Pharmacology/Therapeutics I Block I Handouts – 2017-18

1. Principles of Pharmacology – Fareed
2. Drug Absorption & Distribution - Byron
3. Drug Elimination & Multiple Dosing – Byron
4. Clinical Pharmacokinetics – Quinn
5. Drug metabolism – Clipstone
6. Pharmacology of Drug Transporters – Clipstone
7. Pharmacogenomics - Clipstone
8. Pharmacodynamics I - Battaglia
9. Pharmacodynamics II – Battaglia
10. Drug Toxicity – Clipstone
11. Drug Discovery and Clinical Trial - Clipstone

PRINCIPLES OF PHARMACOLOGY: AN OVERVIEW

Date: August 1, 2017 – 9:30 am

KEY CONCEPTS AND LEARNING OBJECTIVES

1. **Identify some of the major drug categories for the treatment of various diseases.**
2. **Discuss the chemical nature of drugs with reference to their origin.**
3. **List the different origins and sources of drugs and the different types of drug formulations.**
4. **Describe the different routes of administration of drugs.**
5. **List some of the factors that affect drug absorption, drug distribution and drug excretion.**
6. **Describe Fick's law of diffusion and its application to predict distribution of drugs.**
7. **Distinguish the major difference between First Order elimination and Zero Order elimination.**
8. **Distinguish between a multicomponent distribution model and a single compartment distribution model.**
9. **Define receptors and their role in the mediation of drug response and differentiate between a receptor agonist and antagonist.**
10. **Discuss the differences between generic versions of a drug versus the branded product.**
11. **Define the bioavailability of a drug in reference to the mode of administration.**
12. **Identify the main phases and purposes of the drug approval process.**

PRINCIPLES OF PHARMACOLOGY: An Overview

A. WHAT IS PHARMACOLOGY?

Pharmacology represents an integrated body of knowledge that deals with the actions of chemical and biologics on cellular functions.

1. Medical Pharmacology is the area of pharmacology that covers the use of drugs in the prevention (prophylaxis) and treatment of diseases.

2. Toxicology is the area of pharmacology concerned with the undesirable effects of chemicals and biologicals on cellular functions.

3. Pharmacokinetics describes the effects of the body on drugs (absorption, distribution, excretion) and pharmacodynamics describes the action of drugs on the body such as the mechanism of action and therapeutic and toxic effects.

4. Pharmacology is the most integrated multidisciplinary science. It requires knowledge of all of the basic and clinical sciences to understand the mechanism of action of drugs.

B. MAJOR DRUG CLASSES FOR THE TREATMENT OF VARIOUS DISEASES

1. **Autonomic drugs-** These drugs target the involuntary, unconscious portion of the nervous system.

    a. Cholinoceptor-activating and cholinesterase-inhibiting drugs
    b. Cholinoceptor blockers and cholinesterase regenerators
    c. Sympathomimetics
    d. Adrenoreceptor blockers

2. **Cardiovascular drugs**
    a. Antihypertensive agents
    b. Drugs used in the treatment of acute coronary syndrome (ACS)
    c. Drugs used in the treatment of heart failure
    d. Anti-arrhythmic drugs
    e. Diuretic agents

3. **Drugs effecting smooth muscle cells**
    a. Histamine, serotonin and ergot alkaloids
    b. Vasoactive peptides
    c. Prostaglandins and their modulators
    d. Nitric oxide donors and inhibitors
    e. Bronchodilators

4. **Drugs that act on the central nervous system**
    a. Sedative/hypnotic drugs
    b. Alcohols

c. Anti-seizure drugs
d. General and local anesthetics
e. Skeletal muscle relaxants
f. Anti-Parkinsonian drugs
g. Anti-psychotic drugs
h. Anti-depressant drugs
i. Opioids analgesics and antagonists
j. Drugs of abuse

5. Drugs with actions on blood, inflammation and gout

a. Anti-anemia drugs and hematopoietic growth factors
b. Drugs used in the management of thrombosis
c. Anti-hyperlipidemic agents
d. Non-steroidal anti-inflammatory agents

6. Endocrine drugs

a. Hypothalamic and pituitary hormones
b. Thyroid and anti-thyroid drugs
c. Corticosteroids and antagonists
d. Gonadal hormones and inhibitors
e. Pancreatic hormones, anti-diabetics and hyperglycemic drugs
f. Drugs that affect bone mineral homeostasis

