

Morphine-induced Myoclonus in a Patient with End-stage Renal Disease

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Introduction and Patient Profile: Pain is a common complaint, and pain control is frequently challenging. End-stage renal disease (ESRD) patients constitute a special population in whom commonly prescribed medications, including pain medications, must be adjusted or discontinued for safety. We describe a patient with ESRD in whom myoclonus developed after he received 60 days of morphine.

Interventions and Outcomes: Morphine was discontinued, and symptoms resolved.

Discussion: Morphine is hepatically metabolized to morphine-3-glucuronide (M3G), which is renally cleared. In patients with ESRD, M3G and other metabolites are neither renally cleared nor easily removed by dialysis, increasing the risk of neuroexcitatory symptoms such as myoclonus. The use and dosing of renally cleared medications in ESRD patients should be carefully reviewed by prescribers and pharmacists.

Keywords: end-stage renal disease; dialysis; myoclonus; morphine; opioid rotation.

INTRODUCTION AND PATIENT PROFILE

The patient presented is a 59-year-old African-American man with end-stage renal disease (ESRD). ESRD is a subset of chronic kidney disease (CKD) stage 5, in which patients undergo dialysis or receive a kidney transplant. Patients with CKD stage 5 have a glomerular filtration rate (GFR) < 15 mL/min, and such patients frequently do not have sufficient nephron mass to properly filter toxins from the blood and to maintain fluid and electrolyte balance.

The patient presented with an infected stage 4 decubitus ulcer. He reported discharge from the ulcer as well as increasing pain, for which he had been prescribed morphine sulfate 30 mg orally twice daily starting 60 days prior to admission. The ulcer, located in the sacrococcygeal region, was the site of *Pseudomonas* and *Klebsiella* osteomyelitis, for which the patient had recently completed 6 weeks of treatment with doripenem. He was afebrile and without leukocytosis, and computed tomography of the spine revealed acute-on-chronic osteomyelitis. The patient was empirically retreated with meropenem and local wound care therapy. The patient continued to receive dialysis three times weekly, with only one missed session due to pain from the infected ulcer. He was continued on

scheduled morphine and acetaminophen–codeine for breakthrough pain.

The patient noted a jerking movement in the upper extremities that had progressively worsened over the previous 2 weeks. At first, this symptom was an inconvenience, but it soon progressed to an interference with his activities of daily living. He was unable to feed himself because he could not hold utensils or cups. Neurology diagnosed him with myoclonus, which was attributed to uremia. Uremia seemed an unlikely cause, however, since myoclonus did not correlate with levels of blood urea nitrogen (BUN), which were low and at baseline because of adequate dialysis. Moreover, he did not have other symptoms of uremia such as nausea, vomiting, hiccups, peripheral neuropathy, pericarditis, asterixis, or altered mental status.

The differential diagnosis for myoclonus also included seizures, osteomyelitis, and side effects of other medications. The patient had no history of seizures, and neurology ruled out this possibility. Osteomyelitis was also believed to be unlikely because the patient had been undergoing treatment with antibiotics and his infection improved during the course of hospitalization. Finally, there had been no changes to the

patient's medication regimen besides the morphine previously mentioned.

INTERVENTIONS AND OUTCOMES

After ruling out other causes of myoclonus, the patient was evaluated for the possibility of opioid-induced myoclonus. Pain management specialists agreed to switch his regimen from morphine sulfate to hydromorphone hydrochloride 4 mg orally every 4 hours and a fentanyl 25 µg transdermal patch every 72 hours. After discontinuing his morphine, his myoclonus resolved within 2 days.

