ST VINCENT'S HEALTH AUSTRALIA

Methadone Pharmacology

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UNDER THE STEWARDSHIP OF MARY AIKENHEAD MINISTRIES

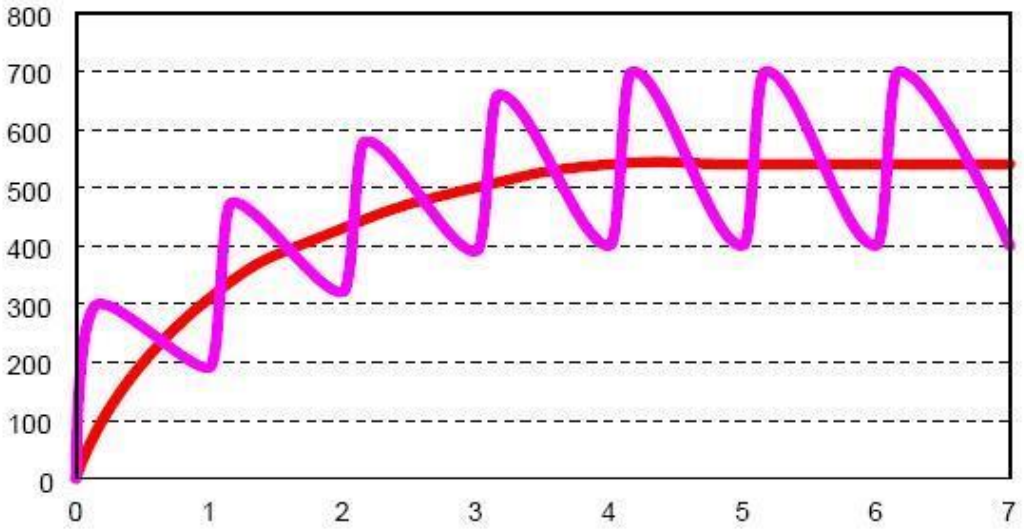
Methadone pharmacology

- 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-glycoprotein

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 : steady-state

- 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.

Metabolism

Methadone is primarily broken down in the liver via the cytochrome P450 enzyme system with:

CYP 3A4

CYP 2D6 (to a lesser extent) (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 & faeces.

Methadone is also secreted in:

- sweat
- saliva
- breast milk (Lauren M. Jansson et al., 2008).

Inter-individual variation

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 Methadone

Constriction of pupils
Itching/scratching
Sedation/somnolence
Hypoventilation
Loss of consciousness
Respiratory depression
Pinpoint pupils
Hypotension
Bradycardia
Pulmonary oedema

Dry mouth > dental decay

^ QT interval (doses over 100mg methadone)

Central sleep apnoea

Difficulties with micturition

Loss of libido(10-15% of males on methadone describe impotence)

Irregular menses

Craving for sweet foods

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 (other opioids, benzodiazepines, other..)

nb. alcohol (combination of non-fatal doses of both may lead to fatal effect)

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

Brands of methadone (1)

Both brands contain “methadone hydrochloride” 5mg/mL as the active ingredient

The two brands of methadone contain different excipients :

- Excipient in **Biodone Forte**: Water, permicol red
- Excipient in **Aspen Methadone Syrup (GSK)**: Caramel, ethanol, glycerol, sodium benzoate, sorbitol solution 70% (noncrystallising), purified water and SC345280 anise spice

Brands of methadone (2)

The 'Pharmacotherapy, Advocacy, Mediation and Support-service' (PAMS) – VIVAIDS (the Victorian Drug User Organisation) has received many reports from patients on methadone who report that their dose no longer 'holds' them after changing from methadone syrup to Biodone Forte.

A possible theory for this is that the excipients such as sorbitol and ethanol which are in Aspen Methadone Syrup, (however not in Biodone Forte Oral liquid) may impede the absorption of methadone in some patients, leading to variable plasma concentration and a possibly increased medication half-life.

A possible solution to this when changing to Biodone Forte oral liquid from Aspen Methadone Syrup, may be to either titrate up the dose of methadone, or alternatively split the daily dose to twice daily.

Another consideration is that the patient may have an 'Allergy' or intolerance to one of the excipients in Biodone Forte (such as permicol red), which is not contained in the Aspen Methadone Syrup.

Drug Interactions with methadone (1)

Potential Inducers of CYP3A4:

- Anti-epileptics (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)

Drug Interactions with methadone (2)

Potential Inhibitors of CYP3A4:

- SSRIs / SNRIs
- Antibiotics- erythromycin
- HIV drugs- zidovudine, ritonavir
- Broad spectrum anti-bacterials and antifungals
- Calcium channel antagonists - nifedipine, verapamil, diltiazem
- Hormones- progesterone, ethinylestradiol, dexamethasone
- Miscellaneous- midazolam, quinidine, cyclosporin, vinblastine, cimetidine

Drug Interactions with methadone (3)

Other interactions with CYP enzymes:

- Induction : alcohol, tobacco
- Inhibition : allopurinol, chloramphenicol, ciprofloxacin**,** isoniazid, **disulfiram**

Methadone - summary

- Pharmacology different to most other drugs
- Safety considerations
- Inter-individual variation
- Drug interactions


any
questions?