Using Methadone to Control Pain in Patients During Final Stages of Life

John F. Manfredonia, DO

Methadone hydrochloride is an effective, inexpensive, and relatively safe opioid to use in treatment of patients with chronic pain. Because it is the only long-acting analgesic available in liquid form, methadone is especially valuable in management of pain during the final stages of life. However, because methadone has an inherently long duration of action with wide variations, a possibility of accumulation and overdosage exists. Therefore, physicians must be judicious and conscientious when prescribing this opioid. Physicians must also closely monitor patients during the titration phase and educate them with regard to basic pharmacologic properties and potential side effects. A plan to start at low doses and proceed slowly is applicable to methadone.

J Am Osteopath Assoc. 2007;107(suppl 4):ES17-ES21.

Chronic pain, one of the most common conditions for which people seek medical treatment, affects more than 85 million Americans.[1] In end-of-life care, in which the primary focus is a reduction or elimination of suffering, many patients still endure uncontrolled pain. In recent years, healthcare consumers have become more sophisticated, demanding better pain control. Thus, physicians need to be familiar and competent with various treatment options including pharmacotherapy to manage their patients' chronic pain.

Dr Manfredonia is board certified and a Fellow of the American Academy of Hospice and Palliative Medicine.

Address correspondence to John F. Manfredonia, DO, FACOFP, FAAHPM VistaCare Area Medical Director, 6420 E Broadway Blvd, Suite B-200, Tucson, AZ 85710.

E-mail: john.manfredonia@vistacare.com

Although the primary responsibility of physicians is to nurture the physical and psychological well-being of their patients, it is also important that they serve as stewards of financial resources. A resurgence in the understanding of pharmacologic and pharmacokinetic properties of methadone hydrochloride coupled with its low cost has led to increased use of this agent in management of chronic pain.

Methadone, a synthetic opioid agonist developed in the late 1940s, has been used for more than 40 years to treat patients who are addicted to narcotics. Although substantial information exists regarding such use of methadone, only limited data are available with respect to pain management. It is only within the past decade that there has been a renewed focus on its use in treatment of patients with chronic pain. The National Guideline Clearinghouse guideline titled "VA/DoD clinical practice guideline for the management of opioid therapy for chronic pain"[2] recommends use of an agent with a long duration of action, such as a controlled-release morphine or methadone, when initiating a trial of opioid therapy for continuous pain.

Initial interest in methadone for pain management emerged in caring for terminally ill cancer patients, but recent attention now includes management of nonmalignant pain. Methadone is achieving greater acceptance in end-of-life care because it is the sole long-acting opioid in liquid form. It is highly lipophilic and readily absorbed through buccal mucosa. Methadone has a wide spectrum of absorption and formulations that allows administration via multiple routes: oral, sublingual, rectal, subcutaneous, intramuscular, intravenous, epidural, intrathecal, and percutaneous endoscopic gastrostomy (PEG) tube.

Formulations

Methadone hydrochloride is available in the United States in multiple formulations, including 5-mg, 10-mg, and 40-mg scored tablets. These tablets, unlike sustained-release formulations of other opioids can be divided or crushed[3]; the 5- and 10-mg tablets can be administered to treat moderate to severe pain in patients who fail to respond to nonnarcotic analgesics. Methadone hydrochloride is also available in solution form in concentrations of 5 mg/5 mL, 10 mg/5 mL, and 10 mg/mL for oral administration, and a 10-mg/mL solution for parenteral administration.[4]

Pharmacokinetics

Methadone, a highly lipophilic drug, is rapidly absorbed with extensive tissue distribution.[5] Unlike morphine sulfate, methadone has no active metabolites; hepatic metabolism has no significant

This continuing medical education publication is supported by an educational grant from Purdue Pharma LP.

