Complex Pain: Methadone

Frank D Ferris, MD, FAAHPM, FAACE
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- Tri-County Health Network
- Volunteers of America
- WCAHEC
Objectives

• Pharmacokinetics
• Risk of side effects
• Dosing principles
• Drug interactions
Methadone

- Synthetic, developed over 60 years ago
- Chemical structure unrelated to opium derivatives
- Racemic mixture
  - L-methadone: mu-receptor agonist
  - R-methadone: N-methyl-D-aspartate (NMDA) receptor antagonist, antitussive
- Presynaptic blockade of serotonin, norepinephrine reuptake
Methadone Uses

• Conventional opioids ± coanalgesics
  Effective – likely pure nociceptive or mild mixed pain
  Ineffective – likely windup with activation of NMDA receptors

• Methadone
  Lower doses – mu-receptor agonism
  Higher doses – NMDA receptor antagonism
Methadone pharmacokinetics does not follow first order kinetics.
Methadone
Pharmacokinetics

- Oral bioavailability 41 – 99 %
- $t_{C_{\text{max}}} = 2 – 4$ hrs
- Lipophilic $\rightarrow$ rapid redistribution fat
  \[ t_{1/2} = 2 – 3 \text{ hrs} \]
- 60 – 90 % binds to alpha-1-acid-glycoprotein
- Analgesic action 4 – 8 hrs, longer with repeat dosing

Dose Q12H or Q8H
Methadone Accumulation In Tissues 15 – 30 days
Methadone Pharmacokinetics

- Extensively metabolized in liver by N-demethylation ➔ inactive metabolites
  Cytochrome
  **Major:** P450-3A4
  **Minor:** P450-2D6

- If excreted, most in feces, < 10% in urine
  No adjustment for oliguria or anuria
Methadone Pharmacokinetics

• Biphasic elimination

  Initial phase: $t_{1/2} = 12 - 24$ hrs
  Second phase:
    $\beta t_{1/2} = 15 - 60$ hrs (as long as 130 hrs)

  May still $\Rightarrow$ side effects
Plasma Concentration

Elimination Half-Life ($t_{1/2}$)

$= \text{time it takes for the body to excrete half the dose}$

Methadone all routes

$\beta \ t_{1/2} \approx 60+ \text{ hrs}$

$\approx 2.5+ \text{ days}$

Initial Phase

$12 - 24 \text{ hrs}$
Complete Elimination

$\beta \ t_{\frac{1}{2}} = 15 - 60 \text{ hrs (as long as 130 hrs)}$

$\Rightarrow 5 \times t_{\frac{1}{2}} \approx 15 - 30 \text{ days}$
Risk of side effects...
Accumulation ➔ Risk
Late Onset Side Effects

10 – 30+ days
Methadone Side Effects

- Generally same as other opioids
  - Sedation ➔ Delirium
  - Nausea
  - Pruritus
- Constipation
  - May develop at a slower pace
- Mild antidiuretic effect
  - Edema
Methadone Side Effects

- Rarely associated with methadone
  Myoclonus – are they also on gabapentin?
  Hallucinations
  Respiratory depression
- QT interval prolongation
  Associated with high dose, > 200 mg / 24 hrs
  Avoid hypokalemia, hypomagnesemia
  Caution when combining with P450-3A4 inhibitors
…QTc Prolongation Clinical Guideline

- Disclosure
- Clinical history
- Screening electrocardiogram
- Risk stratification
- Drug interactions screen

Ann Intern Med. 2009; 150: 387-395
## Association between Opioid doses and QTc

<table>
<thead>
<tr>
<th>Opioid</th>
<th>N</th>
<th>R²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>25</td>
<td>0.09</td>
<td>0.0165</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>27</td>
<td>0.35</td>
<td>0.0016</td>
</tr>
<tr>
<td>Morphine</td>
<td>23</td>
<td>0.03</td>
<td>0.4466</td>
</tr>
<tr>
<td>Tramadol</td>
<td>16</td>
<td>0.11</td>
<td>0.1994</td>
</tr>
</tbody>
</table>

