CLINICAL TOXICOLOGY

Dr Asia S Abdullah

asia_abdullah65@yahoo.com

Pharmacokinetics and Pharmacodynamics

The Basics

- Absorption
- Distribution
- Metabolism
- Elimination
- Compartment modelling

Absorption

- Absorption
- The process by which xenobiotics enter the bloodstream
- Variety of mechanisms by which this can occur,
  - passive diffusion,
  - facilitated diffusion,
  - active transport

Absorption

Routes of Absorption

- Oral
- Inhalation
- Intravenous
- Intramuscular
- Rectal
- Oral mucosa
- Intrathecal
- Dermal
- Ocular
- Intranasal

Absorption

- Bioavailability – the amount of drug which is absorbed relative to the amount administered.
- I.V. administered drugs are 100% bioavailable
- For other routes of administration – unlikely that all will be absorbed.
- Factors affecting bioavailability,
  - Solubility
  - Concentration
  - Surface area
  - Blood supply
  - pH

Absorption

Bioavailability: Solubility

To enter blood drugs must be in solution

- Rate of disintegration for tablets
- Formulation of drug (e.g. coated or sustained release slower than tablets or capsules)
- Aqueous medium more rapidly absorbed than oily medium or solid form
- Generally salts more water soluble than free acids or free bases

Absorption

Bioavailability: Concentration

- The greater the concentration gradient , the faster the rate of absorption of drug

- Therefore, concentrated formulations absorbed more rapidly than dilute formulations

Absorption

Bioavailability: Surface area

- Small intestine – microvilli provide large surface area to facilitate absorption
- Stomach also has large surface area

Absorption

Bioavailability: Blood supply

- Increased blood flow can enhance absorption
- Shock – absorption may b retarded in Shock

Absorption

Bioavailability: pH

- Lipophilic drugs cross biological membranes more easily than hydrophilic drugs
- Drugs that exist in an unionised form will be more lipophilic than drugs in the ionised form
- Degree of ionisation can be calculated using the Henderson-Hasselbach equation

Absorption

Bioavailability: pH

Henderson-Hasselbach Equation

Acid drugs

$pH = pKa + \log \{[ionised]/ [unionised]\}$

Basic drugs

$pH = pKa + \log \{[unionised]/[ionised]\}$

Absorption

- Stomach: pH 1 – 3.5
- Upper small intestine: pH 5 – 6
- Lower small intestine: pH 8

Absorption

Example: Quinidine

The drug Quinidine is a medication used to treat abnormal heart rhythms and is administered orally. It is a weak base and has a pKa of 7.0.

A patient being treated with Quinidine has died. On the day he died the patient took some antacid medication. Taking the antacid medication raised the pH of his stomach to pH=5.0.

Homework:

If the pH in the stomach is normally 4.0, is it possible that administration of the antacid resulted in the patient's death?

Explain in detail why or why not?

Distribution

- The transfer of a substance from one part of the body to another

  For example – Blood to tissues

- Highly perfused tissues receive most of the absorbed drug initially

- Less perfused tissues take longerto reach equilibrium with blood

Distribution

Factors affecting distribution,

- Lipid solubility (e.g. thiopental vs pentobarbital)
- pH (use Henderson-Hasselbach equation to predict when the drugs are unionised).
- Plasma protein binding

Distribution

Apparent Volume of Distribution (Vd)

Drugs distribute into body fluids to varying degrees:

Average 70kg man has 42L total body water

– 27L intracellular

– 15L extracellular (plasma, fluid component of blood, interstitial fluid, CSF, GI fluids etc)

- Drugs may distribute into any or all of the total body water
- Vd represents amount of fluid in which a drug dose appears to be distributed if total dose had remained in the blood

Distribution

Apparent Volume of Distribution (Vd) – Continued

Vd = D/C

– D is dose

– C is blood concentration of drug.