DISCUSSION

Morphine, although effective for pain control, can be dangerous at high concentrations. The presentation of morphine toxicity may vary from myoclonus to respiratory depression and coma. The most severe consequences of morphine intoxication are apnea or aspiration of gastric contents. Therefore, in patients who have difficulty excreting morphine, such as those with CKD stages 4–5, morphine is not recommended.¹ Unmetabolized morphine is eliminated without difficulty in patients with CKD; however, only a fraction of an administered morphine dose remains unmetabolized. Most of the parent compound is metabolized by the liver to products that are not effectively renally cleared in patients with CKD. These metabolites thus accumulate, and the ratio of metabolites to morphine may be increased by 5.5–13.5% in patients with CKD.² Although both morphine and its metabolites are partially cleared by hemodialysis, rebound of serum levels can occur between dialysis sessions due to mobilization from tissue stores.³

Morphine undergoes glucuronidation by uridine 5'-diphospho-glucuronosyltransferase (UGT2B7) in the liver. The products are morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). M6G is more potent than morphine itself and is responsible for most analgesic effects. M3G has little affinity for the opioid receptor, and therefore does not play a role in pain relief.⁴

Once a threshold concentration of M3G is reached, neuroexcitatory effects including myoclonus and seizure may occur.⁵ The exact mechanism of neurotoxicity is unknown, but activation of *N*-methyl-D-aspartate receptors, leading to a rise in intracellular calcium and subsequent neurotransmitter release has been postulated. Interestingly, only morphine metabolites, not morphine itself, cause these side effects.⁵ Those that develop these symptoms have been changed from

systemic to intraventricular morphine with resolution of symptoms, likely because direct injection of morphine into the cerebrospinal fluid bypasses hepatic metabolism and generation of M3G.⁵

One approach to the treatment of neuroexcitatory side effects is opioid rotation, in which one opioid is switched to another in order to diminish toxicity of specific metabolites or to improve effectiveness. With this strategy, substitution of a chemically distinct opioid at an equivalent dose results in similar analgesia while avoiding side effects.⁶ In one study, patients with CKD who did not tolerate morphine were switched to oxycodone, whereupon concentrations of morphine metabolites were five to six-fold lower. Higher doses of oxycodone than morphine were thus tolerated with improved pain control.⁷

In this case, the regimen was changed from morphine to hydromorphone and fentanyl. Hydromorphone is hepatically metabolized to hydromorphone-3-glucuronide (H3G), which is structurally similar to M3G and mimics its neuroexcitatory effects.⁸ Hydromorphone, as morphine, should be used cautiously in patients with CKD, with a recommended starting dose of 0.5–1.3 mg every 6 hours.^{9,10} The patient was prescribed 4 mg every 4 hours as needed, but we were unable to follow up with him after discharge to determine whether he required the maximal dosage of hydromorphone prescribed, and if so, whether myoclonus recurred. One study showed that patients with CKD who were changed from morphine to hydromorphone experienced greater pain relief with fewer side effects.¹⁰

The use of opioids to control pain is problematic in patients with decreased kidney function. CKD alters the pharmacokinetics of opioid metabolism, specifically, the rate of elimination, volume of distribution, carriage by serum proteins, and acid–base status. Furthermore, many commonly used opioids have not been well studied in patients with CKD or ESRD, and more research, including epidemiology and extent of the problem, is needed to develop guidelines for pain control in this population.

LEARNING POINTS

1. Patients with CKD stage 5 have a GFR < 15 mL/min and an inability to properly filter the blood and maintain fluid and electrolyte balance. ESRD is a subset of CKD stage 5, in which patients require dialysis or kidney transplantation.

2. Morphine and its metabolites are renally excreted, so morphine should be used cautiously or avoided in patients with CKD or ESRD.
3. Morphine metabolism produces two products, M3G and M6G. M6G is responsible for the analgesic effects of morphine, while M3G produces the neurotoxic side effects.
4. Morphine toxicity symptoms include pinpoint pupils, nausea, vomiting, constipation, myoclonus, coma, and respiratory depression.
5. One way to treat morphine toxicity is with opioid rotation, in which morphine is switched to another opioid with a different chemical structure.
6. More research is needed to develop guidelines regarding opioid use in CKD and ESRD patients.

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