Methadone: Pharmacology and perioperative application

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Professor of Biochemistry and Molecular Biophysics
Washington University in St. Louis
Adjunct Professor of Pharmaceutical Sciences
St. Louis College of Pharmacy
Director, The Center for Clinical Pharmacology
## Disclosures:

<table>
<thead>
<tr>
<th>Company</th>
<th>Activity</th>
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<tr>
<td>TEN Healthcare</td>
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<td>Astra-Zeneca</td>
<td>Grand Rounds lecture</td>
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<tr>
<td>Medicines Co</td>
<td>Attended a consultants meeting</td>
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Clinical dilemma:

**Challenge #1: Analgesia**
- >80% of pts report inadequate postop pain relief; no meaningful progress in postop pain treatment in the last 20 yr
- Acute postop pain is the major risk factor for chronic postop pain
  (Kehlet: Lancet 2006;367:1618-25)

**Challenge #2: Postoperative respiratory depression**
- Respiratory depression after major surgery is 0.3, 1.1, 17%, even with PCA (naloxone, hypoventilation, or O₂ desat as indicator)
- Most serious respiratory depression occurs 1st 24 hr postop
- “No pt shall be harmed by opioid respiratory depression”

**Challenge #3: The opioid epidemic**
- US is awash in opioids (diversion, abuse, addiction, overdose)
- Heroin is substitution therapy for prescription opioid addiction
- Prescription opioids & heroin caused 28,647 deaths in 2014
Clinical dilemma:

?How to provide effective analgesia throughout the intraoperative and postoperative periods while minimizing opioid side effects?

- Rapid onset
- Duration of analgesia = duration of pain

Intraoperative

<table>
<thead>
<tr>
<th>T</th>
<th>R</th>
<th>E</th>
<th>N</th>
<th>D</th>
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<tbody>
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<td>fentanyl</td>
<td>sufentanil</td>
<td>alfentanil</td>
<td>remifentanil</td>
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PACU

Postop

transition

hydromorphone or morphine load → PCA
## Onset of effect and elimination of opioids

<table>
<thead>
<tr>
<th></th>
<th>Onset</th>
<th>Elimination</th>
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<tr>
<td></td>
<td>$t_{1/2}k_{e0}$</td>
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<tr>
<td>remifentanil</td>
<td>1 min</td>
<td>ultrafast</td>
</tr>
<tr>
<td>alfentanil</td>
<td>1 min</td>
<td>0.5 hr</td>
</tr>
<tr>
<td>sufentanil</td>
<td>6 min</td>
<td>1 hr</td>
</tr>
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<td>fentanyl</td>
<td>5 min</td>
<td>8 hr</td>
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<tr>
<td>methadone</td>
<td>8 min</td>
<td>8-10 hr</td>
</tr>
<tr>
<td>morphine</td>
<td>2-4 hr</td>
<td>2-3 hr</td>
</tr>
</tbody>
</table>

Lötsch: J Pain Symptom Manage 2005;29:S90-103
Methadone

- μ opioid receptor agonist
- NMDA (N-methyl-D-aspartate) receptor antagonist
- Acute, chronic, periop, cancer pain; palliative care
- Cornerstone of therapy for opiate addiction, HIV/AIDS
- Adults & children; IV, IM, oral, subQ, intranasal, rectal
- Rapid IV onset \( t_{1/2} \approx 8 \text{ min} \), long duration \( t_{1/2} \approx 20-40 \text{ hr} \)
- Long half-life (infrequent dosing)

- Methadone enantiomers: PK & PD differences
- Extensively metabolized; 10-20% unchanged in urine
- Primary route: N-demethylation to EDDP
- Metabolism = inactivation; no active metabolites
Intraoperative Methadone: Rediscovery, Reappraisal, and Reinvigoration?
Evan D. Kharasch, MD PhD
January 2011 ● Volume 112 ● Number 1

- Adult methadone 20 mg IV at induction:
  - 1/3 discharged without additional opioid
  - 1/3 oral opioids only
  - 1/3 IV opioid

- Significantly lower postop opioid requirements
- Significantly less postop pain, despite PCA
- No difference in the incidence of side effects
- Cost-effective

