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Title of Lecture: Pharmacokinetics II – Metabolism and Excretion (Problem 17, Lecture 2, 2009)
Pharmacokinetics II
Metabolism and Excretion

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Clinical Pharmacology Lectures

1. Pharmacokinetics I
   Absorption & Distribution

2. Pharmacokinetics II
   Metabolism & Excretion

3. Pharmacodynamics

4. Individualising drug therapy

5. Quality use of medicines
Acknowledgements

• NIH Fundamentals of Clinical Pharmacology

• Professor Evan Begg
  Christchurch, New Zealand

http://www.icp.org.nz
Quiz

• What is pharmacokinetics?

• What are the steps of pharmacokinetics?
Quiz

• What is pharmacokinetics?
  – What your body does to the drug
  – The quantitative analysis of the time course of drug

• What are the steps of pharmacokinetics?
  – Absorption
  – Distribution
  – Metabolism
  – Excretion
Drug X

- Intravenous dose 600 mg bd
- Oral dose 400 mg tds
- Volume of distribution 150 L

- Calculate the bioavailability
Drug X

- Intravenous dose 600 mg bd
- Oral dose 400 mg tds
- Volume of distribution 150 L

- Calculate the bioavailability

\[ \text{Bioavailability} = \frac{AUC_{po}}{AUC_{iv}} = \frac{400 \times 3}{600 \times 2} = 1 \]
Drug XX

- Target plasma concentration 30 mg/L
- Volume of distribution 20 L
- Half life 4 hours

- Calculate the loading dose
Drug XX

- Target plasma concentration 30 mg/L
- Volume of distribution 20 L
- Half life 4 hours

- Calculate the loading dose

\[
\text{Loading dose} = Vd \times \text{target plasma concentration} \\
= 20 \text{ L} \times 30 \text{ mg/L} \\
= 600 \text{ mg}
\]
Loading dose depends on volume of distribution

Maintenance dose rate depends on clearance
Maintenance dose

• Based on concepts of clearance and half life
Drug Clearance
Half life

- Elimination half life is the time required for the plasm concentration (or total body stores) of a drug to fall to half of the concentration.

\[ t_{1/2} = \frac{0.693 \ V_d}{CL_E} \]

- \( T_{1/2} \) = elimination half life
- \( V_d \) = volume of distribution
- \( CL_E \) = elimination clearance
Drug Elimination
Distribution and Elimination

Blood, liver, kidneys -> Central <-> Peripheral -> Muscle, fat

Amounts in:
- Body
- Peripheral Pool
- Central Pool

Amount of Drug (mg)

Amount Eliminated (mg)

Tozer and Rowland, 2006
Biotransformation

Lipid soluble drugs

Biotransformation

Less lipid soluble metabolites

Excretion (renal or hepatobiliary)
Biotransformation

Extrahepatic microsomal enzymes
(oxidation, conjugation)

Hepatic microsomal enzymes
(oxidation, conjugation)

Hepatic non-microsomal enzymes
(acetylation, sulfation, GSH,
alcohol/aldehyde dehydrogenase,
hydrolysis, oxidation/reduction)

Markey, NIH, 2002
Effect of biotransformation: metabolites

• Increased water solubility

• Inactive metabolites

• Active metabolites
  – Similar activity to parent drug
  – Greater activity than parent drug (inactive parent drug = ‘prodrug’)
  – Toxic
  – Reactive, eg
    • paracetamol hepatotoxicity
    • Chemical carcinogenesis and mutagenesis
Richard Tecwyn Williams

• 1942: investigated metabolism of TNT toxicity in munitions workers
• Developed concept of Phase I and 2 metabolic reactions:
  – Phase 1: Biotransformation – metabolic oxygenation, reduction, hydrolysis
    • Change in biological activity (up or down)
  – Phase 2: Conjugation
    • Detoxification
Nonpolar drug

Limited renal excretion due to extensive tubular reabsorption of lipid soluble drug

Nonpolar drug with acceptor group

Increased excretion due to decreased tubular reabsorption (drug is less lipid soluble)

Conjugated drug

Marked increase in excretion due to active tubular secretion and low tubular reabsorption
Time course of drug and metabolite

Tozer and Rowland, 2006
Saturable metabolism
Drug Metabolism Interactions

• Drug metabolism inhibited or induced by co-administration of other drugs
• Phase 1 (CYP 450) most studied
• Phase 2 interactions also occur
• Usually competitive binding to enzyme
• Onset and offset depend on half-life of inhibitor or inducer
Proportion of drugs metabolised by CYP450 isozymes

