

The Clinician

The Outcome Resources Drug Information Newsletter



Methadone for the Treatment of Chronic Pain

Jim Joyner, Pharm.D, C.G.P.

Introduction: Methadone is a potent synthetic opioid with unique characteristics that offer some distinct advantages over other opioid drugs. It was developed as an analgesic in Germany in the late 1940s. Despite its advantages, the level of Methadone prescribing for chronic pain has remained relatively low until recently. Two primary reasons for the lack of widespread use of Methadone for chronic pain include; the difficulty of titrating the dosage when initiating Methadone therapy, and the fact that Methadone may carry some negative stigma since it is best known as a treatment of opioid drug addiction.

Prescriptive Authority: Regulations restrict the prescribing of Methadone for treatment of addiction to FDA approved drug treatment programs. These restrictions *do not* apply when Methadone is prescribed to treat pain, however, some healthcare professionals have been reluctant to prescribe it due to fear of scrutiny by regulatory agencies (1). Methadone is a schedule II controlled substance that may be prescribed for treatment of pain by any physician with valid Drug Enforcement Agency registration.

Pharmacokinetics: Methadone is a fat soluble drug which is widely distributed and bound to various tissues. The

extensive distribution and tissue binding is responsible for the long half-life of the drug and extended duration of analgesic effect upon continuous chronic use. (2) The Methadone distribution phase is complete in 4 to 6 days at which time a “steady-state” condition is achieved between drug levels in the plasma and drug tissue levels. It is because of this extensive distribution phase that the drug may appear to have a shorter duration of analgesic action initially, then exhibit a longer half-life & extended duration of action once the distribution phase is complete. During the last few days of the distribution phase after Methadone therapy is initiated the clinician should be alert for signs of drug accumulation and possible adverse effects (somnolence, delirium, respiratory depression). Methadone is primarily eliminated by metabolism in the liver to inactive metabolites.(3) There is no need for dosage adjustment of Methadone in patients with renal impairment such as those often required with Morphine which has a potentially toxic metabolite that can accumulate and cause toxicity in these patients.

Dosage: For opioid naïve patients, a starting dose of 2.5mg orally every Q8hr has been suggested. (4) In frail, elderly patients the starting dose may need to be reduced to 2.5mg Q12h. The duration of analgesic effect of a single dose may be in the range of 4 to 6

In this issue

Methadone for Chronic Pain	1
Ann’s Pearls of Wisdom	4
Martin McDonough Credentialed in Pain Man- agement	4

Summer 2006

Volume 1
Issue 2

Methadone (continued)

hours for many patients during the initial distribution phase when starting Methadone treatment, therefore, a need for PRN doses should be expected in order to titrate to the therapeutic dose during this period. Breakthrough pain can be managed by using Methadone doses equal to 25-50% of the total daily routine dose at intervals of every 4 hours as needed during the distribution phase. At the end of the distribution phase on approximately Day 5, the total amount of PRN Methadone required for the previous 24 hours is added to the routine total daily dosage and administered in divided doses at 8 or 12 hour intervals. Alternatively, oral morphine solution may be used on a PRN basis for management of breakthrough pain. For patients who will be converted from another opioid to Methadone, there are a variety of published methodologies available. Outcome Resources pharmacists use the following guidelines for conversion which were derived from Ayonrinde and Bridge (Med J Aust 2000)

and Ripamonti (Cancer Pain & Palliative Care 1999):

Methadone Conversion Guide:

- ◆ Convert current opioid dose to the total daily dose of oral Morphine equivalent (see Opioid Conversion Table below)
- ◆ Convert the oral Morphine equivalent to the total daily dose of oral Methadone (see Morphine to Methadone ratio table; page 3)
- ◆ Divide total daily Methadone dose into 3 or 2 doses and administer at 8 or 12 hour intervals

Example: We have a patient on Fentanyl patch 300mcg/hr that we want to convert to Methadone. Fentanyl is converted to an oral Morphine equivalent of 600mg/day using the opioid conversion table. The oral morphine equivalent is then converted to oral Methadone 60mg/day using the Morphine to Methadone ratio table. This total daily dose is then given in divided doses at 20mg Q8hr. This may be further converted

to a Q12h regimen at 30mg Q12h for many patients allowing for greater convenience and compliance.

