Slide 1

Clearance

MBChB 221B

Dr Stephen Jamieson
Dept of Pharmacology and Clinical Pharmacology
Auckland Cancer Society Research Centre

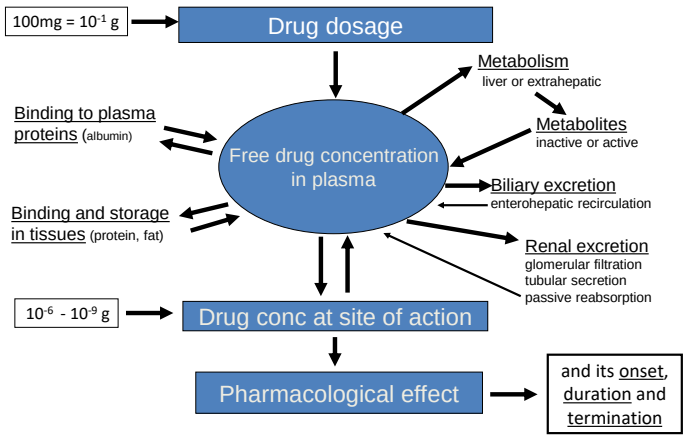
Slide 2

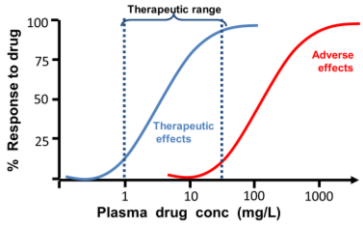
Learning objectives

- Understand the importance of pharmacokinetics
- Learn the definition of clearance
- Understand the physiological determinants of clearance
- Be able to define clearance classes
- Appreciate the applications of clearance concepts to clinical practice

Slide 3

Summary of drug disposition



Slide 4	**Pharmacokinetics** • Pharmacokinetics is the study of the concentration-time profile of a drug in the body. – Blood (plasma) – Tissues – Saliva, milk, urine, faeces • Important pharmacokinetic parameters include: – Clearance, Volume of distribution, Half-life	
Slide 5	**Why is Pharmacokinetics important** • Knowledge of PK allows more rational dosing – Can identify therapeutic window • Gives drug its best chance of achieving efficacy and minimising side effects  	
Slide 6	**Why is Pharmacokinetics important** • Knowledge of PK allows more rational dosing – Can identify therapeutic window • Gives drug its best chance of achieving efficacy and minimising side effects – Identifies optimal routes of administration and schedules of dosing • e.g. oral or IV • e.g. once daily or 3x daily	

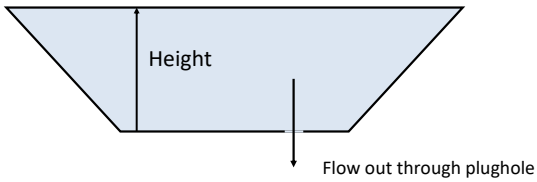
Slide 7

Clearance (CL)

- Volume of plasma irreversibly cleared of drug per unit time (L/h)
- Describes the relationship between concentration and elimination of the drug from the body
  - Clearance (L/h) = Elimination rate (mg/h) / concentration (mg/L)
- Plasma clearance = sum of clearances from individual organs
  - $CL_{plasma} = CL_{renal} + CL_{hepatic} + Cl_{other}$

Slide 8

Bathtub model of CL



Flow out = plughole size *x* height
Elimination rate = Clearance *x* Concentration

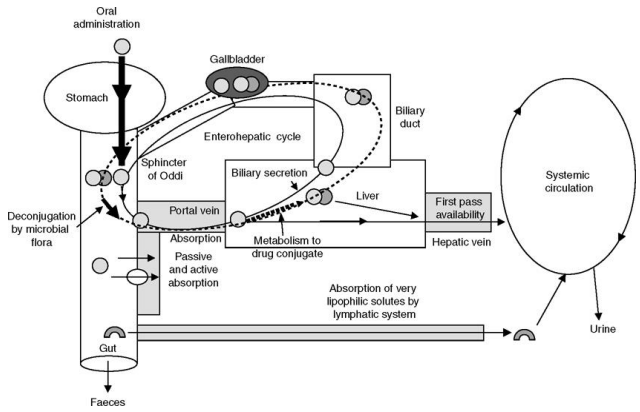
Slide 9

Drug elimination

- Processes by which a drug is removed from the body
  - Metabolism
    - Predominantly in liver
  - Biliary excretion in liver
  - Excretion by glomerular filtration or tubular secretion in the kidney

Slide 10

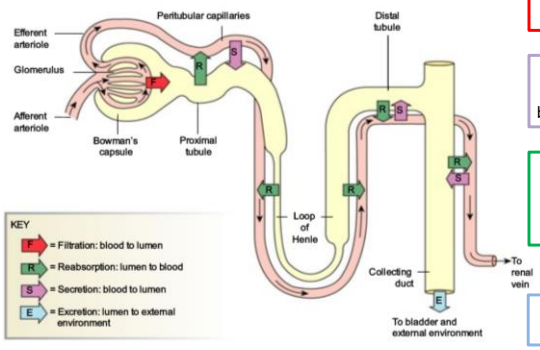
Hepatic elimination



Roberts et al. Clin Pharmacokinet. 41:751-790, 2002

Slide 11

Renal excretion



Glomerular capillaries very porous. Most drugs will be filtered

Active transport of drugs / metabolites by drug transporters

Small, non-ionised, lipophilic drugs reabsorbed by passive diffusion

Drug excreted in urine

Silverthorn. Human physiology, an integrated approach, 3rd Ed. Chapter 19: the kidneys.

