



Regional Palliative Care Services

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Methadone for Pain



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History

Methadone is a synthetic opioid, meaning it is not found naturally occurring and must be chemically derived in a lab.¹ It was developed in Germany in the late 1930's but was only first used for medical purposes in 1946.^{1,2} Following numerous fatalities as a result of respiratory depression, the use of methadone quickly subsided until its recent rise in popularity again over the last decade.³

Pharmacology

Methadone, like morphine, is a highly potent μ opioid receptor agonist, where once absorbed the drug binds to opioid receptors activating them to produce an analgesic response.⁴ This however only accounts for part of methadone's analgesic properties.⁴ It also has two non-opiate analgesic receptor activities: N-methyl-d-aspartate (NMDA) receptor antagonism and monoamine reuptake inhibition.⁴ The NMDA receptor plays a role in the development of central hypersensitisation and opioid tolerance.¹ Methadone binds non-competitively to the NMDA receptor preventing opioid toler-

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ance and NMDA induced hyperalgesia.¹ This action makes methadone a great opioid in the treatment of neuropathic and chronic pain.^{1,4} The combination of μ receptor agonist and NMDA antagonism produces an additive analgesic response while limiting opioid tolerance.⁴

Methadone is highly lipophilic and exhibits rapid, almost complete absorption when administered via the oral or rectal route.^{1,3,5} Methadone can be given parenterally, however given the fast onset and extensive oral/rectal bioavailability, parenteral administration in most instances provides little benefit.⁶ For the imminently dying, for those patients unable to swallow, or when the rectal route is undesirable, methadone can be given buccally or sublingually as it is readily absorbed via the buccal or sublingual mucosa at a rate similar to the oral/rectal

route.^{6,7,8} Though there is limited research and guidelines to support buccal/sublingual administration, the buccal/sublingual route has been used successfully in the palliative care setting.

Following absorption, methadone undergoes a rapid and extensive initial distribution phase within the body, followed by a slow and prolonged elimination phase.^{1,4} A single dose of methadone has a short duration of action due to the rapid and extensive initial absorption, but after repeat doses, a tissue reservoir is created resulting in long duration of action.¹ Methadone does not require metabolism to an active form, it begins to work as an analgesic almost as soon as it is absorbed (~ 30 minutes).^{1,3,5} Elimination occurs mainly via the liver where it is metabolised into inactive metabolites.⁵ Renal excretion occurs at higher doses; however there are no concerns for accumula-

tion in the presence of renal impairment as it is poorly dialysed and is the preferred opioid for patients with renal failure.⁵

Methadone exhibits a wide and unpredictable half-life from person to person, which can vary from 6 to 60 hours.³ This extremely long half-life does not correlate with methadone's observed duration of analgesia (6 to 12 hours), which can lead to accumulation if the dose is increased too quickly, resulting in increased risk of sedation and respiratory depression.⁵

Indications

Methadone is generally not considered first line in the treatment of chronic pain, however it can be extremely effective for syndromes that require high doses of opioids such as neuropathic and incidental pain.⁹ Other indications include moderate to severe cancer pain, nociceptive pain and inadequate pain control

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or dose limiting side effects while on another opioid.^{4,5,9} Methadone may even be considered for opioid-naïve or morphine-intolerant patients, especially when long term treatment is anticipated.⁵

Contraindications

Methadone is contraindicated in patients who are allergic to methadone or its preservatives, however it can be well tolerated by patients who have allergies to other opioids.^{4,5} If a patient does have a rare true opioid allergy such as anaphylaxis or urticaria, methadone may still be tried, but the initial dose should be given under close medical supervision.⁵ Methadone should not be used in patients with severe COPD, acute asthma or respiratory depression.⁴ Concurrent administration of methadone with an antidepressant from the class of monoamine oxidase inhibitors (MAOI) such as phenelzine, is also contraindicated.^{4,9}

Methadone should be used with caution in the elderly, those with liver disease, those who are opioid naïve or who have an intolerance to low dose opioids.^{4,5} Caution should also be exercised in individuals with cardiac disease and those who are on other medications which are known to cause QT prolongation^{4,5} In such instances, an electrocardiogram (ECG) should be performed prior to initiating methadone.⁵ If the patient's QT interval is prolonged, a risk vs benefit analysis should be considered.⁵ Repeat ECG's are only needed as clinically indicated, or when a patient's dose exceeds 150 mg per day.⁵ An extensive list of medications known to prolong the QT interval can be found in Northern Health's Pain and Symptom Management Guidelines (2008) on page 157.

