Morphine toxicity in renal failure
Ferraz Gonçalves, MD

INTRODUCTION

A 60-year-old female with a plasmacytoma of the right clavicle, diagnosed in March 2000, was treated surgically. The follow-up revealed a multiple myeloma of K light chains. The patient was treated with chemotherapy (melphalan and prednisolone) and later with the VAD regimen (vincristine, adriamycin, and dexamethasone). In June 2003 she underwent a bone marrow autotransplantation. In March 2005 a relapse was detected, with concurrent renal failure and hypercalcemia. She was treated with intravenous fluids, furosemide, calcitonin, and pamidronate, and following that she began treatment with thalidomide and cyclophosphamide.

In September 2005 she was admitted to the hematology-oncology service, again with renal failure and hypercalcemia. As she also had osseous lower back pain, she was started on tramadol in increasing doses, which was later changed to modified-release morphine (30 mg every 12 hours). A few days later she was referred to palliative care.

On admission to the palliative care unit, she was diagnosed with mild lower back pain and mild somnolence. She maintained the morphine treatment she had been subject to for the previous few days. She also continued with the other drugs she had been using, including antidepressants (amitriptyline 50 mg and trazodone 100 mg at bedtime) and bromazepam (3 mg at bedtime); she had been on all of the sedative medications for months. On the second day, she had no pain and was mildly somnolent. On the third day she was very drowsy, opening her eyes only when strongly stimulated; respiratory rate was eight to nine breaths/minute, hemoglobin saturation (SaO₂) was 83 percent, body temperature was 39°C, and on physical examination there were widespread rhonchi. Serum creatinine was 2.8 mg/dL (normal range: 0.6 to 1.2 mg/dL), and ionized calcium was 3.8 mEq/L (normal range: 2.3 to 2.8 mEq/L). She was treated with naloxone 0.4 mg (1 mL) diluted in 9 mL of normal saline solution (total volume 10 mL), with 1 mL delivered every two minutes until SaO₂ greater than 90 percent was achieved. She needed to be given naloxone four times—6 mL, 4 mL, 9 mL, and 6 mL, respectively—over a period of 12 hours. She was also hydrated and was started on intravenous antibiotics and 90 mg of pamidronate after hydration; the morphine and all oral medications were suspended. The following day she was somnolent but responsive, with SaO₂ greater than or equal to 90 percent and with no fever. On the fifth day she was awake but confused, with the pain controlled and SaO₂ greater than or equal to 90 percent; creatinine was measured at 2.4 mg/dL and ionized calcium at 3.5 mEq/L. Cognitive function recovered quickly afterwards, and calcium normalized slowly after the patient was started on dexamethasone. After the patient was discharged, the pain was controlled by a daily oral dose of 400 mg of tramadol, with normal-release morphine prescribed 10 mg orally as needed. In the follow-up at the outpatient clinic, she needed to change to a moderate-to-severe-pain opioid, and she started transdermal fentanyl 25 μg/h; this was gradually increased to 75 μg/h without toxicity.

DISCUSSION

There are several reasons for why this patient developed deep sedation and respiratory depression. She had renal failure, hypercalcemia, and an infection, and she was taking sedative medication and morphine, all of which can cause sedation. However, the improvement with administration of naloxone suggests that morphine was the main culprit behind the respiratory depression.

Morphine is primarily metabolized in the liver, and the most important metabolites, morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G), are excreted in the urine. Minor metabolites are normorphine, morphine-3,6-diglucuronide, and morphine sulfate. In renal failure there is a decrease in the clearance of morphine metabolites, resulting in a rise in their plasma concentrations. The increase in the plasma concentration of morphine is typically small, since morphine continues to be metabolized.1 The role and effect of the M3G is still unclear, but it is not believed to be a significant analgesic. M6G, on the other hand, is a more potent analgesic than morphine. There has been particular interest in the role of M6G in the analgesic and adverse properties of morphine,1,5 especially in cases of renal failure. The accumulation of M6G...
has been seen as the main cause for morphine toxicity in renal failure. However, there are many patients with high concentrations of M6G due to renal failure who do not show signs of toxicity. The explanation could be the existence of protective genetic factors or the development of tolerance. There also might be other risk factors that contribute to toxicity, such as drug interactions or disease states. Another factor could be the roles of other morphine metabolites. Therefore, the exact mechanism of morphine toxicity in renal failure is not yet fully understood.