Medication interactions...
Methadone
Drug Interaction – P450 Inhibitors

• **P450 Inhibitors** may ↑ methadone concentration
  - Grapefruit juice
  - Diazepam
  - SSRIs
    - Ketoconazole, other imidazoles; Fluconazole better
    - Ciprofloxacin, other quinolones
    - Erythromycin, other macrolides
    - Atypic antidepressants, e.g., nefazodone
Methadone
Drug Interaction – P450 Inducers

- **P450 Inducers** may ↓ methadone concentration
  - Corticosteroids
  - Risperidone
  - Carbamazepine
  - Phenytoin
  - Phenobarbital
  - Rifampin
  - Antiretroviral drugs, e.g., ritonavir, nevirapine, nelfinavir, efavirenz
Methadone Interaction Potential
Alcohol, Cigarettes

• Alcohol
  Acute use may ↑ methadone AUC (effect)
  Chronic use ↓ methadone concentration

• Cigarettes
  Induce metabolism
  May ↓ methadone concentration
Methadone
Effect on other Medications

• Methadone may ↑ concentrations of
  Codeine, hydrocodone
  Haloperidol
  Phenothiazines, e.g., chlorpromazine
  Tricyclic antidepressants
  Beta blockers
  Dextromethorphan
  Zidovudine, aka Retrovir
Cost advantage...
# Relative Cost - 1 Month Supply Equivalent to morphine 10 mg q4h

<table>
<thead>
<tr>
<th>Medication</th>
<th>Relative AWP Cost 1 Month Supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine IR tabs</td>
<td>1.0</td>
</tr>
<tr>
<td>Morphine ER tabs (generic)</td>
<td>3.9</td>
</tr>
<tr>
<td>Methadone tabs</td>
<td>0.5</td>
</tr>
<tr>
<td>Methadone oral solution</td>
<td>1.0</td>
</tr>
<tr>
<td>Methadone SC / IV</td>
<td>19.0</td>
</tr>
<tr>
<td>Oxycodone IR tabs</td>
<td>1.5</td>
</tr>
<tr>
<td>Oxycodone ER tabs (generic)</td>
<td>6.9</td>
</tr>
</tbody>
</table>
Dosing...
Methadone Dosage Forms

Oral, rectal, buccal, parenteral routes

**Tablets:** 5, 10, 40 mg – in US, 40 mg only for methadone maintenance

**Solution:** 1 mg / ml, 2 mg / ml, 10 mg / ml

**Parenteral:** 10 mg / ml or compounded

Local irritation at SC sites diminished with addition of dexamethasone

**Rectal:** compounded
Methadone Dosing

• Equianalgesic dose varies dramatically depending on the extent of previous exposure to opioids
Sarah 67 F

- Pancreatic Ca x 6 months
  Significant epigastric mass w enlarged LN
  Liver metastases
- 5 – 9 / 10 aching burning epigastric pain
- Dexamethasone 8 mg PO QAM
Methadone Initiation Dosing as Primary Opioid

- Start methadone 5 – 10 mg PO q12 or q8 hrs for 4 – 7 days (dosing for analgesia)
- Titrate to effect
  - ↑ dose 50%, continue for 4 – 7 days
  - Continue ↑ dose every 4 – 7 days until stable pain relief
- **Breakthrough pain**
  - Use an alternative IR opioid PO q1h PRN
  - Substance use – methadone 5 mg q3h PRN
Sarah 67 F

- Pancreatic Ca x 6 months
  - Significant epigastric mass w enlarged LN
  - Liver metastases
- 5 – 9 / 10 aching burning epigastric pain
- Dexamethasone 8 mg PO QAM +
- Morphine ER 160 mg Q12H +
  - Morphine IR 45 mg PO Q1H x 8 / day
  => only partial relief
Methadone Conversion
Replace Other Opioid with Methadone

