Objectives

I. Pharmacology Of Methadone

II. Practical Application of Pharmacology in Methadone Maintenance
Part I

Pharmacology of methadone
Opioids

• Natural derivatives of the poppy plant are opium, morphine, codeine

• Heroin (diacetylmorphine) is a semi-synthetic derived from morphine

• Synthetics are hydromorphone, oxycodone, meperidine, fentanyl, methadone
Methadone Molecular Structure

methadone
\[ C_{21}H_{27}NO \]

codeine
\[ C_{18}H_{21}NO_{3} \]
morphine
\[ C_{17}H_{19}NO_{3} \]
Opioid Receptor Types

- Mu
- Kappa
- Delta
- ORL-1

G-Protein Coupled Receptor
Opioid Receptor Effects

- Agonist
- Antagonist
- Agonist – Antagonist
- Partial Agonist
Opioid Receptor Function

- Mu1 (supraspinal analgesia, bradycardia, sedation)
- Mu2 (respiratory depression, euphoria, physical dependence)
- Delta (spinal analgesia, respiratory depression, dysphoria)
- Kappa (sedation, spinal analgesia, respiratory depression)
Antagonists

- Naloxone
- Naltrexone

Blocks Mu, Kappa and Delta receptors

*Useful for methadone (or other opioid) overdoses.*
*Beware of difference in half-life.*
Mu Agonists

- heroin (diacetylmorphine)
- morphine
- codeine
- hydromorphone
- oxycodone
- meperidine
- fentanyl
- methadone
Partial Agonists

- buprenorphine (partial Mu agonist, Kappa antagonist)
- Suboxone (buprenorphine & naloxone 4:1)
Methadone Basic Pharmacokinetics

EXCELLENT ORAL BIO-AVAILABILITY (80–90%)

ALMOST PURE MU AGONIST ONSET 30 MINS

PEAK 2–4 HRS

BIPHASIC ELIMINATION

Very lipophilic
Effect on N-methyl d-aspartate (NMDA) Receptors

- two isomeric forms “l” (levo) and “d” (dextro)
- methadone in Canada contains a mix of the two isomeric forms
- l-isomeric or (R)-methadone has an agonist effect on opioid receptors
- d-isomeric (S)-methadone has an antagonist effect on NMDA receptors
- meperidine, dextropropoxyphene, tramadol also have effect on NMDA receptors
Methadone Biphasic Elimination

Analgesic half-life is similar to short-acting opioids
Maintenance half-life (withdrawal suppression) is prolonged
Methadone Pharmacology

- Potent Mu agonist (potential of single dose overdose)
- N-Methyl-D-aspartic acid (NMDA) antagonist (blocks tolerance)
- Delta agonist activity (blocks euphoria)
- Analgesic half-life is similar to short-acting opioids
- Blocks other opioids at higher doses
- Analgesic properties of methadone differ significantly from maintenance properties
- Maintenance half-life (withdrawal suppression) is prolonged (24–36 hours)
- Accumulation with repeated use for pain can result in sedation and respiratory depression in the non-tolerant patient
Steady State in Days

TIME (multiples of elimination half-time)
Dose level remains constant

Payte — Adapted from Goodman and Gilman
Methadone as an Analgesic

- Short analgesic half-life (similar to morphine)
- Usually prescribed q8h
- Accumulated toxicity. Accumulation with repeated use for pain can result in sedation and respiratory depression in the non-tolerant patient
- Potential for sedation and respiratory depression
- When switching to methadone from another opioid agonist, there is a much more unpredictable degree of incomplete cross-tolerance than with other opioids
- Standard analgesic equivalency tables cannot be used
Methadone Side-Effects

- Sedation
- Respiratory depression
- Hypotension
- Constipation/nausea or vomiting
- Stomach pain
- Gastroesophageal reflux syndrome
- Sleep disturbance
- Dysphoria
- Perspiration
- Pruritus
- Opioid-induced edema
- Endocrine effects
- Depressed libido
Toxicity

- Concurrent use of sedative hypnotics
- Stimulants
- Alcohol
- Medications that interfere with methadone metabolism
- Deteriorating liver function
Methadone and QT Prolongation

Factors which predispose to QTc prolongation and torsades de pointes

- High methadone doses (>150 mg daily)
- History of cardiac disease (arrhythmias, susceptible heart)
- Endocrine or electrolyte disturbances
- Co-administration of another QTc prolonging drug*

* Methadone Maintenance Program: Clinical Practice Guideline 2014, Section 1.6.2 Toxicity

Recommend An Ecg Be Recorded When One Or More Of The Above Factors Are Identified
Methadone Metabolism

- Extensive bio-transformation in liver
- Metabolized by Cytochrome P450-3A4
- Some evidence of 2B6 and 2D6 metabolism
- Metabolites (mainly EDDP*) are essentially inactive
- Metabolites and unchanged methadone are excreted in bile and urine
- Metabolism does not rely on renal function

*2-ethylidene- 1,5-dimethyl-3,3-diphenylpyrrollidine
Drug Interactions

Refer list of medications metabolized by cytochrome P450-3A4*

• inhibitors
• substrates
• inducers

_Beware of cumulative effect of other central nervous system (CNS) depressants_
Inducer Examples

- Increased Clearance
- Poor Analgesia
- Withdrawal

- Nevirapine (Efavirenz)
  - Protease Inhibitors

- Tegretol (Dilantin)
  - Anticonvulsants

- Smoking (EtOH (Chronic))
  - Other
Inhibitor Examples

- ERYTHROMYCIN
- FLUCONAZOLE
- KETOCONAZOLE
  - Antibiotics
  - Antifungal agents

