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Title of Lecture: Clinical Pharmacology
(Problem 17, Lecture 1, 2009)
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
  http://www.cc.nih.gov/training/training/principles/info.html

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Definitions

• Pharmacology
  – Study of drugs and their actions in living organisms

• Clinical Pharmacology
  – Study of drugs in humans
  – Includes drug
    • Discovery
    • Development
    • Use
    • Evaluation
History

• Only relatively recent emphasis on drug therapy and rational prescribing.
• ‘a surgeon who uses the wrong side of the scalpel cuts his own fingers and not the patient; if the same applied to drugs they would have been investigated very carefully a long time ago.’

Rudolph Buchheim, 1849
Established first laboratory of experimental pharmacology
PHARMACEUTICAL PROCESS
Is the drug getting into the patient?

PHARMACOKINETIC PROCESS
Is the drug getting to its site of action?

PHARMACODYNAMIC PROCESS
Is the drug producing the required pharmacological effect?

THERAPEUTIC PROCESS
Is the pharmacological effect being translated into a therapeutic (or toxic) effect?
Pharmacokinetics

• What your body does to the drug
• The quantitative analysis of the time course of drug:
  – Absorption
  – Distribution
  – Metabolism
  – Excretion
Pharmacokinetics Improves Drug Dose Selection

• Traditional:
  – Look up ‘usual’ dose in MIMS/AMH
  – Memorise ‘usual’ dose

• Improved:
  – Individualise dosing
  – Apply pharmacokinetics and the ‘target concentration strategy’
  – Useful when drug has a low therapeutic index and pharmacokinetics account for much of the inter-patient variability in response
Target Concentration Strategy

Estimate Initial Dose
- Target level
- Loading dose
- Maintenance dose

Begin therapy

Assess therapy
- Patient response
- Drug level

Refine dose estimate and Adjust dose

Tozer and Rowland, 2006
Absorption

- Site of administration to plasma
- Depends on route of administration

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Administration

↓

Cross lipid barriers/ cell walls

↓

Distribute

↓

Cellular target
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Movement of drugs across cell membranes

- Simple diffusion
- Passive transport
- Active transport

Fulton, UCSF
Routes of Administration
Oral Absorption

• Passive non-ionic diffusion
  – Majority of drugs
• Specialised transporters
  – Large neutral amino acid transporter
    • L-dopa, Methyldopa, Baclofen
  – Oligopeptide transporter (PEPT-1)
    • Amino beta lactams, ACE inhibitors
  – Monocarboxylic acid transporter
    • Salicylic acid, pravastatin
Oral (enteral): absorption from mouth, stomach and small intestine

- Stomach: minority

- Small Intestine: majority
  - Passive > Active
  - Rate ~ 75% in 1-3 hours. Depends on:
    - Motility eg diarrhoea decreases absorption
    - Blood flow
    - Food – enhance or impair
    - Particle size and formulation
    - Physico-chemical factors
      - Unionised
      - Lipid soluble

- Rate of gastric emptying rate limiting step
Gastric Emptying Rate Affects Paracetamol Absorption

Gastric emptying is:
-Delayed by propantheline
-Stimulated by metaclopramide

FIG. 3—The effect of propantheline and metoclopramide on paracetamol absorption in a 22-year-old man.

Nimmo et al., Br Med J, 1973
Effects of Food on Oral Drug Absorption

• Poor acid stability: prolonged gastric exposure → degradation
  – eg erythromycin, azithromycin, isoniazid

• Require acid environment
  – eg itraconazole, ketoconazole

• Fat or bile acids enhance absorption
  – eg tacrolimus, carbamazepine

• Bind to fibre, reducing absorption
  – eg digoxin

• Bind to calcium (chelate), reducing absorption
  – eg tetracyclines, quinolones
Formulation

• Rate of disintegration of tablet
  – Tablet compression
  – Bulk excipients

• Rate of dissolution of drug particles in intestinal fluid
  – Particle size: smaller dissolve quicker

• Modified Release
  – Reduce frequency of oral administration
    • eg morphine, nifedipine, paracetamol extend
  – Deliver contents to site of action
    • eg mesalazine: pH sensitive coating – 5-ASA released in distal small bowel and colon
Routes of Administration
Sublingual Administration

• From blood vessels at base of tongue
• Lipid soluble drugs only
  – nitroglycerin
• Small surface area
  – potent drugs only
• Avoids first pass metabolism
• Rapid absorption: minutes
Routes of Administration
Rectal Formulations

• Avoid first pass metabolism
• Erratic absorption because of rectal contents
• Acceptable to patients?
• Useful if unable to take oral medications
  – eg paracetamol, oxycodone, NSAIDS
• Useful if unable to get IV access
  – eg diazepam in status epilepticus
• Direct effect on large bowel
  – eg corticosteroids in Inflammatory Bowel Disease
Routes of Administration
Parenteral: Intravenous

