Objectives

- To discuss the use and effectiveness of methadone
- To discuss the pharmacokinetics and pharmacodynamics of methadone
- To discuss how methadone compares with other narcotics
- To discuss dosing options of methadone
- To discuss potential complications of methadone
- To discuss the need for additional and current research on *perioperative* use of methadone for analgesia & acute pain management.
Historically…

- **METHADONE, the beginning** -- German scientists synthesized methadone during World War II because of a shortage of morphine. Although chemically unlike morphine or heroin, methadone produces many of the same effects.

- Introduced into the United States in 1947 as an analgesic (Dolophine), Methadone is primarily used today for the treatment of narcotic addiction.

- The effects of methadone are longer-lasting than those of morphine-based drugs. Methadone's effects can last up to 24 hours, thereby permitting administration only once a day [as in heroin detoxification and maintenance programs].
What is Methadone?

...the pharmacodynamics

- A synthetic opioid *agonist* at the *mu* opioid receptor.
  - *Mu* receptors produce the most profound analgesia
- It has *antagonistic* activity at the NMDA receptor
  - This counteracts opioid tolerance in experimental models of pain, possibly explaining the lesser escalation of dosage required in patients treated with methadone compared with morphine
  - This also results in increased efficacy against hyperalgesia and may explain methadone’s greater effectiveness against neuropathic and other chronic pain states not responsive to other therapies

Manfredi & Houde, 2003
Toombs & Kral, 2005
Methadone is a racemic mixture containing both an L-isomer and D-isomer:
- the *l*-isomer is responsible for the drug's analgesic effects and is 8 to 50 times more potent than the D isomer.
- the *d*-isomer exhibits significantly less analgesic action and lacks respiratory depression activity and addiction liability, but it does have antitussive effects.
Activation of the μ receptor by an agonist such as methadone causes:

- analgesia
- sedation
- decreased respiration
- euphoria
- reduced BP, HR
- pruritis
- nausea
- miosis &
- decreased bowel motility

Some of these effects, such as sedation, euphoria and decreased respiration, tend to disappear with continued use as tolerance develops.

Analgesia, miosis and reduced bowel motility tend to persist; little tolerance develops to these effects.

Stimulation of μ1-receptors blocks (supraspinal) pain while stimulation of μ2-receptor causes respiratory depression and constipation.
What is Methadone?

...the pharmacodynamics

- Binds to mu, kappa, and delta opioid receptors producing analgesia as well as usual opioid side effects.
- Inhibits reuptake of serotonin and norepinephrine (which are typical TCA actions).
- Is also an antagonist of NMDA receptors which can help prevent central sensitization and reduce opioid tolerance.
What is Methadone?

…the pharmacokinetics

- Onset: 10-20 min
- Peak: 1-2 hrs
- Duration:
  - 3-6 hrs with single dosing
  - 8-12 hrs with repeated dosing
- Vd: 2-6 L/kg, highly lipophilic
- Metabolism: hepatic, no active metabolites
What is Methadone?

…the pharmacokinetics

- Highly protein bound; however, tissue binding predominates over binding to plasma proteins [accumulation of the drug occurs in these tissues with repeated dosing], i.e. maintains plasma conc.
- **Half-life** elimination: 8-59 hrs. [avg = 22hrs].
  - Prolonged with alkaline pH
  - Decreased during pregnancy
  - Shorter in children than adults
- Excretion: urine
  - <10% as unchanged drug
  - Increased with urine pH <6
Indications of methadone treatment for pain states

- Cost $$$
- Neuropathic pain
- Morphine allergy
- Pain refractory to other opioids
- Uncontrolled pain
- Low level of side effects
Application of Perioperative Methadone use in Anesthesia:

A Case Study--
Case Study--Patient Presentation:

- 60 yo male, inpatient
- Pulmonologist
- ASA 2
- No Prior Charts/Records
- Ht: 71 in/Wt: 72 kg
- Allg: INH
- Meds:
  - Zantac
  - Decadron
  - Morphine PCA

PMH:
- +PPD s/p inh
- Asthma [rare symptoms]

PSxH-no anesthetic problems
- Rt C6-C7 foramenotomy 1987
- Left L4-L5 diskectomy 1989

Pre-op VS:
- 97.9 -72 -13; 126/72
- MP 1
- limited cervical extension
- MET > 4
Chief Complaint

- Increased low back pain, right leg pain & weakness [4/5]
- Acute right foot drop- determined to be improving
- L4-L5 stenosis/spondylosis
- Right L4-L5 radiculopathy
- Patient described this presentation as: “much like mirror image of 16 years ago”
Fig. 1 * indicates pain-sensing structures

http://www.hughston.com/hha/a_12_1_1.htm

Lumbar dorsal ramus syndrome (Bogduk, N., 1980)