- LUVOX
- PROZAC
- PAXIL
- AMITRYPTYLLINE
  - SSRI'S / TCA'S

- ETOH (ACUTE)
  - Other

- Decreased Clearance
- Increased Serum Levels
- Toxicity
Part II

Practical Application Of Pharmacology in Methadone Maintenance
Challenges

- high inter-individual variability
- high intra-individual variability (tolerance)
- interaction with other medications
- long elimination half-life
Indications and Dose Forms

Treatment of opioid dependence (maintenance) and treatment of pain (not first line)

- 10 mg/ml

  *most common, Methadose® is a red, cherry-flavoured solution and, unless diluted, does not require refrigeration, it is ingested under supervision (“witnessed ingestion”) at the pharmacy*

- 10 mg/ml
- 1 mg tablets
- 5 mg tablets
- 10 mg tablets
- 25 mg tablets

Is contraindicated in individuals with known hypersensitivity to the drug. It is also contraindicated in any situation where opioids are contraindicated such as patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), and in patients with acute bronchial asthma or hypercarbia. High risk for QTc prolongation.
## Initial Dose

<table>
<thead>
<tr>
<th>DEGREE OF TOLERANCE</th>
<th>DOSE RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NON-TOLERANT</td>
<td>10 mg +/- 5</td>
</tr>
<tr>
<td>UNKNOWN TOLERANCE</td>
<td>20 mg +/- 5</td>
</tr>
<tr>
<td>KNOWN TOLERANCE</td>
<td>20 to 30 mg</td>
</tr>
</tbody>
</table>
Methadone Initiation

- There is no clear relationship between the amount of heroin used and the dose of methadone required to stabilize the patient.
- Doses are adjusted gradually until “tolerance threshold” is attained.
- Each dose will have a greater effect until steady-state is achieved (potential for accumulated toxicity).
- Methadone induction is a dangerous period for risk of overdose.

Most programs recommend at least five days between dose adjustments in the range of 5–10 mg.

More rapid dose escalations could be achieved by daily monitoring three to four hours post ingestion (peak methadone blood level) for the first three to five days after initiation or dose adjustment is required. This will reduce the risk of overdose. Prescribers should not allow weekends to interrupt this process and select a start date accordingly.
Most patients will receive stability on maintenance doses of 60–120 mg daily. Methadone doses must always be individualized and based on clinical response.
Risk Factors for Methadone Toxicity

- Use of other central nervous system (CNS) depressants
- Lack of tolerance
- Respiratory illness
- Age
- Liver disease
- Use of medications which affect methadone metabolism
Methadone Stabilization Doses

It is important to stabilize a patient on an effective dose while avoiding the risk of overdose. An effective maintenance dose should have the following results:

- Reduce or eliminate withdrawal symptoms
- Reduction or eliminate drug craving
- Will not induce sedation or drug craving
- Block the euphoric effects of illicit opioids

Most patients will receive stability on maintenance doses of 60–120 mg daily. Methadone doses must always be individualized and based on clinical response.
Heroin Use by Methadone Dose

Payte — J.C. Ball, November 18, 1988
Retention in Treatment

Payte — Adapted from Caplehorn and Bell: The Medical Journal of Australia
Protocol for Missed Doses

• Utilize PharmaNet as a tool, communicate with pharmacist, hospital and other allied health care professionals

• Always review reasons for missed doses with patient (may need updated plan)

• There may be a rapid change in tolerance when methadone ingestion is interrupted or discontinued

• One to two days missed dose: Administer usual dose as long as no other contraindication

• Three to four consecutive days missed: If dose is 30 mg or less, continue; if dose is greater than 30 mg, start at 50% of previous dose

• Five or more consecutive days missed: Restart methadone and then titrate dose upwards as usual
Tolerance

Uncommon due to NMDA effect, but consider:

• Other drug withdrawal?
• Medication interactions?
• Environmental factors?
• Personal stressors?
• Alcohol?
• Rapid metabolizer (e.g. high dose, pregnancy)?
Tolerance Strategies

- Cognitive behavioural interventions
- Increased contact, counselling, support
- Other drug withdrawal management
- Raise dose?
- Split dose (if stable)?
- Methadone blood levels?
Split Doses

Split doses are an alternative way of providing methadone to patients who have demonstrated rapid metabolism to methadone.

These patients experience symptoms of opioid withdrawal from four to six hours before the next dose of methadone is administered in a 24-hour dosing schedule.

A split-dose protocol involves administration of half the daily requirement of methadone every 12 hours.

- Naturally high metabolizers
- Pregnancy
- Concurrent medication use (P450 3A4 enzyme inducers)

*Split doses should only be used in patients who have clinically demonstrated rapid metabolism. Because of the difficulty in ensuring witnessed ingestion twice daily, they should not be used simply when requested by a patient, particularly if stability has not been attained.*
Methadone Blood Levels

• Peak/trough ratio is more important than individual serum methadone levels

• Serum methadone pre-dose = Trough

• Serum methadone two to four hours post-dose = Peak

• Peak/trough ratio is usually 2.0 or less

• Peak/trough ratio >2.0 suggests rapid metabolism
Split Dose Simulation

- Single
- High Single
- Split

INTOXICATION
NORMAL
WITHDRAWAL

0  8  16  24 hours
Split Dose Induction

• **DAY 1:**
  – 100% of dose observed
  – 50% of dose to take in 12 hours

• **DAY 2:**
  – 50% of dose every 12 hours
Summary

• Understanding pharmacology key
• Many drug interactions are clinical relevant
• PROPERLY PRESCRIBED Methadone is EFFECTIVE and SAFE
• The correct methadone dose is highly variable
• Frequent assessments are important
THANK YOU!