Most drugs metabolised by more than one isozyme
CYP450 Substrates, Inhibitors and Inducers

• Whether a drug is a substrate, inhibitor or inducer of a specific CYP are distinct issues
  – Drugs can that are not metabolised by a specific CYP can still inhibit that isozyme
    • Quinidine: metabolised by CYP3A4, inhibits CYP2D6
  – Drugs which are metabolised by a specific CYP may not potently inhibit that isozyme
    • Venlafaxine: metabolised by CYP3A4, not a potent inhibitor of CYP3A4
Examples of CYP 450 Substrates, Inhibitors & Inducers

<table>
<thead>
<tr>
<th>CYP3A4</th>
<th>Substrates</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Midazolam</td>
<td>Ritonavir</td>
<td>Rifampin</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin</td>
<td>Ketoconazole</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Felodipine</td>
<td>Grapefruit juice</td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>Quinidine</td>
<td>Nil clinically relevant</td>
</tr>
<tr>
<td></td>
<td>Amitryptiline</td>
<td>Fluoxetine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Codeine</td>
<td>Cimetidine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ritonavir</td>
<td>Fluvoxamine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clofibrate</td>
<td>Cimetidine</td>
<td>Smoking</td>
</tr>
<tr>
<td></td>
<td>Theophylline</td>
<td>Ciprofloxacin</td>
<td>Omeprazole</td>
</tr>
<tr>
<td></td>
<td>Caffeine</td>
<td></td>
<td>Cruciferous veg</td>
</tr>
</tbody>
</table>

See Australian Medicines Handbook and [http://medicine.iupui.edu/flockhart/](http://medicine.iupui.edu/flockhart/) for more complete lists.
Medications withdrawn due to severe ADRs related to CYP 450 drug interactions

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Liability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terfenadine</td>
<td>QT prolongation</td>
</tr>
<tr>
<td>Astemizole</td>
<td>Ventricular arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Non-sedating antihistamines</td>
</tr>
<tr>
<td>Mibefradil</td>
<td>CYP3A4 inhibition</td>
</tr>
<tr>
<td>(Ca Channel Blocker)</td>
<td></td>
</tr>
</tbody>
</table>
Clinical use of CYP metabolic interactions

- Saquinavir & ritonavir
  - Saquinavir (substrate of CYP3A4) poorly absorbed, tds
  - Combination with ritonavir (inhibits CYP3A4)
  - Allows for bd dosing and decreased dose saquinavir

- Cyclosporin & ketoconazole
  - Cyclosporin (substrate of CYP3A4) expensive
  - Combination with ketoconazole (inhibits CYP3A4)
  - Allows for lower dose cyclosporin
St. John’s Wort: CYP3A4 induction effects

- 8 normal volunteers
- Indinavir AUC determined before and after 14 days
- SJW 300 mg tds
- Indinavir AUC decreased by 57% in presence of SJW
- Could lead to failure of therapy

*Piscitelli SC et al. Lancet 2000;355:547-8*
Variability in Drug Metabolism

• Genetic factors
  – Polymorphisms

• Environmental factors
  – inducers/inhibitors of CYP450

• Age
  – Development: poor in foetus/neonates
  – Children: greater than adults
  – Old age: reduced phase I (healthy) + reduced phase II (frail)

• Disease
  – Liver disease, CCF
Pharmacogenetics

- Genetically determined alterations in drug response
- Polymorphism
  - 2 more alleles occur at 1 locus
  - each with appreciable frequency
  - in same population
Normal Distribution

Activity

Frequency
Polymorphic Distribution

Pratt WB and Taylor P, fig 7.5b
GENETIC POLYMORPHISMS

**Pharmacokinetic**
- Transporters
- Plasma protein binding
- Metabolism

**Pharmacodynamic**
- Receptors
- Ion channels
- Enzymes
- Immune molecules
Cytochrome P450 2D6 Polymorphisms

• Hydroxylation

• Epidemiology
  – Poor metabolisers:
    • 7% Caucasians, 3% Polynesians, 1% Asians
    • Homozygous for two recessive loss-of-function alleles
  – Ultrarapid metabolisers:
    • 1-7 % Caucasians, >25 % Ethiopians
Fig. 1. Frequency distribution of the $\log_{10}$ 0- to 8-hour urinary debrisoquine to 4-hydroxydebrisoquine ratio in an unselected group of white British subjects ($n = 324$) after a 10mg oral dose of debrisoquine hemisulphate (Lennard et al. unpublished data). Debrisoquine 4-hydroxylation is controlled by 2 alleles at a single gene locus. Poor metabolisers (■) are homozygous for an autosomal recessive allele and usually have ratios $> 20$ (Evans et al. 1980).
CYP 2D6 Substrates
Metabolism co-segregates with desbrisoquine

