Methadone

Safe and Effective Use in Hospice Pain Management

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Pain in advanced illness

• Two attitudes can disservice patients
  - Avoidance
  - Careless Use

• Critical balance between *do no harm* and *reduction of suffering*
• Under-treatment is common
• Many patients and caregivers worry about addiction and stigma
Objectives

• Discuss the history of methadone.
• Review the risks and benefits of methadone use.
• Recognize the appropriate use of methadone in the hospice population.
• Demonstrate methadone dosing and monitoring strategies.
Test Your Knowledge

True or False

Treatment with methadone is generally expensive  
Methadone can safely be used in opioid naïve patients  
Methadone is a naturally occurring opioid  
Methadone is only effective for neuropathic (nerve) pain  
Patients will not get pain relief from the first few doses of methadone, it needs to reach steady state first.  
Methadone is safe to use in patients with kidney disease
History

- Methadone was developed in 1937 by German scientists at IG Farben
- Brought to market officially in 1943 and was widely used by the German army during WWII under the name *Polamidon*
- After the war, Eli Lily introduced methadone to the U.S. as Dolophine
- Marketed as a safer alternative to morphine because it does not cause as much sedation or nausea
WHEN RELIEF OF PAIN

is of paramount importance

When severe pain must be controlled promptly and with certainty, Methadone Hydrochloride is given with advantage. This synthetic analgesic agent is less likely to produce nausea, vomiting and respiratory depression than is morphine in comparable analgesic doses. It is effective not only on intramuscular injection, but also when administered orally.

Methadone Hydrochloride is indicated whenever pain must be controlled—in trauma, biliary or renal colic, painful orthopedic conditions, and acute cardiac episodes associated with severe discomfort. Methadone Hydrochloride is also useful for controlling withdrawal symptoms in the treatment of morphine addiction. Because its action is largely analgesic and to only a slight extent sedative, it should not be given for preanesthetic purposes.

Methadone Hydrochloride (Massengill) is supplied in tablets of 2.5 mg., 5.0 mg., and 7.5 mg., and in 1 cc. ampuls containing 10 mg. Also available in 10 cc. vials. Methadone Hydrochloride is under the jurisdiction of the Harrison Narcotic Act.

THE S. E. MASSENGILL COMPANY
Bristol, Tenn.-Va.
NEW YORK • SAN FRANCISCO • KANSAS CITY
Dr. Vincent Dole and his wife, Dr. Marie Nyswander, sought to change the perceptions and treatment options for heroin addicts

- 1964: 6 patients
- 1967: 300 patients
- 1971: 25,000 patients

Unfortunately, methadone could not distance itself from the heroin epidemic of the 1970’s and 1980’s
History

• After 1973, methadone saw limited use until a growing body of research in the 1990’s shed light on the positive effects it was having on neuropathic pain control

• Started to see a resurgence of use for chronic pain and cancer patients

• 2006 FDA Public Health Advisory warning of increasing reports of death and life-threatening side effects

• To this day, conflicting perceptions and unfamiliarity continue to hinder appropriate methadone utilization
Ask the Audience - Methadone Perceptions

• What are some concerns you have experienced in your practice regarding methadone?

• How do patients respond when methadone is first brought up as a treatment option?

• What strategies do you currently employ when changing a patient’s pain regimen?
Nociceptive vs. Neuropathic Pain
Nociceptive vs. Neuropathic Pain

Nociceptive:

- Inflammatory
- Muscle, tissue, or organ pain
- Often pain with movement
- Dull, aching, or throbbing
- Includes bone and arthritic pain
Neuropathic:

- Shooting, stabbing, radiating, burning, tingling, numb, electrical
- Allodynia – pain from a stimulus that normally does not provoke pain
- Hyperalgesia – increased sensitivity to a stimulus that is normally painful
  - Damage to peripheral nerves
  - Lack of opioid rotation
Methadone and Neuropathic Pain