Gourlay: Anesthesiology 1982; 57:458-67
Intraoperative Methadone Improves Postoperative Pain Control In Patients Undergoing Complex Spine Surgery

- **Inclusion:** Adults undergoing multilevel thoracolumbar spine surgery with instrumentation and fusion
- **Exclusion:** preop methadone, morbid obesity (BMI>36), chronic renal failure, cirrhosis, hepatic failure
- **TIVA propofol** (50-150 µg/kg/min titrated to BIS)
- **sufentanil** (0.75 µg/kg bolus + 0.25 µg/kg/h infusion) or **methadone** (0.2 mg/kg single bolus dose)
- **supplement:** 0.1 µg/kg sufentanil for inadequate anesthesia
- **Postop PCA** (fentanyl, morphine, or hydromorphone)

Anesth Analg. 2011;112:218-23
Patients receiving methadone had:

- Significantly lower postop opioid requirements (median 98 vs 219 mg morphine equivalents 0-72 hr postop)
- Significantly less postop pain, despite PCA
- No difference in the incidence of side effects

“A single intraoperative bolus of methadone improves postoperative pain control for patients undergoing complex spine surgery”

Anesth Analg. 2011;112:218-23
Intraoperative Methadone for Cardiac Surgery

- Patients undergoing cardiac surgery with cardiopulmonary bypass (n=156)
- Randomized to methadone (0.3 mg/kg) or fentanyl (12 μg/kg) intraop
- Half at induction, remainder infused over next 2 h
- Maintenance of anesthesia with sevoflurane
- Postop nurse-administered morphine

<table>
<thead>
<tr>
<th></th>
<th>Methadone</th>
<th>Fentanyl</th>
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</thead>
<tbody>
<tr>
<td>N (M:F)</td>
<td>77 (52:25)</td>
<td>79 (63:16)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65 ± 10</td>
<td>66 ± 11</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88 ± 18</td>
<td>83 ± 17</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>56 ± 14</td>
<td>56 ± 12</td>
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<tr>
<td>Sleep apnea</td>
<td>14 (18%)</td>
<td>9 (11%)</td>
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</table>

Operative procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Methadone</th>
<th>Fentanyl</th>
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<tbody>
<tr>
<td>CABG</td>
<td>35 (45%)</td>
<td>43 (54%)</td>
</tr>
<tr>
<td>Valve</td>
<td>35 (45%)</td>
<td>28 (35%)</td>
</tr>
<tr>
<td>CABG and valve</td>
<td>6 (8%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
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<tr>
<td>Anesthesia time (hr)</td>
<td>6.1 (5.4-7.1)</td>
<td>6.2 (5.5-7.1)</td>
</tr>
<tr>
<td>CPB time (hr)</td>
<td>1.9 (1.6-2.3)</td>
<td>2.0 (1.6-2.2)</td>
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</table>
### Postoperative analgesic requirements

<table>
<thead>
<tr>
<th></th>
<th>methadone</th>
<th>fentanyl</th>
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</thead>
<tbody>
<tr>
<td><strong>Time of 1st morphine rescue (h)</strong></td>
<td>6.5 (3.25-9.25)*</td>
<td>3.75 (1.5-5.75)</td>
</tr>
<tr>
<td><strong>Morphine (mg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st 24 hr</td>
<td>6 (4-12)*</td>
<td>10 (6-22)</td>
</tr>
<tr>
<td>0-72 hr total</td>
<td>8 (4-14)*</td>
<td>14 (8-28)</td>
</tr>
<tr>
<td>Morphine dose ≥20 mg first 24 hr</td>
<td>2 (3%)*</td>
<td>23 (29%)</td>
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* P<0.05 vs fentanyl