• Calculate total conventional opioid and equivalent methadone dose

• Morphine 160 mg ER PO Q12H + Morphine 45 mg IR PO x 8 / day = Morphine 680 mg daily
# Equianalgesic Dosing - Chronic Pain

## Changing Routes of Administration

<table>
<thead>
<tr>
<th>PO / PR</th>
<th>IV / SC / IM</th>
<th>Epidural</th>
<th>Intrathecal</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1</td>
<td>0.1</td>
<td>0.01</td>
</tr>
</tbody>
</table>

## Changing Analgesics

### Opioids

<table>
<thead>
<tr>
<th>Oral / Rectal Dose (mg)</th>
<th>Analgesic</th>
<th>Parenteral SC / IV / IM Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>Meperidine</td>
<td>50</td>
</tr>
<tr>
<td>150</td>
<td>Tramadol</td>
<td>-</td>
</tr>
<tr>
<td>150</td>
<td>Codeine</td>
<td>50</td>
</tr>
<tr>
<td>150</td>
<td>Hydrocodone</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>Morphine</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>Oxycodone</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Oxymorphone</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Hydromorphone</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Levorphanol</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>Fentanyl</td>
<td>0.050 mg*</td>
</tr>
</tbody>
</table>

*1000 mcg = 1 mg; must convert to mg to calculate equianalgesic dose

### Transdermal Fentanyl

Morphine 50 mg PO in 24 hrs ≈ Fentanyl 25 mcg transdermal patch q 72 hrs

## Methadone

<table>
<thead>
<tr>
<th>Daily Morphine Dose (mg/24 hrs PO)</th>
<th>Conversion Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine PO</td>
<td>Methadone PO</td>
</tr>
<tr>
<td>&lt;100</td>
<td>3 : 1</td>
</tr>
<tr>
<td>101-300</td>
<td>5 : 1</td>
</tr>
<tr>
<td>301-600</td>
<td>10 : 1</td>
</tr>
<tr>
<td>601-800</td>
<td>12 : 1</td>
</tr>
<tr>
<td>801-1000</td>
<td>15 : 1</td>
</tr>
<tr>
<td>&gt;1001</td>
<td>20 : 1</td>
</tr>
</tbody>
</table>

## Methadone SC / IV Dosing

1. Convert from daily Morphine Equivalent PO Dose/24 hrs to Methadone PO Dose/24 hrs using the Methadone PO Dosing Table above
2. Then ÷ 3 to convert to Methadone SC Dose/24 hrs

## Adjusting for Incomplete Cross Tolerance

<table>
<thead>
<tr>
<th>Rating</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>100%</td>
</tr>
<tr>
<td>Moderate</td>
<td>75%</td>
</tr>
<tr>
<td>Excellent</td>
<td>50%</td>
</tr>
</tbody>
</table>

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### METHADONE

<table>
<thead>
<tr>
<th>Daily Morphine Dose (mg/24 hrs PO)</th>
<th>Conversion Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Morphine PO</td>
</tr>
<tr>
<td>&lt;100</td>
<td>3</td>
</tr>
<tr>
<td>101 - 300</td>
<td>5</td>
</tr>
<tr>
<td>301 - 600</td>
<td>10</td>
</tr>
<tr>
<td>601 - 800</td>
<td>12</td>
</tr>
<tr>
<td>801 - 1000</td>
<td>15</td>
</tr>
<tr>
<td>&gt;1001</td>
<td>20</td>
</tr>
</tbody>
</table>

### METHADONE SC / IV DOSING

1. Convert from daily Morphine Equivalent PO Dose/24 hrs to Methadone PO Dose/24 hrs using the Methadone PO Dosing Table above
2. Then ÷ 3 to convert to Methadone SC Dose/24 hrs
Methadone Conversion
Replace Other Opioid with Methadone

- Morphine 160 mg ER PO Q12H + Morphine 45 mg IR PO x 8 / day = Morphine 680 mg daily
- **Morphine 680 ≈ 12**
  - Methadone X 1

