ProCare **HospiceCare** *May/June Edition 2018*

On-Demand Clinical News

Pain Management: The Use of Methadone in Hospice and Palliative Care

By: Kiran Hamid, RPh

Methadone's unusual pharmacokinetic properties make it a unique medication for pain management at end of life. Methadone is a synthetic opioid and exerts its actions as an analgesic primarily through binding with mu opioid receptors. It also acts as an NMDA receptor antagonist, which accounts for its role in neuropathic pain and reducing the effects of opioid withdrawal.

Pharmacokinetics of Methadone

Although it is thought that methadone has a very long onset of action, its analgesic effects can start in as little as 30 minutes. Methadone has good oral bioavailability, but this can vary greatly, and it emphasizes the importance of individualized dosing. Methadone's duration of action is shorter acting at first, about 4-8 hours with single doses, and then increases as it accumulates in the body's tissues to up to 22-48 hours with chronic dosing. When patients cannot swallow, methadone tablets may be crushed and given sublingually (SL) or the liquid concentrate may be given SL. Methadone can also be given parenterally via the intramuscular, subcutaneous, or intravenous routes. The tablets or the oral solution of methadone can also be given rectally. Methadone is a lipophilic substance and is widely distributed to tissues throughout the body, including the liver, kidneys, lungs, intestines, muscles, and brain. With repeated dosing, the body accumulates a reservoir of methadone. This reservoir reaches equilibrium where it is constantly absorbing and releasing methadone at a particular rate; this mechanism contributes to the overall steady state and its long half-life

Methadone is metabolized in the liver by N-demethylation to inactive metabolites. It also undergoes metabolism via the cytochrome P450 system. Because of this, it can lead to numerous drug-to-drug interactions. Patients with severe liver disease should initiate at lower doses and titrate slowly, as they may not be able to metabolize methadone as efficiently.

Methadone is primarily eliminated in the urine and feces. Although it is predominantly excreted via the renal route, in the presence of kidney failure, there is increased fecal excretion, both of metabolism products and methadone itself. This way, methadone may be considered safe for kidney failure in patients undergoing dialysis.

Continued on Page 2

Advantages and Disadvantages of Methadone Therapy

Methadone may have a bad reputation, but it is important to remember its many advantages for our hospice patients. Although it can be very effective for pain management, not every patient may be a suitable candidate for methadone therapy.

Advantages of Methadone
• Very effective for nociceptive and especially neuropathic pain
• Multiple routes of administration
• Methadone tablets can be crushed and it is available in a liquid concentrate
• Because it is a synthetic opioid, it has a lower risk of true allergic reaction
• No active metabolites
• Can be initiated in an opioid-naïve patient at very low doses
• May help reduce symptoms of opioid toxicity and opioid tolerance
• Very low cost

Disadvantages of Methadone
• May not be appropriate for the actively dying patient (it can take up to 5 days or more to reach steady state)
• Long and unpredictable half-life
• No exact dose conversion with other opioids; requires careful dose titration
• Numerous drug-to-drug interactions
• Stigma surrounding its use for opioid addicts
• May not be suitable for a patient who lives alone or in a poor caregiving environment
• May not be suitable for patients with significant cardiac history

The Use of Methadone in Hospice and Palliative Care continued from page 1

Adverse Effects of Methadone

In general, methadone appears to be better tolerated than other opioids, and this is most likely due to its lack of active metabolites. Similar to other mu opioid agonists, methadone can cause CNS depression, constipation, nausea/vomiting, and itching. Respiratory depression can be a very critical adverse effect of methadone. Since methadone accumulates in the body, its peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, especially in the early dosing period, or when increasing doses. Another important adverse effect of methadone is its potential to cause QT prolongation. As the QT interval increases, so does the risk for life-threatening arrhythmias such as polymorphic ventricular tachycardia or Torsades de Pointes (TdP). Many studies have reported on QT interval prolongation caused by methadone, but it is important to note that most studies showed a dose-dependent effect on increasing QT interval. Risk factors that can increase the possibility of QT prolongation include history of advanced heart disease, especially a history of arrhythmias or bradycardia, electrolyte imbalances caused by depletion from vomiting, diarrhea or diuretics, being female (women have a naturally longer QT interval than men), and administration of other medications that can prolong the QT interval.

