from the hospital. The thoracostomy procedure was critical in improving her symptoms and allowing her home discharge. Without it, premature sedation until death was the only available option. This time she spent at home under hospice care was essential for the patient and her family members in receiving good end-of-life care.

In conclusion, decisions at the end of life are complex and should be individualized. The presence of a DNR order should not prevent patients from receiving needed medical therapy including invasive procedures if consistent with the patient's wishes. Consultants are not always familiar with available palliative care options, and candid discussion about available therapeutic options, empowering patients and their families to participate in decisions while balancing the benefits and risks of treatments, is essential at the end of life. As early palliative care could be associated with prolonged survival,[8] good palliative care at the end of life could be associated with longer survival and prevent premature sedation.

Ahmed Elsayem, MD
Department of Emergency Medicine
The University of Texas M. D.
Anderson Cancer Center
Houston, Texas, USA
E-mail: aelsayem@mdanderson.org

Marvin Delgado-Guay, MD
Eduardo Bruera, MD
Department of Palliative Care
and Rehabilitation Medicine
The University of Texas M. D.
Anderson Cancer Center
Houston, Texas, USA

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References

1. Teno JM, Casey VA, Welch LC, Edgman-Levitan S. Patient-focused, family-centered end-of-life medical care: views of the guidelines and bereaved family members. J Pain Symptom Manage 2001;22:738–751.

2. Hales S, Chiu A, Husain A, et al. The quality of dying and death in cancer and its relationship to palliative care and place of death. J Pain Symptom Manage 2014;48:839–851.

3. Garrido MM, Balboni TA, Maciejewski PK, Bao Y, Prigerson HG. Quality of life and cost of care at the end of life: the role of advance directives. J Pain Symptom Manage 2015;49:828–835.

4. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 1991;7:6–9.

5. Beller EM, van Driel ML, McGregor L, Truong S, Mitchell G. Palliative pharmacological sedation for terminally ill adults. Cochrane Database Syst Rev 2015;CD010206.

6. Cherny NI. Sedation for the care of patients with advanced cancer. Nat Clin Pract Oncol 2006;3:492–500.

7. Aziz H, Branco BC, Braun J, et al. The influence of do-not-resuscitate status on the outcomes of patients undergoing emergency vascular operations. J Vasc Surg 2015.

8. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733–742.

Methadone for Pain: What to Do When the Oral Route Is Not Available

To the Editor:

Methadone has an important role in the management of severe chronic pain, whether from cancer or other causes. Patients taking methadone for pain in situations such as advanced cancer or end-stage renal failure have often exhausted all other available opioids and appropriate adjuvant analgesics.[1] Methadone is available in different forms around the world, including liquid (with and without preservative) and tablets. As people approach end of life, it is expected that they will stop eating. Many patients experience a period of time before death when they are unable to take oral medications. As they approach this time, many do not want to risk compromising their pain control by having to change their opioid to one that has already been shown to be either ineffective or to cause severe side effects. Equianalgesic dosing charts do not apply to switching from methadone to other opioids, and having to switch to a different opioid, such as morphine or hydromorphone, puts the patient at risk of underdosing or overdosing, as well as very likely to experience side effects and lack of analgesia.

Sterile methadone for injection is not reliably available in many other parts of the world,[2] and injections themselves may not be desired or available in a home setting, so alternatives to the oral route other than injection are necessary for patients unable to swallow or absorb oral methadone. This situation also can occur at times other than end of life such as during episodes of bowel obstruction, cancer treatment-induced vomiting, head and neck cancer, or dysphagia. Palliative care teams need to be familiar with nonoral, noninjectable routes of administration so that satisfactory analgesia from methadone can be maintained throughout the whole course of illness.

The following case report illustrates how seamless transition from the oral route of methadone

administration to an alternative, noninjectable route can allow continuation of pain control for a peaceful death outside of the hospital setting.

