

METHADONE

Dr. Kim Wolff
Senior Lecturer in the Addictions

Treatment Philosophy

- Britain: to prescribe a dose that will prevent withdrawal symptom complaints for the whole dosing interval (24 h)
- USA: to prescribe a dose that will block euphoric effects of the drug (blockade)

Much Researched

- Reduces illicit heroin use (Schuster, 1991)
- Reducing injecting drug behaviour & HIV
- Reduces acquisitive crime
- Social stabilisation (employment)
- Need to stay in treatment to achieve these effects (NTORS, 2001)

Oral Administration of Methadone

Oral efficiency is determined by the balance between lipid solubility and susceptibility to first pass metabolism.

Methadone is a lipid-soluble drug and is therefore well absorbed from the gastro-intestinal tract, particularly from the small intestine.

The extent to which a drug is absorbed from its site of administration into the systemic circulation is known as its BIOAVAILABILITY (F)

Drug bioavailability is more simply the fraction of methadone dose absorbed intact by any given route relative to a reference formulation, e.g. an intravenous injection which gives the equivalent to 100% absorption (F=1)

- Oral bioavailability of methadone = 95%
- Gluteal bioavailability of methadone = 66%
- Deltoid bioavailability of methadone = 91%

Therefore if it needs to be an intra-muscular dose, the deltoid site is better, especially in patients with a relatively high adipose to lean tissue ratio, in the gluteal region.

Absorption

The route of administration is an important determinant, since it will predetermine the type and number of membranes that methadone must traverse before absorption and distribution can occur.

- **Intravenous:**
 - Rapid onset of action since methadone reaches circulation in 15 secs
 - Absorption is rapid, predictable and the onset of effects occur after about 30 minutes
- **Intramuscular:**
 - Absorption is much more variable, the extent of muscular, blood flow and diffusion of the surrounding tissue determine entry into the systemic circulation
- **Oral:**
 - Methadone is unusual opioid in that it is very effective when given orally because largely it is not subject to a 'first pass effect'. Absorption from the gut into the systemic circulation takes 0.5-1.0h.

Distribution

The distribution of methadone is complex. Being a lipophilic drug, methadone preferentially leaves the systemic circulation and localises in tissues, including: liver, kidney, lung, spleen and brain.

Distribution of a drug can be divided into two phases:

1. A rapid, initial phase (30min – 2h) when the plasma concentration drops due to the distribution of methadone into tissues (α phase)
2. A slow decline in plasma concentration which is accompanied by a parallel decline in tissue concentration (β phase). The β phase of distribution involves both the metabolic reactions and the excretion of the drug.

The half-life of the β phase is often referred to as the terminal 'elimination' half-life ($1/2 \beta$)

Steady-state Considerations

- It takes 5 – 6 half-lives for a drug to reach steady-state. This is when the plasma concentration of a drug evens out and the rate of drug administration and the rate of drug elimination are equal.
- Dosing schedules are worked out according to the half-life of a drug.

Terminal Elimination Half-life

The half life of any drug is the time required for the plasma concentration to fall by 50 %.

The half-life of a drug therefore provides a measure of the irreversible drug loss from the blood.

The plasma half-life of methadone is about 36h. Therefore, once daily dosing is appropriate.

Heroin has a half-life of 2 mins and morphine 4 hrs.

Metabolism

- Once absorbed, methadone is transported via the portal vein to the liver where metabolism occurs
- N-Demethylation to EDDP is quantitatively the most important metabolic route, EDDP appearing as the major urinary metabolite in man.

The principal enzymes involved are the cytochrome P-450 enzymes.

- The metabolism of methadone is actually self-induced with chronic dosing
- Methadone metabolism is slowed down in patients with chronic liver disease or in the elderly.

Other enzymes to note

- CYP3A4 is not genetically polymorphic
- Other enzymes involved CYP2B6, CYP2C19, CYP2D6, CYP2C9
- Metabolism complex and variable (Irbaine, 2001)
- Metabolism not significantly genetically linked

Mechanism of Action

- Mu Opioid agonist
- NMDA (N-methyl aspartate receptor) antagonist
- This property reported to protect against tolerance. Hence can prescribe methadone in fixed daily doses (Trujillo, 1995)

Elimination

- Most drugs are eliminated from the body via metabolism in the liver and/or by excretion of the drug/metabolites by the kidneys.
- The efficiency of elimination by the liver is expressed as an extraction ratio. Therefore an hepatic extraction ratio of 0.7 (i.e. morphine) tells us that 70% of blood flowing through the liver will be completely cleared of the drug.

