BIOP211 – Pharmacology

Tutorial Session 3 – Pharmacokinetics and drug distribution, metabolism and excretion

3.1 Choose any drug/class of drugs, and list both the Adverse Drug Reactions, ADR, and also important drug interactions (DDI).

Using your textbook (or other resource), discuss how these ADRs and interactions come about.

Examples for causes of drug interactions include but may not be limited to:

- Competition for absorption or protein binding
- Competition for metabolism by same enzyme
- Induction or inhibition of metabolic enzymes

3.2 Answer true or false to these questions:

a. The rate of drug clearance affects the steady state.
b. The half-life of a drug is affected by the volume of distribution.
c. In general, if a dose of a drug is missed, a double dose should be taken in order to maintain the therapeutic effect.
d. Dosing regimen should only be guided by the drug half-life.
e. Saturable metabolism is when the enzyme metabolising the particular drug reaches maximum capacity.

Summary Pharmacokinetics

Pharmacokinetics

‘The study of the kinetics of a drug during the process of absorption, distribution, metabolism and excretion.’

- Absorption
  - Process by which unchanged drug proceeds from the site of administration into the blood.
  - 4 methods of absorption – absorption across biological membranes; membrane openings or pores; passive transport; active or carrier transport
- Distribution
- Metabolism
- Elimination

See Unit “Principles of Pharmacology”

- Sections on “Drug Absorption, Distribution, Metabolism and Excretion” Chapter introduction and figures

Bioavailability is ‘the fraction of unchanged drug reaching the systemic circulation following administration by any route’ and will be less than 100% due to such factors as incomplete absorption, metabolism by the gut and liver biotransformation.

This is affected by the extent of absorption and 1st pass metabolism.

See Unit “Principles of Pharmacology”

- Sections on “Drug Absorption”, “Key Pharmacokinetic Concept – Drug Bioavailability”, “Key Pharmacokinetic Concept – Hepatic First-Pass Effect”

Routes of administration

Route of drug administration can affect both the rate at which onset of action occurs and the extent of the response. The major categories are:

- parenteral – subcutaneous, intramuscular, intravenous, Intrathecal, epidermal
- inhalation
- topical
Distribution
Once a drug has been absorbed into the systemic circulation, it is distributed to various target sites. Factors affecting distribution are:

- Plasma protein binding
- Tissue binding
- Blood brain barrier
- placental barrier
- Blood supply
- Capillary permeability
- Cardiovascular function

Metabolism
Most metabolism processes are carried out by enzymes and occurs in 2 phases which overlap. Some Pharmacology texts prefer to refer to them by their names only, as there is so much overlap.

**Phase I** or preferably Functionalisation Reactions (oxidation / reduction and / or hydrolysis) mostly due to cytochrome P450 (CYP) isoforms sometimes the metabolites are more active than the pro-drug with longer half lives; sometimes the metabolites are toxic

**Phase II** or preferably Conjugation Reactions (endogenous cofactor UDP-glucuronate, sulphate, acetyl CoA or glutathione) involves the coupling of a drug /metabolite with an endogenous substrate to be excreted.

1st Pass Metabolism
refers to how much drug is left to enter systemic circulation after it has undergone liver biotransformation

higher 1st pass metabolism → higher oral doses needed

Excretion
Drugs continue to exert a pharmacological/toxic effect until it is eliminated. Route of excretion:

- kidneys
- hepatic
- expired air
- sweat and saliva
- breast milk

Dosing Regimens
From a dosing point of view, the most important pharmacokinetic parameters are:

- Therapeutic range
- steady state
- clearance (ability of an individual organ to or the whole body to eliminate a drug), needed to calculate maintenance dose rate = clearance X target steady-state plasma drug concentration
• volume of distribution, needed to calculate loading dose = volume of distribution X desired plasma concentration
• half life elimination (major indicator of the duration of action of a drug)
  o amount of time needed for the concentration of the drug in plasma to halve
  o the pharmacokinetic parameters used to calculate $t_{1/2}$ are clearance and volume of distribution

Dosing issues: elderly, neonates and children, pregnancy, lactation.

See Unit “Principles of Pharmacology”

- Sections on “Pharmacokinetics and Dosing Regimens” Chapter Introduction and figure, Hepatic Clearance, Renal Clearance, “Key Pharmacokinetic Concept – Volume of Distribution” and “Key Pharmacokinetic Concept – Half-life”; and
- “Drug Use During Pregnancy”, “Drug Use During Lactation”, “Drug Metabolism in Children” and “Drug Use in the Elderly”

Pharmacogenomics

Branch of pharmacology which deals with the influence of genetic variation on drug action and elimination.

See Unit “Introduction to Pharmacology”

- Section on Human genome targets: pharmacogenomics

See Unit “Principles of Pharmacology”

- Section on Pharmacogenomics and adverse drug reactions

Textbook Location of Readings


Chapter 6 Drug Absorption, Distribution, Metabolism and Excretion

Chapter 8 Pharmacokinetics

Revision Questions / Activities from the Reading Guide

1. Define biotransformation. Briefly describe the enzyme systems involved in biotransformation of drugs and other exogenous substances.
2. Name the 2 phases in metabolism and outline what happen in each phase.
3. How many half-lives does it take for a drug with a $1/2$ life of 5 hours and an initial concentration of 24 mg to reach less than 1 mg?

Reference list


http://www.medicinescomplete.com/ (see link on LibGuides for online access Pharmacology - Endeavour College of Natural Health LibGuides - LibGuides at Endeavour College of Natural Health)

Interactive clinical pharmacology, Hittlab NZ and Christchurch Hospital / University of Otago

Christchurch, New Zealand available at Pharmacology - Endeavour College of Natural Health LibGuides - LibGuides at Endeavour College of Natural Health

Subscribed database called Cochrane Database, available from the Pharmacology - Endeavour College of Natural Health LibGuides - LibGuides at Endeavour College of Natural Health


https://www.ebs.tga.gov.au