- Direct delivery to plasma
  - no absorption required
- Rapid effect
- Avoids first pass metabolism
- Risks: infection, embolism
Parenteral: Intramuscular

- Low water solubility drugs
- Slow release
  - eg depot fluphenazine in oil to slow diffusion
- Painful
Parenteral: Subcutaneous

- Insoluble suspensions
- Slow, even absorption
Subcutaneous Insulins

- Ultra-short and short acting:
  - soluble (clear)
- Intermediate acting:
  - large crystals (cloudy)
- Long acting:
  - Insulin glargine:
    - Soluble in acid (clear in vial)
    - Insoluble at body pH
    - After injection crystals form and insulin is absorbed slowly.
  - Insulin detemir:
    - Fatty acid attached to insulin molecule.
    - Complex binds albumin in the s/c space and in plasma.
    - Insulin gradually dissociates from albumin and can then diffuse into blood stream to reach tissue insulin Rcs.
Routes of Administration
Inhaled Medications

- **Formulations:**
  - Powders
  - Aerosol solutions
  - Nebulised solutions

- **Delivery to bronchioles**
  - ~10%
  - Depends on type of inhaler and how used

- **Local effects**
  - eg oral candida

- **Some systemic absorption**
  - Salbutamol: tremor
  - Corticosteroids: osteoporosis
  - Ipratropium bromide: anticholinergic ‘dry mouth’ in 15% patients
Routes of Administration
Topical: Intranasal Formulations

- Direct therapeutic effect
  - Sodium chromoglycate for rhinitis
- Systemic effect
  - Sumatriptan in migraine (vomiting)
- Local toxicity
  - Cocaine – necrosis of nasal septum

Saddle-nose deformity
Villa, J Can Dent Assoc, 1999
Routes of Administration
Topical: Eye Drops

• Absorption through conjunctival sac epithelium
• Local effects in eyes with minimal systemic effects
• Some systemic absorption
  – eg timolol for glaucoma may precipitate bronchospasm in asthma
Routes of Administration
Topical: Cutaneous Administration

• Local effect on skin
  – Steroids

• Slow systemic absorption (patch)
  – Lipid soluble drugs only
    • Oestrogen
    • Opioids – Fentanyl, Buprenorphine
• 77 year old woman found dead
• Applied heating pad over fentanyl patch, which was also site of her pain
• Increased fentanyl absorption due to heat
• Possible application of 2\textsuperscript{nd} patch without removing 1\textsuperscript{st}
First pass metabolism of oral drugs
First Pass Metabolism in Gut Lumen

– Gastric acid inactivates benzylpenicillin
– Proteolytic enzymes inactivate insulin
First Pass Metabolism in Gut Wall

– Monoamine oxidase – metabolises monoamines
  • Irreversible MAO inhibitors + amine-containing foods
    – Tyramine not metabolised by MAO in gut wall
      » enters systemic circulation
      » releases NAd from stores in nerve endings causing hypertensive crisis
First Pass Metabolism in Gut Wall

- **CYP 3A4**
  - Blocked by grapefruit juice
  - Many drugs inducers, inhibitors, substrates

![Graph showing plasma Simvastatin concentration over time with data points for water and grapefruit juice administration.](image)

Administration of 40mg Simvastatin with

- Water
- Grapefruit juice

*Lilja et al., Br J Clin Pharmacology, 1994*
First Pass Metabolism in Gut Wall

• P-glycoprotein (enterocytes to gut lumen)
  – Interactions b/w inhibitors (eg verapamil, macrolides) and substrates (eg digoxin)

Administration of 0.75mg digoxin with

- placebo
- clarithromycin

Rengelshausen et al., Br J Clin Pharmacol, 2003
Hepatic First Pass Metabolism

- Reduced amount of parent drug
- Metabolites
  - More water soluble - facilitates excretion
  - Activity
    - Decreased
    - Increased: Pro-drugs
      - Inactive precursors, metabolised to active metabolites
      - eg cyclophosphamide, simvastatin, ramipril, perindopril
      - Reduced first pass metabolism – reduced bioavailability of pro-drugs
Oral availability


Bioavailability: the % of an ingested dose of a drug that enters systemic circulation
Bioavailability: implications for oral and parenteral dosing

• High bioavailability, dose same for IV and po routes
  – eg metronidazole, fluconazole, amoxicillin

• Low bioavailability, lower dose for parenteral than po routes
  – eg morphine: 10 mg s/c or IM = 30 mg po
Bioavailability after oral administration of different formulations

- $C_{\text{max}}$: maximum plasma drug concentration
- $T_{\text{max}}$: time required to achieve a maximal concentration
- AUC: total area under the plasma drug concentration-time curve

