ST VINCENT'S HEALTH AUSTRALIA

Methadone Pharmacology

Victorian Opioid Management ECHO
Department of Addiction Medicine
St Vincent's Hospital Melbourne 2018

UNDER THE STEWARDSHIP OF MARY AIKENHEAD MINISTRIES

Methadone toxicology will be dealt with in a separate presentation

Metabolism

Methadone is primarily broken down in the liver via the cytochrome P450 enzyme system with CYP 3A4 and, to a lesser extent, CYP 2D6 the main isoforms involved (Eap, et al., 2002).

Approximately 10% of methadone administered orally is eliminated unchanged. The rest is metabolised and the (mainly inactive) metabolites are eliminated in the urine and faeces.

Methadone is also secreted in sweat and saliva and, in small amounts, breast milk (Lauren M. Jansson et al., 2008).

Methadone is highly bound to plasma proteins, in particular to α1-glycoprotein. Its mean free fraction is around 13%, with a 4-fold inter-individual variation (Eap, et al., 2002)

There is up to a **17-fold inter-individual variation** of methadone blood concentration for a given dosage, with variations in metabolism accounting for a large part of this variation (Eap, et al., 2002).

Effects of Opioids (e.g. methadone, heroin, morphine)

- Constriction of pupils
- Itching/scratching
- Sedation/somnolence
- Lowered blood pressure
- Slowed pulse
- Hypoventilation
- Loss of consciousness
- Respiratory depression
- Pinpoint pupils
- Hypotension
- Bradycardia
- Pulmonary oedema

Methadone pharmacology

Onset of effects- 75% oral bioavailability. Detected in plasma 15-45 mins after ingestion

Peak plasma concentration- 2.5-4 hours (Eap, Buclin, Buchanan 2002)

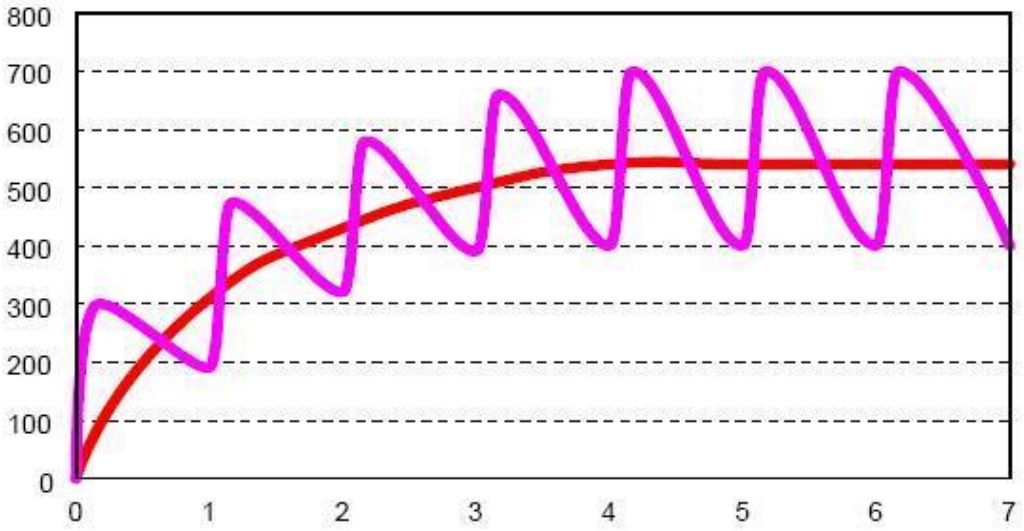
Duration of effects 20-36 hours: elimination t½ (Eap et al 2002, Humeniuk, Ali, White, Hall & Farrell 2000)

Methadone is highly bound to plasma proteins, in particular to α1-glycopro

Most deaths in early phase of treatment occur on Day 3-4

Steady State Simulation - Methadone Maintenance

Steady State attained after 4-5 half-lives -1 dose every half-life



Time in days (24 hrs.= methadone half-life)
Dose remains same - Effect increases

In the graph above the wavy line represents the blood levels of methadone as well as the "effect" it has on the individual patient.

Methadone Toxicity

Usual triad of opioid toxicity (respiratory depression, pinpoint pupils, coma) may be preceded by:

Drowsiness

Slurred speech

Poor balance (unsteady gait)

Note: additive effects of other sedatives

Due to methadone's unique pharmacokinetics – long time between ingestion and maximum effect, and t½ (leading to accumulation in tissues)

Pharmacodynamic Drug Interactions

= what the drug does to the body

Most methadone-related deaths occur in conjunction with other CNS depressants

- opioids
- benzodiazepines
- alcohol (combination of non-fatal doses of both may lead to fatal effect)
- tricyclic antidepressants (TCAs) – respiratory depression, pulmonary oedema, QTc

Pharmacokinetic Drug Interactions

= what the body does to the drug

Potential interactions between methadone and drugs which cause inhibition/induction of hepatic enzymes (esp. CYP3A4)

Potential Inducers of CYP3A4

Antiepileptics (phenytoin, carbamazepine, phenobarbitones). Not valproate or benzodiazepines

Glucocorticoids

Rifampicin, Rifabutin

(Rifampicin commonly used to treat TB, resistant Staphylococcal infections (Staph aureus, Staph epidermidis- SBE, osteomyelitis)

Potential Inhibitors of CYP3A4 metabolism

SSRIs

SNRIs

Antibiotics- erythromycin

HIV drugs- zidovudine, ritonavir

Broad spectrum antibacterials and antifungals

Calcium channel antagonists- nifedipine, verapamil, diltiazem

Hormones- progesterone, ethinylestradiol, dexamethasone

Miscellaneous- midazolam, quinidine, cyclosporin, vinblastine, cimetidine)

Other pharmacokinetic interactions

Alcohol and tobacco induce enzymes which affect methadone metabolism

Common inhibitors include: allopurinol, chloramphenicol, **ciprofloxacin, disulfiram**, isoniazid

Final comments

Methadone reaches steady state in the body (where drug elimination equals the rate of drug administration) after a period equivalent to 4-5 half lives or approximately 3-10 days. Once stabilisation has been achieved, variations in blood concentration levels are relatively small and good suppression of withdrawal is achieved.

As many as one-third of patients on methadone doses of 60mg/day may experience withdrawal symptoms in the latter part of the inter-dosing interval. A smaller volume of distribution, suggesting shortened terminal half-life, with greater binding to α1-acid glycoproteins may be a factor in this variability (Dyer, 2005).

If dose increases or multiple dosing within a twenty-four hour period do not prevent withdrawal symptoms, transfer to buprenorphine should be considered


any
questions?