METHADONE USE IN HOSPICE PATIENTS WITH NEUROPATHIC PAIN

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Goals of this Presentation

1. Gain a better understanding of the benefits/risks of methadone use.
2. Recognize how methadone helps neuropathic pain.
3. Discuss initiation of methadone to opioid naïve patient.
4. Discuss converting patients on other opioids to methadone.
5. Present an easy-to-follow algorithm or plan for introducing or converting to methadone.

History

• Available since mid-1940s
• Large clinical studies published in 1950s
• Used for addiction in mid-1960s
• Single-dose studies and reported equianalgesic dose ratio appeared in 1967 — Dangerously misleading
History

1970s & 1980s
Methadone’s dangers found out the hard way

1990s
The era of enlightenment

2000 and Beyond
Using methadone with care & expertise

History

• Prior to 1985
  – When long-acting morphine preparations were introduced, Methadone was commonly prescribed for cancer-related pain as it had a longer duration of action than morphine.
  – It was well appreciated, though, that methadone had a higher risk of respiratory depression due to drug accumulation with chronic dosing.
  – This was an effect not associated with other opioids, for which there is no drug accumulation in the setting of normal renal function.

History

• Prior to 1990
  – There was a widespread belief that opioids were relatively ineffective in treating neuropathic pain.

• Since 1990
  – There has been a much greater understanding that opioids are an effective part of neuropathic pain treatment.
History

• Prescriptions for methadone have greatly increased in the past ten years.

• The reason for this increase is likely related to two factors:
  – Reduced cost relative to other potent opioids
  – Basic science data suggests that methadone may be particularly useful in treating neuropathic pain.

Mechanism of Action

• Methadone is a racemic mixture

• One stereoisomer acts as a mu-opioid receptor agonist

• The other acts as a NMDA receptor antagonist

Mu-agonist

• Methadone hydrochloride is a mu-agonist

• It is a synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine

• The most prominent of which involves the central nervous system and organs composed of smooth muscle.
NMDA Receptor Antagonist

NMDA receptor antagonist which plays an important role in

- Prevention of opioid tolerance
- Potentiation of opioid effects
- Efficacy for neuropathic pain syndromes

Mechanism of Action (other)

- Methadone also inhibits reuptake of serotonin and norepinephrine
  - Similar manner to newer anti-depressants,
  - Some of which are effective against neuropathic pain (e.g. venlafaxine)
- Methadone has demonstrated efficacy in animal models of neuropathic pain

Pharmacology

- 80% oral bioavailability
- Lipid soluble
- Almost completely absorbed in GI Tract
- Metabolized in liver to inactive metabolites but excreted in the urine, feces
Pharmacology

• Rapid, extensive distribution phase
• Slow elimination phase (because it is lipophilic)
• Clinical effect depends upon whether it is a first dose vs. part of ongoing regimen

Pharmacology
Side Effect Profile

• Constipation
• Sedation
• Nausea and vomiting
• Sweating
• Circulatory depression
  – QTC prolongation
• Respiratory depression

QTC Prolongation

• The effect of initiation of methadone on QTC interval in cancer patients
  A study reported in the Journal of Palliative Medicine supports the safety of methadone to treat patients with advanced cancer in the palliative care setting.
• Researchers from the University of Texas M.D. Anderson Cancer Center investigated the effect that methadone had on 100 palliative care cancer patients’ QTC interval at baseline, two weeks, four weeks, and eight weeks after starting methadone.
• Investigators found prolonged QTC intervals of greater than 430 ms in males and greater than 450 ms in females in 28% of patients at baseline
• But significant QTC intervals of 500 ms or more rarely occurred after methadone initiation.
• The team found no clinical evidence of torsades de pointes, ventricular fibrillation, or sudden death.
Advantages of Methadone

• Extended dosing interval (a long acting opioid)
• Only long-acting liquid opioid
• Rapid absorption from mucous membranes

*Roxanol is NOT absorbed from the mouth

Advantages of Methadone

• Great for opioid rotation when other opioids – especially the "morphine derivatives" are not effective, require high doses or have intolerable side effects
• Rapid onset of action
• Long half-life after steady state is established.
• Great for use in patients with hepatic and renal failure because there are no active metabolites.