7. Chemotherapeutic agents

a. Antibiotics
b. Anti-fungal agents
c. Anti-viral chemotherapy
d. Anti-protozoal drugs
e. Anti-helmentic drugs
f. Cancer chemotherapy
g. Immuno-modulators

8. Drugs used in the treatment of gastrointestinal disorders

a. Drugs used in acid-peptic diseases

b. Drugs stimulating GI motility

c. Laxatives

d. Anti-diarrheal agents

e. Anti-emetics

9. Vaccines, complex biologic drugs and immune globulins

a. Active immunization-goal is 1^{o} immune response with memory

b. Passive immunization- goal is short-term protection in specific populations

10. Stem cell therapy

a. Stem cell therapy is the use of stem cells to treat or prevent a disease or condition

b. Stem cell therapy to treat various diseases, such as cancer, diabetes and neurodegenerative disorders are being clinically tested.

11. Monoclonal antibodies

C. THE NATURE OF DRUGS

1. Inorganic ions
2. Non-peptide organic molecules and organomimetics
3. Small peptides and peptidomimetics
4. Natural and recombinant proteins
5. Nucleic acids and their analogues
6. Lipids and lipid derived agents
7. Carbohydrates and their derivatives

The molecular weight of drugs varies from 7 daltons (Li^+) to > 100,000 daltons (antibodies, vaccines, enzymes)

D. ORIGIN AND SOURCE OF DRUGS

1. Microbes
2. Plants
3. Animals
4. Inorganic elements and compounds
5. Synthetic organic compounds
6. Synthetic organomimetics
7. Biotechnology derived products
8. Biologics and products of human origin/recombinant equivalents
9. Cell therapies

E. DRUG FORMULATIONS

1. Liquid
2. Tablets
3. Suppositories
4. Sprays and inhalants
5. Ointments
6. Transdermal patches
7. Drug coating on medical devices (stents, catheters, extracorporeal circuits)
8. Drug implants

9. Micro and nanoparticles
10. Targeted drug delivery

F. ABSORPTION OF DRUGS

1. Route of absorption

   a. Intravenous
   b. Intramuscular
   c. Subcutaneous
   d. Buccal and sublingual
   e. Rectal
   f. Inhalation
   g. Transdermal
   h. Other

2. Blood flow

3. Concentration

G. MOVEMENT (TRANSPORTATION) OF DRUGS IN THE BODY

4. Permeation

   a. Aqueous diffusion
   b. Lipid diffusion
   c. Transport by special carriers
   d. Endocytosis

5. Fick's law of diffusion
   a. Predicts the rate of movement of molecules across a barrier.
   b. The concentration gradient (C_1- C_2) and permeability coefficient for the drug and the thickness of the barrier impact drug diffusion.

$$\text{Rate} = (C_1 - C_2) \times \frac{\text{Permeability coefficient}}{\text{Thickness}} \times \text{Area}$$

H. AQUEOUS AND LIPID SOLUTION OF DRUGS

1. Aqueous diffusion
2. Lipid diffusion
   The pH of the medium determines the fraction of drug which is charged (ionized) versus uncharged (non-ionized). If the pK, of the drug and pH on the medium are known, the amount of ionized drug can be predicted by means of Henderson-Hasselbalch equation.

3. Ionization of weak acids and bases

$RNH_3^+ \leftrightarrow RNH_2 + H^+$

$RCOOH^+ \leftrightarrow RCOO^- + H^+$

I. DISTRIBUTION OF DRUGS

1. Determinants of distribution
   a. Size of the target site (organ)
   b. Blood flow
   c. Solubility
   d. Binding

2. Apparent volume of distribution and physical volume

J. METABOLISM OF DRUGS

1. Drug metabolism as a mechanism of termination of drug action
2. Drug metabolism as a mechanism of drug activation
3. Drug elimination with out metabolism

K. ELIMINATION OF DRUGS

1. First order elimination

   First order elimination implies that the rate of elimination is proportional to the concentration.

   The higher the concentration of drug the greater amount of drug is eliminated per unit time.