Excretion

- Methadone as a basic drug is subject to the ion-trapping mechanism of the kidney.
- The renal clearance of methadone is universally related to urinary pH. Normally, only 1-3% of the oral dose of methadone is excreted unchanged in urine.
- When urinary pH falls below 6, renal clearance of methadone increases.
- Therefore, measuring methadone in urine will only tell us that methadone has been consumed at some point over the previous 2-3 days.
- Accurate information regarding methadone dosing can be collected using plasma methadone monitoring.

Drug Interactions

- Disulfiram – abnormally low plasma methadone levels
- Desipramine – Raised levels of desipramine
- Chronic alcohol consumption may cause the onset of opiate withdrawal symptoms whilst binge drinking (drunk on a single occasion) may increase the toxicity of methadone.

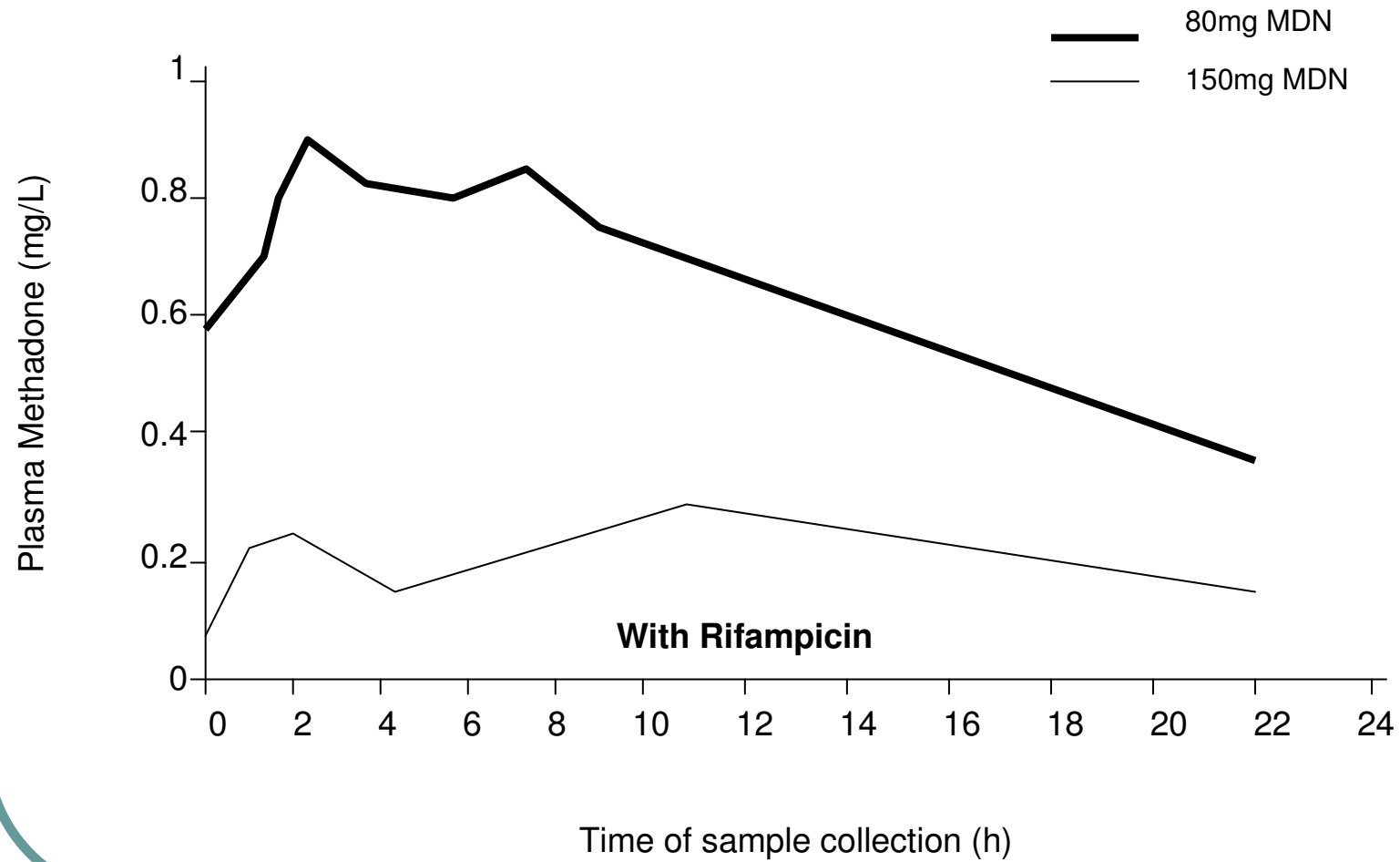
Drug interactions: inducing

Co-medication with enzyme inducing drugs causes the onset of opioid withdrawal symptoms e.g. –

