Rotation among opioids to minimize side effects and improve analgesia is a common clinical strategy in pain and palliative care. Methadone is frequently prescribed during opioid rotation, either by mouth or intravenously (IV) with patient-controlled analgesia (PCA) at home. However, there is a lack of consensus on rotation strategies from other opioids to methadone, as well as on conversion ratios. As a result, strategies for achieving rotation vary widely, among not only providers, but also institutions.

Clinical decisions surrounding opioid rotation must take into consideration the patient's overall medical condition, the expertise and comfort level of the prescribing physician, the medical evidence, and institutional guidelines, in addition to goals of care. The following case study and discussion refers to all of these aspects of opioid rotation and depicts an example of conversion and use of parenteral methadone for refractory pain due to cancer.

**CASE PRESENTATION**

Mr A is a 64-year-old retired engineering consultant with stage IV non–small-cell lung cancer, who presented to the palliative medicine outpatient clinic with worsening low back pain, delirium, anorexia, and marked decline in physical functioning. The patient had been diagnosed with metastatic disease to the spine, hip, liver, and brain and had been on multiple chemotherapy regimens. The palliative care team was asked to respond to his urgent pain crisis. The patient’s specific pain complaints included worsening mid-lower back pain over the past week, rated at a severity of 7/10 on a numerical rating scale (NRS) with minimal relief from immediate-release breakthrough medication (80–100 mg liquid oxycodone in 24 hours). He also had been taking a standing dose of oxycodone extended release dosed at 60/40/60 mg 3 times/day. He had experienced 1 episode of vomiting, creating the possibility that 1 dose was not absorbed the previous night. He experienced minimal pain relief with ibuprofen 600 mg. He described the pain as dull and aching, without any radicular component. Relieving factors were recumbence on a heating pad, but worsened on resuming an upright position. He did not report any motor weakness or sensory impairments.

Other symptoms included worsening delirium, which was compounded by use of oxycodone, and also profound fatigue and lassitude. He also reported tremors, dysphagia with medication, and associated gagging, nausea, and vomiting. He was tolerating liquids inconsistently but not solid foods. He had not had a bowel movement in 2 weeks, despite oral naloxone and lactulose. He had begun to develop some urinary retention over the last few days and complained of difficulty starting a stream.

**MEDICAL HISTORY**

Mr A had been diagnosed with an 858 mutation in the epidermal
growth factor receptor gene and initially was prescribed erlotinib, then subsequently switched to gefitinib. He experienced cancer progression despite multiple combination chemotherapy regimens. He also had been treated with palliative external beam radiotherapy to his hips, lumbar spine, and brain, and he underwent a vertebroplasty after a spinal lesion caused significant disability. Mr A also had a history of prostate cancer; he was treated with surgery in 1994 and was thought to have no evidence of disease. Additional diagnoses included chronic obstructive pulmonary disease from chronic tobacco use, gastroesophageal reflux disease, dyslipidemia, and restless legs syndrome.

He was taking multiple medications, including phenytoin sodium prescribed to him following a seizure caused by brain metastasis, which created a possibility for drug interactions if he were prescribed methadone. He reported some cancer history in his family.

**Physical Examination and Laboratory Results**

On physical examination, Mr A did not appear to have any signs of cutaneous hyperalgesia, although he did have myoclonus. Neurologic findings did not suggest cord compression or worsening lesion to the spine, although he was experiencing mild confusion and difficulty with word finding. He did have point tenderness throughout his thoracic and lumbar spine. Laboratory reports showed anemia with elevated liver function tests. Radiology showed diffuse metastatic disease to the C-spine and interval development of a deposit at the T2 pedicle with some extension.

Our assessment suggested severe cancer pain that was unresponsive to increased oxycodone titration, along with likely neurotoxicity and opioid-related side effects resulting from the rapid titration. Initially, we were concerned that the symptoms Mr A presented may be attributed to opioid-induced hyperalgesia (OIH) syndrome, secondary to escalating doses of oxycodone; however, he was found to have local tenderness and no cutaneous hyperalgesia. He reported that he had some mental clarity before the titration of oxycodone. The decision was made to admit the patient to the palliative care service and to initiate rotation to parenteral methadone for analgesia and management of side effects.