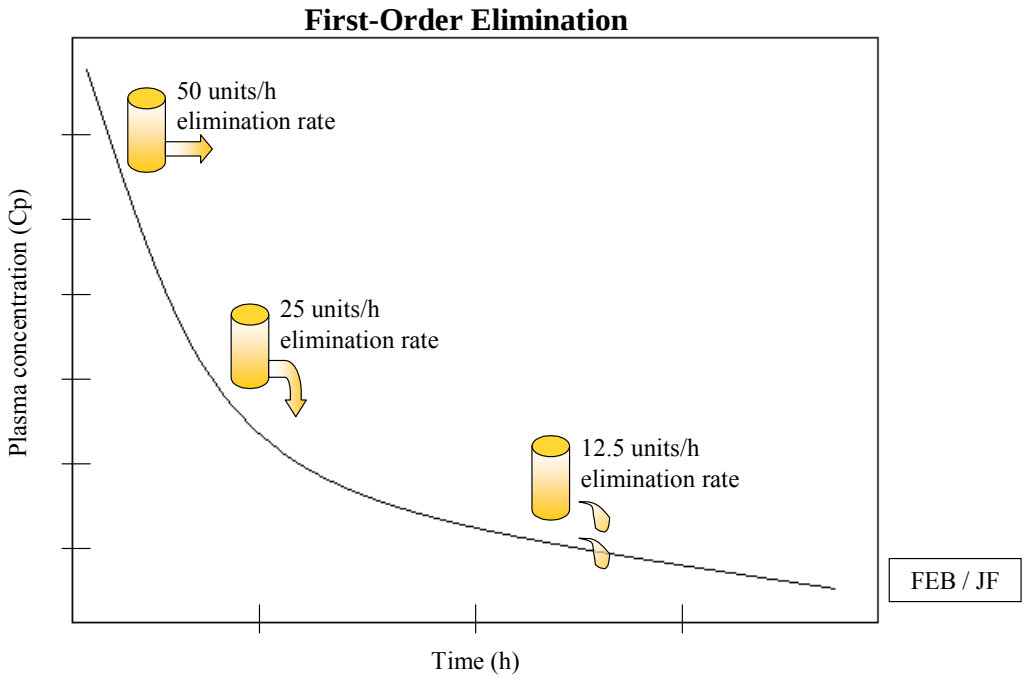


Figure 1. First-order kinetics of drug elimination. The rate of elimination is proportional to the circulating levels of the drug. (more common)

2. Zero order elimination

Zero order elimination implies that the rate of elimination is constant regardless of the concentration.