≈ Methadone 57 mg or 60 mg daily
# Methadone Conversion

3-step conversion over 3 days

<table>
<thead>
<tr>
<th>Day</th>
<th>Conventional Opioid</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>↓ Conventional opioid dose by 1/3</td>
<td>Add 1/3 of methadone dose</td>
</tr>
<tr>
<td>2</td>
<td>↓ Conventional opioid dose by 1/3</td>
<td>Add 1/3 of methadone dose</td>
</tr>
<tr>
<td>3</td>
<td>Stop conventional opioid</td>
<td>If pain controlled, stop. If still in pain, ↑ to total methadone dose</td>
</tr>
</tbody>
</table>
# Methadone Conversion

## 3-step conversion over 3 days

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Conventional Opioid</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional opioid dose by 1/3</td>
<td>680 mg to 460 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day 2</th>
<th>Conventional Opioid</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional opioid dose by 1/3</td>
<td>460 mg to 230 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day 3</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop conventional opioid</td>
<td>If pain controlled, stop. If still in pain, up to total methadone dose</td>
</tr>
</tbody>
</table>
Methadone as Coanalgesic
Minimize Risk of Side Effects

• Ideal for mixed pain
  Neuropathic component
• Continue previous opioid, routine + BT dosing
• Add methadone 2.5 – 5 mg Q12H or Q8H hrs
• Titrate to effect
  Every 4 – 7 days
  ↑ methadone 2.5 mg Q12H or Q8H hrs
• Once effective analgesia, ↓ other opioid ?
  Concurrent nociceptive pain control
Other Cases...
Methadone Summary

• Opioid mu-receptor agonist + NMDA receptor antagonist
• Tissue accumulation
• Prolonged elimination $t_{1/2}$
  Delayed onset side effects 15 – 30 days
  Coanalgesic vs. conversion
• Many drug interactions
Complex Pain: Ketamine

Frank D Ferris, MD, FAAHPM, FAACE
Ketamine

• Is it here to stay or is it just the flavor of the month?

• History
  
  Rapid - acting IV dissociative general anesthetic
  
  • C III prescription

Palliative uses – off label
Ketamine – Possible Uses

- Systemic Pain
- Depression
- Mucositis
- Wound Management
  - Dressing changes
Ketamine Action

- N-methyl-D-aspartate (NMDA) / glutamate receptor antagonist
  - Inhibits the excitatory effects of glutamate and aspartate
  - Interacts with other receptors
Ketamine – Pharmacokinetics

- Substrate of CYP3A4
- Ketamine $\rightarrow$ Norketamine
  (equipotent analgesic)

<table>
<thead>
<tr>
<th></th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>15 – 30 min</td>
<td>15 – 120 min</td>
</tr>
<tr>
<td>PO</td>
<td>30 – 60 min</td>
<td>?</td>
</tr>
</tbody>
</table>
Ketamine – Side Effects …

- High doses (1 - 2 mg / kg IV) – not commonly used in palliative care
  - Somnolence
  - Tachycardia
  - Excessive salivation
  - Psychotomimetic phenomena
Ketamine – Side Effects

• Low doses – more common as doses increase
  • Nausea
  • Sedation
  • Confusion
  • Dissociative feelings (less with PO)
  • Hypertension (transient)

• Management
Ketamine – Side Effects

- Chronic use may result in toxicity to:
  - Urinary
  - Hepatobiliary
  - Neuropsychiatric
Ketamine - Monitoring

- Think efficacy and safety
- Efficacy
  - When to assess
  - Improvement in pain / functionality
- Safety
  - Cystitis
  - Opioid doses
  - Psychotomimetic effects
**Ketamine – Dosage Forms**

- **Injectable solution**
  - 10 mg / mL, 20 mg / mL, and 50 mg / mL

- **Compounded products**
  - Oral solution 50 mg / mL
    - Stable for 30 days at room temperature
  - Topical formulations 0.5 % - 20 %
  - Mouthwash 4 mg / mL
Proper Patient Selection ...