**Opioid Rotation to Methadone**

We began by reviewing Mr A’s opioid requirements in the previous 24 hours: oxycodone 240 mg is approximately equal to morphine 360 mg. Assuming a 5:1 or 10:1 morphine-to-methadone conversion, we calculated his dose at approximately 60 mg of methadone daily. Assuming approximately 70% to 95% bioavailability orally is approximately equal to IV, the team decided to assume a 1:1 conversion of orally to IV, as opposed to the typical starting dose of half of the oral dose for IV conversion. IV methadone PCA was administered with a basal rate of 2.5 mg an hour and a PCA dose of 2.5 mg with the ability to titrate every 30 to 40 minutes. Loading doses of 5 mg were also available in case of pump failure or extreme pain.

**Inpatient Follow-up**

Mr A responded remarkably well. On day 1, his pain severity dropped on an NRS from 7/10 to 2/10 following only 2 PCA doses in 24 hours. We initiated a trial of olanzapine for his delirium. Within the first day, we noted some decrease in his myoclonus, nausea, and vomiting, and he had a bowel movement. Functionally, he was able to ambulate in the corridors in the hallway, whereas previously he had been barely able to rise from his chair. On day 2, the IV methadone was discontinued, and the basal rate was converted to a methadone elixir of 20 mg taken sublingually 3 times/day, maintaining the 1:1 conversion. The IV methadone PCA was continued for breakthrough pain. On day 3, IV PCA was discontinued as the patient reported excellent analgesia. Delirium persisted, although he had fewer vomiting episodes. He was started on buccal mucosal fentanyl 200 µg in the hospital for breakthrough pain with good effect and discharged home that evening with the Visiting Nurse Association’s “bridge to hospice” program for continuing palliative and
supportive care. He was seen for follow-up in the outpatient cancer clinic 5 days later and was markedly improved. In the home setting his cognitive function improved. He was taking the sublingual methadone elixir 20 mg 3 times daily, fentanyl 200 µg once daily, and continuing the olanzapine twice daily for treatment of delirium and nausea. He rated his pain as 2/10, and his function had improved vastly. He was able to perform activities of daily living at home and outdoors.

This case study illustrates a patient who had a severe toxic reaction to opioids who was successfully rotated to methadone with markedly decreased toxicity and adequate analgesia.

METHADONE CONVERSION: A REVIEW OF THE LITERATURE

Was the palliative care team’s decision to undertake a 5:1 or 10:1 (morphine to methadone) conversion ratio for this patient rational according to the medical literature? There is significant variability in the medical literature and across institutions surrounding methadone conversion practices. In the literature, the equianalgesic tables are based on single-dose studies. The morphine-to-methadone ratio is typically reported as 1:1 for parenteral dosing, and 3:1 or 3:2 for oral dosing. The earlier equianalgesic tables recommended a conversion ratio of 10 mg of morphine to 1 mg of methadone. For hydromorphone, the equianalgesic conversion ratio to methadone was reported as 1:1 conversion for hydromorphone less than 330 mg, and 1.6:1 for higher doses of hydromorphone. Further study revealed that prior opioid dose was a significant determinant of the conversion ratio. At equivalent morphine doses of less than 1 g/day, the median dose ratio between morphine and methadone was 5.42. For higher doses of morphine, the median dose ratio was 16.84. The first prospective trial to define equianalgesic dose ratios for morphine to methadone established the conversion standard of 4:1 for morphine doses less than 90 mg, 8:1 for doses 90 to 300 mg, and 12:1 for higher morphine doses. A subsequent study of rapid switching from morphine to methadone in patients with cancer found that a fixed ratio of 5:1 was safe and effective in patients with cancer who had poor morphine response. Building on these findings, a recent study confirmed that doses of the prior opioid exposure are significant determinants for the dose ratio conversion for methadone and further defined morphine doses as part of the conversion. Whereas the opioid rotation calculations in this study ranged from 3:1 for morphine doses less than or equal to 100 mg to 20:1 for doses greater than 1000 mg, from a clinical perspective the proposed calculations create a ceiling for the starting dose of methadone when converting from morphine (eg, daily oral morphine dosages of 300 mg, 600 mg, 900 mg, and 1200 mg all convert to 60 mg of methadone). Finally, in a small study, terminally ill patients with cancer who rotated from morphine to methadone had a mean conversion ratio of 5.2, with wide interpatient variability ranging from 1.3 to 11.