When ordering methadone, clinicians should ask patients about any history of structural heart disease, arrhythmia, or syncope, and warn patients of the risk of arrhythmia before prescribing methadone. Patients and caregivers should be educated to seek medical attention immediately if any non-specific signs and symptoms of QT prolongation occur such as syncope, seizures, or palpitations. Every effort should be made to decrease the risk of modifiable risk factors, such as dehydration due to nausea, vomiting, or diarrhea, and drug interactions with QT prolonging medications. The bottom line is that methadone at the doses we typically use in our hospice patients can be safely administered as long as the potential for QT interval prolongation is recognized and appropriate clinical actions are taken in its presence.

Drug Interactions

Unfortunately, methadone participates in plenty of drug interactions with other medications. Its adverse effects of sedation, CNS depression, and respiratory depression are additive with other opioids. Increased CNS depression and oversedation can occur with benzodiazepines such as lorazepam, anti-psychotics, and alcohol. And because methadone acts to inhibit the re-uptake of serotonin and norepinephrine, it can theoretically interact with SSRI anti-depressants and increase the risk of serotonin syndrome. More importantly, medications that cause QT prolongation can have additive effects with methadone. Examples of these medications that are commonly seen in hospice care include amiodarone, quetiapine, haloperidol, citalopram, ciprofloxacin, ondansetron, and fluconazole. As previously mentioned, since methadone is extensively metabolized by the CYP 3A4 enzymes in the liver, medications that act to inhibit or induce these enzymes can affect methadone serum levels. Enzyme inhibitors, such as fluconazole, diltiazem, and HIV protease inhibitors can decrease the metabolism of methadone, increasing its serum levels. Enzyme inducers, such as phenobarbital, phenytoin, and carbamazepine, can increase methadone's metabolism, reducing its serum levels.

Continued on Page 3

ProCare 20/20

2018 Conference Event

Atlanta, GA

August 16, 2018

FOCUSED on Hospice Care

Featured Speakers:

Meri Madison, PharmD, Nate Hedrick, PharmD,
Kristin Speer, PharmD, and Kiran Hamid, RPh

The Use of Methadone in Hospice and Palliative Care Continued from page 2

As a nurse, we have the opportunity to heal the heart, mind, soul and body of our patients, their families and ourselves. They may forget your name, but they will never forget how you made them feel.

- Maya Angelou

Dosing Methadone

There are several dosing strategies that exist regarding methadone, and methods are still evolving. Many studies have found no evidence to support the superiority of one dosing strategy over another. The lack of prospective and comparative studies concerning dosing strategies highlights the need to carefully individualize the dosing regimen of methadone. Titration should be based on patient response and not solely based on equianalgesic dosing tables.

Two things that are consistent among the different dosing methods are: (1) the use of oral morphine as the standard opioid to use in the conversion, and (2) unlike other opioids, conversion to methadone is not based on a linear model. The non-linear conversion from other opioids to methadone is thought to be due to methadone's unique mechanism of mu receptor agonism paired with *N*-Methyl-d-Aspartate (NMDA) antagonism; this is believed to diminish the tolerance developed with opioid increases.

When initiating methadone, one of the first steps is to determine whether the patient is opioid naïve; for opioid naïve patients, the rapidity of dose escalation is the differentiating factor in a given clinical situation. Dosing is typically started lower at about 2.5mg – 5 mg po q8h or q12h, and should be dosed even lower in an elderly, frail patient. Dose should be gradually titrated and with close monitoring.