All equi-analgesic ratios are approximations and are intended to be used as tools to guide the clinician in the determination of an equivalent dosage. Final decisions regarding the appropriate conversion doses should be tempered by individual patient clinical factors including current level of pain, history of compliance with the previous regimen, renal and/or hepatic function, and potential drug interactions.

Advantages of Methadone: Unlike other opioids, Methadone has significant ability to inhibit the NMDA receptor (n-methyl-d-aspartate receptor) at therapeutic doses.⁽⁵⁾ Activation of the NMDA receptor produces central nervous system sensitization, so this pharmacological effect makes Methadone a much more effective drug for neuropathic pain than other opioids. There is also evidence that inhibitory activity at the NMDA receptor sites reduces the possibility of tolerance to Methadone when compared to that exhibited by other opioids.⁽⁶⁾

In addition to being a long-acting opioid that may be dosed at 8 to 12 hour intervals, Methadone is available in a variety of dosage forms:

Tablets: 5mg, 10mg, and 40mg (dispersible tablet)

Oral solution: 5mg/5ml, 10mg/5ml

Oral concentrate: 10mg/ml

Sterile injection: 10mg/ml.

Methadone is well absorbed by the sublingual route which may be of critical importance in patients that are unable to swallow and in whom

Opioid Conversion Table

DRUG	EQUIVALENT ORAL DOSE	EQUIVALENT PARENTERAL DOSE
Morphine	30mg	10mg
Hydromorphone	7.5mg	1.5mg
Oxycodone	20mg	-
Methadone	See methadone conversion guide	
Hydrocodone	30mg	-
Codeine	200mg	-
Propoxyphene	180mg	-
Meperidine	300mg	75mg
Fentanyl patch	25mcg patch is approximately equivalent to 50mg	

Total Daily Oral Morphine Dose Morphine to Methadone Ratio

<100mg	5:1
101-749mg	10:1
>750mg	12:1

infusion therapy is not feasible.⁽⁷⁾ Although oral morphine solution is often administered by the sublingual route, there is evidence to suggest that it is poorly absorbed because of its low lipid solubility.⁽⁷⁾ Methadone may offer distinct advantages over oral morphine solution when the sublingual route of administration is indicated.

One of the most impressive advantages to this unique opioid is its very low cost compared with other potent opioid drugs. Methadone is about one-tenth of the cost of an equivalent dose of the Fentanyl patch (generic)

of the patients reported improvement in pain control and reduction of adverse effects following rotation to Methadone.⁽⁸⁾ Morphine has been associated with a variety of adverse effects including pseudo-allergy (itching, flushing, sweating) and tremors. Methadone is synthetic and belongs to a distinctly different structural class than Morphine, making it a good alternative to patients exhibiting the pseudo-allergy symptoms. In patients receiving Morphine who have renal impairment, an active metabolite, Morphine-3-

Methadone Side Effects

**Constipation Somnolence
Sweating Nausea/vomiting
Respiratory depression**

for a patient on Morphine that is exhibiting neurotoxic side effects.

Drug interactions: There are a variety of potential drug interactions with Methadone. Many of the potential interactions cited in the literature have not been associated with documented clinical effects, even though alterations in Methadone plasma concentrations may be statistically significant. This may be due to the pharmacodynamics of the drug, specifically; long half-life, extensive distribution, and extensive tissue binding. These factors may blunt the clinical impact of some potentially interacting drugs that may induce or inhibit inactivation of Methadone in

Cost Comparison of Fentanyl Patch vs Methadone

(15 day supply of equianalgesic doses)

Fentanyl Patch 50mcg/72h = \$95.00

Methadone 5mg BID = \$9.00

Cost based upon actual claims data from Outcome Resources March 2006

and one-seventh the cost of Morphine extended release tablets (generic).