Drug Interactions

Most of the drug interactions seen with methadone are related to inducers or inhibitors of the cytochrome P450 enzyme system which is involved in drug metabolism.⁴ Specifically, drugs which inhibit or induce enzyme CYP 3A4 are mainly responsible for most interactions, but to a lesser extent CYP 1A2 and CYP 2D6 are also involved.⁵ Inducers of CYP 3A4 reduce methadone levels (eg. Phenytoin, carbamazepine), while inhibitors of CYP 3A4 increase methadone levels (eg. Fluoxetine, cimetidine).⁵ An extensive list of medications involved in these interactions can be found on page 154 of Northern Health's Pain and Symptom Management Guidelines (2008).

Acute use of alcohol and/or benzodiazepines will potentiate the risk of sedation and respiratory depression.⁵ Chronic use of alcohol will actually increase clearance of methadone, but as the liver deteriorates methadone levels will tend to accumulate.⁵ Other drugs to be aware of are those which are known to cause QT interval prolongation.⁵ It is important to consult a pharmacist when starting methadone or when adding/removing medications, to assess for any interactions which may exist.⁹



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Side Effects

Methadone's side effects are similar to those seen with other opioids: sedation, nausea, dry mouth, sweating, pruritus, constipation.³ However, methadone is considered to be less sedating and causes less nausea and constipation than other opioids.^{3,4} In addition, because methadone does not have any active metabolites, it has a lower potential to cause delirium and opioid induced neurotoxicity.^{3,5} Respiratory depression is the most serious risk when the initial dose of methadone is too high or increased too quickly.⁵

Dosing/Conversion

Because of methadone's long/unpredictable half-life associated with the risk of delayed overdose, physicians who have not had a lot of experience prescribing methadone are encouraged to consult one of Northern Health's Palliative Care physicians or pharmacist when starting a patient on methadone.^{5,10} There are many published guidelines for the conversion to methadone, however no one method has been shown to be superior over another.⁵ In an outpatient setting, the preferred method is "start low, go slow", especially with opioid naïve patients, or those at high risk for adverse reactions.⁵

Methadone's equianalgesic ratio is quite variable and the higher the previous opioid dose the more potent methadone will be.⁵ Regardless of the calculated equivalent dose, methadone should never be started at more than 30 mg every 8 hours, even if the previous total daily dose of the oral morphine equivalent is very high.⁵ Single daily doses of methadone are not effective for analgesia and methadone must be administered in divided doses every 6 to 12 hours when being used for pain.¹⁰ When initiating or titrating methadone, it is important to provide a short acting opioid such as hydromorphone for breakthrough pain, as it usually takes between 3 to 5 days to reach steady state.⁵ Doses should be adjusted in

increments of 10% to 20% and no more frequently than every 3 days to avoid the risk of accumulation.⁵ A copy of an equianalgesic dosing guide is available in Northern Health's Pain and Symptom Management Guidelines (2008) on page 152.

Methadone is available in Canada as an oral liquid (Methadose 10mg/mL), oral tablets (Metadol 1 mg, 5 mg, 10 mg, 25 mg), as a powder for compounding and as an injectable product which must be specially ordered through Health Canada for subcutaneous administration (Synastone 10mg/mL).⁵ Compounding pharmacies can prepare custom made capsules, suppositories, or liquid methadone at different concentrations if a specific dose or alternate route of administration is desired.⁵ The dose ratio for the oral to rectal route is 1:1, while the parenteral product should be dosed at 50% to 80% of the oral equivalent dose.^{4,5}

Benefits/Barriers

Methadone is an inexpensive opioid at around one-tenth the cost of other opioids.⁴ It appears to provide more effective analgesia with less risk of opioid induced neurotoxicity, and may be especially useful for cancer pain which can require high doses of opioids.⁴ Even so, many patients are reluctant to try methadone because of the stigma and common perception that it is used for addiction.⁵ Other barriers include the requirement for physicians to obtain a special license to prescribe methadone and the challenge of getting injectable methadone, which can take up to 3 months to acquire from Health Canada.^{3,5} Nonetheless methadone should be considered in those patients who are experiencing inadequate pain control with dose-limiting side effects from another opioid, in individuals with renal failure, those with neuropathic pain and those with moderate to severe cancer pain.^{4,5,9} Methadone's unique pharmacology while complex, offers characteristics and advantages not seen with other analgesics.

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Palliative Care Education Sessions

Webinar/teleconference
Every Thursday and last Wednesday of month
2:00 p.m. to 3:00 p.m. (PST)

A team of experts in palliative care will be presenting a series of interdisciplinary webinars on palliative care. All individuals from all care settings are invited to attend. A specific subject will be taught each month and sessions will be repeated for the first three Thursdays of that month to allow more people to participate.