- Rifampicin
- Phenobarbitone
- Phenytoin
- Zidovudine (AZT)

- Disulfiram

Methadone



Drug assessment and stabilisation

- At onset of treatment, individuals respond differently to methadone
- Auto-induction of methadone
 - Metabolism of methadone speeds up with daily dosing until steady state reached
 - Quite feasible that some individuals may experience discomfort after 1-2 weeks of dosing
- Blood sample taken at onset of treatment can be used to predict plasma concentration at steady state
- Should help with dosage decisions.

Sedation, nausea – “Toxicity”

- Plasma methadone level too high for dose prescribed
 - Elderly patient
 - Chronic liver disease
 - Co-medication with enzyme inhibitor e.g. Ritonavir
 - Consumption of extra methadone in addition to daily prescribed dose

Signs Opioid Overdose

- Adult respiratory arrest (with a pulse)
- Pin point pupils (not universal esp in children)
- SNORING (shallow respirations rate <8/min)
- Bradycardic & hypertensive

Methadone overdose (Wolff 2002)

- Cause death usually respiratory depression
- Generally found at home, in bed
- Lethal dose in non-tolerant = 25 mg
- Lethal dose in child = 5-10 mg
- **MUST** give infusion Naloxone

Factors that alter clearance

- Clearance decreased
 - Hepatic disorders
 - Chronic (cirrhosis)
 - Acute Viral hepatitis (may or may not change)
 - Chronic active hepatitis or
 - Obstructive jaundice

Drug dosage may need reducing in patients with hepatic function impairment

Tolerance

- Methadone is a mu agonist
- Produces effect by occupation of receptor sites
- Continuation of the desired effect requires increasing amounts of receptor occupancy – increased dosage
- Tolerance is built up slowly (time frame diff for each effect)
- Tolerance is lost after 2-3 doses are missed