Checklist

- **Phenanthrene Derivatives**
  - ☐ Codeine
  - ☐ Hydrocodone
  - ☐ Oxycodone
  - ☐ Morphine sulfate
  - ☐ Hydromorphone hydrochloride
- **Phenylpiperidine Derivatives**
  - ☐ Meperidine hydrochloride
  - ☐ Fentanyl
- **Diphenylheptane Derivatives**
  - ☐ Methadone hydrochloride
  - ☐ Propoxyphene

Figure 1. *Opioid family categories. (Source: Killion K, ed.* Drug Facts and Comparisons. *54th ed. St Louis, Mo: Facts and Comparisons; 2000:784-797.)*

Table 1
Some Medications That Can Decrease or Increase Methadone Level When Coadministered

Decrease Level	Increase Level
Antibiotics	Cimetidine
Rifampin	Ciprofloxacin
	Fluconazole
Anticonvulsants	Fluoxetine
Phenytoin	Ketoconazole
Phenobarbital	Macrolide antibiotics
Carbamazepine	Nifedipine
	Sertraline hydrochloride
Antipsychotics	Tricyclic antidepressants
Risperidone	Zidovudine
Antiretrovirals	
Ritonavir	
Nevirapine	

Source: Ripamonti C, Bianchi M. The use of methadone for cancer pain. *Hematol Oncol Clin North Am.* 2002;16:543-555.

Table 2
Conversion Ratio of Oral Morphine to Methadone

Morphine Sulfate	Ratio	Methadone Hydrochloride
⩽100 mg	3:1	?? mg–33 mg
101 mg–300 mg	5:1	20 mg–60 mg
301 mg–600 mg	10:1	30 mg–60 mg
601 mg–800 mg	12:1	50 mg–67 mg
801 mg–1000 mg	15:1	53 mg–67 mg
⩾1000 mg	20:1	50 mg–__ mg

Source: Gazelle G, Fine P. Fast Facts and Concepts #075. Methadone for the treatment of pain. September 2002. End-of-Life Physician Education Resource Center. Available at: http//www.eperc.mcw.edu. Accessed January 15, 2005.

effect on methadone concentrations, clearance, or clinical disposition.[6] Renal and/or hepatic impairment does not alter clearance or dosing of methadone. It is predominantly excreted in the feces; however, acidification of the urine will increase renal excretion. It has a prolonged and variable elimination phase with a plasma half-life ranging from 4.2 hours to 190.0 hours.[5,7-9] The mean plasma half-life of methadone is probably 15 to 60 hours,[7] though even this range is extremely variable and dependent on single versus multiple dosing, individual adipose stores, and protein binding. This wide variation in half-life contributes to a substantial possibility of toxic accumulation.

Methadone binds with mu-, delta-, and, to a lesser extent, kappa-opioid receptor sites (*Figure 1*)[10] and has a rapid onset of action; analgesic effects occur within 30 to 60 minutes and peak between 2.5 and 4.0 hours. Its oral bioavailability, though variable, generally exceeds 80%.

Adverse Effects

Adverse reactions that occur during methadone administration are similar to those found with other mu-opioid agonists, including pruritus, nausea, constipation, confusion, sedation, and respiratory depression. In addition, excess sweating (diaphoresis) and flushing can occur. Because life-threatening toxicities may not become observable for 2 to 5 days after initiation of methadone therapy, caution should be taken at commencement of dosing; increases should be carefully monitored.[3] Fatal or life-threatening respiratory depression and cardiac arrhythmias in methadone-naïve patients receiving oral doses continue to be reported by the US Food and Drug Administration (FDA) as recently as November 27, 2006.[11] Therefore, the need for appropriate attention to dosing and side effects is always indicated.

Drug Interaction

Cytochrome P450 is the main isoenzyme involved in methadone biotransformation,[5] yet little clinical information is known regarding its drug interactions. Because a majority of medications are metabolized via this pathway, physicians