### Postoperative analgesia

<table>
<thead>
<tr>
<th></th>
<th>Pain at rest (0-10)</th>
<th>Pain with coughing (0-10)</th>
<th>Overall satisfaction with pain management</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>methadone</td>
<td>fentanyl</td>
<td>methadone</td>
</tr>
<tr>
<td>15 min</td>
<td>3 (1-5)*</td>
<td>5 (2-8)</td>
<td>90 (75-95)*</td>
</tr>
<tr>
<td>2 hr</td>
<td>3 (1-5)*</td>
<td>4 (2-7)</td>
<td>90 (75-97)*</td>
</tr>
<tr>
<td>4 hr</td>
<td>2 (1-4)</td>
<td>3 (1-6)</td>
<td>90 (80-98)*</td>
</tr>
<tr>
<td>8 hr</td>
<td>2 (0-4)*</td>
<td>4 (2-6)</td>
<td>90 (80-100)*</td>
</tr>
<tr>
<td>12 hr</td>
<td>2 (0-4)*</td>
<td>4 (2-5)</td>
<td>90 (80-100)*</td>
</tr>
<tr>
<td>24 hr</td>
<td>2 (1-4)*</td>
<td>4 (2-7)</td>
<td>95 (90-100)*</td>
</tr>
<tr>
<td>48 hr</td>
<td>2 (0-3)*</td>
<td>3 (1-5)</td>
<td>95 (90-100)*</td>
</tr>
<tr>
<td>72 hr</td>
<td>2 (0-3)*</td>
<td>3 (0-5)</td>
<td>100 (90-100)*</td>
</tr>
</tbody>
</table>

* P<0.05 vs fentanyl

Murphy: Anesthesiology 2015:122:1112-22
Intraoperative Methadone for Cardiac Surgery

- Postoperative morphine requirements reduced 40%
- Severity of postoperative pain decreased by 30-40%
- Enhanced patient-perceived quality of pain management
- No difference vs fentanyl in opioid-related complications: Nausea, vomiting, itching, hypoventilation, hypoxemia, sedation
- No difference vs fentanyl in complications: respiratory, cardiac, renal, neurologic, infectious
Methadone disposition and clinical effect

Kharasch: Anesth Analg 2011;112,13-6
Methadone vs morphine PCA for postoperative pain

- Total hip arthroplasty
- Bupivacaine spinal anesthesia
- PCA morphine vs methadone
  - 1 mg, 6 min lockout, 4 hr limit 20 mg
  - 1 mg/hr continuous infusion
  - 750 mg po paracetamol q6hr

Methadone PCA:
- Lower opioid consumption
- Lower pain scores at rest and with movement (knee flexion)

Neto: J Anesth 2014;28:505-10
Methadone cost-effectiveness

Opioid component of general anesthetic:
Target plasma concentration to ~50%MAC reduction
• fentanyl 2 µg/kg/hr
• remifentanil 0.25 µg/kg/min
• methadone 20 mg

*Patient charge:
CADD pump $62/day
CADD extension $13 (use up to 3d)
hydromorphone 50mg CADD $172
morphine 100mg CADD $299

fentanyl IV $18/250 µg
remifentanil IV $66/2 mg
methadone IV $18/10mg
methadone 10mg tablet $5

*BJH Pharmacy, Sept 2011
## Methadone Cost-Effectiveness

### 3 day Cost Modeling

<table>
<thead>
<tr>
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<th>Intraoperative</th>
<th>PACU/Postoperative</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td><strong>Intraoperative</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl IV</td>
<td>$36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remifentanil IV</td>
<td></td>
<td>$131</td>
<td></td>
</tr>
<tr>
<td>Methadone IV</td>
<td>$36 $36</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PACU/Postoperative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CADD pump (3d)</td>
<td>$186 $186</td>
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</tr>
<tr>
<td>Extension set</td>
<td>$13 $13</td>
<td></td>
<td></td>
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<tr>
<td>Morphine CADD</td>
<td>$299/$598</td>
<td>$299/$598</td>
<td></td>
</tr>
<tr>
<td>Methadone IV</td>
<td></td>
<td>$72 $18</td>
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<tr>
<td>Methadone po</td>
<td></td>
<td></td>
<td>$15</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>$534/$833</td>
<td>$629/$928</td>
<td>$108 $70</td>
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</table>
Guide to perioperative methadone use

Principles:
- Initial methadone bolus must be large enough so that blood concentrations are >MEC after the distribution phase
- The higher the initial concentration, the longer the duration

Practice:
- Inpatient; case duration >45 min
- 20 mg IV bolus (2 cc) in OR before induction (15 mg if “physiologically” >60 yr, due to declining methadone elimination & increased risk of respiratory depression with age)
- No/minimal additional intraop opioid (occasional fentanyl, 50-100 µg)
- PACU: 2-3 mg IV methadone at >5-10 min intervals (if pt complains of pain, unstimulated RR>10). Max 5-10 mg or call
53 yo F, total shoulder; 65 kg, mild asthma inhaler, citalopram