Slide 12

Physiological basis for clearance

- Liver and kidney are the 2 organs most responsible for drug clearance
  - Organ clearance can not exceed blood flow to that organ
- Liver blood flow ≈ 90 L/h
  - Cleared by metabolism and biliary excretion
- Kidney blood flow ≈ 70 L/h
  - Cleared in urine
  - Glomerular filtration rate ≈ 6 L/h
  - Tubular secretion (variable rate)
  - Tubular reabsorption

Slide 13

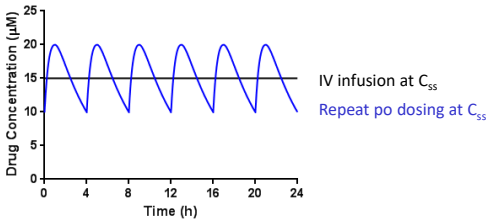
Clearance of common drugs

- Hepatic CL drugs
  - High (40-90 L/h)
    - Propranolol, verapamil, morphine
  - Low (<20 L/h)
    - Theophylline (3 L/h), warfarin (3 L/day)
- Renal CL drugs
  - High
    - Benzyl penicillin (≈ 36 L/h, Filtration & secretion)
  - Low
    - Gentamicin (≈ 6 L/h, filtration)
- Drugs cleared by multiple routes
  - Digoxin: liver (2.5 L/h) and kidney (6.5 L/h)
  - Glyceryl trinitrate (150 L/h): plasma, liver, etc

Slide 14

Maintenance dose rate (MD)

- Dose rate to achieve and maintain a target concentration
  - Steady state concentration (C_{ss})



Slide 15

Maintenance dose rate (MD)

- Dose rate to achieve and maintain a target concentration
  - Steady state concentration (C_{ss})
    - Dose rate in = rate of elimination

Maintenance dose (mg/h) = CL (L/h) x target concentration (mg/L)

- A rapidly cleared drug will need a large maintenance dose to keep drug concs at target levels

Slide 16

Maintenance dose calculation

- Calculate the dose rate of theophylline for a patient with asthma to maintain a target concentration of 10 mg/L
  - The clearance of theophylline is 2.8 L/h
  - Maintenance dose rate (mg/h)
    = CL (L/h) x target conc (mg/L)
    = 2.8 x 10
    = 28 mg/h

Slide 17

Clearance Classification

- Constant
  - Independent of concentration and organ blood flow
  - First-order or linear elimination
  - e.g. glomerular filtration, most metabolism
- Concentration-dependent
  - CL changes with concentration
  - Mixed order or non-linear elimination
  - e.g. tubular secretion of penicillin, metabolism of phenytoin
- Flow-dependent
  - CL approximates organ blood flow
  - e.g. morphine CL = 60L/h

Slide 18

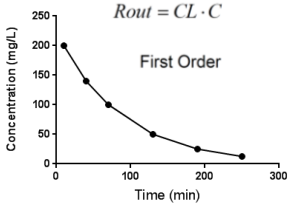
Concentration-dependent clearance

$$Rout = \left[\frac{V\max}{Km + C}\right] \cdot C$$

Mixed Order

$$Rout = \left[\frac{V\max}{Km + C}\right] \cdot C$$

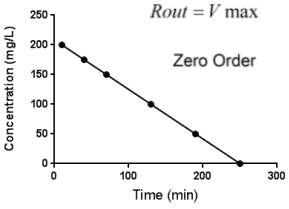
$$Rout = CL \cdot C$$



First Order

$$Rout = \left[\frac{V\max}{Km + C}\right] \cdot C$$

$$Rout = V\max$$

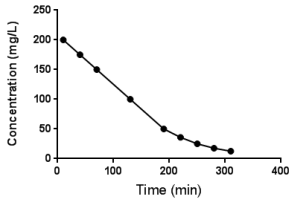


Zero Order

Slide 19

Mixed order kinetics: phenytoin

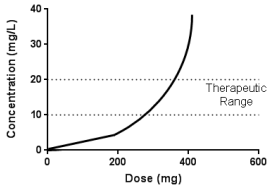
- At low concentrations, phenytoin metabolism is a first-order process
- At higher concentrations, metabolism is saturated



Slide 20

Mixed order kinetics: phenytoin

- At low concentrations, phenytoin metabolism is a first-order process
- At higher concentrations, metabolism is saturated
- Small increases in dose, cause large increases in plasma drug levels



Slide 21

Applications

- Additional elimination processes
  - Haemodialysis
    - Blood is filtered to remove drug
    - Theophylline CL = 4 L/h
  - Haemoperfusion
    - Passing blood through a cartridge to adsorb drug
    - Theophylline CL = 9 L/h
  - Gut adsorption by charcoal
    - Prevents drug absorption
    - Theophylline CL = 6 L/h