Since August 27th 2015 we have been pleased to offer presentations from guest medical residents every fourth Wednesday of the month. These interactive sessions will be recorded and repeated on the following Thursday and all recordings will be provided on the external website at the end of the month. To access these videos please use the following link:
<https://northernhealth.ca/Professionals/PalliativeCareEndofLifeCare.aspx>

If you or someone you know is interested in being added to our distribution list, please contact Sandra.Schmaltz@northernhealth.ca

Upcoming topic for March:
Dehydration and Hypodermoclysis

Contest ~ QUIZ: Methadone

Test your knowledge on Methadone by answering the following quiz and enter for a chance to win.

CONTEST & PRIZES

All submissions will be entered in a chance to win a prize, and all submissions who correctly answered all questions will have an additional chance to win a prize. Only one entry per person. Contest winner will be notified using the contact information provided in your entry.

DEADLINE: Contest closes **March 15, 2016.**

1. Methadone was first discovered in _____, in the late _____.
 - a. Paris, 1930's
 - b. Germany, 1946
 - c. Paris, 1946
 - d. Germany, 1930's
2. Methadone is:
 - a. A synthetic opioid
 - b. Is inexpensive compared to other opioids
 - c. Has a negative stigma associated with its use
 - d. All of the above
3. Methadone undergoes a _____ and _____ initial distribution phase, followed by a _____ and _____ elimination phase.
 - a. Rapid, prolonged, slow, extensive
 - b. Rapid, extensive, slow, prolonged
 - c. Slow, prolonged, rapid, extensive
 - d. Slow, extensive, rapid prolonged
4. A single dose of methadone has a long duration of action.
 - a. True
 - b. False
5. Methadone has no active metabolites.
 - a. True
 - b. False
6. Methadone has a predictable, but long half-life.
 - a. True
 - b. False
7. Methadone is contraindicated for use in patients with:
 - a. A known allergy to methadone or its preservatives
 - b. Diabetes
 - c. Severe COPD
 - d. A and C
8. Methadone has many drug interactions:
 - a. True
 - b. False
9. Methadone's potential side effects include:
 - a. Dry mouth, sweating, pruritus
 - b. Sedation, that improves with stable dosing
 - c. Less nausea and constipation than other opioids
 - d. All of the above
10. Methadone's equianalgesic ratio is quite _____ and the _____ the previous opioid dose the more _____ methadone will be.
 - a. Potent, lower, variable
 - b. Variable, lower, potent
 - c. Potent, higher, variable

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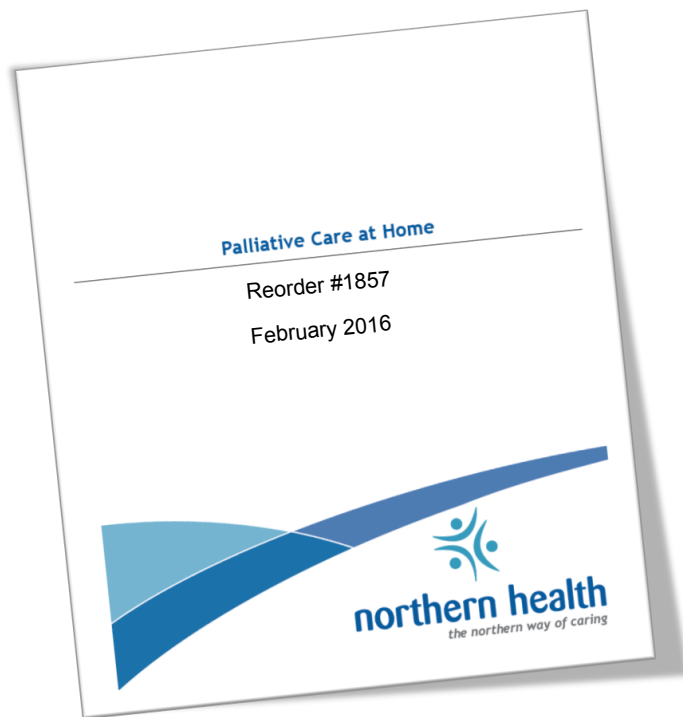
Name: _____

Address: _____

Contact (Email / Tel): _____

Fax to Sandra Schmaltz @ 250-565-5596
or email Sandra.Schmaltz@northernhealth.ca

What's New?



The Northern Health Palliative Care Consultation Team has now finalized the regional *Palliative Care at Home Manual*. Our focus for the regional binder is to make it non community specific. The binder is available in NHA Document Source online catalogue for ordering and the re-order number is #1857.

For any questions please contact the Palliative Care Nurse Consultant in your health service delivery area at:

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Northeast 250-795-6134

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