For opioid-tolerant patients, a number of different equianalgesic dose ratio (EDR) tables can be used to determine the dose of methadone. When converting to methadone, lower morphine equivalent daily doses have lower conversion ratios than higher morphine equivalent daily doses. As previously mentioned, methadone dose conversion is not a linear process due to its NMDA antagonist properties and subsequent reduction of opioid tolerance. So when methadone is initiated, the patient feels more opioid-sensitive. Monitoring patients closely when initiating/titrating methadone is critical, since conversion tables can underestimate the potency of methadone. Dose ratios in many conversion tables sometimes do not apply to repeated doses of opioids. There may be large inter-patient variability in the conversion; a single ratio may not be applicable to all patients. The use of high but ineffective doses of a previous opioid may result in overestimation of the equivalent dose of methadone. This is why it is generally recommended to reduce the calculated methadone dose by about 25% to account for incomplete cross-tolerance. Another important point to remember is that the dose conversion tables are not bi-directional. They cannot be used in reverse (i.e. the morphine to methadone conversion ratio is not be the same as the methadone to morphine ratio).

Dosing of methadone should be calculated and determined only by experienced clinicians. Patients should be assessed frequently (e.g. daily) when methadone is initiated and when the dose is increased. Once stable dosing is established, follow-up can be completed as clinically warranted.

Methadone can provide effective pain relief for patients at end of life. It is important to evaluate the benefits of methadone therapy versus any risks and to monitor patients closely while on methadone. When used appropriately, methadone can greatly increase comfort for patients at end of life.

Continued on Page 4

References:

1. Story P. Primer of Palliative Care, 3rd Ed. AANPM 2004.
2. Strain, Eric and Stritzer, Maxine. (2006). *The Treatment of Opioid Dependence*. New York: JHU Press.
3. Cruciani, R. and Knotkova, H. (2014). *Handbook of Methadone Prescribing and Buprenorphine Therapy.* New York*:* Springer Science & Business Media.
4. Lexi-Comp OnlineTM , Lexi-Drugs OnlineTM , Hudson, Ohio: Lexi-Comp, Inc.; January 2018.
5. McPherson ML. (2010). Demystifying Opioid Conversion Calculations: A Guide to Effective Dosing. Bethesda, MD: ASHP.
6. 6. Moaleji, N. and Pangarkar, S. (2016, April). Oral Methadone Dosing Recommendations for the Treatment of Chronic Pain. Retrieved from https://www.pbm.va.gov/PBM/clinicalguidance/clinicalrecommendations/Methadone_Dosing_Recommendations_for_the_Treatment_of_Chronic_Pain_July_2016.pdf
7. Habershaw, A. (2012, May). Methadone and QTc Prolongation. Retrieved from https://www.urmc.rochester.edu/medialibraries/urmcmedia/medicine/palliative-care/patientcare/documents/methadoneandqtcprolongation.pdf
8. Reddy S, Hui D, El Osta B, et al. The Effect of Oral Methadone on the QTc Interval in Advanced Cancer Patients: A Prospective Pilot Study. J Palliative Med. 2010;13:33-38.

Upcoming Lunch and Learn Presentations

May

Pediatric Considerations in End of Life Care

Presenter: Madeline Vallejo, PharmD

Dates: Tuesday, May 8, 2018 at 3:00PM ET; Wednesday, May 9, 2018 at 12:00PM ET

June

Focusing on End-Stage Cardiac Disease in the Hospice Patient

Presenter: Tracey Gordon, PharmD

Dates: Tuesday, June 12, 2018 at 3:00PM ET; Wednesday, June 13, 2018 at 12:00PM ET

RSVP by contacting Suzanne Stewart, Lunch and Learn Coordinator, at:
1-800-662-0586 ext. 3303 or sstewart@procarerx.com

Missed a Lunch and Learn?

Log onto PHC's website, click on "Resources and Education", "Client Resources", and "Lunch and Learn" to listen to audio and view handouts from previous programs. (https://phc.procarerx.com/resource/edutools/l-l)

ProCare HospiceCare welcomes all suggestions and comments. If you would like additional information about our services, have ideas for articles, or wish to submit a comment, email us at **resources@procarerx.com**.

ProCare HospiceCare

1267 Professional Pkwy., Gainesville, GA 30507

Executive Editor: Meri Madison, PharmD
Editor: Kristin Speer, PharmD, BCPS