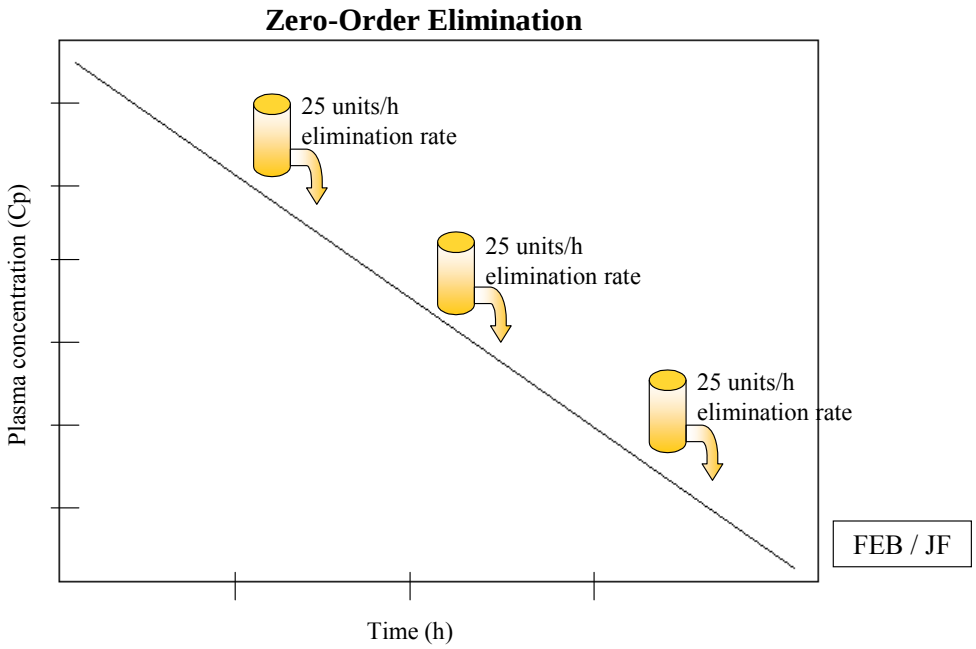
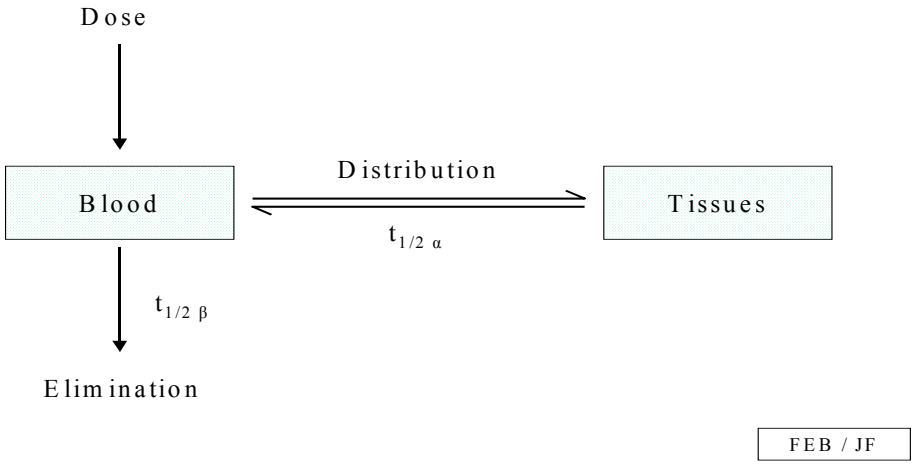


Figure 2. Zero-order kinetics of drug elimination. The rate of elimination is constant and independent of circulating levels of the drug. (less common)

L. PHARMACOKINETIC MODELS

1. Multicomponent distribution

Many drugs undergo an initial distribution phase followed by a slow elimination phase. Mathematically this process can be modeled by means of a two compartment model.



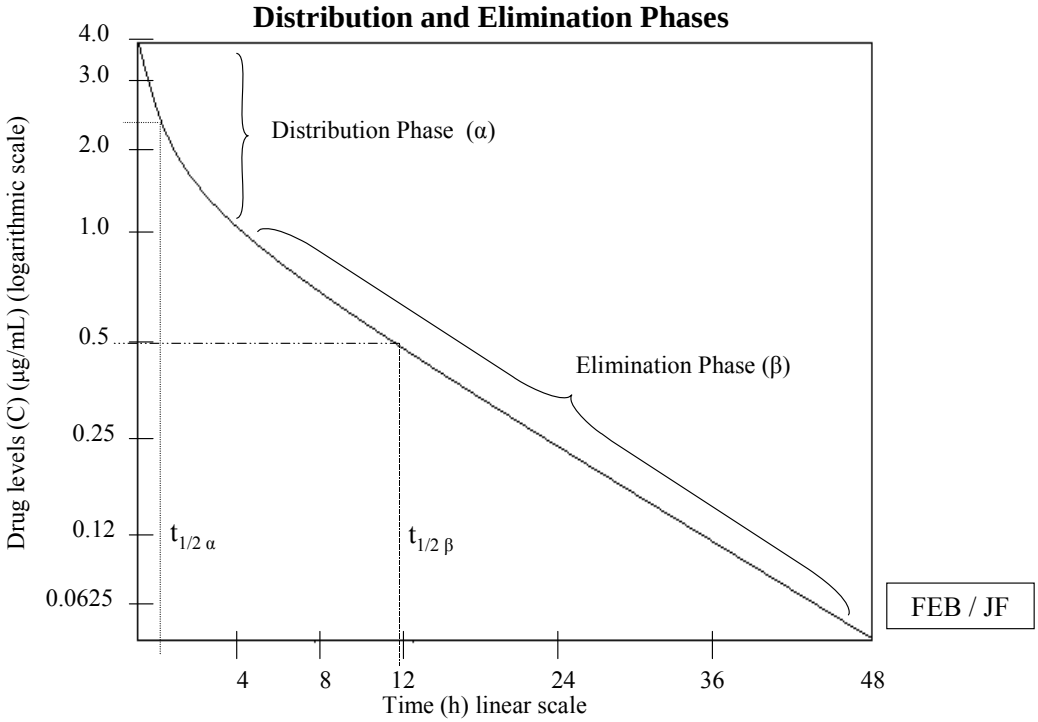


Figure 3. Circulating levels of a drug after an intravenous bolus. The initial curvilinear portion of the data represents the distribution phase (α), whereas the linear portion of the curve represents the elimination phase (β).