Advantages of Methadone

Inexpensive

• 10mg tabs $0.14 each
• Methadone Conc. 10mg/ml $7.50/90ml
• Methadone Inj. 10mg/cc $84.10/20cc
• Roxanol 20mg/cc $17.00/30cc
Cost of a 15 day Supply for Various Opioids

Cost of a 15 day supply of equivalent doses:

- **Oxycodone CR** (generic Oxycontin) 80mg/day $110.00
- **Fentanyl Patch** (generic Duragesic) 50mcg $95.00
- **Morphine CR** (generic MS Contin) 100mg/day $65.00
- **Methadone** 10mg /day $9.00

Advantages of Methadone

- Available in various dosage forms (pill, elixir, IV, suppository, sublingual or even subcutaneous, and can be crushed and put through NG or GT tubes)
- Used appropriately, it can change lives that seemed hopelessly entrenched in symptom burden

Disadvantages of Methadone

- Large inter-individual variation in pharmacokinetics
- Equianalgesic ratios formerly used underestimated relative potency
- Stigmatized by some patients or providers due to its association with addicts
- It is unfamiliar to many, and thus it is the scapegoat for many unexpected events
Drugs that Increase Activity of Methadone

- Ketoconazole or Fluconazole
- Grapefruit juice
- HIV Protease Inhibitor
- Antidepressants: Prozac, other SSRIs, Effexor
- Elavil (amitriptyline)
- Tagamet (cimetidine)
- Antibiotics: Ciprofloxacin, erythromycin, Flagyl, Biaxin
- Acute alcohol use

Drugs that Decrease Activity of Methadone

- Rifampin
- Carbamazepine
- Phenytoin
- Corticosteroids
- St. John’s Wort
- Barbiturates
- Risperdal
- HIV retrovirals
- Spironolactone
- Verapamil
- Estrogens
- Chronic alcohol consumption

Choosing the Right Patient for Methadone

No reason it can not be used first line, first time in the right patient
When is Methadone the Right Choice?

• Complex pain syndromes
• Poorly treated neuropathic pain
• High doses, poor pain relief on other opioids – those who need opioid rotation
• Unacceptable side effects that could be signs of opioid neurotoxicity (hyperlgesia, myoclonus, delirium)

When is Methadone the Right Choice?

• “Debility and decline” patients with a pain component such as arthritis
• COPD, CHF
• ALS (Amyotrophic Lateral Sclerosis)

When is Methadone the Right Choice?

• Cirrhosis of the liver — may be the drug of choice...
• Chronic Renal Failure — may be the drug of choice...

Because there is no accumulation of toxic metabolites as there is with MS, oxycodone and hydromorphone.
Morphine to methadone conversion

Methadone behaves as a much more potent opioid the higher the dose of the prior opioid.

Morphine to Methadone Conversion Ratios

<table>
<thead>
<tr>
<th>Daily Morphine</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50mg</td>
<td>5:1</td>
</tr>
<tr>
<td>51-100mg</td>
<td>use 10mg/day</td>
</tr>
<tr>
<td>101mg-749mg</td>
<td>10:1</td>
</tr>
<tr>
<td>&gt;750mg</td>
<td>12:1</td>
</tr>
</tbody>
</table>

50mg methadone is the upper limit for a single starting dose.

Opioid Conversion Table

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Dose</th>
<th>Parenteral Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30mg</td>
<td>10mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5mg</td>
<td>1.5mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20mg</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>See methadone guidelines</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30mg</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>200mg</td>
<td></td>
</tr>
<tr>
<td>Fentanyl Patch</td>
<td>25mcg patch approx. = 50mg</td>
<td>Oral Morphine/day</td>
</tr>
</tbody>
</table>
**Morphine Conversion Factors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Multiply by this factor to equal oral Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone oral</td>
<td>4</td>
</tr>
<tr>
<td>Hydromorphone IV</td>
<td>20</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1.5</td>
</tr>
<tr>
<td>Morphine IV, SC</td>
<td>3</td>
</tr>
<tr>
<td>Methadone</td>
<td>See methadone guidelines</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.15</td>
</tr>
<tr>
<td>Fentanyl patch</td>
<td>25mcg patch approximately = 50mg Oral Morphine/day</td>
</tr>
</tbody>
</table>

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**Starting Methadone in a Patient Not on Strong Opioids**

- Start low, often at 2.5mg to 5mg po q12hrs titrate to q8 hrs if needed and use Roxanol for breakthrough pain
- Reassess frequently
- Seldom have to titrate

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**Starting Methadone in a Patient Not on Strong Opioids**

- Monitor carefully by phone or in person
- Watch especially for signs of accumulation between 4 – 7 days
- Watch for somnolence, delirium, respiratory depression, etc.
Starting Methadone in a Patient Not on Strong Opioids

• On day 7 of methadone use, look at the Roxanol use in prior 48hrs, divide by 5 to get the methadone equivalent.

• Divide this by 4 (to get from 48 to 12 hrs) and add this to the existing q 12 h methadone dose.

Converting a Patient Already on Strong Opioids to Methadone

• This will be more difficult and require more attention if pain is poorly controlled on current opioid.

• Convert total 24 hr opioid dose to 24 hr Oral Morphine Equivalent (OME)
  (No need to account for limited cross tolerance)

• Divide the 24 hr OME dose by 10 to determine 24 hr methadone dose.