• Most effective opioid for neuropathic pain

• Active N-methyl-D-aspartate (NMDA) receptor antagonist
  • Reduces CNS sensitization to pain/hyperalgesia
  • Reduces CNS amplification of pain sensation

• Few other known NMDA receptor antagonists:
  • Dextromethorphan
  • Ketamine
  • Memantine
Pharmacokinetics

Patients can feel analgesia with the very 1st dose
Pharmacokinetics

- **Half-life**
  - Long, but variable (4-130 hours)
  - Increases with repeat dosing

- **Duration of action**
  - 3-6 hrs with INITIATION of dosing
  - Increased to 8-24 hours with REPEATED dosing
  - Takes 5-7 days to reach steady state
Routes of Administration

• Multiple dosage forms
  • Tablet (5 mg, 10 mg, 40 mg)
  • Liquid Concentration (10 mg/mL)
  • Injection (10 mg/mL)

• Well-absorbed from multiple routes of administration
  • Oral, Rectal, Subcutaneous, IV, Sublingual, Vaginal

<table>
<thead>
<tr>
<th>PO Methadone to IV Methadone</th>
<th>IV Methadone to PO Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO:IV 2:1</td>
<td>IV:PO 0.7:1</td>
</tr>
</tbody>
</table>
Wait...what if my patient vomits her dose?

<table>
<thead>
<tr>
<th>Vomitus consists only of a small amount of mucous material</th>
<th>Do not replace the dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emesis &lt; 15 minutes after dose</td>
<td>Consider replacing 50% to 75% of the dose; but if the dose is more than 120 mg, consider replacing only 50%</td>
</tr>
<tr>
<td>Emesis 15-30 minutes after dose</td>
<td>Consider replacing 25% to 50% of the dose</td>
</tr>
<tr>
<td>Emesis &gt; 30 minutes after dose</td>
<td>Do not replace the dose</td>
</tr>
</tbody>
</table>

Keep in mind that there is probably more risk replacing part or all of a dose, due to the potential to over-dose the patient if they did not eliminate it all.
Hepatic and Renal Considerations

- Safe in renal failure - No active metabolites
- Dose should still be reduced in severe impairment
- Does undergo hepatic metabolism so should be avoided in severe liver disease.

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Preferred Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &gt; 40</td>
<td>Morphine, Oxycodone, Hydromorphone, Methadone</td>
</tr>
<tr>
<td>CrCl = 30-40</td>
<td>Oxycodone, Hydromorphone, Methadone</td>
</tr>
<tr>
<td>CrCl = 10-30</td>
<td>Oxycodone, Methadone</td>
</tr>
<tr>
<td>CrCl &lt; 10</td>
<td>Oxycodone, Methadone</td>
</tr>
</tbody>
</table>
Pharmacokinetic Concepts

Liver Metabolism – Normal Process

CYP enzyme

(mainly CYP3A4, CYP2B6)

Active methadone

100% inactive methadone
NO ACTIVE METABOLITES
Pharmacokinetic Concepts

Liver Metabolism – CYP inhibitors and Liver Failure

CYP inhibitors (mainly CYP3A4, CYP2B6)

CYP inhibitors and/or 2B6 INHIBITORS
(Think: Methadone TOXICITY)

- verapamil
- sertraline*
- nicardipine
- metronidazole
- haloperidol
- fluconazole
- doxycycline
- paroxetine
- desipramine*
- clotrimazole
- erythromycin
- clarithromycin
- amiodarone
- caffeine
- diltiazem
Pharmacokinetic Concepts

Liver Metabolism – CYP Inducers

CYP3A4 and/or 2B6 INDUCERS
-(Think: methadone REDUCTION/WITHDRAWAL)
carbamazepine (Tegretol®)
dexamethasone
oxcarbazepine (Trileptal®)
phenytoin*
phenobarbital*
nevirapine*
primidone*

