared with the original nociceptive stimulus, and may be accompanied by myoclonus.^{7,8} One feature of OIH is a paradoxical increase in pain following opioid administration. Although the incidence of OIH is not defined in the literature, it should be suspected

when repeated dose escalations do not improve analgesia or a pain exacerbation results from opioid dose titration.⁹ Given the potential for declining renal function with advanced illness and aggressive opioid use that is often needed to manage pain and dyspnea, hospice and palliative care patients may be at increased risk for opioid metabolite accumulation with subsequent hyperalgesia and allodynia. Hospice and palliative care clinicians should recognize signs and symptoms associated with OIH to avoid subsequent opioid titrations that may worsen pain or lead to further neurotoxicity. We describe the case of a hospice patient who developed allodynia initially from morphine then with hydromorphone to illustrate the importance of recognizing this adverse effect in clinical practice and to discuss potential management strategies.

Case Description

A 43-year-old female patient diagnosed stage IIIB non-small cell lung cancer with bilateral rib metastases was admitted to home hospice. Her past medical history was significant for osteoarthritis, depression, and anxiety. Upon hospice admission the patient reported neuropathic pain from

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her lower back extending down her legs and somatic pain in her knees. Based on the results of magnetic resonance imaging (MRI) of the lumbar spine, her back pain was thought to be related to degenerative changes at L5–S1. Approximately 5 months after hospice enrollment the patient was rotated from fentanyl patches to morphine sulfate extended release 100 mg twice daily due to inadequate analgesia. Fifteen days after the patient was started on morphine, she experienced new onset generalized pain with tactile stimulation that escalated into severe pain to light touch and the inability to move without excruciating pain. The patient rated her pain as a 6/10 on a 0 to 10 scale when lying completely still and a “15 to 20”/10 with movement. Her pain medications consisted of morphine sulfate ER 100 mg orally twice daily, morphine sulfate 60 mg sublingually every 2 hours as needed for pain (approximately 2 doses/day), gabapentin 1200 mg orally 3 times daily, and ibuprofen 800 mg orally 3 times daily. Recent renal function labs were not available in this outpatient setting, so new labs were ordered to evaluate kidney function. Morphine sulfate and ibuprofen were discontinued. The gabapentin dose was decreased and ibuprofen was stopped due to suspected renal impairment, although the results of the patient’s renal function testing were later found to be within normal limits. The hospice team followed up with the patient’s pain physician and her opioid regimen was changed to oxycodone ER 40 mg orally 3 times daily and hydromorphone 8 to 16 mg orally every 2 hours as needed for pain. Her allodynia resolved over the next week.

Sixteen days later, the patient reported an escalation in her back pain with radiation to her legs with movement. She rated this pain as 4/10 when lying completely still and 8 to 9/10 with movement. Nortriptyline 50 mg orally at bedtime was added for additional neuropathic pain coverage and gabapentin was increased to 1200 mg orally 3 times daily. Nine days later, the patient’s allodynia reemerged and peripheral edema was noted. Gabapentin was tapered and carbamazepine 200 mg orally twice a day was initiated as an alternative neuropathic pain treatment. The patient’s breakthrough hydromorphone use gradually increased over the 25 days postopioid rotation, although exact outpatient dose and frequency of administration was not consistently documented.

After the 25-day period the patient reported increased vivid dreams with the sensation of crickets crawling on her. A maximum oral hydromorphone dose of 16 mg, 6 to 7 times daily was noted at this time by the hospice nurse. The patient was transferred to the hospital for initiation of a fentanyl patient controlled analgesia (PCA) and monitoring. Three days later she was discharged home on an intravenous (IV) fentanyl PCA with a 100 mcg/hour basal rate and bolus dose of 25 mcg IV every 15 minutes as needed for pain. The only remaining pain the patient reported after fentanyl PCA initiation was mild somatic knee pain.

Discussion

Both animal and human studies have reported M3G- and H3G-associated OIH and allodynia. Wright and colleagues evaluated the excitatory effects and comparative potency of M3G and H3G after intracerebroventricular (IVC) administration.³ Rats received ICV H3G, M3G, or artificial cerebrospinal fluid (aCSF) injections and were observed for behavioral changes. Results showed H3G administration

produced dose-dependent excitatory behavior induction similar to M3G administration. Smith found that ICV administration of M3G was a potent antagonist of morphine and M6G analgesia.¹⁰ Rats administered 2.5 μ g or 3 μ g ICV M3G 15 minutes prior to or after 20 μ g ICV morphine were observed to have an increase in the incidence of allodynia, hyperalgesia, excessive grooming, tremor, wet dog shakes, opioidergic system activation indicated by raised tails (Straub tail), seizures, and death compared with rats administered morphine 20 μ g ICV alone. Results showed rats given M3G 10 mg intraperitoneal (IP) 30 to 40 minutes prior to morphine 1.5 mg IP had significantly reduced analgesic response compared with morphine 1.5 mg IP alone ($p < 0.05$).