- Again, think safety and efficacy
- **Efficacy**
  - **Systemic Analgesia**
    - Escalating pain, poor response or intolerant to opioids
    - Acute > chronic
    - Neuropathic or somatic
    - Hyperalgesia or allodynia
Proper Patient Selection

- Safety
  
  Caution use in patient’s with
  
  - ICP
  - Psychiatric illness
  - Pulmonary hypertension
  - Decompensated heart failure
  - Significant hepatic dysfunction
  - Scenarios where hypertension can be detrimental
Patient Case 1

• A 35 year old male needs treatment for “comfort care” including pain, diarrhea, and depression – transitioning to inpatient hospice

  Diagnosis – HIV, severe colitis, CKD

  Prognosis – weeks to months

  Vitals – 140’s / 90’s, HR mid 90’s

  Medications (NKDA) – maintenance meds stopped, fentanyl patch, hydromorphone
Patient Case 2

- A 51 year old female needs treatment for severe pain

  Diagnosis – metastatic lung cancer to bone

  Prognosis – weeks

  PMH – polysubstance drug abuse and COPD

  Medications ( NKDA ) –
  Morphine CADD 30 – 15 – 15,
  Lorazepam 1 mg bid, prednisone 10 mg daily
  and albuterol nebs q 4 hrs
## Systemic Pain

<table>
<thead>
<tr>
<th>Dose</th>
<th>Time to Effect</th>
<th>Time to Peak</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SC / IV</strong></td>
<td></td>
<td></td>
<td><strong>Assess benefit</strong></td>
</tr>
<tr>
<td>• Push: 10 – 25 mg Q6-8H</td>
<td>• Min to hrs</td>
<td>• Hours</td>
<td>• Reduces Pain</td>
</tr>
<tr>
<td>( 0.2 – 0.5 mg / kg )</td>
<td></td>
<td></td>
<td>• Opioid use</td>
</tr>
<tr>
<td><strong>SC / IV Infusion:</strong></td>
<td></td>
<td></td>
<td>• Improved functionality</td>
</tr>
<tr>
<td>0.1 – 0.2 mg / kg / hr,</td>
<td></td>
<td></td>
<td>• Tolerance may develop with</td>
</tr>
<tr>
<td>titrate to effect or side</td>
<td></td>
<td></td>
<td>chronic use</td>
</tr>
<tr>
<td>effects ( Max reported is</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.6 gm in 24 hrs )</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Systemic Pain

<table>
<thead>
<tr>
<th>Dose</th>
<th>Time to Effect</th>
<th>Time to Peak</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral / Rectal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 2.5 – 5 mg Q8H, titrate to effect</td>
<td><strong>Hrs</strong></td>
<td><strong>Weeks</strong></td>
<td><strong>Taper</strong></td>
</tr>
<tr>
<td>• Up to 0.5 – 1.0 mg / kg Q8H</td>
<td><strong>Max initial dose is 50 mg Q8H</strong></td>
<td></td>
<td>• Slowly with chronic use</td>
</tr>
<tr>
<td>• Conversion from IV / SC : 50 – 100 % of 24 hr. dose in divided doses</td>
<td><strong>Max initial dose is 50 mg Q8H</strong></td>
<td></td>
<td>• Monitor for withdrawal</td>
</tr>
</tbody>
</table>
Patient Case 3

- A 61 year old male needs treatment for severe mucositis

  Diagnosis – Tonsil cancer

  Prognosis – years to curable

  PMH – HTN, smoking, and BPH

  Medications (NKDA) – nicotine patch, lisinopril, hydromorphone 8 – 16 mg Q1H prn and tamsulosin 0.4 mg daily
# Mucositis