Vd < 1: Hydrophilic drugs and strongly plasma protein bound drugs

Vd > 1: Lipophilic

Vd is a theoretical value and may be greater than total body water (sequestered drugs)

Vd changes with age, gender, disease, and body composition

Metabolism

The process by which the structure of a xenobiotic is altered to facilitate removal from the body

Two general phases,

- Phase I
- Phase II

Metabolism

Phase I Metabolism

- Enzymatic transformation of functional groups
- Cytochrome P450 monooxygenases most widely studied.
  - Isozymes (The existence of isozymes permits the fine-tuning of metabolism to meet the particular needs)
  - In lipid bilayer of smooth ER
- Common mode of activity

Phase I Metabolism

- Many P450 enzymes can be induced by drugs and environmental chemicals
  - Requires increase in protein binding sites and in turn protein synthesis in binding inhibition
  - Takes time.
- Some drugs selectively inhibit P450 isozymes
  - Competition for active site
- Drugs that induce or inhibit are often routinely prescribed
  - Cannot underestimate the significance of this!

Phase I Metabolism

- Other phase 1 processes
  - Oxidases: Monoamine oxidase, flavin-containing monooxygenases
  - Hydrolytic: Cholinesterase
- Though Phase 1 is generally a detoxification process, some metabolites are active
  - Parathion – paraoxon
  - Prazepam – nordiazepam (pro-drug)

Phase II Metabolism

- Conjugation reactions
  - Derivatisation of drug or phase I metabolite with endogenous substance
  - Purpose is to increase water solubility (elimination)
- Most common is glucuronidation
  - Uridine diphosphate-glucuronic acid reacts with hydroxyl or amino groups to form conjugates of glucuronic acid
  - Catalysed by glucuronyltransferases (microsomal enzymes)
  - Glucuronide conjugates are inactive
  - Exception: Morphine-6-glucuronide which has greater analgesic potency than morphine

Phase II Metabolism

- Drugs and metabolites may be conjugated with more than one substance

– Glucuronide and sulphate conjugates of morphine identified

- Usually preceded by phase I metabolism though structure determines if phase I is needed

- Oxazepam rapidly cleared by conjugation without Phase I metabolism

Metabolism

First Pass Effect

·Enzymes in GI tract can metabolise drugs before they enter bloodstream

Drugs taken orally are transferred to general circulation via liver

– Absorbed from small intestine

– Enter portal circulation

– Transported to liver

In the liver metabolism may occur prior to entry into heart and general circulation

Drugs with significant first pass effect may require administration by other routes

Drugs affected include propranolol, lidocaine

Excretion

- Final removal of xenobiotics or their by-products from the body

Most commonly via kidney and liver

Volatiles can be eliminated via lungs (hence breath alcohol testing)

Some drugs can be eliminated into breast milk

Some drugs can be eliminated into sweat

- Drug elimination referred to as 'clearance' (removal from plasma)
- Defined as volume cleared per unit of time

– Therefore does not indicate how much drug is removed but represents the volume of plasma from which the drug is completely removed

- Total body clearance is sum of individual organ clearances

Excretion

Hepatic Excretion

- Substances cleared by liver form bile (stored in gall bladder).

  Bile enters intestines where final elimination occurs in faeces.

- Factors affecting clearance,

– Blood flow to liver

– Ability of liver to extract drug from blood

- Difficult to assess

– Poor absorption vs hepatic excretion

– Reabsorption from bile

Renal Excretion

Renal excretion is function of filtration, secretion, reabsorption

Filtered at glomerulus if less than 50,000 amu (atomic mass units)

– Proteins not filtered

– Protein bound drugs not filtered

– Drugs not protein bound are filtered v. efficiently and rapidly by filtration.

Protein bound drugs cleared to greater extent by secretion

– Carrier proteins

– Active process

– Saturable (co-administration of drug secreted by same carrier protein?)

Passive or active reabsorption of drugs may occur

– Lipid solubility, pH

– Acidification and alkalisation of urine

Pharmacokinetics

Some assumptions made to simplify and allow mathematical models to be used – one assumption is the concept of body compartments

- One Compartment Model
  - Assumes instantaneous distribution after administration
  - Drug distributes evenly throughout body
- Two Compartment Model
  - Rapid distribution in central compartment
  - Slower distribution in peripheral compartment