Pharmacokinetics: Absorption and distribution

Why are pharmacokinetic properties crucial to drug action?

- Drug has **to reach** the target tissue and target molecule to create a response
- Drug has to achieve an **adequate concentration** at the target molecule
- Drug has to **stay long enough** at the target tissue/molecule
- All these things involve pharmacokinetics

Typical pharmacokinetic problems of drugs

- Poor absorption after oral administration
- Drug given orally is metabolized (inactivated) in gastrointestinal system and liver before it reaches systemic circulation
- Drug does not distribute from systemic circulation to target tissue
- Drug disappears very fast from the body

The drug journey through the body: introduction to ADME

- Absorption
- Distribution
- Metabolism
- Excretion

Routes of administration

- **Enteral**
  - Intraoral (sublingual, buccal)
  - Oral (p.o.)
  - Rectal
- **Parenteral**
  - Injection
    - Subcutaneous (s.c.)
    - Intramuscular (i.m.)
    - Intravenous (i.v.)
  - Local administration (inhalation, intrathecal, skin, cornea, vagina, nasal, etc.)

Absorption: Drug has to cross the membrane
Absorption from the intestine

- Drug has to go through membrane(s)
- Drugs are mostly absorbed from the small intestine (there is large surface area!)
- Absorption may be affected by
  - Properties of drug
  - Diseases
  - Other factors, such as eating
- Absorption $\rightarrow$ portal circulation $\rightarrow$ liver $\rightarrow$ heart and lungs $\rightarrow$ arterial circulation

Formulation affects the time of absorption and $T_{\text{max}}$ and $C_{\text{max}}$ values

Food and absorption

- Food may affect the absorption of drugs
- Normally, presence of food delays absorption but does not affect the total amount of drug which is absorbed
- Drugs that are poorly absorbed may their absorption further impaired by the presence of food in the stomach

First-pass (pre-systemic) metabolism

Bioavailability

- Fraction of absorbed drug that passes unchanged into the systemic circulation
- “Dose minus unabsorbed minus first-pass metabolism divided by dose”
- Normally applied to orally administered drugs but can be used for other routes of administration
Bioavailability % = \( 100 \times \frac{Y}{X} \)

Measurement of bioavailability

\[
\text{Bioavailability} = \left( \frac{\text{AUC}_{\text{p.o.}}}{\text{AUC}_{\text{i.v.}}} \right) \times 100\%
\]

Enterohepatic circulation

Absorption of drug to portal circulation

Secretion of drug through bile into intestine

Distribution

1. Central
2. Peripheral
3. Central
4. Peripheral

Volume of distribution \((V_d)\)

- Theoretical volume:
  - Defined as the volume of fluid required to contain the total amount of drug in the body at the same concentration as that present in the plasma
- \(V_d = \frac{\text{total amount}}{\text{plasma concentration}}\)
- \(V_d \text{ small} \rightarrow \text{drug is mostly in plasma}\)
- \(V_d \text{ large} \rightarrow \text{drug is mostly in tissue}\)

Disease may affect distribution: the example of CNS penetration
Plasma protein binding

- Only unbound (free) drug molecules can cross membranes

Membrane transporter proteins and distribution of drugs

- Membrane transporter proteins move drugs through membranes
- These proteins affect distribution of drugs
- Transporter proteins expression may differ extensively in various tissues

Significance of transporter proteins in drug therapy

- Affects distribution of drugs
  - Advantage if drug concentrates in target tissue
  - Disadvantage if drug concentrates in tissue or cell population leading to harmful effects
- Variation in drug effects due to
  - Drug interactions (other drug may affect transporter activity)
  - Genetic polymorphism (decreased or increased transporter activity)

Membrane transporter proteins: P-glycoprotein

Elimination

- Metabolism
- Excretion
Renal excretion of drugs

Clearance

Theoretical plasma volume containing the amount of drug that is removed from the body in unit time

\[
\text{Clearance (ml/min)} = \frac{\text{Excretion (mg/min)}}{\text{Plasma concentration (mg/ml)}}
\]

Lipophilic drugs have to be metabolized to more water-soluble forms for renal excretion

Detoxification of foreign chemicals (including drugs)

Liver cytochrome P450 (CYP) system
Causes of variation in drug elimination

- Genetic polymorphism
- Other individual factors
  - Age
  - Gender
  - Diseases
- Environmental factors
  - Drugs
  - Alcohol, tobacco
  - Food

Half-life ($T_{1/2}$)

First-order kinetics = equal amount in percentage is eliminated in unit time.

Zero-order kinetics = equal amount in mg is eliminated in unit time.

Accumulation

Accumulation: plasma concentration of drug increases until rate of elimination matches rate of addition. Plasma level thereafter remains constant (= “steady-state”). Time to steady state is always 4-5 half-lives.

Accumulation: water level rises until hydrostatic pressure equals rate of inflow and outflow. Water level then remains constant.

Steady state concentration

Steady state is achieved after 4-5 half-times regardless of dose. Dose influences plasma concentration at steady state.

Disappearance of drug after cessation of treatment

After the tap is closed the water level decreases, first quickly but as the hydrostatic pressure decreases, leakage will be slower. Disappearance happens in the reverse way to accumulation. Therefore, after 5 half-lives the drug has been practically eliminated.
Linear and saturating kinetics

2 x 200 mg or 4 x 100 mg administration

Bioequivalence

Drug interactions

Drug interactions
- Many patients use several drugs concomitantly
- Many elderly patients routinely use more than 5 drugs concomitantly
- Drugs may interact with other drugs

Two general mechanism of drug interactions
- Drug A may modify the effect of drug B by
  - pharmacodynamic interaction
    - concentrations of drug B at its site of action are not changed
  - pharmacokinetic interaction
    - concentrations of drug B at its site of action are changed
Drug interactions may be beneficial or harmful

- Beneficial interactions
  - Combination of drugs to increase efficacy is very common
  - Blood pressure treatment, pain medication, etc. (pharmacodynamic interaction)
  - Stalevo (pharmacokinetic interaction)

- Harmful interactions
  - Drug A attenuates the efficacy of drug B
  - Combination may cause increase in side-effects

Examples of harmful pharmacodynamic interactions

- Drugs may affect the same physiological response through different mechanisms
- Drugs may affect the same receptor (agonist and antagonist)
- Drugs may affect the same intracellular signaling cascade

Pharmacokinetic drug interactions

- Drugs may affect the
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
  - of other drugs

CYP-function and the effects of altered function

CYP-enzyme metabolizes drug X

- Drug X alone
- Drug X + Drug Y (CYP-inhibitor)
  - (Multiple fold increase in concentration)

- Drug X + Drug Z (CYP-inducer)
  - (Lower concentrations)
Consequences of CYP-induction/inhibition

**Induction of metabolism**
- Drug → Metabolite
- Drug response diminished → treatment less/not effective

**Inhibition of metabolism**
- Drug → Metabolite
- Drug response increased but also adverse effects increased

CYP-enZYme activity and drug half-life

More CYP450 activity → shorter half-life

P-glycoprotein and drug interactions

Drug development
- Basic research
  - Validated target
  - Screening
- Preclinical
  - Efficacy
  - Safety/toxicology
- Clinical
  - Ph I - First in human
  - Ph II - First in patients
  - Ph III Multi site trial

Thank You!