Sjogren and coworkers described a case series of cancer patients who developed hyperalgesia or allodynia with morphine use that resolved following opioid rotation.⁸ The first case was a 19-year-old female with gliosarcoma who was titrated up to 20 g per day of morphine IV over a 14-month period. She experienced hyperalgesia, myoclonus, and allodynia that resolved with rotation to oral methadone. The second case described a 55-year-old female breast cancer patient with bone pain. This patient was being treated with 60 mg of sustained-release morphine daily when she began to experience severe pain and allodynia from wearing clothing. She was switched to oral ketobemidone 40 mg per day, and the pain she previously experienced with touch was alleviated. A third case was that of a 68-year-old woman with breast cancer and bone metastases who developed allodynia while taking 1000 mg of sustained-release oral morphine daily. After rotation to a subcutaneous sufentanil infusion at 1.2 mg per day, the patient’s allodynia resolved. The fourth case report was that of a 10-year-old boy with an astrocytoma and cerebral infiltration who experienced allodynia on 750 mg per day of oral morphine equivalent. The patient’s allodynia disappeared within 2 days of methadone rotation.

In addition to the above case series, Sjogren et al. reported the cases of six patients, four with cancer-related pain and two with chronic, nonmalignant pain who were receiving moderate to high dose morphine via IV, oral, or intrathecal (IT) routes who developed hyperalgesia, allodynia, and/or myoclonus.¹¹ Each of the patients’ symptoms resolved upon rotation to an alternative opioid without active metabolites as such oral methadone, continuous IV sufentanil, or IT fentanyl. The authors obtained plasma and CSF M3G, morphine-6-glucuronide (M6G), and morphine levels from each patient to determine if elevated levels correlated with hyperalgesia, allodynia, and/or myoclonus. Unfortunately, the laboratory results were highly variable and no significant pattern was established. In each case once the morphine was stopped and was substituted with an alternative opioid, the patient’s allodynia disappeared, which is similar to what we observed in our patient.

Parisod and colleagues describe a case of allodynia after a single IT morphine dose in a 66-year-old male paraplegic patient.¹² The patient experienced persistent neuropathic pain from a previous spinal cord injury below T8 that was refractory to IT fentanyl, IV lidocaine, T7–T10 laminectomy, lumbar sympathetic blocks, and a transcutaneous electrical nerve stimulation (TENS) unit along with oral clonazepam, valproic acid, carbamazepine, gabapentin, mexiletine, amitriptyline, doxepin, clonidine, and paracetamol with dextropropoxyphene. Within 2 hours of receiving a 0.5 mg IT morphine

bolus dose the patient reported allodynia over the T6 and T7 dermatomes on his right side. Four days later the patient was given another 0.2-mg intrathecal injection of morphine after which the allodynia recurred.

In a study by Smith et al. 14 opioid-tolerant cancer patients with inadequate analgesia from oral or subcutaneous morphine received ICV morphine and CSF and plasma samples were drawn for morphine, M3G, and M6G concentrations to determine whether intraspinal morphine levels cause neuroexcitatory adverse effects including hyperalgesia.¹³ It was found that plasma and CSF concentrations of M3G decreased after the change to ICV morphine, whereas the CSF concentrations of morphine increased approximately 50-fold. Patients reported pain relief with the ICV morphine and a decrease in excitatory side effects implicating morphine metabolites may be responsible for adverse events and tolerance to systemic morphine.

Several case reports describe OIH in humans who received hydromorphone. Patel et al. describe the case of a 55-year-old male with nonobstructive hypertrophic cardiomyopathy who was receiving IV hydromorphone for acute left-sided chest pain and dyspnea.¹⁴ After administration of 4 mg IV hydromorphone on hospital day 1, the patient's wife reported two episodes of "jerking" movements that increased in frequency with dose escalation on day 2. Electroencephalogram (EEG) results on day 3 showed no seizure activity and the patient's renal function was stable with an estimated creatinine clearance (CrCl) ranging from 72 mL/minute to 79 mL/minute throughout the hospitalization. On day 3 the patient's myoclonus resolved after IV hydromorphone was stopped and the patient was rotated to oral oxycodone.

Chung and colleagues report an episode of hydromorphone-induced neurotoxicity in a 61-year-old male with stage IV transitional cell bladder carcinoma and prostate adenocarcinoma.¹⁵ The patient was admitted to the hospital for an exacerbation of left hip pain with radiation down the left leg and was initiated on a hydromorphone PCA. Over the next 8 days, his IV hydromorphone dose escalated from 23 mg/day to 1890 mg/day with subsequent new-onset hyperalgesia, tremors, confusion, and hallucinations. He was rotated to oral methadone 60 mg every 6 hours and oxycodone 10 mg orally every 3 hours for breakthrough pain. The patient reported improved pain and myoclonus resolution 2 days after methadone rotation. His methadone dose was decreased to 40 mg orally every 8 hours at 48 hours and improvement in mental status by 72 hours was noted.