- Codeine (pro-drug)
- Beta blockers
  - Metoprolol, propranolol, timolol
- Antiarrhythmics
  - Amiodarone, flecainide, mexiletine
- Antidepressants
  - Tricyclics, SSRIs
- Neuroleptics
  - Phenothiazines, butyrophenones, atypicals
CYP 2C9 Polymorphisms

- Hydroxylation
- 1-3% Caucasians poor metabolisers
- Poor metabolisers of warfarin (carriers) – need smaller loading and maintenance doses and have 4x higher risk of haemorrhage
Association between CYP2C9 genotype, S-warfarin clearance, and warfarin dose required for INR 2-3

Scordo et al., 2002
Acetylator Polymorphisms

• N-acetyl transferase (Phase II)
• Epidemiology
  – 60% Caucasians poor metabolisers
  – 20% Asians poor metabolisers
  – 90-95% Mongoloid races fast metabolisers
• Substrates
  – Isoniazid, Hydralazine, Procainamide, Nitrazepam, Caffeine, Dapsone
• Poor metabolisers – increased ADRs
Relationship between onset of lupus syndrome in fast and slow acetylators receiving procainamide

Drug excretion by the kidney

**Fig. 3.3** A diagrammatic representation of a nephron, showing the sites of the three major processes whereby drugs are excreted via the kidney.

Grahame-Smith and Aronson, 2001
Renal Excretion

• Glomerular filtration (20% renal plasma)
  – Free drug (albumin too big)

• Active tubular secretion (80% renal plasma)
  – Free and protein bound drug
  – Carriers (competitive)
    • Acids eg frusemide, thiazides, penicillin, probenecid, uric acid
    • Bases eg morphine, pethidine, amiloride, quinine

• Passive tubular diffusion (reabsorption)
  – Lipid soluble, unionised drugs
  – Depends on urinary pH, eg urinary alkalisation for aspirin overdose
Adjustment of Maintenance Dose of Renally Cleared Drugs

• For renally cleared drugs, drug excretion $\propto$ creatinine clearance

$$
\text{Creatinine clearance (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \times 0.85 \text{ for females}
$$
Probenecid inhibits renal tubule excretion of amoxicillin

Data from Staniforth et al., 1983
Case history

• 72 year male
• Background of:
  – Hypertension
  – Asthma
  – Osteoarthritis
  – Peptic Ulcer disease
Presentation

• Muscle aches
• Swollen ankles
• Headache
Medication History

- "Moduretic"
- "Agon SR"
- "Lipex"
- "Pepcidine"
- "Feldene"
- Puffers
Medications Taken

• “Moduretic”- amiloride/HCT mane
• “Agon SR”- felodipine 20mg daily
• “Lipitor” - atorvastatin 80mg nocte
• “Pepcidine”- famotidine 20mg bd
• “Feldene”- piroxicam 20mg daily
• Puffers – salbutamol prn
What questions would you ask?
Any change in medications?

• Was taking metoprolol for hypertension but had ADRs:
  – wheeze, poor sleep, nightmares

• 3/12 ago, LMO
  – changed metoprolol to felodipine
  – prescribed clarithromycin for presumed chest infection
  – added fluticasone/salbutamol for wheeze (now only salbutamol PRN as asthma better controlled without metoprolol)
Could his medications account for his symptoms?

• Muscle aches
  – ?HMG CoA inhibitor

• Swollen ankles and headache
  – ?Ca channel antagonist
How could this occur?

- Clarithromycin inhibits CYP3A4
- Atorvastatin and felodipine are substrates of CYP3A4
- Reduced clearance results in toxicity
Other problems

• Original dose of felodipine high….
  – Recommended maintenance dose is 5-10mg/day
  – reduce dose with liver disease
Other problems

• Use of NSAIDs in patient with peptic ulcer and use of long-acting NSAIDs in older people
  – ?change to paracetamol
  – may be able to stop H2 antagonist

• Does he have asthma? Does he need the anti-asthma treatment?
Pharmacodynamics …

- Agonists and antagonists
- Dose-response
- Pharmacodynamic variability
- Clinical cases