OR: uneventful GA, LMA, 100 µg fentanyl, methadone 10 mg, paracetamol 1g,

PACU: methadone 8 mg Painbuster (ropivacaine 0.2% 10 ml/hr)

1645: PACU D/C, Painbuster

1800: quite awake

1845: slightly sedated (easily rousable), RR 16

1950: profoundly sedated, unrousable, RR 5 and shallow, "dusky", pulse present, color improved with mask ventilation, no response to 400 µg naloxone

Intubated, ventilated overnight, recovered fully

Caution!!

Do not mix full methadone dose with regional anesthesia
Methadone: Therapeutic mysteries and challenges

- Substantial interindividual variability in PK & PD
- Susceptibility to drug interactions
- Role of P450s and transporters
- Autoinduction of oral methadone clearance
- Consequence: withdrawal, toxicity, respiratory depression, inadequate analgesia, breakthrough pain
- Exponential increase in oral methadone-related deaths (related to increased use for chronic pain)
- First 1-2 weeks of oral methadone treatment the highest risk period for adverse events (overdose)
- Due to erroneous oral induction dosing, mainly for pain
Human hepatic cytochrome P450 (CYP) & drug metabolism

% of total hepatic P450

% of top 200 drugs

% of total intestinal P450

JPET 2006; 34:880-6
Br J Clin Pharmacol 2004;57:687-8
Anal Bioanal Chem 2008; 392:1093-108
**Methadone metabolism and clearance**

**In vitro:**
HLM N-demethylation by CYP3A4
(>7 papers, 1996-2003)

Extrapolation and “Conventional Wisdom”:
• Methadone clearance is determined by CYP3A4
• Methadone is susceptible to CYP3A4 drug interactions
• Methadone product label: “Methadone is a CYP3A substrate. CYP3A drug interactions may alter methadone kinetics and cause adverse effects. Drugs that inhibit CYP3A4 may cause decreased methadone clearance. Expected results would be increased or prolonged opioid effects”

**Involvement of CYP3A4 in vivo:**
CYP3A update

- CYP3A plays a minimal (if any) role clinically in single-dose methadone N-demethylation and clearance.
- CYP3A has no influence on single-dose IV or oral methadone plasma concentrations.
- Methadone does not appear to be a clinical CYP3A substrate.
- Clinical guidelines stating that methadone is a CYP3A4 substrate and warning about CYP3A4 drug interactions need revision.
CYP2B6

- CYP2B6 is a predominant enzyme responsible for methadone metabolism \textit{in vitro}

- CYP2B6 mediates clinical methadone metabolism, clearance, and stereoselective disposition

- Methadone disposition is affected by CYP2B6 drug interactions

- Clinical guidelines that methadone is a CYP2B6 substrate and warning about CYP2B6 drug interactions may improve methadone use, treatment of pain and substance abuse, and patient safety

### Common CYP2B6 allele frequencies

<table>
<thead>
<tr>
<th>CYP2B6 allele</th>
<th>CYP activity</th>
<th>Caucasian</th>
<th>African-American</th>
<th>African</th>
<th>Asian</th>
<th>Hispanic</th>
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</thead>
<tbody>
<tr>
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<tr>
<td>*4</td>
<td>increased?</td>
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</table>

Zanger: Pharmacogenomics 2007;8:743-59  
Rotger: CPT 2007; 81:557-66
Purpose
Assess influence of CYP2B6*6 polymorphism on clinical methadone metabolism and clearance

Hypothesis: CYP2B6*6 hetero or homozygotes have altered methadone metabolism and clearance in vivo

Approach
1. Genotype screen healthy volunteers for CYP2B6 SNPs
2. Enroll cohorts of CYP2B6*1/*1, CYP2B6*1/*6, CYP2B6*6/*6 (n~20 each) (also CYP2B6*4/X)
3. Evaluate IV and oral methadone pharmacokinetics
Oral methadone