The published literature on rotation to IV methadone is limited only to case reports. Four patients with cancer-related pain treated with continuous IV morphine and hydromorphone were switched to IV methadone. Patients experienced excellent analgesia at a dose that, based on conversion charts, was only 3% of the calculated equianalgesic dose of hydromorphone (Table). Another case report described a patient converted to methadone PCA with a 1:1 equianalgesic conversion. He was using a morphine PCA at home (incremental dose of 15 mg every 6 minutes) with a continuous infusion rate of 80 mg/hour, resulting in an average daily con-
sumption of approximately 2200 mg of morphine. Morphine was discontinued and replaced with instituted PCA methadone (incremental dose 10 mg every 6 minutes) with a continuous infusion of methadone at a rate of 40 mg/hour. His initial infusion basal rate was thus reduced by 50%, and the PCA dose by 33%, with satisfactory pain control and no side effects. Over the course of 5 days the treating physicians incrementally reduced infusion and PCA doses to prevent drug accumulation. It is important to recognize that they continued to titrate down based on clinical observations, which are essential to safe and successful conversion. Conversions based on these reports have not been well tested, and therefore serve only as a guide for treatment decisions, based on sound clinical observation and assessment of the patient's status. Only 1 study appears in the medical literature describing conversion of IV fentanyl to IV methadone. In that study, 18 patients were converted from 25 µg/hour of fentanyl to 0.1 mg/hour of methadone without toxicity.12

CONCLUSIONS

The published literature on methadone conversion is far from prescriptive. It constitutes a starting point for an individualized approach to methadone tailored to the patient's condition, age, and individual response. For example, in the case of Mr A, one might argue for initiating treatment with a methadone PCA at a much lower basal rate. However, as this case demonstrates, the patient tolerated higher dosages without any increase in side effects. There is much room for lively debate on proposed conversion rates and approaches to treatment.

DISCUSSION

Dr Shaiova: We have been addressing issues surrounding receptor variability and the fact that very high doses of morphine convert to a very low starting dose of methadone. But within that framework, why is there no real discussion about morphine resistance?

Dr Bruera: Animal studies have demonstrated that methadone has the ability to delay or reverse opioid tolerance in humans. Nonetheless, there is a widespread ideological barrier to accepting the development of opiate tolerance—much the same as the ideological barrier we had surrounding patient pain assessment that took 15 years to penetrate. If there is no opioid tolerance, then how do you explain that a patient who is taking 300 to 600 mg of morphine nonetheless develops a bad toothache or abdominal pain? At that dose, we should be able to amputate the patient's toe! In my opinion, the opiate is starting to fail to have antinociceptive effect, signaling a previous opiate failure rather than nociceptive escalation.

In his presentation, Dr Blinderman mentioned the fact that morphine dosing typically rounds up about 60. That is quite true now, but 10 or 15 years ago it was common for people to be dosed at 5000 to 7000 mg of morphine-equivalent dose before opiate rotation became common practice. Today, such high dosing occurs rarely. I personally think that it is not that nociception has changed in our patients with cancer. I think we are doing something that is limiting tolerance development.

Dr Davis: Morphine is a partial agonist thus you get a therapeutic ceiling at increasing doses. You have to bind more receptors and activate more G proteins for response than full opioid receptor agonists. When you rotate to another opiate, the opioid ligand binds differently, further altering G protein activation, which re-establishes analgesia. Thus, although methadone binds to the same receptor as morphine, it works differently at the cellular level because of differences in receptor activation and the degree to which the receptor is activated.

Dr Shaiova: Dr Pasternak’s recent research shows that when opiate-naïve animals receive equianalgesic doses of 5 different opiates, those treated with morphine or morphine-6-glucuronide do not get analgesia at all.13 However, those dosed with heroin, acetyl-6-morphine, or levorphanol tartrate all obtain analgesia.

Dr Davis: The real question is whether it is appropriate to use a linear equianalgesic conversion to methadone for patients who are taking 450 to 1000 µg of fentanyl per hour.
The question has yet to be answered. We recently converted a patient with OIH from 1000 µg fentanyl to IV methadone with a final ratio of 1:5, although the Mercadante conversion table recommends a ratio of approximately 1:20.14 In normal dose ranges the ratio may be correct, but when you get to the higher doses there is a difference that may be clinically significant. Another important point to consider is that in the cancer setting, inflammatory cytokines down-modulate CYP3A4 expression. You cannot take equianalgesic ratios in the patients without cancer and apply them to patients with cancer.

**Dr Berger:** I would urge a very conservative approach to conversion. I was on 50 µg of IV fentanyl an hour. We started at a dose of 5 mg every 8 hours for 3 days and then went down to 2.5 mg every 8 hours. We reduced the suggested conversion dose by 50%, which is the approach I also take in clinical practice.