Indications for use: Methadone is appropriate for treating chronic severe pain, including cancer pain and neuropathic pain. It is an excellent choice when rotating a patient from other opioid therapy which may be either ineffective or causing intolerable side effects. A study of cancer patients who had uncontrolled pain and/or intolerable adverse effects showed 80%

glucuronide can accumulate and is thought to be associated with neurotoxic symptoms (myoclonus, allodynia, and hyperalgesia).⁽⁹⁾ There is also evidence that Morphine-3-glucuronide may actually antagonize the analgesic effect of Morphine itself.⁽⁹⁾ Since Methadone does not have any active metabolites and the dosage does not need to be adjusted for renal impairment, it is ideal for the patient with renal impairment or

Reasons to use Methadone

- **Morphine allergy**
- **Neuropathic pain**
- **Opioid rotation due to ineffectiveness or intolerable side effects**
- **Renal impairment**
- **Long-acting opioid**
- **Effect sublingually**
- **Cost control**



2217 Plaza Dr. Suite 300
Rocklin, Ca. 95765

Phone: 866-877-2053
Fax: 888-500-9023

President & CEO of Outcome Resources, Martin McDonough, Pharm.D., C.G.P. has recently finished extensive course-work and successfully completed a certification examination to become Credentialed in Pain Management through the American Academy of Pain Management. Congratulations to Martin on this significant accomplishment.

Methadone Drug Interactions

Clinically Significant Drug Interactions

Increased Methadone	Ciprofloxacin(Cipro), Diazepam(Valium), Fluconazole(Diflucan), ethanol(acute use)
Decreased Methadone Effects (reduced effects)	Phenytoin,(Dilantin), Phenobarbital, Rifampin, Nelfinavir(Viracept), Ritonavir(Novir)

Possible Methadone Drug Interactions (Clinical effects not documented in literature)

Increased Methadone blood levels	Cimetidine(Tagamet), Fluoxetine(Prozac), Paroxetine(Paxil), grapefruit juice
Decreased Methadone blood levels	Carbamazepine (Tegretol)

the liver. Refer to the drug interaction table for details. There are various strategies for managing drug interactions, however, if the combination of interacting drugs cannot be avoided a general rule of thumb is to adjust the Methadone dose by 25%; upwards if the interacting drug has been shown to result in decreased Methadone clinical effects or down if the interacting drug has been shown to result in increased Methadone clinical effects. Dosage adjustment may not be necessary for drugs which have the potential for altering enzymatic metabolism of Methadone, yet have not been shown to result in a change in the clinical status of patients. The clinician, however, should be alert to possible changes in the clinical picture when any potentially interacting drug is added or removed.

Conclusion: Methadone is a valuable analgesic with distinct advantages

over other opioids that make it a viable option for treatment of chronic severe pain. Clinicians who prescribe Methadone need to be familiar with its unique pharmacokinetics and the dosing ramifications for safe and effective use of the drug.

References:

1. Baumrucker (2000). Amer. J. Hospice & Palliative Care; 17(3): 153-154
2. Goodman and Gilman. The Pharmacological Basis of Therapeutics 11th Edition
3. Eap, et al. (2002) Clin. Pharmacokinetics 41: 1153-93
4. The College of Physicians and Surgeons of Ontario (Nov 2000)
5. Davis, Walsh (2001) Support Care Cancer; 9:73-76
6. Hewitt (2000) Clin J Pain; 16:S73-79
7. Coluzzi (1998) J Pain & Symptom Management; 16:184-192
8. Mercadante, et al. (2001) J Clin Oncology; 19:2898-2904

9. Anderson, et al. (2003) J. Pain & Symptom Management; 25: 74-91

Ann's Pearls of Wisdom:

Ann McLaughlin, Director of Operations

A little helpful hint to keep the pharmacies from "bugging" you:

Don't forget the 5 pieces of required information every time you order a prescription.

1. Patient's full name
2. Patient's date of birth
3. Patient's ID number (which differs from group to group)
4. Patient's gender
5. Group number

The pharmacy may ask for more information than this, but this is the minimum amount needed for the pharmacy to adjudicate a claim with Outcome Resources.