Scheduled Procedure:

- Planned procedure: L4 laminectomy,
- L4-L5 PLIF,
- L4-L5 Monarch PSF

Laminectomy

The entire lamina is removed from the affected vertebra. In some cases, laminectomy involves two or more vertebrae.

www.augustaortho.com

Posterior Lumbar Interbody Fusion

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Plan of Care:
as proposed and discussed with CRNA and MDA

- IV’s x2 [18g & 16g]
- A-line
- T&S/Cell saver
- Induction
- Positioning
- Maintenance
- Emergence
Postoperative evaluation:

- PACU/DOS
  - Verbalized comfort
  - Denied pain
  - Scaled pain as “0” of 0-10 using the Numerical Rating pain Scale

- GMSF/POD#1
  - PCA morphine “barely using”
  - Ambulating w/assist
Patients’ comments postop:

- Pt reported “I never felt so comfortable without feeling ‘clouded’ after surgery”

- Inquired about “bridging with methadone” and how wonderful it worked for him
Methadone & It’s Use in Anesthesia
When to use methadone?

- *It has been suggested that methadone is suitable as a first-line opioid in selected patients when slow onset and long duration of action are advantageous.*
When to use methadone in anesthesia?
In a double-blind randomized study measuring postop pain:

- 30 Patients undergoing elective abdominal hysterectomies, age <60yrs randomized into 2 groups:
  - Morphine n=15
  - Methadone n=15
- ASA 1 or 2
- No opioids for minimum 24 hrs preop
- No psychiatric hx or h/o drug abuse
- Used 0-10 pain scale
- 0.25mg/kg of study drug given at induction
- Further 3 to 4.5 mg of assigned opioid was given in PACU q15min until pt was pain free for >30min.
- VS/LOC measured q min x10min then q5min

Double-Blind Randomized Trial Comparing Postoperative Analgesia After Perioperative Loading Doses of Methadone or Morphine.
Use of Perioperative Methadone…

The Results:

- Each group with 15pts of similar age and body weight– homogeneous samples
- Pts in the methadone group requested fewer doses of supplementary opioids than the morphine group [p<0.001].
- 10 of 15 pts [67%] in the methadone did not require further parenteral opioid while all pts in the morphine group required at least 2 further doses of morphine
- Pain scores were similar in both groups at time of discharge from the PACU however, *Pain scores in the methadone group declined* subsequently and the scores remained low for the 48hr study period
- The morphine group had a higher total pain score for the 48hr study period (p<0.001) despite having receiving more supplementary doses of morphine.
When to use methadone in anesthesia?

In a double-blind randomized study measuring postop pain:

- 20 patients,
- ASA 1 or 2,
- undergoing surgery involving upper abdominal incision (all surgical procedures lasted for at least 60 min)
- randomly allocated to one of two treatment groups:
  - methadone (n=10) or
  - morphine (n=10)

A Double-blind Comparison of the efficacy of methadone and morphine in postoperative pain control.
Use of Perioperative Methadone....

- Patients were given a 20 mg intraoperative opioid dose ten minutes after induction.
- 5 mg IV increments of opioid from precoded syringes were given for pain reported in the recovery and/or surgical units. (Each patient was administered only one opioid for the duration of the study (60h).
- Scheduled measurements of postop pain were estimated by the linear visual analogue pain scale; blood samples were concurrently measured for methadone concentrations.

A Double-blind Comparison of the efficacy of methadone and morphine in postoperative pain control.
METHADONE AND MORPHINE IN POSTOPERATIVE PAIN

TABLE 1. Duration of Pain Relief, Age, Weight, Type of Operation and Perioperative Opioid Requirements in Methadone and Morphine Study Patients

<table>
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<tr>
<th>Patient Number</th>
<th>Type of Operation</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Sex</th>
<th>Intraoperative Opioid (mg)</th>
<th>Opioid in Recovery Room (mg)</th>
<th>Duration of Pain Relief (h)</th>
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Mean ± SD

Range

Morphine group

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<th>Weight (kg)</th>
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<td>1.6</td>
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</table>

Mean ± SD

Range

Significance

NS = Not significant.

* Represents a Nissen fundoplication.

† Represents a highly selective vagotomy.

A Double-blind Comparison of the efficacy of methadone and morphine in postoperative pain control.
Use of Perioperative Methadone...

