ST VINCENT'S HEALTH AUSTRALIA

Drug Interactions and ORT

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

UNDER THE STEWARDSHIP OF MARY AIKENHEAD MINISTRIES

Methadone/buprenorphine pharmacology and toxicology will be covered in a separate presentation

Torsades de Pointes (TdP) will also be covered in a separate presentation

Some principles

Opioids have many clinically significant interactions

Majority of interactions occur through a pharmacokinetic route ("What the body does to the drug")

Pharmacokinetic interactions usually involve induction/inhibition of cytochrome P450 enzymes (CYP450)

-also drug-induced changes to permeability of blood-brain barrier may occur

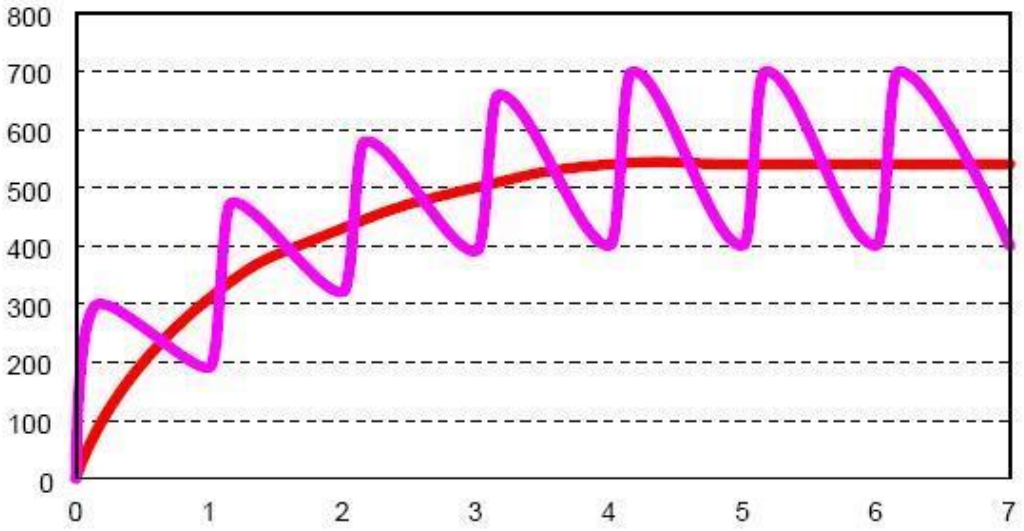
CYP450 enz are found in ER of hepatocytes and epithelium of small bowel

Most drugs are metabolised in liver

6 CYP450 enzymes are responsible for 90% of drug metabolism (CYP 3A4 involved in metabolism of 50% of drugs)

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.

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)

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).

Possible effects of drug-drug interactions

Drugs which the same substrate for the same enzymes may result in changes in the metabolism of either/both drugs

Drugs which inhibit CYP enzymes may cause increase in plasma levels = risk of toxicity/OD

Drugs which induce CYP enzymes may increase drug metabolism and so reduce plasma concentration = reduced efficacy/withdrawal

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)

Methadone

Metabolised by CYP3A2, **2B6**, 2C9, 2C19, 2D6

CYP2B6 is probably the main enzyme

Numerous enzymes = numerous interactions

Also be aware of pharmacodynamic factors (what the drug does to the body)- when methadone used with drugs which suppress respiration- bzds, alcohol

Buprenorphine

Metabolised to norbuprenorphine by CYP3A2

CYP3A4 inhibitors may increase plasma buprenorphine levels but effects unlikely to be problematic due to the ceiling effect of buprenorphine on respiration

CYP3A4 inducers may cause a decrease in plasma buprenorphine and opioid withdrawal symptoms

Deaths have bene reported when buprenorphine combined with bzds.

Some specific drug interactions

Nicotine- may decrease methadone; nicotine cessation (i.e. on hospital admission may increase levels

Omeprazole- can increase in vitro levels of methadone

Quetiapine- increased plasma levels of R-methadone (active enantiomer)

Methadone my limit antithrombotic effect of aspirin

Cimetidine may decrease methadone metabolism and increase plasma concentration

Vardenafil “Levitra” (PDE5 inhibitor), used in erectile dysfunction, may cause TdP with methadone (?? Also Sildenafil and Tadenafil)

Final comments

Need to consider possible interactions

Online resources available:

DRUG–DRUG INTERACTIONS IN OPIOID THERAPY
A FOCUS ON
BUPRENORPHINE & METHADONE
Edited by Professor Elinore McCance-Katz
in Opioid Maintenance

App store (created with a grant from Indivior)


any
questions?