Case

A 45-year-old woman with advanced metastatic rectal cancer was admitted to our acute oncology inpatient unit in a pain crisis. The patient also had a 14 year history of multiple sclerosis but had been able to walk with assistance and a walker until recently. She had a history of T3 N0 Stage 2 colon cancer removed two years previously with negative surgical margins, and she chose not to receive adjuvant radiation or chemotherapy. She had a documented recurrence in the S2 vertebra 17 months later and received 30 Gy radiation over 10 fractions to the pelvis but declined palliative chemotherapy. At this time, she developed cauda equina syndrome and lost bowel and bladder control. She was lost to follow-up for some months and received alternative therapies during that time without benefit. Eight months later, she presented with severe sacral/coccygeal pain and was found to have large pelvic metastases invading the sacrum, with multiple sacral fractures and nerve root compression. Transdermal fentanyl was titrated rapidly from 25 μg/h to 75 μg/h, with additional short-acting morphine, with minimal impact on pain. She also received dexamethasone 4 mg daily, gabapentin 300 mg three times a day, and clonazepam 1 mg at bedtime. Doses of all medications were increased to dose-limiting side effects, but pain control was inadequate. Her rural residence precluded an intrathecal infusion.

The patient was switched to oral methadone and reached a dose of 20 mg oral methadone every eight hours, which achieved markedly improved pain control. She was discharged home, and the dexamethasone was stopped. Gabapentin and clonazepam were continued.

Over the next two months, the methadone was increased gradually up to a peak dose of 42 mg every eight hours, with breakthrough rescues of 20 mg up to three times a day. She was restarted on dexamethasone. She was admitted to hospital a month later because of psychosocial distress, with poor medication compliance. Pain control was again achieved with the methadone administered as prescribed. With counseling, the patient and family accepted that she was approaching end of life and agreed to transfer to a residential hospice. In hospice, the methadone was gradually reduced to 25 mg every eight hours with good pain control.

A month later, she developed difficulty swallowing. Having to do rectal bowel care for some time had led to her and her family being comfortable with this route as a possible way of continuing the methadone therapy. The same 10 mg/mL solution that had been dispensed for oral use was administered rectally by syringe as 2.5 mL (25 mg) every eight hours. All other oral medications were discontinued. This treatment provided excellent ongoing pain control, and she died peacefully 10 days later, having been on methadone for just over five months in total.

Comment

There are three nonparenteral options for methadone administration when the oral route is not available: transmucosal, rectal, and transdermal. The transmucosal and rectal routes are the easiest to switch to because they rarely require any special compounding. Acceptability to the patient is an important consideration in selecting the preferred route when multiple alternatives are available. With all opioid drug or route changes, it is important to be vigilant for variation in bioavailability for at least a couple of half-lives (in methadone's case, at least a week), and predicted doses may need to be adjusted when the effect of the opioid after switching is observed to be greater or less than anticipated.

Rectal Route

The aqueous methadone liquid can be administered rectally at the same dose as given orally previously. A lubricated needleless plastic syringe can be used to deliver the liquid into an empty rectum and, if the volume to be delivered is small, it can be flushed in with warm water. If a patient is difficult to position for intermittent dosing, administration via a catheter inserted rectally and left in place could be considered. Obviously, if the patient was incontinent of stool or the rectum was full of stool, this would not be effective. Methadone absorption from suppositories is poor and variable (35%–58%), but rectal bioavailability of methadone aqueous liquid is approximately 80%,[3–5] which is much the same as when swallowed.

Transmucosal Route

The sublingual space offers good absorption, but patients need to be able to keep their mouth closed long enough, and the buccal route (between the lower molars and the inside of the cheek) requires less patient cooperation for administration. It has been reported[6–8] that up to 1.5 mL of the concentrated 10 mg/mL oral solution can be absorbed in one dose, with doses repeated at 5–10 minute intervals if more than 15 mg per dose is required. More concentrated solutions have been reported in the past to be able to be easily compounded, however Health Canada recommends that this only be done in situations where no appropriate commercially available product is available,[9] and methadone powder is no longer widely available. This may limit the dose able to be administered

via the buccal or sublingual route. A case series of 25 patients from Toronto[6] found that using an oral:transmucosal 1:1 dosing ratio worked very well, with 88% of the patients needing no subsequent dose adjustments.

Alkalinization of an acidic solution may facilitate more rapid absorption, which would be more convenient for patients. The three 10 mg/mL methadone oral concentrated solutions currently available in North America are potentially quite acidic, the manufacturers' brochures reporting a pH between 4.5 and 6.5 (Methadose® [Mallinckrodt Canada, Pointe-Claire, Quebec, Canada] and Dolophine® [Boehringer Ingelheim Canada, Burlington, Ontario, Canada]), or between 1.0 and 6.0 (Metadol® [Paladin Labs, St-Laurent, Quebec, Canada]).