Forero et al. note a case of OIH and opioid neurotoxicity in a 52-year-old male with chronic low back pain from disk herniation.¹⁶ Over the course of 17 years, the patient received numerous interventions for his poorly controlled pain including a L5-S1 laminectomy, nonsteroidal anti-inflammatory drugs, acetaminophen, oral opioids, nerve blocks, medial branch ablations, physiotherapy, intrathecal morphine, and a spinal cord stimulator. An intrathecal hydromorphone pump was placed at year 11 and the dose was titrated to 12 mg/day over the next 6 years. During year 17, the patient experienced new-onset generalized burning and aching pain that he rated as 9/10. He was admitted to the hospital for a suspected disconnection between the intrathecal catheter and implanted pump. A pump revision was completed under general anesthesia and the patient was started on a hydromorphone PCA. Postoperatively he developed severe lower back spasms and

pain with bilateral radiation down his legs and feet. These symptoms increased with the administration of 12 mg of IV hydromorphone and 10 mg IV morphine over 30 minutes. No evidence of a catheter tip granuloma was observed on computed tomography (CT) scan. The patient emergently received a 15-mg IV ketamine bolus (0.25 mg/kg/bolus) with resolution of his pain and spasms. A ketamine infusion at 3 mg/hour (50 mcg/kg/hour) was started and his IT hydromorphone dose was decreased to 2.5 mg/day. The ketamine infusion was stopped 12 hours later without additional spasms or reemergence of the generalized aching and burning pain. The patient was discharged home 30 hours after his postoperative pain exacerbation on 2.5 mg/day of IT hydromorphone with continued back pain at a level the patient considered acceptable.

Potential opioid-induced neuroexcitatory treatment options include opioid rotation, adjuvant pain medications (e.g., ketamine) for opioid-sparing effects, managing unwanted symptoms such as hallucinations or myoclonus, or increasing opioid clearance with administration of IV fluids.⁵ The primary intervention for my case patient allodynia with both morphine and hydromorphone was opioid rotation to promote metabolite excretion of the previous offending agent. Because the hospice team had incomplete hospital medical records, it is unknown if the patient received IV fluids to promote H3G metabolite excretion or a neuroleptic agent to manage the patient's associated delusions. Converting to one-fourth to one-half the equianalgesic dose is recommended during opioid rotation to a structurally different opioid.^{17,18} During the first allodynia occurrence, the patient was converted to scheduled extended-release oxycodone and as needed oral hydromorphone. Utilizing an equianalgesic conversion ratio of 7.5 mg oral hydromorphone to 20 mg oral oxycodone, the equianalgesic oxycodone equivalent of the patient's oral hydromorphone breakthrough use (96 mg to 112 mg oral hydromorphone = 256 mg to 299 mg oral oxycodone) exceeded the patient's scheduled oxycodone regimen. Oxycodone produced greater analgesic effects compared with morphine in healthy adult volunteers with experimentally induced hyperalgesia.¹⁹ The potential for oxycodone metabolites to produce allodynia and hyperalgesia is not established in the medical literature. It was also noted that when hydromorphone was discontinued and the patient was rotated to fentanyl, an agent within the phenylpiperidine opioid class and with no active metabolites, the patient's allodynia resolved and my patient who was discussed in the case description section had improved analgesia.

Chronic opioid use is also proposed to cause OIH through inhibition of the central glutamate transporter system resulting in increased glutamate availability to the N-methyl-D-aspartate (NMDA) receptors and NMDA receptor activation.²⁰⁻²³ Given methadone's inactive metabolites and NMDA receptor antagonist properties, rotation to methadone would also have been a reasonable pharmacologic option. Unfortunately, our case patient would not accept a methadone trial due to a previous episode of suspected pulmonary inflammation. Fentanyl and methadone maintain analgesia without producing active metabolites. Additional allodynia treatment options include initiation of neuropathic pain adjuvant medications, for example, ketamine, nortriptyline, carbamazepine, and gabapentin.

Both M3G and H3G metabolite accumulation can induce allodynia and hyperalgesia.^{3,8,10-12} It has also been described

that when opioid rotation occurs to an agent with inactive metabolites allodynia or hyperalgesia may resolve.^{2,24} As far as we know, this is the first case of OIH secondary to both morphine and hydromorphone reported in a hospice patient, which resolved following opioid rotation. Hospice and palliative care clinicians should recognize OIH signs and symptoms in order to avoid subsequent opioid titrations that may contribute to the cycle of increasing pain or distressing allodynia.

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Author Disclosure Statement

No competing financial interests exist.

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