2. Single compartment distribution

A few drugs may behave as they are distributed to only one compartment (vascular compartment). Others have more complex distributions that require more than two compartments for construction of accurate models.

M. **RECEPTORS FOR DRUGS**

Drug effects result from their interactions with endogenous macromolecules in the patients that are called receptors. Upon interaction with the receptor, a drug can initiate biophysical and biochemical events leading to the observed drug effects. Drugs can bind to receptors with a variety of different bonds, which include covalent, electrostatic, and weaker bonds (hydrophobic, Van der Waals and hydrophilic).

1. Types of receptors
   a. Type I receptors: plasma membrane
      - Acetylcholine and norepinephrine

   a. Type II receptors: cytoplasm
      - Steroid hormones

   c. Type III receptors: nucleus
      - Anticancer drugs

2. Agonists: is a drug capable of fully activating the effector system when it binds to the receptor.

3. Antagonists: structural similarity to agonist and interact with receptor but does not cause same molecular change in receptor, therefore inhibits interaction of agonist with receptor.

4. Chain of events following a drug – receptor interaction

   Ach + receptor → Na^+ influx → action potential → increased free Ca^{2+} → contraction

   - Depends on particular receptor and particular type of cell.

5. Exceptions to drug actions mediated by specific receptors
   a. Volatile anesthetics
   b. Metal chelating agents
   c. Osmotic diuretics

6. Regulation of receptors
   a. Down-regulation (pharmacodynamic tolerance or desensitization): repeated administration of catecholamines decreasing number of alpha-receptors.
   b. Up-regulation (pharmacodynamic sensitization): thyroid hormone increasing number of beta-receptors in myocardium.

7. Receptor Changes In Diseases
   a. Antibodies to acetylcholine receptors in motor end-plates.
      Clinical application: Myasthenia gravis.
   b. Decreased number of receptors for plasma LDL (low density lipoproteins)
      Clinical application: Familial hypercholesterolemia.

N. DRUG ANTAGONISMS

1. Competitive antagonism: reversible competition for agonist receptor binding sites without inducing a biological response, such as: Naloxone to reverse opioid overdose and flumazenil which is an antidote to benzodiazepines.

2. Non-Competitive antagonism: Irreversible binding with receptor preventing agonist binding to receptor, such as DFP which combines with acetylcholinesterase to prevent acetylcholine from binding to acetylcholinesterase.

O. DRUG NOMENCLATURE

1. Type of drug names
   a. Chemical name: utilizes rules of organic chemistry.
   b. Code name: assigned to drug by pharmaceutical manufacturer.

c. Generic name (nonproprietary name): if drug is admitted to United States Pharmacopoeia, the generic name becomes the official name of drug.
d. Tradename (proprietary name) (trademark) (registered name): a superscript R or TM follows trade name.
1) If drug is marketed by more than one pharmaceutical company, then the same drug may have several trade names but only one official generic name.

2. Use of generic or tradename of a drug
a. Textbooks
b. Lectures, handouts and examinations in this course
c. National Board Examinations (USMLE)
d. Prescription of drugs
1) A pharmacist may substitute a generic drug for a trade name drug unless the physician indicates "no substitution" on the prescription.
2) The physician can indicate the manufacturer for a generic drug.
3) Clinical application: Advantage of generic drugs is saving the patient money. Disadvantage of generic drugs is patient may receive a preparation of drug that is of inferior quality to a trade name drug.
e. Expressions of drug product equivalence related to generic drug substitution
1) Chemical equivalence: related to amount of drug per tablet.
2) Biological equivalence: related to pharmacokinetics involving bioavailability.
3) Therapeutic equivalence: related to clinical response that will provide same efficacy and toxicity (hopefully same lack of toxicity).
Clinical implications: most of the generic drugs are comparable in their safety and efficacy profile with the branded products. Very few exceptions.