Transdermal Route

The usual vehicle for transdermal drug delivery is pluronic lecithin organogel, but this is not useful for transdermal delivery of methadone.[10] Love and Bourgeois[11] have recently published a report on transdermal methadone in Lipoderm®, which is a compounding base produced by Professional Compounding Centers of America, Houston, TX. The 5% cream (10 mg/0.2 mL) comprised methadone powder 2.65 g, ethoxydiglycol 4.2 mL, and Lipoderm® cream 47 g. They report that the formula can be modified to a range from 2 mg/0.2 mL up to 25 mg/0.2 mL.

The extent of absorption from this cream has not been tested, but the reported patients used doses ranging from 7.5 to 50 mg every eight hours, with a 30% reduction from the prior oral dose being chosen for determining the starting topical dose.

In conclusion, there is no need for patients to stop methadone when the oral route is no longer available. Injectable methadone may be unavailable or not desired, and the rectal, transmucosal, or transdermal routes are acceptable alternatives. The choice of alternative route depends on patient-specific factors, and it is important to have a number of options to be able to meet the needs of all patients. Concerns about loss of the oral route should not be a barrier to accessing methadone for those patients who experience inadequate analgesia or intolerable side effects with other opioids. Further research is needed on factors that might affect bioavailability such as the optimal pH of aqueous solutions, optimal cutaneous site selection and formulations for transdermal application.

Philippa Hawley, FRCPC
Pain and Symptom Management/Palliative Care Program
BC Cancer Agency
Vancouver, British Columbia, Canada
Division of Palliative Care
Department of Medicine
University of British Columbia
Vancouver, British Columbia, Canada
E-mail: phawley@bccancer.bc.ca

Petrina Wing, RN, CHPCN(C)
Vancouver Coastal Health
Sunshine Coast Home Care Services
Sechelt, British Columbia, Canada

Shalini Nayar, FRCPC
Pain and Symptom Management/Palliative Care Program
BC Cancer Agency
Vancouver, British Columbia, Canada
Division of Palliative Care
Department of Medicine
University of British Columbia
Vancouver, British Columbia, Canada

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References

1. Leppert W. The role of methadone in opioid rotation—a Polish experience. Support Care Cancer 2009;17:607–612.

2. World Health Organization. Cancer pain relief: with a guide to opioid availability, 2nd ed. Geneva: WHO, 1996.

3. Moolenaar F, Fiets G, Visser J, Meijer DK. Preliminary study on the absorption profile after rectal and oral administration of methadone in human volunteers. Pharm Weekbl Sci 1984;14:237–240.

4. Ripamonti C, Zecca E, Brunelli C, et al. Rectal methadone in cancer patients with pain. A preliminary clinical and pharmacokinetic study. Ann Oncol 1995;6:841–843.

5. Dale O, Sheffels P, Kharasch ED. Bioavailabilities of rectal and oral methadone in healthy subjects. Br J Pharmacol 2004;58:156–162.

6. Spaner D. Effectiveness of the buccal mucosa route for methadone administration at the end of life. J Palliat Med 2014;17:1262–1265.

7. Hagen NA, Fisher K, Stiles C. Sublingual methadone for the management of cancer related breakthrough pain: a pilot study. J Palliat Med 2007;10:331–337.

8. Weinberg DS, Inturrisi CE, Reidenberg B, et al. Sublingual absorption of selected opioid analgesics. Clin Pharmacol Ther 1988;44:335–342.

9. Alberta Health Services. Long term care formulary. Available at: https://pharmacists.ab.ca/sites/default/files/CompoudingMethadoneAddendum.pdf. Accessed May 2, 2015.

10. Sylvester RK, Schauer C, Thomas J, Steen P, Weisenberger A. Evaluation of methadone absorption after topical administration to hospice patients. J Pain Symptom Manage 2011;41:828–835.

11. Love R, Bourgeois K. Topical methadone: an alternative for pain control in end-of-life management. J Palliat Med 2014;17:128.