Active Methadone
# Opioid Cost Comparison

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Avg cost:</th>
<th>Per dose</th>
<th>Per 15 days supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxyContin®</td>
<td>$ 5.39</td>
<td>$ 226</td>
<td></td>
</tr>
<tr>
<td>OxyFast®</td>
<td>$ 3-6</td>
<td>$ 180</td>
<td></td>
</tr>
<tr>
<td>Morphine Sulfate ER</td>
<td>$ 2.13</td>
<td>$ 85</td>
<td></td>
</tr>
<tr>
<td>Fentanyl Patch*</td>
<td>$ 16/patch</td>
<td>$ 80</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>$ 0.13</td>
<td>$ 5</td>
<td></td>
</tr>
</tbody>
</table>

*5 fentanyl patches/box, each patch lasts for 72 hrs.
QT Prolongation and Methadone

- QT prolongation
- Torsades de Pointes (TdP)
- Ventricular tachycardia (FATAL)
QT Prolongation and Methadone

Risk Factors

• Female
• Impaired liver function
• Arrhythmias, CAD/MI, CHF
• QT prolonging medications (amiodarone, quetiapine, haloperidol, chlopromazine, citalopram, paroxetine, fluoxetine, sotalol, trazodone, Ranexa, ondansetron)
• Electrolyte imbalances (hypokalemia, hypomagnesemia), also caused by diuretics, laxatives, vomiting and diarrhea
• Doses greater than 200 mg of methadone per day
QT Prolongation: Clinical Approach

- Avoid in multiple risk factors; reduce controllable risk factors (dehydration, nausea/vomiting/diarrhea, QT drugs)
- Arrhythmia alone is not a contraindication and many clinicians still use in this setting
- Risk vs benefit discussion with patient and caregivers
- Monitor for new/increased tachycardia, syncope, palpitations, diaphoresis (indicating new arrhythmia)
- Consider baseline/periodic EKG in patients with longer prognoses
When to Use Methadone

- Patients with rapidly escalating drug requirements (greater than 200 mg of morphine equivalents a day)
  - Full Conversion
  - Adjunct Dosing
- Patients with dose-limiting side effects from other opioids
  - Nausea, constipation, hallucinations, myoclonus
- Patients having trouble swallowing pills who need long-acting pain control
- Patients or caregivers with a history of drug addiction or diversion
Methadone Dosing

• Add up total oral morphine equivalents (OME)
• Use morphine : methadone conversion factor
• Divide daily dose into 2-3 doses per day
• Use breakthrough medication during titration
• Monitor daily for pain levels and new/worsening adverse effects
• Increase total daily dose no more frequently than every 5 days
• Patients on greater than 200 mg of morphine/day may need to cross-taper
Methadone Dosing

- Methadone is dosed using a non-linear conversion
- The higher the dose of oral morphine equivalents a patient is taking, the greater you divide to get your methadone dose
- Methadone (NMDA blockade) reverses tolerance/increases sensitivity to opioids
- Increased opioid sensitivity = lower methadone dose required

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<tr>
<th>24 Hour Oral Morphine Equivalent</th>
<th>Morphine : Methadone (per 24 h)</th>
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<tr>
<td>&lt;30 mg/24 h</td>
<td>2 : 1</td>
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<td>30 – 99 mg/24 h</td>
<td>4 : 1</td>
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<td>100-299 mg/24 h</td>
<td>8 : 1</td>
</tr>
<tr>
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<tr>
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<td>&gt;1000 mg/24 h</td>
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Story P, et al.
Methadone Dosing

- During initial titration
  - Utilize *other* immediate-release opioid, dosed q2-4hr prn
    - Morphine IR, oxycodone IR, hydromorphone IR
    - *IF* methadone must be used for breakthrough pain, start low and limit to 3 prn doses/day
- Calculate breakthrough dosing
  - One breakthrough dose = 5% - 15% of total daily dose of oral morphine equivalents (OME)
  - **Good rule of thumb**: 10% of the total daily dose of OME
Methadone Dosing: Clinical Pearls

• If more than 3 breakthrough doses are needed per day to treat baseline pain, contact prescriber with recommendation to increase methadone.

