Authors’ Response

To the Editor:
We are delighted to hear of Dr. Reddy’s success with a percutaneous approach. It represents a logical extension of the principles and experience summarized in our article. More study is needed to enable the optimal application of these techniques for the benefit of our patients.

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Methadone for Refractory Cancer Pain

To the Editor:
In the United States, moderate to severe chronic cancer pain typically is treated with morphine, hydromorphone, oxycodone or fentanyl. Individualization of the dose through a process of dose titration usually is successful in achieving a favorable balance between analgesia and side effects. Occasionally, pain is poorly responsive to this approach, and rarely pain can be refractory to even highly aggressive opioid dose escalation. In this situation, a variety of strategies may be employed, including the use of nonopioid adjuvant analgesics and various interventional approaches. A trial of methadone in this setting offers another option, which may have effectiveness beyond expectations.1,2

We present a case in which it was necessary to increase the dose of opioid 50-fold over a five-day period. In response to poor pain control and dose-limiting side effects, the opioid was rotated to intravenous (IV) methadone at 10% of the previous opioid dose, with good effect. This case illustrates the process of aggressive dose titration followed by opioid rotation to methadone.

Case Report

A 64-year-old man was diagnosed more than one year ago with rectal carcinoma. He had known abdominal, left iliopsoas muscle and pulmonary metastases. He underwent an anterior-peritoneal resection with a palliative colotomy and received systemic chemotherapy and local radiation to the tumor bed.

He was brought to the emergency room for a progressive new pain, lower extremity numbness, and weakness increasing over 24 hours. His pain was in the lower extremities, right greater than left. He had pre-existing rectal and abdominal pain, for which he was receiving methadone 60 mg orally every 6 hours around the clock.

On physical examination, he was found to have left lower extremity plegia and mild proximal weakness of the right lower extremity. Deep tendon reflexes were absent except the right knee jerk, which was +1. He was unable to ambulate secondary to pain and weakness. An emergent MRI with gadolinium of the lumbar spine showed pathologic collapse of the L4 vertebral body, osteolytic lesions of L3 and L5, and a large metastasis in the left psoas muscle.

On the day of the admission, the patient was continued on methadone 60 mg orally every 6 hours and started on hydromorphone 4 mg orally every 3 hours for breakthrough pain. The pain was poorly relieved and began to escalate in a crescendo manner. Pain consultation was requested. Our team discontinued his other opioids and began treatment with IV fentanyl 100 μg/hour with 50 μg every 15 minutes as needed, which was administered via a patient controlled analgesia (PCA) device. He also was given intravenous dexamethasone 24 mg initially and 4 mg every 6 hours thereafter.

Pain was unrelieved the next day. The basal rate of the fentanyl was increased to 150 μg/hour with 175 μg every 10 minutes as needed, which was administered via a patient controlled analgesia (PCA) device. He also was given intravenous dexamethasone 24 mg initially and 4 mg every 6 hours thereafter.

Pain was unrelieved the next day. The basal rate of the fentanyl was increased to 150 μg/hour with 175 μg every 10 minutes as needed. Three hours later, there was inadequate analgesia and the fentanyl was increased to 200 μg/hour with 200 μg every 6 minutes as needed. The pain control was still suboptimal and the next day the infusion was increased to 300 μg with 300 μg every 6 minutes as needed. The patient reported only slight relief and continued to use the supplemental doses on a regular basis. During the following two days, the basal infusion rate was increased first to 400 μg/hour and then to 500 μg/hour. The supplemental
dose was increased to 400 μg every 6 minutes as needed.

The patient began to experience somnolence and he was switched to IV hydromorphone 3 mg/hour with 3 mg every 10 minutes as needed. This was the calculated to be equianalgesic to the fentanyl dose. The dose of the hydromorphone was increased over the next six hours to a basal rate of 18 mg/hour, with 12 mg every 6 minutes as needed.

He used frequent supplemental doses. During one period, he used 308 mg of hydromorphone over 6 hours (51 mg/hour) without effective pain control. Somnolence and confusion occurred. He was then switched to intravenous methadone, with a one time loading dose of 40 mg. The basal rate was 24 mg/hour with 10 mg every 20 minutes as needed. He became almost pain-free on this regimen within a short time. Five days later, he underwent a posterior spinal fusion for stabilization. He continued receiving methadone at the same dose, but required a temporary increase in the supplemental dose. Over the next few days, however, he became pain-free on a basal rate of 24 mg/hour and needed few supplemental doses.

One week after surgery, he started palliative radiation therapy to the spine, and shortly thereafter, his analgesic requirement decreased. He was intermittently somnolent as the methadone dose was decreased. His methadone dose gradually was decreased to 6 mg/hr. Pain remained well controlled and he died of sepsis 10 weeks later.