**Dr Blinderman:** But shouldn't we consider the patient setting? The hospice patient at home with metastatic cancer pain, the postoperative patient who is being opioid rotated, or the patient with chronic pain syndrome—these are all very different clinical settings with different treatment goals. In the case of Mr A, we were very happy to see that he was very functional and that was a primary therapeutic goal. And in your case, Dr Berger, sedation and compromised functioning would not have represented an acceptable quality of life because you were eager to return to your medical practice. Therapeutic goals must be balanced against the individual's needs, concerns, and quality of life.

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**Dr Perlov:** Another practical consideration is how to establish the dose you are converting from. For example, consider the patient who is well controlled on 200 mg daily of oxycodone. Then for a reason, which often is not fully understood—be it progression of disease or opioid tolerance or psychological suffering—the patient experiences an increase in pain. You may triple the dose without significant improvement in pain. Which dose of oxycodone do you use for conversion, 200 mg or 600 mg?

**Ms Derby:** Yes, the equianalgesic table is our starting point, and it is so variable, particularly for oxycodone and morphine. Another question that I have is when you determine the 24-hour dose of drug A, do you use around-the-clock dosing or do you also factor in the rescues? That could change the final equianalgesic dose tremendously.

**Dr Bruera:** This is a very good point because if you dosed at 200 mg yesterday and at 800 mg today, you should probably establish an oxycodone conversion dose somewhere between 200 to 800 mg because the patient truly is not stable at 800 mg. Another important consideration for conversion is nonopiate receptor side effects. Patients who need to be rotated because of myoclonus and hyperalgesia, as opposed to opioid tolerance, may require a much more conservative conversion strategy.

**Dr Shaiova:** And in the setting of illicit drug use, the conversions become extremely difficult. We are converting street bags of heroin to methadone. For drug abusers, those who are on methadone maintenance of 90 mg/day and who use 6 bags of heroin a day, we initiate them on 15 mg of IV methadone on day 1, and it is still inadequate analgesia.

**Dr Bruera:** When a provider is treating an illicit drug user who requires analgesia, the provider should consult with a palliative care expert immediately. Such cases are entirely too complex to be treated by nonspecialists. On the other hand, hospice physicians, oncologists, general internists, and other nonspecialists use methadone quite well in other patient populations. The need for extreme caution is based on the patient population.

**Ms Derby:** I think assessment is really the key here. We see many medication errors attributed to opioids, and patients are treated with naloxone, when in fact the sedation is caused by lorazepam.

**Dr Shaiova:** Or patients with lung cancer may be given naloxone because they are somnolent and delirious when in fact they need an O2 cannula to deliver oxygen.

**Dr Inturrisi:** I would agree that everyone focuses on the conversion number. But it is all of the other considerations that may be even more important. You can miss the number, but if you monitor carefully, you are eventually going to achieve the desired therapeutic
result. Physicians have a tendency to only read the conversion table, but the descriptive text is perhaps even more important. The tables are based on confidence intervals, and the intervals are enormous.

**Dr Pappagallo:** All of these points are well taken. It is also important to stress that primary care physicians must follow these patients closely. It is important for primary care providers and other specialists to assess patients for depression, insomnia, anxiety, in addition to opioid tolerance. The threshold for referral to pain specialists should be very low. Unfortunately, there are only 6 board-certified pain physicians per 100,000 adult patients with chronic pain. If children are included in the ratio, then we only have 4 board-certified pain physicians per 100,000 patients with chronic pain in the United States.¹⁵

**Dr Kalman:** Heart failure as a specialty is quite similar, as there are not enough specialists to treat the millions of patients with heart failure. We encourage the creation of educational programs to impart the specific knowledge of specialized heart failure management to the primary care physician. I believe the pain management field would benefit from this as well, in which the model of specialized care is then carried out by the general physician. The use of physician extenders is also critical.

**Dr Davis:** The problem is deep because we did a study looking at opioid prescribing patterns in patients before referral to a pain specialist. We found errors in dosing approximately 80% of the time. These errors covered a broad range, such as around-the-clock dosing for chronic pain, provision of laxatives, and combining opioids in a way that did not make sense clinically. Thus the prescribing history is another confounding factor for the pain specialist to consider. And such errors point to a critical need to educate nonspecialists on appropriate assessment, dosing, and monitoring practices.

**REFERENCES**