The Results:

- No significant differences in the patient groups
- No significant difference in the amount of methadone (8 +/- 6.3mg, range 0-20 mg) or morphine (9 +/- 9 mg, range 0-25mg) administered in the recovery room to provide initial pain relief.
- There was a highly significant (p<0.01) difference in the mean duration of pain relief between the methadone (20.7 +/- 20.2 h) and the morphine (6.3 +/- 3.0 h) group.
- The duration of pain relief ranged from 5.5 to 58 h in the methadone group and from 1.6 to 11.4 h in the morphine treatment group.

A Double-blind Comparison of the efficacy of methadone and morphine in postoperative pain control.
Summary & Analysis of Postop Dosing

- Results provide further evidence in support of a **prolonged duration of pain relief with methadone**
- Significantly less (p<0.001) methadone (11.5 +/- 8.5 mg) compared with morphine (41 +/- 14.1 mg) was administered in the surgical ward.
- The significant difference was also apparent when considering the total opioid required for pain relief.

A Double-blind Comparison of the efficacy of methadone and morphine in postoperative pain control.
Pharmacodynamics and Pharmacokinetics of Methadone During the Perioperative Period


Table 1. Methadone Study Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Type of Operation</th>
<th>Age</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Time to First Supplementary Analgesia (hours)</th>
<th>Amount of Narcotic (mg morphine equivalent)</th>
<th>Number of Injections</th>
<th>Minimum Effective Analgesic Concentration (mg/ml)</th>
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Median value (Groups 1, 2, and 3 combined) 27

* Total narcotic includes 20 mg intraoperative methadone.
ND represents not determined.
† P = prolonged analgesia

Pharmacodynamics and pharmacokinetics of methadone during the perioperative period.
Dosing of IV Methadone for moderate to severe pain:

- Optimal dose initiation and titration strategies for the treatment of pain have not been determined.
- Methadone is most safely initiated and titrated using small initial doses and gradual dose adjustments.
- In opioid naïve patients, the usual IV methadone starting dose is 2.5 to 10 mg every 8 to 12 hrs, slowly titrated to effect.
Dosing of IV methadone for moderate to severe pain: some studies reported:

- Lower-than-expected doses of IV methadone were needed for pain relief in cancer patients unrelieved by morphine and hydromorphone.

- When IV hydromorphone dosage could not be further increased due to sedation effects, cancer patients found relief of pain with IV methadone at 2.6% to 3.8% of the calculated equianalgesic dose of hydromorphone.

Manfredi et al, 1997
However,

- “For various reasons, there is significant individual variability in patient response to methadone, making initiation of therapy and rotation to methadone from other opioids, at times unpredictable.
- As such, it does require some special care and knowledge in its use.
- The use of ‘equivalency tables’ to calculate a dose of methadone is unreliable and should be avoided.”
Exactly!
‘Start low, go slow’

- In some patients [elderly/infirm], very small doses of methadone may be quite effective and generally better tolerated
- Remember! A dose can always be increased
- Due to gradual accumulation to a steady state, methadone’s effectiveness as an analgesic may improve gradually after a dose increase, for up to four to five days
‘Start low, go slow’

- Most methadone related deaths [as studied on MMT pts] occur in the first week of therapy, as a result of accumulation, *emphasizing* the importance of careful monitoring during the initiation of therapy.

- Methadone blood levels continue to rise about 5 days after starting treatment or raising a previously stable dose.

- Death by accumulated toxicity may result from increasing a dose before the full effect of the current dose is known.
of importance with dosing:

- When determining the initial IV dose of methadone, the following should be considered:
  - Total daily dose
  - Potency
  - Characteristics of the opioid the patient had been taking, if any
- Patients degree of opioid tolerance
- Age, condition & medical status of the patient
- Concurrent medications
- Type, severity and expected duration of pain
- Acceptable balance between pain control and adverse effects
Caution with dosing

- Individualize
- Equianalgesia not always equal
- Note *acute* vs *chronic* dosing & management information
Considerations with Methadone

- High interindividual variability
  - Equianalgesic doses vary widely person-to-person and day-to-day/week-to-week in same person
- Long half-life
- Varying level of plasma binding protein
- Age, gender, weight (large distribution reservoir)
- Other medications
- Time from start of treatment (auto-induction)/slow onset
Methadone warnings:

- May prolong QT interval
- Use caution with severe volume depletion
- Effects on respiration last longer than its analgesia effects
- Decrease dose with renal impairment
- Caution in patients with liver disease
Equianalgesia not always equal