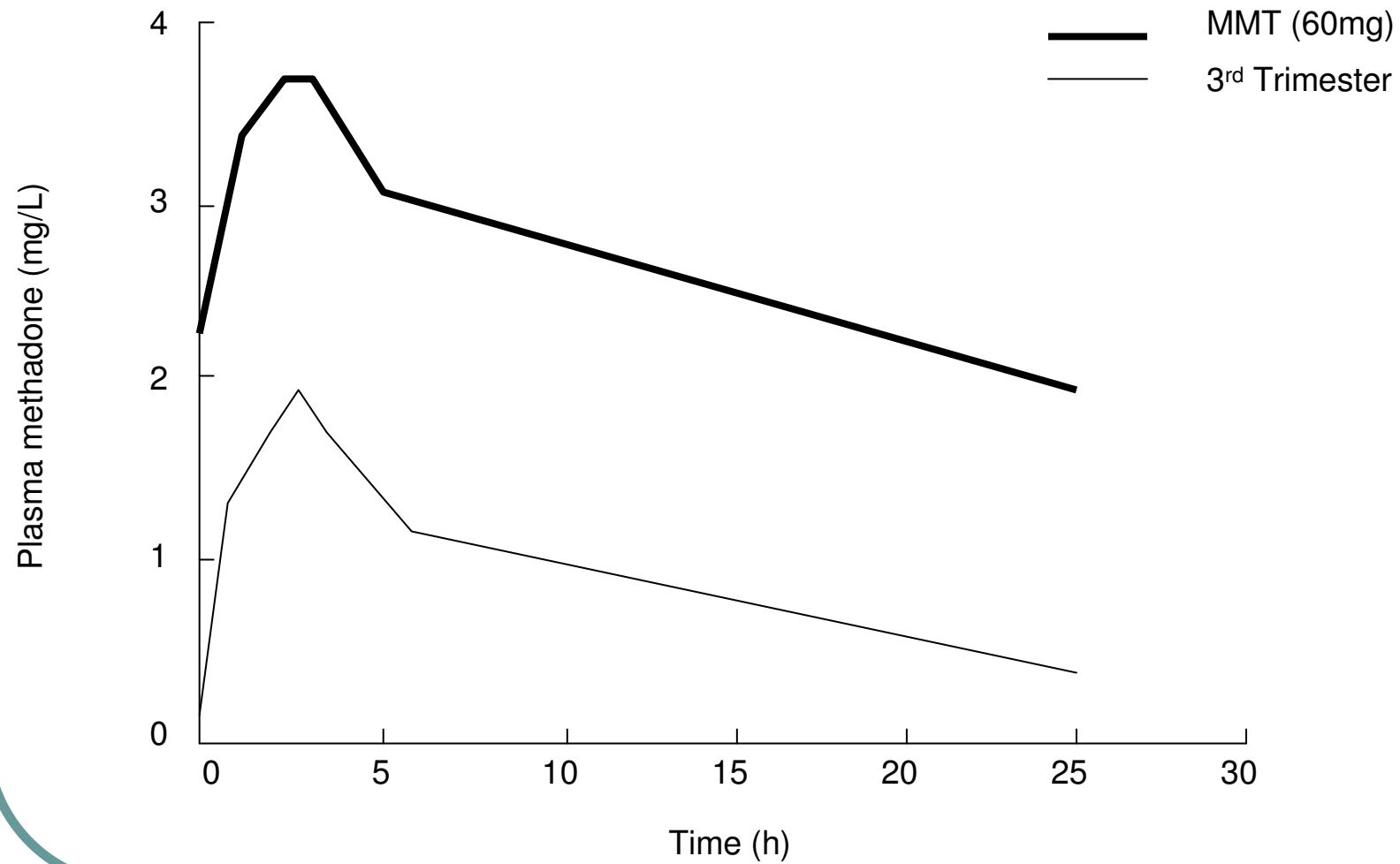
Side Effects

- Constipation
- Sweating
- Poor Dentition
- Nausea
- As for other opiates

Methadone and Pregnancy

- Stability is the primary concern for both mother and child.
- If a woman wished to give up drugs slow reduction of the methadone dose should be encourage with proper medical attention. Dosage reduction should be in small increments (5mg-10mg per week). Detoxification is not recommended during late pregnancy due to the onset of neonatal withdrawal symptoms. The prescription of benzodiazepines should be avoided during pregnancy.
- Pregnancy is often a very stressful time. The most important thing is to avoid chaotic behaviour and the use of illicit drugs. Nutritional supplements are also good practice.

Methadone



Withdrawal Symptom Complaints

- **Bingeing with Alcohol**
- Chronic alcohol dependence may incur metabolic adaptation (increased levels of cytochrome P-450 like enzymes) which may speed up the metabolism of methadone
- Methadone is metabolised by cytochrome CYP3A4 enzymes and this system is induced due to the metabolism of alcohol by pathways other than the acetyl dehydrogenase system

Methadone & Sleep

- Sleep disturbance can influence quality of life
- If withdrawing from drugs may sleep badly (Beswick 2003)
- Reducing doses of opioids or BZ disrupts sleep (Kaendler, 1996)
- Early recognition of sleep disturbance and appropriate interventions are recommended

Methadone and Exercise

- Little has been documented about the impact of exercise on the efficacy of methadone
- Pre-clinical work rats: exercise increases the concentration of endogenous opioid peptides (beta-endorphin beta).
- This effect had also been observed in humans and purportedly provides that “feel good” factor after exercising.
- In methadone dependent exercising rats consumed significantly less methadone than non-exercising controls (McLachlan et al, 1994)!
- **Methadone dosing should not need adjustment**
- In humans exercise would not be expected to have a deleterious effect on those stabilised on the drug.
- Strenuous exercise in the unfit would be likely to cause aches, joint pains, muscle strain, stiff limbs and sometimes gastrointestinal motility that should not be confused with symptoms of methadone withdrawal.

Important considerations when taking a drug history

- Sequence questions from the least to the most threatening –
 - Smoking, Alcohol, Medications, Licit Drugs, Illicit Drugs
- Ask the appropriate questions –
 - a) Not: Do you use marijuana? (closed end question)
 - b) Instead: How much marijuana are you using (open-ended question)
- Be specific as to the period of use:
 - a) First question: How much did you drink (smoke) in the month before you learned you were pregnant?
 - b) Follow-up question: Have you changed your use since learning you were pregnant?
- Be specific about the type of drug:
 - a) Not: Do you drink alcohol? (smoke marijuana) Answer: No
 - b) Instead: What do you like to drink? (smoke) Answer: Wine coolers (marijuana)
- Search for guilt feelings:
 - a) Do you worry that drugs you used early in pregnancy may have injured your baby?
- Remember:
 - Partners drug use is critical
 - Marijuana is often not considered a drug
 - Changes in drug use pattern are important - at night after children are asleep, early morning before work and during work