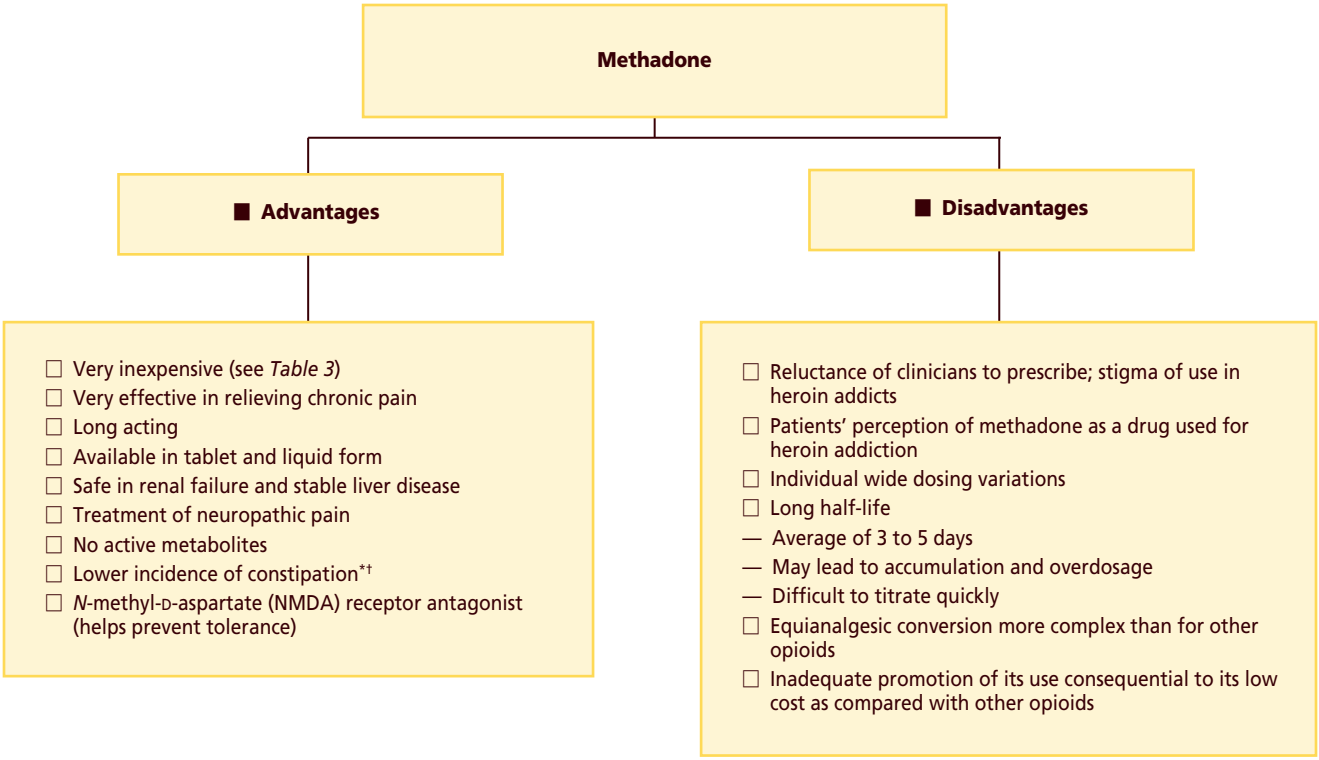

Figure 2. *Advantages and disadvantages associated with the use of methadone. (*Ripamonti C, Bianchi M. The use of methadone for cancer pain,P>Hematol Oncol Clin North Am.* 2002;16:543-555; Bruera E, Sweeney C. Methadone use in cancer patients with pain: a review. J Palliat Med. *2002;(1):127-138.)*

must be sensitive to co-administration of other drugs that could result in either an increase or a reduction of methadone levels (*Table 1*[5]).

Clinical Advantages

Although initially used in patients with cancer, methadone is being increasingly used in the end-of-life care setting for patients with nonmalignant pain syndromes. As the only long-acting opioid liquid formulation, methadone provides an attractive alternative to the expensive transdermal fentanyl patch in patients with debilitating states of advanced dementia or with arthritis, in deconditioned bedridden individuals with adult failure to thrive who have generalized pain or allodynia, and when patients can no longer swallow pills. The high bioavailability and long duration of action following rectal administration offer an alternative to intravenous administration.[10] Another advantage to methadone is the fact that because it is synthetic and has no cross-allergenicity, it may be used in patients with morphine allergy.[3] Additionally, the relatively slow development of action and long duration serve to reduce establishment of reward behaviors that can occur with faster-acting and shorter-duration opioids.[3]

Whereas methadone and fentanyl have been shown to be safe in patients with renal failure,[6] morphine and codeine should be avoided because their active metabolites accumulate. Clinical data in the literature regarding the use of hydromorphone and oxycodone with renal failure are sparse, and because both of these medications are primarily excreted in the urine and also have the potential for toxic accumulation, they should be used with caution. An additional advantage of methadone is its property as an *N*-methyl-D-aspartate (NMDA) receptor antagonist. This action contributes to a reduced propensity to develop opioid tolerance as compared with morphine, and a possibly greater efficacy in treating patients with neuropathic pain.[5,6,8,12] (*Figure 2*)

Equianalgesic dosing of methadone is more complex than it is for other opioids. Unlike morphine, methadone exhibits wide variations in half-life among patients and must be cautiously prescribed, especially in individuals currently medicated with an opioid.