<table>
<thead>
<tr>
<th>Drug</th>
<th>IM</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>0.15 mg</td>
<td>0.12 mg SL</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td></td>
<td>20 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>2 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Meperdine</td>
<td>100 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Methadone</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td></td>
<td>20 mg</td>
</tr>
</tbody>
</table>
Equianalgesia not always equal

Dose Equivalents for opioid analgesics in opioid-naive adults and children >= 50 kg body weight

<table>
<thead>
<tr>
<th>Opioid agonist</th>
<th>Oral</th>
<th>Parenteral</th>
<th>Dosing interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30 mg</td>
<td>10 mg</td>
<td>Q 3-4h</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5 mg</td>
<td>1.5 mg</td>
<td>Q 3-4h</td>
</tr>
<tr>
<td>Meperidine</td>
<td>300 mg</td>
<td>100 mg</td>
<td>Q 2-3h</td>
</tr>
<tr>
<td>Methadone</td>
<td>20 mg</td>
<td>10 mg</td>
<td>Q 6-8h</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Variable **</td>
<td>____</td>
<td>Transdermal patches q3days</td>
</tr>
</tbody>
</table>

http://www.echt.chm.msu.edu/blockiii/pain/BlockIIIcorecompetency/equianalgestic_table.htm
Equianalgesia not always equal

### Equianalgesic Chart

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parenteral (mg)</th>
<th>Oral (mg)</th>
<th>Duration (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine sulfate</td>
<td>10</td>
<td>30</td>
<td>2–4</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
<td>2–4</td>
</tr>
<tr>
<td>Oxycodone</td>
<td></td>
<td>20</td>
<td>2–4</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
<td></td>
<td>2–4</td>
</tr>
<tr>
<td>Methadone</td>
<td>5</td>
<td>10</td>
<td>6–8</td>
</tr>
<tr>
<td>Meperidine</td>
<td>75–100</td>
<td>300</td>
<td>2–4</td>
</tr>
</tbody>
</table>

[https://www.hoparx.org/HOPA2006/nesbit.pdf](https://www.hoparx.org/HOPA2006/nesbit.pdf)
Equianalgesia not always equal...

Parental morphine to IV methadone conversion for chronic administration for patients with chronic pain:

<table>
<thead>
<tr>
<th>Total daily baseline IV morphine dose</th>
<th>Est daily IV methadone requirement % of total daily morphine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to 30 mg</td>
<td>40% to 66%</td>
</tr>
<tr>
<td>30 to 50 mg</td>
<td>27% to 66%</td>
</tr>
<tr>
<td>50 to 100 mg</td>
<td>22% to 55%</td>
</tr>
<tr>
<td>100 to 200 mg</td>
<td>15% to 34%</td>
</tr>
<tr>
<td>200 to 500 mg</td>
<td>10% to 20%</td>
</tr>
</tbody>
</table>
Suggested safe & effective starting doses when rotating patients from other IV opioids to IV methadone with PCA

<table>
<thead>
<tr>
<th>Initial Opioid</th>
<th>Basal</th>
<th>New Opioid</th>
<th>Basal</th>
<th>Demand</th>
<th>Clinician Activated bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>morphine</td>
<td>10 mg</td>
<td>methadone</td>
<td>1 mg</td>
<td>1 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>dilaudid</td>
<td>1.5 mg</td>
<td>methadone</td>
<td>0.3 mg</td>
<td>0.3 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>fentanyl</td>
<td>250 µg</td>
<td>methadone</td>
<td>1.25 mg</td>
<td>1.25 mg</td>
<td>5 mg</td>
</tr>
</tbody>
</table>
Methadone drug interactions:

**Methadone Treatment**

<table>
<thead>
<tr>
<th>Clinical significance</th>
<th>Increase methadone concentration/effects</th>
<th>Decrease methadone concentration/effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented clinical effects</td>
<td>Ciprofloxacin (Cipro), clonazepam (Valium), ethanol (acute use), fluconazole (Diflucan), urinary alkalinizers</td>
<td>Amprenavir (Agenerase), efavirenz (Sustiva), nevirapine (Viramune), phenobarbital, phenytoin (Dilantin), rifampin (Rifadin), ritonavir (Norvir), urinary acidifiers</td>
</tr>
<tr>
<td>Documented enzyme effects</td>
<td>Cimetidine (Tagamet), fluoxetine (Prozac)</td>
<td>Carbamazeine (Tegretol)</td>
</tr>
<tr>
<td>Clinical effects uncertain</td>
<td>Omeprazole (Prilosec), quinidine, paroxetine (Paxil)</td>
<td></td>
</tr>
<tr>
<td>Predicted interaction</td>
<td>Delavirdine (Rescriptor), grapefruit juice or fruit</td>
<td></td>
</tr>
<tr>
<td>No current clinical evidence</td>
<td>Ketoconazole (Nizoral), macrolide antibiotics (erythromycin, clarithromycin [Biaxin], troleandomycin [TAO]), tricyclic antidepressants, verapamil (Calan)</td>
<td>Ethanol (chronic use)</td>
</tr>
</tbody>
</table>