Methadone Use at The Elizabeth Hospice

• Educate Staff Monthly
  – New Staff
  – Refresher

• Strong physician support

• Started use ~4 years ago
Methadone Use at Elizabeth Hospice

- Initially conversion of those
  - Not helped with other opioids or
  - With intolerable side effects
- Now convert most patients from other opioids to methadone
- Now start most patients on methadone as narcotic of choice

Patient Example

Adam Able

68 year old man with severe chest pain due to CA of the lung who also has left arm tingling is on 120mg tid of MS Contin, but since his last MS dose increase has experienced myoclonic jerking and more agitation. Opioid rotation to methadone is considered so that he can avoid opioid neurotoxicity and be helped with his left arm neuropathic pain. How would you convert him from morphine to methadone?

Problem

- 360 mg OME is equivalent to ___ mg of methadone. For convenience of dose forms, give ___ mg am and ___ mg pm for 12 hr dosing or ___ mg for 8 hr dosing.
- Use Roxanol for breakthrough using ~ 10-20% of OME of the past 24h narcotic doses given q1h pm.
Answer

• 360 mg OME is equivalent to 36 mg of methadone. For convenience of dose forms, give 15 mg am and 20 mg pm for 12 hr dosing or 10 mg for 8 hr dosing.

• Use Roxanol for breakthrough using ~ 10-20% of OME of the past 24h narcotic doses to guess at what might be needed i.e., 40-50mg q1h

Patient Example

Bert Brouha

54 year old patient with end-stage liver disease on 25mcg Duragesic (fentanyl TD). Pain is under poor control. He was not offered any breakthrough pain Meds.

Problem

• Convert to oral morphine equivalent (OME) - 25mcg Duragesic = about ___ mg qd of OME

• Divide ___ OME by 5 = ___mg/24 methadone

• Start with ___mg methadone q12h

• Since pain was poorly controlled on Duragesic, expect more Roxanol use.

• On Day 7 add up Roxanol use in prior 48hrs, lets say 100mg.

• Divide by ___ to get the methadone equivalent, divide that by ___ to get the 12h dose and add that amount of methadone to his current 12hr dose of ___mg (from above calculation in #1) giving him a new 12hr dose of ___
**Answer**

- Convert to oral morphine equivalent (OME) - 25mcg
  Duragesic = about 50 mg q.d  of OME
- Divide 50mg OME by 5 = 10mg/24 methadone
- Start with 5mg methadone q12h
- Since pain was poorly controlled on Duragesic, expect more Roxanol use.
- On Day 7 add up Roxanol use in prior 48hrs, lets say 100mg.
  Divide by 10 to get the methadone equivalent, divide that by 4 to get the 12hr dose and add that amount of methadone to his current 12hr dose of 5mg (from above calculation in #1) giving him a new 12 hr dose of 7.5mg

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**Patient Example**

Christine Chang

45 year old lady with ovarian cancer metastatic to the peritoneum and retroperitoneal area with post renal failure (obstruction of ureters bilaterally). She is developing more sedation on her oral hydromorphone (Dilaudid) dose of 5mg q8h. Opioid rotation is requested to improve pain control and avoid sedation.

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**The problem:**

- Day 1 Convert 15 mg of hydromorphone to OME ___ mg/d & divide by ___. Give ___mg (closest MD dose) q12h.
- Adding Roxanol in doses of ___ to ___ q1h for breakthrough
- Day 2-5 carefully assess and reassess in person and by phone for pain control, side effects
- Day 7 CC has used 100mg Roxanol in 48hr and so her 12hr dose of methadone should be increased by ___mg to a total of ___mg q12h
- Day 5-7 Watch for____ and need for dosage adjustment.
Answer

- Day 1 Convert 15 mg of hydromorphone to OME 60mg/d & divide by 5. Give 5 mg (closest MD dose) q12h.
- Adding Roxanol in doses of 5 to 20mg q1h for breakthrough
- Day 2-5 carefully assess and reassess in person and by phone for pain control, side effects
- Day 7 CC has used 100 mg of Roxanol in 48hr and so her 12hr dose of methadone should be increased by 2.5 mg to a total of 7.5 mg q12h or 5 mg q8h
- Day 5-7 Watch for sedation and need for dosage adjustment

Morphine to Methadone Conversion

- Conversion we have learned today is ONLY for conversion of other opioids TO methadone
- Principles of conversion FROM methadone to morphine or other opioids is not the same and requires another set of rules!

Methadone Bottom Line

- Methadone is a unique opioid that has a role in symptom management
- Worst fear scenarios have not played out with extensive use at MD Anderson Cancer Center (even by non-specialists) and with extensive use at Hospice Care Team with non-specialists
- Treat it like any other useful tool—it requires a skilled operator
- Don’t be too hesitant to administer it
Methadone Bottom Line

- Methadone is an analgesic of indisputable value that continues to gain acceptance in chronic pain management.
- Methadone has no active metabolites.
- Methadone is an inexpensive long-acting opioid with a rapid onset of action available in various dosage forms.
- Methadone is an excellent alternative from both a clinical and economic perspective.

Questions??

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