**Comment**

We present a patient with crescendo pain due to progressive rectal carcinoma. He was switched from oral methadone at a dose of 60 mg every six hours (equal to 5 mg/hour IV based on standard equianalgesic dose tables) to IV fentanyl and then hydromorphone. The dose of the latter drug reached a level that was roughly 50 times the calculated equianalgesic dose of the original oral methadone. He had poor pain control and was somnolent and confused. We then switched back to IV methadone at a dose of 24 mg/hour (roughly five times the dose he had been receiving orally) and he achieved excellent pain control, without side effects. This methadone dose was only 10% of the equianalgesic hydromorphone dose that he had received during the six hours prior to the change. This outcome may illustrate the unique pharmacology of this drug.

Methadone is a synthetic opioid μ agonist, which was developed more than 40 years ago, initially for the treatment of pain. Until recently, it was seldom used for pain and had its major role in the treatment of heroin addiction. Recently, interest in its analgesic utility has grown. When administered as the racemate, methadone contains a d-isomer, which antagonizes the N-methyl-D-aspartate (NMDA) receptor. This mechanism, which could contribute both a partial reversal of opioid tolerance and to an independent analgesic action, may underlie the remarkable degree of incomplete cross-tolerance sometimes observed when patients receiving high doses of another μ agonist opioid are rotated to methadone for refractory pain.

Methadone can be successfully used to treat some patients with pain that is poorly responsive to escalating doses of other opioid drugs. Given the potential for methadone to have an unexpectedly high potency in this setting, a switch to methadone should be accompanied by a large reduction in the calculated equianalgesic dose, e.g., 75–90%. The variable potency, combined with a similar degree of variation in kinetics, implies that the use of methadone requires careful monitoring.

Our patient illustrates the potential utility of a switch to methadone in the context of crescendo pain. Although we do not know for certain whether a simple 5-fold increase in the initial oral methadone dose over a period of days would have yielded excellent analgesia, it is unlikely that this is so given the inability of a much larger increase in another opioid to benefit the patient. Rather, it is more likely that the treatment with fentanyl and hydromorphone, changed the potency of the methadone, presumably via the NMDA interaction, and established the mechanisms that ultimately led to methadone’s efficacy.

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References

Cryoneuroablation for Pain in a 12-Year-Old Girl

To the Editor:
Cryoneuroanalgesia is an established treatment for management of painful nerve disorders of the back, thorax, feet, and face. We report a case of cryogenic denervation of a portion of abdominal wall for urgent pain control in a desperate adolescent.

Case Report
A 12-year-old female presented with escalating right lower quadrant pain. She described it as sharp, constant at 2/10 visual analog scale (VAS) intensity, with occasional fleeting spasms of 9/10 VAS, and increasing severity over 10 months. It did not have any burning or dysesthetic qualities, and did not radiate. She had taken acetaminophen, ibuprofen, and codeine with no improvement.

Several physicians had failed to find cause for the pain, despite investigations that included ultrasonography and CT scanning. She had missed a considerable amount of school, had been threatened with school failure for the year, and had expressed suicidal thoughts.

She had a history of Hashimoto’s thyroiditis, but was now euthyroid on replacement therapy. She was otherwise well, with no known allergies. Physical examination revealed no abnormalities apart from right lower quadrant discomfort. A single point in the right lower quadrant was exquisitely tender on palpation. It was focal, and she could consistently localize it by pushing, with one finger, cranial to the external inguinal ring. Pain was exacerbated by walking and by extending her back to stretch the abdominal muscles.

A tentative diagnosis of neurpathic abdominal wall pain was made, and supported by complete response to injection of a small volume of local anesthetic. She was started on carbamazepine, and referred to a pediatric psychologist familiar with chronic pain management. The carbamazepine was stopped after 2 weeks because of rash, facial swelling, and thrombocytopenia. It was replaced with gabapentin, escalated over 1 week to 2700 mg/day. The pain intensity subsided, but she remained uncomfortable and unwilling to return to school. Several injections of local anesthetic with methylprednisolone were given in an attempt to interrupt the pain cycle; these were all at the same site, same depth (one loss of resistance, leaving needle tip between external and internal abdominal oblique planes), and same volume (less than 2 ml).

The pain continued to escalate despite therapy. She failed repeated trials of anti-inflammatory and opioid analgesics. After considering surgical exploration, the patient was scheduled to undergo cryogenic denervation.

The procedure was performed with an argon-based CRYOCare™ Surgical System machine (Endocare, Irvine, California). Under mild sedation, the overlying skin and deeper abdominal wall tissues were infiltrated with 1% lidocaine. A 1 cm skin incision was made, and the skin retracted away from the cryoprobe entry site. The cryoprobe was placed through an