<table>
<thead>
<tr>
<th>Dose</th>
<th>Time to Effect</th>
<th>Duration of Effect</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 4 mg / mL Swish 5 mLs for 1 min and expectorate Q3H prn pain</td>
<td>• Minutes</td>
<td>• Up to 3 hrs.</td>
<td>Assess benefit</td>
</tr>
<tr>
<td></td>
<td><strong>Side effects should be minimal unless the mouthwash is mistakenly swallowed</strong></td>
<td></td>
<td>• Reduced Pain Opioid use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Improved oral intake</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Taper</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Not likely required</td>
</tr>
<tr>
<td>Dose</td>
<td>Time to Effect</td>
<td>Dosage forms</td>
<td>Additional Comments</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------------------</td>
<td>------------------------------------</td>
<td>-------------------------------------------</td>
</tr>
</tbody>
</table>
| • Apply to entire wound bed prior to wound care | • Onset ≈ 10 – 15 min, up to 1 hr depending on vehicle | • Gel, cream, ointment, or spray  
• Avg. cost $ 70 – 100 per 30 gm jar or 30 mL bottle (without insurance) | • No good trials  
• Systemic absorption occurs, peaks at 6 – 10 hrs after application |
# Depression

<table>
<thead>
<tr>
<th>Dose</th>
<th>Time to Effect</th>
<th>Repeat Dosing</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV: 0.5 mg / kg infused over 30 min to 1 hour</td>
<td>Hours to days **consider using ideal body weight in patients with BMI &gt; 30</td>
<td>1 – 8 weeks depending on dosing strategy and effectiveness</td>
<td>Viewed as a “last line” option. Informed consent - ?</td>
</tr>
<tr>
<td>Oral: 0.5 mg / kg with varying frequency</td>
<td>up to 3 mg / kg</td>
<td>Dosing 2 – 3 times weekly appears to be effective</td>
<td></td>
</tr>
</tbody>
</table>
Ketamine Summary

- Proper patient identification is key
- Monitor for efficacy and side effects
- Look for future data as we get more experience
Acknowledgements

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Complex Pain: Lidocaine

Frank D Ferris, MD, FAAHPM, FAACE
Lidocaine

- A common drug with both familiar and unfamiliar uses

- History
  - Amide Local anesthetic
  - Class IB anti-arrhythmic
Lidocaine – Possible Uses

- Cough
- Mucositis
- Topical pain
- Uncontrolled neuropathic pain
- Wound Management
Lidocaine - MOA

- Sodium channel blocker
  - Believed to work through peripheral, spinal, and supraspinal mechanisms
Lidocaine - Pharmacokinetics

• IV

  Onset – 30 to 60 minutes
  Duration – hours

• Hepatic metabolism

  CYP1A2 (major) and CYP3A4 (minor)

• Metabolite

  Monoethylglycinexylidide (MEGX)

  May contribute to analgesia and toxicity with continuous infusion
# Lidocaine – Side Effects...

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Blood Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lightheadedness</td>
<td>1 mcg/mL</td>
</tr>
<tr>
<td>Peri-oral numbness</td>
<td>2 mcg/mL</td>
</tr>
<tr>
<td>Metallic taste</td>
<td>2 – 3 mcg/mL</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>5 – 6 mcg/mL</td>
</tr>
</tbody>
</table>

**Adverse Drug Reaction** *(Stop Infusion Immediately)*

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Blood Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blurry vision</td>
<td>6 mcg/mL</td>
</tr>
<tr>
<td>Twitching</td>
<td>8 mcg/mL</td>
</tr>
<tr>
<td>Seizures</td>
<td>10 mcg/mL</td>
</tr>
<tr>
<td>Bradycardia, HR &lt; 50</td>
<td>20 – 25 mcg/mL</td>
</tr>
</tbody>
</table>
Lidocaine – Side Effects

• Topical / Patch
  Mild
  Rash
  Erythema
Lidocaine – Side Effects

- Oral lidocaine (2 – 4 %)
  - Cough
  - Aspiration
  - * Be careful NOT to eat or chew for 60 min after use
Lidocaine - Monitoring

- **Think efficacy and safety**
- **Efficacy**
  - When to assess depends on dosage form
  - Improvement in pain / functionality
- **Safety**
  - Side effects
  - HR, BP, RR, lidocaine levels
Lidocaine – Dosage Forms

- Injectable formulation
- Topical products
  - Oral – solution, viscous
  - Cream, gel, jelly, lotion
  - Patch
- Nebulized
Proper Patient Selection ...