There are several approaches to prescribing methadone. In end-of-life care where some patients have noncancer pain syndromes and debilitated elderly patients have moderate pain, a reasonable approach is to start at 2.5 mg to 5 mg every 12 hours. Additional increases are determined based on the frequency and amount of short-acting opioid used for breakthrough or incidental pain, and titrated accordingly every 5 days. Although no method of conversion has emerged as being superior, two examples of established protocols[13] for both initiating and converting to methadone follow.

New Start: Opioid-Naïve Patients

This is the easiest method for initiating treatment with methadone in opioid-naïve patients:

Resources

BOOKS

- ***Drug Information Handbook***. 13th ed. Hudson, Ohio: Lexi-Comp Inc; 2005
- ***Goodman & Gilman's The Pharmacological Basis of Therapeutics***. 10th ed. New York, NY: McGraw Hill; 2002

WEB SITES

- **American Pain Foundation** http://www.painfoundation.org
- **American Association for Cancer Pain Initiative** http://www.aacpi.org
- **American Chronic Pain Association** http://www.theacpa.org
- **Partners Against Pain** http://www.partnersagainstpain.org
- **American Academy of Pain Medicine** http://painmed.org

Figure 3. *Print and Web site resources.*

- Start methadone at 2.5 mg to 5 mg every 6 to 12 hours.
- Titrate every 3 to 5 days until adequate analgesia is achieved.
- When steady state is achieved, switch to every 8- to 12-hour dosing schedule.
- Use a short-acting opioid during the titration phase as needed for breakthrough or incidental pain. An example in an opioid-naïve patient would be 15 mg of morphine or its equianalgesic equivalent opioid every 2 hours as needed. Monitor the frequency and amount of the short-acting opioid, and adjust the methadone accordingly. In an opioid-tolerant patient, use 10% to 15% of the total morphine equianalgesic 24-hour dose every 2 hours as needed.
- **Note:** If adequate analgesia is attained on the second day or if sedation occurs, monitor closely and consider reducing the dose of methadone because of the delayed volume distribution during the titration phase (usually 3-5 days). If the patient has adequate analgesia, especially if accompanied by sedation prior to the third day before consistent blood levels have been attained, then there is greater risk for toxic accumulation.

Conversion From Morphine to Methadone

- Discontinue administration of morphine.
- Start dosing with methadone every 6 hours for four to six doses; then, decrease frequency to every 8 to 12 hours.
- Use an immediate-release opioid for rescue dosing.

Table 2[13] provides the conversion ratio of oral morphine to methadone.

Switching From Another Opioid to Methadone

The process of switching from another opioid to methadone, especially when high doses are being used, is more complex. Several conversion protocols are available.[13-15] One example is:

- Discontinue administration of current opioid.
- Start administering methadone at a fixed oral dose every 3 hours as needed: Administer a fixed dose of methadone hydrochloride that equals 10% of prior daily oral morphine equivalent with a maximum dose of 30 mg.[14,15]

Example—If prior daily opioid dose equals 150 mg of oral morphine sulfate equivalent per day; then, use 15 mg of methadone hydrochloride every 3 hours as needed. (Note: This is not a 1:10 ratio unless only one dose is given in 24 hours: 1:10 ratio would be 15 mg/d, not 15 mg per dose.)

On day 6, calculate total amount of methadone taken during previous 48 hours and convert to twice-daily methadone dose. If the patient actually took the 15 mg dose every 3 hours on days 4 and 5, then the correct dosing would be 60 mg every 12 hours.

Example—Patient is taking 600 mg of oral morphine sulfate equivalent per day. Because the oral morphine equivalent is greater than 300 mg/d, use 30 mg of methadone hydrochloride as initial fixed dose after terminating morphine administration and give 30 mg of methadone hydrochloride every 3 hours as needed. If the patient requires eight doses of 30 mg each for a total of 240 mg days 4 and 5 (120 mg/d); then, on day 6, adjust methadone dose to 40 mg orally every 8 hours or 60 mg every 12 hours.[14,15]

Figure 3 provides a list of additional print and Web site resources.