As occurred with the case described above, the toxicity of morphine generates a vicious cycle initiated by somnolence and decreased liquid intake, leading to further deterioration of renal function and then a decrease in respiratory rate; this is eventually followed by respiratory infection and, if this cycle is not interrupted, death.

On the occurrence of renal failure, alternative opioids (for moderate to severe pain) to morphine can be considered. Methadone or its metabolites do not accumulate in renal failure because they are excreted almost exclusively via the feces; therefore, methadone can be a very useful drug in patients with renal failure. Hydromorphone also seems to be safe, even in end-stage renal failure, as was concluded in a recent retrospective study; however, high doses of hydromorphone in patients with renal failure can be associated with nausea and delirium. Buprenorphine is a partial agonist that can be administered by parenteral, sublingual, and transdermal routes; it is another opioid that can be useful in selected cases of pain in patients with renal failure, for whom it appears to be a safe drug. Fentanyl, which can be administered by intravenous, subcutaneous, and transdermal routes, also seems to be safe in such patients; however, life-threatening respiratory depression can occur in patients with severe renal failure who are administered transdermal fentanyl. Alfentanil and sufentanil are also safe drugs for patients in renal failure; however, they must be used intravenously or subcutaneously.

Although there are a number of alternatives to morphine for patients with renal failure, for various reasons they are not an option in certain circumstances. If we consider this in a worldwide context, we will find that not all the options described above are always available. For example, in relation to oral opioids, in Portugal methadone is available for treating drug addicts but not for pain control, and hydromorphone and sublingual buprenorphine are not available at all; transdermal buprenorphine and fentanyl are available, but these formulations are not flexible enough for dose titration, and we can easily think of countries in which these drugs are unavailable because they are too expensive. Injectable drugs can be useful in inpatients, but they are usually not suited for an outpatient clinic, although syringe drivers can be used in this setting. The point is that although morphine is not the ideal drug for pain control in renal failure, there are circumstances in which useful alternatives to morphine are not available. Morphine can be used in patients with renal failure, although it must be used carefully. A normal-release preparation is preferred to a modified-release one because, as it has a shorter half-life, it is more flexible and can be reduced or suspended if significant toxicity develops, with effects that are not as prolonged. In this situation, low dosages and schedules that are broader than the usual four-hour one can be used, with extra doses as required and with close monitoring; it is a prudent way of using morphine in renal failure. Alternatively, the dose titration can be done with a normal-release preparation administered every three to four hours as required until the pain is controlled, and then changed, with the same total 24-hour dose, to a regime of every six, eight, or 12 hours. If extra doses are still needed, the dose can be increased by about a third approximately every three or four days.

The goal of the treatment of respiratory depression due to chronic use of morphine or other opioids is to prevent death. If that danger is not present, though, because the patient can ventilate adequately, there is no need to intervene beyond careful observation and reducing or temporarily withdrawing the dose of the opioid and starting later on with a lower dose. In more severe cases, naloxone can be used via intravenous, subcutaneous, and/or intramuscular routes. It can be used as both a bolus and a continuous infusion, but I favor the intravenous use of naloxone in small boluses. The reason is that the goal, in patients chronically using opioids, is to mitigate the risk of death due to respiratory failure, as stated above, and not to immediately normalize the level of consciousness; if a complete reversal of adverse effects is attempted, pain, withdrawal syndrome, and the activation of the sympathetic system, with tachycardia, arrhythmias (including ventricular fibrillation), and high blood pressure may ensue. Therefore, what must be done in these cases is to provide small boluses of naloxone, as described in this case report, under close surveillance. If an oximeter is available, attempts should be made to ensure \( \text{SaO}_2 \) greater than or equal to 90 percent; if such equipment is not available, then the goal is to attain a respiratory rate greater than or equal to 10 breaths/minute and the reversal of cyanosis. The action of naloxone is short-lived, with a serum half-life of about one hour; therefore, repeated doses may be necessary.

ACKNOWLEDGMENTS

This paper was supported in part by the North Section of the Portuguese League Against Cancer.

Ferraz Gonçalves, MD, Unidade de Cuidados Continuados, Instituto Português de Oncologia, Porto, Portugal.
REFERENCES