Pharmacology of Methadone and Physician-Pharmacist Collaborative Care

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Objectives

- Methadone Pharmacology
- Adverse Effects
- Drug Interactions
- Dosing
- Missed Doses
- Overdose
- Pharmacist-Physician Collaboration
Methadone

- Developed in 1941 by IG Farbenindustrie
- Post WW2 marketed in US by Eli Lilly as Dolophine for pain
- 1962 methadone used in Vancouver as part of withdrawal program
- 1963 Dole and Nyswander in New York began testing methadone for maintenance therapy
Methadone Pharmacology

- Synthetic opioid
- Structurally unrelated to opiates
Methadone Pharmacology

- Agonist at the $\mu$-opioid receptor
- Uses: analgesia and withdrawal management in opioid dependent individuals
- No rush/euphoria in stabilized patients
- Blocks euphoria from heroin and other opioids
- Excellent oral bioavailability
- Long duration of action allows once daily dosing in methadone maintenance therapy (MMT)
- Note: when used for pain dosing is typically TID
Absorption

- Following oral dosing, methadone is detected in the plasma within about 30 minutes.
- Peak plasma levels are 2-4 hours after ingestion.
- PO bioavailability is 90%.
Distribution

- Highly protein bound to both plasma proteins and tissue proteins
- $V_D = 4.5\text{L/kg}$
- $t_{1/2} = 22\text{ hours (15-40 hours)}$
- 5-7 days to reach steady state with repeated dosing
- Withdrawal typically suppressed for 24-36 hours with therapeutic doses
Metabolism

- Primarily metabolized by cytochrome P450 3A4 to the inactive metabolite EDDP
- Also metabolized to a lesser extent by CYP 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6
- Weak inhibitor of 2D6
Excretion

- Methadone is excreted both as unchanged drug and as metabolites in urine and feces.
- Amount of methadone excreted in urine increases as pH decreases.
Adverse Effects

- Sweating – may be due to dose being too high or too low

- Sedation - tolerance develops to this side effect but caution is advised during initiation and with dose increases

- Constipation - inhibits propulsive contractions of the intestines while increasing non-propulsive segmental contractions. Increases tone of anal sphincter. Need to treat with stimulant laxative that works at the myenteric plexus (i.e., Senna, bisacodyl)
Adverse Effects

- Weight gain - reported by many patients. Can cause water retention and decreased metabolism.

- Psychoactive effects - patients may experience some euphoria when starting on methadone or during dose increases. When stabilized methadone will block euphoria from other opioids.
Adverse Effects

- Insomnia - generally improves as patient is stabilized. Look into other causes of insomnia such (i.e. anxiety). Instruct patient on good sleep hygiene

- Sexual problems - may decrease desire and/or performance. Once stabilized some patients may experience an increase in desire
Adverse Effects

- **Neuroendocrine**: increased prolactin, affects HPA and HPG axis but with chronic use tolerance develops to these affects. Most women will report normal periods once stabilized.

- **Dental**: may inhibit saliva production which causes dry mouth and increased plaque production. Good oral hygiene practices should be encouraged.

- **Urinary**: some people report difficulty voiding but tolerance usually develops quickly.
Adverse Effects

- QT interval: QT interval prolongation with high doses.
- ECG recommended for patients on high doses.
Drug Interactions

PHARMACOKINETIC INTERACTIONS

- P450 3A4

- Drugs that inhibit CYP 3A4 – decrease methadone metabolism. Interaction occurs quickly (1-2 days). Watch for signs of toxicity (sedation, respiratory depression)

- Drugs that induce CYP 3A4 – increase methadone metabolism. Interaction is slow to occur with peak effect after 1-2 weeks. Watch for signs of withdrawal.

- Antagonist/partial-agonists-precipitate withdrawal
Drug Interactions

Decrease plasma levels

- Barbiturates
- Carbamazepine
- Ethanol (chronic)
- St. John’s Wort
- Nelfinavir*
- Phenytoin
- rifampin

Increase plasma levels

- Amitriptyline
- Ciprofloxacin
- Clarithromycin
- Erythromycin
- Ethanol (acute use)
- Fluconazole/itraconazole
- Fluvoxamine
Drug Interactions

PHARMACODYNAMIC INTERACTIONS

• Additive effects of drugs with similar side effect profile

• Be very careful with other CNS depressants and methadone-increased risk of respiratory depression and sedation
Dosing

- Start low and go slow!
- 15-30mg to start
- Remember it takes 5 days for plasma levels to reach steady state
- Increase by 5-10 mg every 3-5 days as tolerated. Avoid prescriptions that have dose increases without patient assessment.
- Incomplete cross-tolerance
Dosing

- Overdose can be fatal but opioid withdrawal is not. Always balance risk versus benefit.
- Patient should take dose at same time each day
- Some patients are rapid metabolizers and may require split dosing (also pregnant women)
Missed Doses/ Vomited Doses

- Tolerance is lost relatively quickly
- After 3 missed doses, the patient must have a dose reduction - requires a new prescription
- Emesis must be witnessed by a health care professional
  - Within 15 mins - consider replacing 50-75% of dose
  - Within 15-30 mins - consider replacing 25-50% of dose
- After 30 mins - do not replace
Overdose

- CNS and respiratory depression
- Treat with naloxone for a minimum of 24 hours with an additional 12 hours of monitoring
- Can run as an infusion or give small bolus doses hourly
Pharmacist-Physician Collaboration

- Pharmacist is often the healthcare provider that the patient has the most contact with. Will see methadone patients at least once a week if not more.

- Pharmacists develop a professional relationship with their methadone patients so they are able to assess their condition when they come in for their dose.

- Pharmacists are in an excellent position to identify when patients may be needing more support or referral to other healthcare professionals.
Collaboration

Examples of situations that should be reported to physicians:

• patient exhibiting unusual or unacceptable behaviour
• Patient has not picked up dose
• Patient refuses part or all of their dose
• Patient appears intoxicated or impaired
• Patient vomits dose
• Patient fails to provide lock box
Collaboration

- A good working relationship is not only professionally satisfying but is also good for patient care.
Questions?