*Information from references 6, 8, and 26 through 28.*
Estimated monthly drug costs

Comparative cost analysis of commonly prescribed opioids:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>5 mg orally three times daily (90 pills)</td>
<td>$8.00</td>
</tr>
<tr>
<td>Sustained-release morphine (generic)</td>
<td>30 mg orally twice daily (60 pills)</td>
<td>$101.50</td>
</tr>
<tr>
<td>Sustained-release morphine (MS Contin)</td>
<td>30 mg orally twice daily (60 pills)</td>
<td>$113.50</td>
</tr>
<tr>
<td>Sustained-release oxycodone (Oxycontin)</td>
<td>20 mg orally twice daily (60 pills)</td>
<td>$176.50</td>
</tr>
<tr>
<td>Transdermal fentanyl (Duragesic)</td>
<td>25 mcg per hour (10 patches)</td>
<td>$154.00</td>
</tr>
</tbody>
</table>

*—Estimated cost to the pharmacist based on average wholesale prices, rounded to the nearest half dollar; in Red book: Montvale, N.J.: Medical Economics Data, 2004. Cost to the patient will be higher, depending on prescription filling fee.
So, why don’t we use methadone?
Some comments:

- “for heroin addicts”
- “stigma”
- “never used it” “don’t know it”
- “Never heard of it being used in anesthesia”
- “government regulations & MMT”
- “I don’t know, it’s a great drug”
- “I don’t think the hospital has it.”
‘Anesthesia and Methadone’: Review of the Literature

- Research, publications & information on the use of methadone in Anesthesia is dated and challenging to find.
‘Anesthesia and Methadone’:
Review of the Literature

‘Anesthesia and Methadone’: Review of the Literature

‘Anesthesia and Methadone’: Review of the Literature

‘Anesthesia and Methadone’: Review of the Literature


However, ongoing research pending:

- Clinical trials
- Increase the research in anesthesia to provide for evidence based practice.
On the horizon…

Methadone Clinical Trials

- Methadone - **Comparison of A Single Dose Combination of Methadone and Morphine With Morphine Alone for Treating Post-Operative Pain** - This study is currently recruiting patients (Current: 08 Jun 2006)
- Methadone - **Phase III Randomized Controlled Study of Morphine and Nortriptyline in the Management of Postherpetic Neuralgia** - This study has been completed (Current: 08 Jun 2006)
- Methadone - **Project Pain - 1** - This study is currently recruiting patients (Current: 08 Jun 2006)
- Methadone - **Sublingual Methadone for the Management of Cancer Breakthrough Pain** - This study is currently recruiting patients (Current: 08 Jun 2006)
- Methadone - **Switching From Morphine to Methadone. A Clinical, Pharmacological and Pharmacogenetic Study** - This study is currently recruiting patients (Current: 08 Jun 2006)
- Methadone - **Treatment of Chronic Pain After Spinal Cord Injury (SCI) or Amputation** - This study is no longer recruiting patients (Current: 08 Jun 2006)

http://clinicaltrials.gov
In Summary…
Methadone & It’s Use in Anesthesia

- Pros & Cons of pharmacokinetics & pharmacodynamics
  - Benefits of prolonged duration of pain control with less frequent dosing
  - Less drug required; with better pain control & less side effects
  - Difficult drug to manage because:
    - Has long and variable half-life, with slow onset of analgesia
    - It takes 2 weeks to reach steady state
    - Accumulation can result in prolonged sedation and difficulty in managing fluctuations in pain

- More cost effective
- May be more effective than other opioids for neuropathic pain because of NMDA receptor activity
References

- http://clinicaltrials.gov/ct/show/NCT00142519
- http://www.anesthesiaforum.com/Methadone.htm
References

- www.hughston.com/hha/a_12_1_1.htm
- http://www.ucsf.edu/pain/orientation/opioid%20analgesics.PDF#searchopioidpharmacokinetics
- http://www.vasg.org/opioid_analgesics.htm
References

- Micromedex® healthcare series drugdex drug evaluations: methadone
THANK YOU
CRNA WEEK 2007
at Good Morning America