R-methadone

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>R-methadone (ng/ml)</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>48</td>
<td>4</td>
</tr>
<tr>
<td>72</td>
<td>6</td>
</tr>
<tr>
<td>96</td>
<td>8</td>
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S-methadone

<table>
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<tr>
<th>Time (hr)</th>
<th>S-methadone (ng/ml)</th>
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<td>0</td>
</tr>
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<td>24</td>
<td>5</td>
</tr>
<tr>
<td>48</td>
<td>10</td>
</tr>
<tr>
<td>72</td>
<td>15</td>
</tr>
<tr>
<td>96</td>
<td>20</td>
</tr>
</tbody>
</table>

Kharasch: Anesthesiology 2015;123:1142-53
Oral methadone

R-methadone

S-methadone

CYP2B6 Genotype

Oral Clearance CL/F (ml/kg/min)

Kharasch: Anesthesiology 2015;123:1142-53
Modeling: Daily oral methadone & CYP2B6 genetics

Time (hr)

R-methadone (ng/ml)

Single-dose

CYP2B6*6/*6
CYP2B6*1/*6
CYP2B6*1/*1
CYP2B6*4/X
CYP2B6*6 carriers, compared with CYP2B6*1/*1 subjects:
- Higher plasma methadone concentrations
- Decreased methadone systemic clearance
- Decreased methadone hepatic clearance
- Decreased methadone metabolism (N-demethylation)

CYP2B6*4 carriers, compared with CYP2B6*1/*1 subjects:
- Lower plasma methadone concentrations
- Increased methadone systemic clearance

- CYP2B6 polymorphisms influence methadone concentrations, because of altered methadone metabolism and thus clearance
- Genetic influence is much greater and really only important for) oral vs IV methadone
- CYP2B6 genetics explains, in part, interindividual variability in methadone elimination
- CYP2B6 genetics may identify subjects at risk for methadone toxicity and drug interactions
Autoinduction of clinical methadone clearance

- Initiation of oral methadone use is challenging
- 20% of accidental methadone deaths occur in 1st 2 wk of Rx
- Risk during this period 10- to 100-fold greater
- Methadone CL undergoes time-dependent autoinduction

<table>
<thead>
<tr>
<th>Wolff: Addiction 2000; 95:1771-83</th>
<th>First dose</th>
<th>Steady-state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (L/hr)</td>
<td>3.1</td>
<td>10.2</td>
</tr>
<tr>
<td>$t_{1/2}$</td>
<td>128</td>
<td>48</td>
</tr>
</tbody>
</table>

- Hazard if steady-state CL values used to guide initial dosing
- Methadone upregulates CYP2B6 and its own metabolism

Campbell: Anesth Analg, 2013; 117:52-60
Modeling: Daily oral methadone & CYP2B6 genetics

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>R-methadone (ng/ml)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>48</td>
<td>20</td>
</tr>
<tr>
<td>72</td>
<td>30</td>
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<tr>
<td>96</td>
<td>40</td>
</tr>
<tr>
<td>120</td>
<td>50</td>
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<tr>
<td>144</td>
<td>60</td>
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<tr>
<td>168</td>
<td>70</td>
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<tr>
<td>192</td>
<td>80</td>
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<tr>
<td>216</td>
<td>90</td>
</tr>
<tr>
<td>240</td>
<td>100</td>
</tr>
</tbody>
</table>

Single-dose:
- CYP2B6*6/*6
- CYP2B6*1/*6
- CYP2B6*1/*1
- CYP2B6*4/X

Steady-state:
- CYP2B6*1/*1
- CYP2B6*4/X
Oral methadone
Methadone prescribing and adverse events

- “The darling of the pain management community”
- Total prescriptions rose 1300% (0.3-3.9 million) 1997-2006

- Adverse events increased 1800% between 1997-2004
- Fatalities increased 390% 1999-2004 (drug with greatest increase)
- 6th most frequently suspected drug in death & serious nonfatal outcomes

http://www.dpt.samhsa.gov/ppt/methadone%20ARCOS%202007-20-07.ppt
http://www.dpt.samhsa.gov/pdf/MethadoneBackgroundPaper_72007_2_.pdf
http://www.deadiversion.usdoj.gov/drugs_concern/methadone/methadone_presentation0407_revised.pdf
Methadone prescribing and adverse events

- Methadone contributed to 1 in 3 prescription painkiller deaths in 2009
- 5,000 die annually of methadone-related overdose
- Six times as many people died of methadone overdose in 2009 than 1999

http://www.cdc.gov/vitalsigns/MethadoneOverdoses/index.html
Opioid clinical effects and PK-PD assessment

Dose

Blood

concentration measurements

\[ ke_0 \]

uptake

\[ efflux \]

Effect compartment

Effect

EEG
Analgesia
Nausea
Respiratory depression
Miosis

Plasma PK

Brain PK

Concentration vs. Time

concentration measurements(!)

