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FAST FACTS AND CONCEPTS #75

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Introduction Methadone, a potent opioid agonist, has many characteristics that make it useful for the treatment of pain when continuous opioid analgesia is indicated. Although available for decades, its use has gained renewed interest due to its low cost and potential activity in neuropathic pain syndromes. This Fast Fact will introduce methadone's pharmacology and clinical use as an analgesic.

Pharmacology Unlike morphine, methadone is a racemic mix; one stereoisomer acts as a NMDA receptor antagonist, the other is a mu-opioid receptor agonist. The NMDA mechanism plays an important role in the prevention of opioid tolerance, potentiation of opioid effects, and efficacy for neuropathic pain syndromes, although this latter impression is largely anecdotal.

Methadone is highly lipophilic with rapid GI absorption and onset of action. It has a large initial volume of distribution with slow tissue release. Oral bioavailability is high, ~ 80%. Unlike morphine there are no active metabolites and biotransformation to an active drug is not required. The major route of metabolism is hepatic with significant fecal excretion; renal excretion can be enhanced by urine acidification (pH <6.0). Unlike morphine, no dose adjustment is needed in patients with renal failure since there are no active metabolites.

Prescribing Methadone is available in tablet, liquid and injectable forms; oral preparations can be used rectally. Parenteral routes include IV bolus dosing or continuous infusion. Any clinician with a Schedule II DEA license can prescribe methadone for pain; a special license is only required to prescribe methadone for the treatment of addiction. In some jurisdictions, it is necessary to apply the words "for pain" on the prescription.

Cautions Unlike morphine, hydromorphone, or oxycodone, methadone has an extended terminal half-life of up to 190 hours. This half-life does not match the observed duration of analgesia (6-12 hours) after steady state is reached. This long half-life can lead to increased risk for sedation and respiratory depression, especially in the elderly or with rapid dose adjustments. Rapid titration guidelines for other opioids do not apply to methadone. Given recent reports that high-dose methadone may be associated with development of QT interval prolongation and Torsades de Pointes, EKG monitoring may be appropriate when changes in dosage are made (depending upon life expectancy and goals of care).

Potency An important property of methadone is that its apparent potency, compared to other opioids, varies with the patient's current exposure to other opioids. See below for a suggested dosing guide for opioids tolerant patients (Reference 1).

Daily oral morphine dose equivalents oral methadone	Conversion ratio of oral morphine to
< 100 mg	3: 1 (i.e. 3 mg morphine =
1 mg methadone)	
101-300 mg	5: 1
301-600 mg	10: 1

601-800 mg	12: 1
801-1000 mg	15: 1
>1001 mg	20: 1

Due to incomplete cross-tolerance, it is recommended that the initial dose is 50-75% of the equianalgesic dose.

Key Points

- Compared to morphine, methadone is inexpensive, may provide improved analgesia in neuropathic pain and will provide a longer duration of action. Dosing intervals at the start of treatment are q 4-6 hours, and may increase over time to q 6-12 hours.
- Methadone is not indicated in poorly controlled pain where rapid dose adjustments are needed; do not increase oral methadone more frequently than every 4 days.
- Dose conversion to: from other opioids and methadone is complex; consultation with pain or palliative specialists familiar with methadone use is recommended • Patient and family education is essential as they may misinterpret prescription of methadone to mean that their physician believes that they are an addict.

References

1. Ayonrinde OT, Bridge DT. The rediscovery of methadone for cancer pain management. *Med J Austral.* 2000; 173:536-40.
2. Bruera E, Sweeney C. Methadone use in cancer patients with pain: a review. *J Pall Med.* 2002; 5(1):127-38.
3. Iribarne C, Dreano Y, Bardou LG, et al. Interaction of methadone with substrates of human hepatic cytochrome P450 3A4. *Toxicology.* 1997; 117:13-23
4. Krantz MJ, Lewkowiez L, Hays H, et al. Torsade de Pointes associated with very-high-dose methadone. *Ann Intern Med.* 2002; 137:501-4.
5. Morley JS, Makin MK. The use of methadone in cancer pain poorly responsive to other opioids. *Pain Rev.* 1998; 5:51-8.
6. Rowbotham MC. The debate over opioids and neuropathic pain. In: Kalso E, McQuay HJ, Wiesenfeld-Hallin Z, eds. *Opioid Sensitivity of Chronic Noncancer Pain.* (Progress in Pain Research and Management, Vol 14). Seattle, WA: IASP Press; 1999: pp 307-317.

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