• If breakthrough pain is caused by movement or is episodic, pre-treat with short acting opioids.

• Hold methadone for lethargy, respirations < 9/min, decreased responsiveness, or other signs of opioid toxicity.

• Although it is as effective as other opioids, do not use methadone PRN for shortness of breath – use short acting opioid instead.
Mrs. Jones (Part 1)

- 60 yo female admitted to hospice with dx of breast cancer
- CC: Back pain; Rating 10/10; Describes as stabbing and burning
- Hx: Diabetes, Non-smoker, 5’5” 105 lbs
- Current meds:
  - MS Contin 30mg PO q8h
  - Morphine IR 10mg PO q2h prn BTP (using 5 doses/day)
- Total Oral Morphine/day: 140mg
Methadone Dosing

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Story P, et al.
Mrs. Jones (Part 1)

• Methadone equianalgesic dosing ratio: 8:1
• 140 divided by 8 = 17.5mg per day
• Dose reduce by 25% = 13.125 mg
  • When switching between opioids
  • Round up to 15 mg (severe pain) or down to 10 mg (pt is not in pain)

Discontinue MS Contin; Start: Methadone 5 mg PO q8h
Roxanol (20mg/mL) 10-20mg PO q2h prn breakthrough pain
Monitor daily for 5 to 7 days
## Management of Side Effects

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<tr>
<th>Common side effect</th>
<th>First line medication(s)</th>
<th>Comments</th>
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| Opioid-induced constipation (stasis)    | Senna-S Reglan                    | Induces motility  
Avoid “all mush, no push!”  
Less severe/frequent with methadone                                    |
| Opioid-induced nausea/vomiting          | Haldol Compazine Reglan           | Dopamine-mediated  
Less severe/frequent with methadone                                        |
| Sedation                                | Oral steroid Ritalin              | Reduces with continued use  
Less severe/frequent with methadone                                         |
| Opioid-induced itching/rash             | Oral diphenhydramine *Hydroxyzine| Uncomplicated itching/rash is a common side effect, not an allergy. Switching opioids may or may not be effective |
Methadone Toxicity

- Signs/symptoms: extreme somnolence, stupor, muscular flaccidity, cold clammy skin, maximally constricted pupils, respiratory depression (Cheyne-Stokes respirations, cyanosis, low RR)²

- Synergistic toxicity: benzodiazepines (lorazepam, diazepam, etc.)

Identify Methadone Toxicity: “Cold, Limp Noodle”
Mrs. Jones (Part 2)

- Today is methadone day 3 (5 mg PO q8h)
- Reports today pain is 9/10
- Has taken 2 x 10 mg Roxanol (20mg/mL) doses in the last 24 hours
- Patient insists the methadone dose should be increased

This is your patient. What should we do? What questions should we ask?
Adjunct Dosing

- Patients may be unwilling to switch completely to methadone
- Consider adding a smaller dose of methadone to a patient’s existing pain regimen
  - Improves pain control
  - reduces side effects
  - reduces cost
- Current regimen is usually decreased
- Methadone is not the only adjunct medication!
  - Steroids
  - Gabapentin
Mr. Smith

• 42 yo male with pancreatic cancer and significant metastases
• Still able to swallow pills whole
• Currently taking: Morphine IV via continuous infusion
  • 25 mg per hour continuous
  • 10 mg bolus q 10 min prn breakthrough pain
• Has used 39 breakthrough doses with 51 attempts in the last 24 hours
• Pain is still 10/10 and he states: “Everything hurts! Even the blanket!”
• Refuses to switch outright to methadone as morphine “has always done the trick in the past”
Summary

Two attitudes that can disservice patients in pain management

- Avoidance
- Careless Use
Questions
References