Case Presentation

A 46-year-old man with head and neck cancer status post radical dissection is taking the following medications:

- ☐ *fentanyl transdermal system, 100 µg, three patches every 72 hours*
- ☐ *oxycodone hydrochloride, 20-mg tablets, three every 12 hours*
- ☐ *oxycodone hydrochloride with acetaminophen tablets (5 mg/325 mg), two every 4 hours*
- ☐ *morphine sulfate immediate release (MSIR), 20 mg every 2 hours*

The approach to pain control in this patient would be as follows:

- Determine the patient's total daily morphine equianalgesic dose:
  - ☐ fentanyl transdermal system, 300 µg in 72 hours (600 mg total)
  - ☐ oxycodone hydrochloride, three 20-mg tablets, twice daily (120 mg total)
  - ☐ oxycodone hydrochloride/acetaminophen, two tablets every 4 hours times four doses (40 mg total)
  - ☐ MSIR, 20 mg every 2 hours times 12 doses (240 mg total)

Total equianalgesic dose equals 1000 mg per 24 hours

In the patient described in the case scenario, pain control was initiated with administration of methadone hydrochloride, 15 mg every 8 hours, with four 8-mg tablets of hydromorphone hydrochloride (32 mg) every 2 hours as needed for pain. The patient utilized 10 doses of hydromorphone daily for 2 days, then 5 to 8 doses per 24 hours for the next 3 days. After the fifth day, his pain was well controlled with 3 doses of hydromorphone daily.

Comment

Methadone is gaining recognition in the arsenal of pain management. With appropriate knowledge and initial, cautious titration, physicians can readily give consideration to administration of methadone as they would to extended-

release formulations of morphine, oxycodone, hydromorphone, and fentanyl. The efficacy, long-acting liquid formulations, multiple routes of administration, and low cost make methadone a noteworthy contender in treatment of patients with chronic pain.

References

1. Moskowitz M. Advances in understanding chronic pain. *Neurology*. 2002;59(5 suppl):S1.

2. National Guideline Clearinghouse. VA/DoD clinical practice guideline for the management of opioid therapy for chronic pain. Available at: www.guidelines.gov./summary/summary.aspx?doc_id=4812&nbr=003474. Accessed January 22, 2007.

3. Toombs JD, Kral LA. Methadone treatment for pain states. *Am Fam Physician*. 2005;71:1353-1358.

4. Waknine Y. Methadone-related fatalities underscore need for careful dosing, *Medscape Medical News*.Available at: www.medscape.com/view article/548340. Accessed January 22, 2007.

5. Ripamonti C, Bianchi M. The use of methadone for cancer pain. *Hematol Oncol Clin North Am*. 2002;16:543-555.

6. Dean M. Opioids in renal failure and dialysis patients [Abstract Review]. *J Pain Symptom Manage*. 2004;28:497-504. Availableat:http://www.das/journal/view/45309477-2N/15183529?source=MI. Accessed January 15, 2005.

7. Doyle D, Hanks GW,Cherny N. *Oxford Textbook of Palliative Medicine*. 3rd ed. New York, NY: Oxford University Press;2004: 24-325.

8. Bruera E, Sweeney C. Methadone use in cancer patients with pain: a review. *J Palliat Med*. 2002; (1):127-138.

9. McCaffery M, Pasero C. *Pain Clinical Manual*. 2nd ed. St Louis, Mo: Mosby; 1999:185-186.

10. Killion K, ed. *Drug Facts and Comparisons*. 54th ed. St Louis, Mo: Facts and Comparisons; 2000:784-797.

11. FDA Alert [11/2006]: Death, narcotic overdose, and serious cardiac arrhythmias. Available at: www.fda.gov/cder/drug/infopage/methadone/. Accessed June 26, 2007.

12. National Guideline Clearinghouse. Asessment and management of chronic pain. Available at: www.guidelines.gov./summary/summary.aspx?doc_id=8363&nbr=004684. Accessed January 22, 2007.

13. Gazelle G, Fine P. Fast facts and concepts #75 Methadone for the treatment of pain. September 2002. End-of-Life Physician Education Resource Center. Available at http://www.eperc.mcw.edu. Accessed January 15, 2005.

14. Morley JS, Makin MK. The use of methadone in cancer pain poorly responsive to other opioids. *Pain Rev*. 1998;5:51-58.

15. Texas Academy of Palliative Medicine. Available at: http://www.tapm.org/vault/Converting_to_Methadone.pdf. Accessed January 15, 2005.