Burkitt, Australian Prescriber, 2003
Bioequivalence

- Pharmaceutically equivalent and equal systemic bioavailability
- Generics
  - must be bioequivalent to innovator (80-125%)
- Phenytoin toxicity outbreak (Australia 1968)
  - ‘Inert’ excipient changed: CaSO$_4$ to lactose
  - Increased solubility and systemic availability
Change in phenytoin excipients results in epidemic toxicity

F Bochner, Proc Aust Assoc Neurol, 1973
AUC A > B: Therapeutic Significance?
AUC A > B: B Ineffective

MEC = Minimum Effective Concentration
AUC A > B: Equally Effective

MEC = Minimum Effective Concentration
Bioavailability of Thyroxine (T4)

• Agents that reduce bioavailability of oral thyroxine
  – may need to ↑ dose T4:
    – Drugs that decrease absorption of oral T4:
      • cholestyramine
      • soy bean formulations
      • sucralfate
      • ferrous sulfate
    – Drugs that increase hepatic metabolism of T4
      • phenobarbitone
      • carbamazepine
      • rifampicin

Stockigt; Aust Prescr 1996;19:47
Effect of route of Administration on Plasma Concentration

Drug Binding and Distribution
Protein Binding

Reversible and rapid

Depends on [free drug], affinity for binding sites, [protein]
Protein binding

• Many drugs bind to plasma proteins
  – Albumin (acidic drugs, eg warfarin, NSAIDs)
  – Alpha-1 acid glycoprotein (basic drugs, eg quinine)
  – Lipoproteins (basic drugs)
  – Globulins (hormones)

• Only free drug can bind to receptors
Clinical implications of changes in protein binding

• Changes in protein binding
  – Disease and nutrition
  – Protein binding displacement interactions
    • eg valproate displaces phenytoin – increases free phenytoin, compensate with increased clearance

• Clinically relevant effects if
  – >90% of drug is protein bound
    • eg phenytoin, warfarin
  – Small volume of distribution
High protein binding, low clearance

- [Free drug] depends on clearance of free drug
- [Total drug] depends on protein binding

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Birkett et al., 1979

Same drug
Same dose
Same clearance

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Birkett et al., 1979
Tissue Binding

• Body Fat
  – Lipid soluble drugs
  – Stable reservoir
  – eg anaesthetics

• Bone
  – Adsorption onto bone-crystal surface
  – Reservoir – slow release
  – eg tetracyclines, heavy metals
Distribution: body fluid compartments

- Plasma Water: 5%
- Interstitial Water: 16%
- Intracellular Water: 35%
- Transcellular Water: 2%
- Fat: 20%

Free drug can move between compartments. Depends on:
- permeability
- binding
- pH partition
- fat:water partition
### Apparent distribution volumes of some common drugs

<table>
<thead>
<tr>
<th>Volume (L/kg body weight)</th>
<th>Compartment</th>
<th>Vd (L/kg body weight)</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>Plasma</td>
<td>0.05-0.1</td>
<td>Heparin, Insulin, Warfarin, Atenolol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1-0.2</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>Extracellular fluid</td>
<td>0.4-0.7</td>
<td>Theophylline</td>
</tr>
<tr>
<td>0.55</td>
<td>Total body water</td>
<td>1-2</td>
<td>Ethanol, Phenytoin, Methotrexate, Paracetamol, Diazepam, Morphine, Morphine, Digoxin</td>
</tr>
</tbody>
</table>
Apparent Volume of Distribution (Vd)

• Vd: volume of fluid required to contain the total amount of drug in the body at the same concentration as that in the plasma

• $Vd = \frac{\text{amount of drug in body}}{\text{plasma concentration}}$

• Loading dose = $Vd \times \text{desired plasma concentration}$
Apparent volume of distribution

Gentamicin

• Absorption
  – Oral: <1% - highly polar cation, ↑ disease
  – Topical: ↑ large wound/burn/ulcer
  – IMI: rapid, peak 30-90 mins, ↓ shock

• Distribution
  – Apparent Vd 25% lean body weight (~ECF)
  – Loading dose = Vd x desired plasma concentration
    = 0.25 L/kg x 12-20 mg/L
    = 3-5 mg/kg
    Apparent Vd increases in sepsis – ? higher loading dose
    Adjust interval or maintenance dose in renal impairment – clearance
    next lecture!
  – High concentrations in renal cortex and endolymph/perilymph
    inner ear – toxicity
Barriers to Drug Distribution

• Blood brain barrier
  – Only lipid soluble drugs can enter brain and CSF
  – ‘Leaky’ in disease – eg penicillin in meningitis

• Placenta
  – Allows passage of lipid and some water soluble drugs - eg opioids, antiepileptics
  – Enzymes in placenta inactivate some drugs
Pharmacokinetics II

• Quiz
• Metabolism
• Excretion
• Pharmacokinetic drug interaction case