• Again, think safety and efficacy
• Efficacy (IV administration)
  Systemic Analgesia
    Acute > chronic
  Neuropathic
  Allodynia
  Escalating pain, poor response with suspicion of neuropathic component
... Proper Patient Selection

- Safety
  - Caution in patient's with
    - Renal insufficiency
    - Cardiac dysfunction
      - 1\textsuperscript{st} & 2\textsuperscript{nd} degree heart block
    - Concurrent class 1 antiarrhythmia therapy
  - Hepatic dysfunction
  - Do not use if amide anesthetic allergy
### Patch (5%)

<table>
<thead>
<tr>
<th>Directions / Dosing</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Apply patch to most painful area</td>
<td>• Avoid exposing application site to external heat sources</td>
</tr>
<tr>
<td>• Patch(es) may remain in place for up to 12 hrs in any 24-hour period</td>
<td>• Remove patch while having MRI scan; can cause burns</td>
</tr>
<tr>
<td>• Up to 3 patches may be applied in a single application</td>
<td>• Less than 5% is absorbed</td>
</tr>
<tr>
<td>• Patches may be cut to appropriate size</td>
<td>• Can be $$$</td>
</tr>
<tr>
<td>• Effect starts in an hour and can take approximately a week to see full effect</td>
<td></td>
</tr>
</tbody>
</table>
Patient Case 1

- A 56 year old male needs treatment for severe neuropathic pain

  Diagnosis – metastatic lung cancer to spine
  Prognosis – weeks
  PMH – HTN and COPD
  Medications ( NKDA ) – haloperidol 1 mg bid, hydromorphone CADD 6 - 3 - 15, prednisone 20 mg daily, albuterol nebs Q4H
# Systemic Pain

<table>
<thead>
<tr>
<th>Dose</th>
<th>Time to Effect</th>
<th>Time to Peak</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Load 100 mg or 2 mg / kg IV / SC over 15 – 20 min</td>
<td>Min to hrs</td>
<td>Min to hrs</td>
<td>Assess benefit</td>
</tr>
<tr>
<td>Wait 30 min to assess pain</td>
<td>Min to hrs</td>
<td></td>
<td>• Reduced Pain</td>
</tr>
<tr>
<td>If pain improved, continue infusion: 0.5 – 3 mg / kg / hr</td>
<td>Min to hrs</td>
<td></td>
<td>Opioid use</td>
</tr>
<tr>
<td>Lidocaine level 8 – 10 hrs after start of infusion</td>
<td>Min to hrs</td>
<td></td>
<td>• Improved functionality</td>
</tr>
<tr>
<td></td>
<td>Min to hrs</td>
<td></td>
<td>• Infusions can be “diagnostic”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Transition to oral sodium channel blocker if IV effective</td>
</tr>
</tbody>
</table>
Lidocaine Infusion

- Worth the hype?
  - Effect seen in studies is small
    - About 1 point on a 10 point scale
    - Experience suggests a greater response
  - Many patients respond though the magnitude of response is small
  - Side effects are real though rarely serious
Mexiletine

• Similar to lidocaine
  Oral class IB anti-arrhythmic use - dependent sodium channel blocker

• Many side effects
  Especially at commercially available doses
Lidocaine Summary

Many common uses, IV infusion requires careful patient selection.

Response to IV infusions are usually short-term, consider alternative agent for long-term use.
Gandhi... You need to be the change you want to see in the world...
Palliative Care
Interdisciplinary Curriculum
A Joint Initiative of the Palliative Medicine Faculty & Staff of

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