Effect

PD

Effect vs. Concentration

Effect vs. Time
Drug effects on opioid pharmacodynamics and brain access

Identify human transporters responsible for opioid brain access

- **In vitro**: Opioid uptake & efflux by expressed human BBB transporters
- **In vitro**: Opioid uptake & efflux by human BBB endothelial cells; transporter inhibitors & knock-downs
- **In vivo**: Opioid pharmacodynamics: transporters modulation
- **In vivo**: Opioid brain pharmacokinetics using Positron Emission Tomography (PET)
Clinical inhibition of brain P-gp by cyclosporine: Effect on methadone pharmacokinetics & pharmacodynamics

CsA 2.5 mg/kg/hr x 2 hr

Methadone infusion (1 hr)

Meissner: Anesthesiology 2014;121:1281-91
Clinical inhibition of brain P-gp by cyclosporine: Effect on morphine pharmacokinetics & pharmacodynamics

CsA 2.5 mg/kg/hr x 2 hr
Morphine infusion (1 hr)

Meissner: Anesthesiology 2013;119:941-53
Clinical inhibition of brain P-gp by cyclosporine: Effect on opioid pharmacodynamics

CsA 2.5 mg/kg/hr x 2 hr

Opioid infusion (1 hr)

Morphine

Methadone

Meissner: Anesthesiology 2013;119:941-53

Meissner: Anesthesiology 2014;121:1281-91
Several case reports of TdP in patients on high-dose methadone

Most prospective, cross-sectional, retrospective studies (n=16 articles): QTc prolongation but not TdP

QTc prolongation (~1/3 of pts, typically <40ms); rarely >500 ms

- Few studies on “hard” endpoints (sudden death or TdP)
- Surrogate clinical marker of arrhythmia potential: QTc prolongation
  - QTc prolongation>450 msec
  - QTc >500 msec threshold for arrhythmia risk

Cruciani: J Pain Symptom Manage 2008;36:545-52
5503 methadone-associated adverse events reported to FDA MedWatch system (1969-2002)

43 (0.78%) events of TdP, 16 (0.29%) QT prolongation

Methadone dose $410 \pm 349$ mg/d (median 345, range 29-1680)

Other risk factors for TdP found in 44 (75%) cases
Methadone, torsades de pointes, and QTc prolongation

Dose-dependency

- QTc increases with dose
- 0.14 ms/mg
- Relevance to low dose?

Time-dependency

- QTc increases over time
- Studies evaluate QTc after weeks-months
- Relevance to initial single dose?

Fanoe: Heart 2007;93:1051-5

Wedam: Arch Intern Med 2007;167:2469-75
# Methadone, torsades de pointes, and QTc prolongation

## Recommendations for ECG screening: Synthesis

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>ECG?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pain or methadone maintenance</td>
<td>&gt;100-150 mg/d</td>
<td>variably recommended</td>
</tr>
<tr>
<td>Methadone maintenance</td>
<td>60-100 mg/d</td>
<td>actively debated</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>10-30 mg/d</td>
<td>not recommended</td>
</tr>
<tr>
<td>Acute perioperative</td>
<td>20-30 mg</td>
<td>??</td>
</tr>
</tbody>
</table>

Methadone: Practical perioperative application

- IV methadone is a long-duration, effective, underutilized, inexpensive, cost-effective alternative to more conventional short-duration opioid paradigms
- IV onset fast; duration of analgesia = duration of pain
- Reduced postop pain and opioid requirements
- 20 mg (15 mg) IV at induction; set it & forget it
- Methadone is often-studied, and more often misunderstood
- Oral methadone more challenging to use, particularly by individuals not familiar with PK characteristics