P. **DRUG-TESTING AND APPROVAL**

1. Pre-clinical testing and toxicology screen
2. Phase I: 10 normal volunteers receive small doses and observed for efficacy and safety
3. Phase II: Small group of patients with disease and observed for efficacy and safety
4. Phase III: large-scale clinical trial in patients with disease and observed for best dosage for treatment of disease.
5. NDA (New Drug application): If the FDA approves the NDA, then the drug goes on the market for general use.

PHARMACOKINETICS I: ABSORPTION AND DISTRIBUTION

Learning Objectives

By the end of the lecture, you should be able to:

1. Define pharmacokinetics according to the acronym ADME.
2. Discuss the mechanisms (aqueous & lipid diffusion, active transport, etc.) by which drugs are absorbed in the body to reach their sites of action.
3. Describe chemical characteristics of drugs (e.g. solubility, pKa) and other factors (e.g. regional differences in blood flow, transporters, non-specific binding) that influence drug absorption.
4. Compare common routes of drug administration, their uses and their limitations.
5. Explain what is meant by a one-compartment and a two-compartment model of drug distribution and how it affects the plasma drug concentration time course.
6. Explain the concept of Volume of Distribution and the effect of plasma protein binding on drug distribution.
7. Recognize that differential drug distribution can create drug reservoirs that affect the time course and magnitude of drug effect.

Drugs used as examples: digoxin, lidocaine, gentamicin, tobramycin, vancomycin, theophylline, warfarin, heparin, phenytoin, chloroquine lidocaine, procainamide, penicillin G, aspirin, ethyl alcohol, propranolol

Recommended Reading:
The Merck Manual Online
Robert S. Porter, MD, Editor, Justin L. Kaplan, MD, Senior Assistant Editor
http://www.merck.com/mmpe/sec20/ch303/ch303a.html

Goodman & Gilman's Manual of Pharmacology and Therapeutics, Chapter 2
Randa Hilal-Dandan, PhD, Laurence Brunton, PhD, Editors

An Outline of Topics for Review

1. Definition of Pharmacokinetics

2. Significance of pharmacokinetic principles in therapeutics:
   a. Design of rational therapeutic regimens.
   b. The time-course of drug action.
   c. Dose- (and/or plasma concentration-) related efficacy and toxicity. How to adjust dosage to achieve therapeutic efficacy and avoid toxicity.
   d. Significance of the area under the plasma concentration vs. time curve.

3. Factors affecting drug absorption:
   a. membrane permeability.
   b. availability of transport processes (active or passive).
   c. available surface area.
   d. pH and concentration gradients.

4. Routes of administration:

   a. oral
   b. sublingual/buccal
   c. rectal

   } enteral (administration through the digestive tract)

   d. inhalation
   e. topical
   f. transdermal
   g. subcutaneous
   h. intramuscular
   i. intravenous
   j. intrasynovial
   k. intrathecal
   l. vaginal
   m. urethral
   n. ocular
   o. nasal
   p. aural
   q. intra-peritoneal
   r. epidural

   } parenteral (given by routes other than the digestive tract, usually injected)

5. Factors affecting drug distribution:

   a. regional differences in blood flow
   b. tissue mass
   c. transport mechanisms
   d. permeability characteristics
   e. ion-trapping
   f. protein binding

6. One-compartment vs. Two-compartment distribution:

   a. One-compartment: a rapid equilibrium is achieved between plasma and tissue distribution following drug administration. Plasma concentration-time profile declines mono-exponentially.

   b. Two-compartment: rapid distribution to a central compartment is followed by slow distribution to other tissues/binding sites (second compartment). This results in a bi-exponential plasma concentration-time profile. With repetitive administration, steady-state concentrations are achieved only after 5-6 elimination half-lives ($t_{½}$). Digoxin, lidocaine, and phenytoin are examples of drugs that display two-compartment pharmacokinetics.

7. Volume of Distribution (V_d)

   V_d describes how large a blood volume would be required to contain the entire administered dose at the measured concentration of drug in the blood.

8. Drug Reservoirs

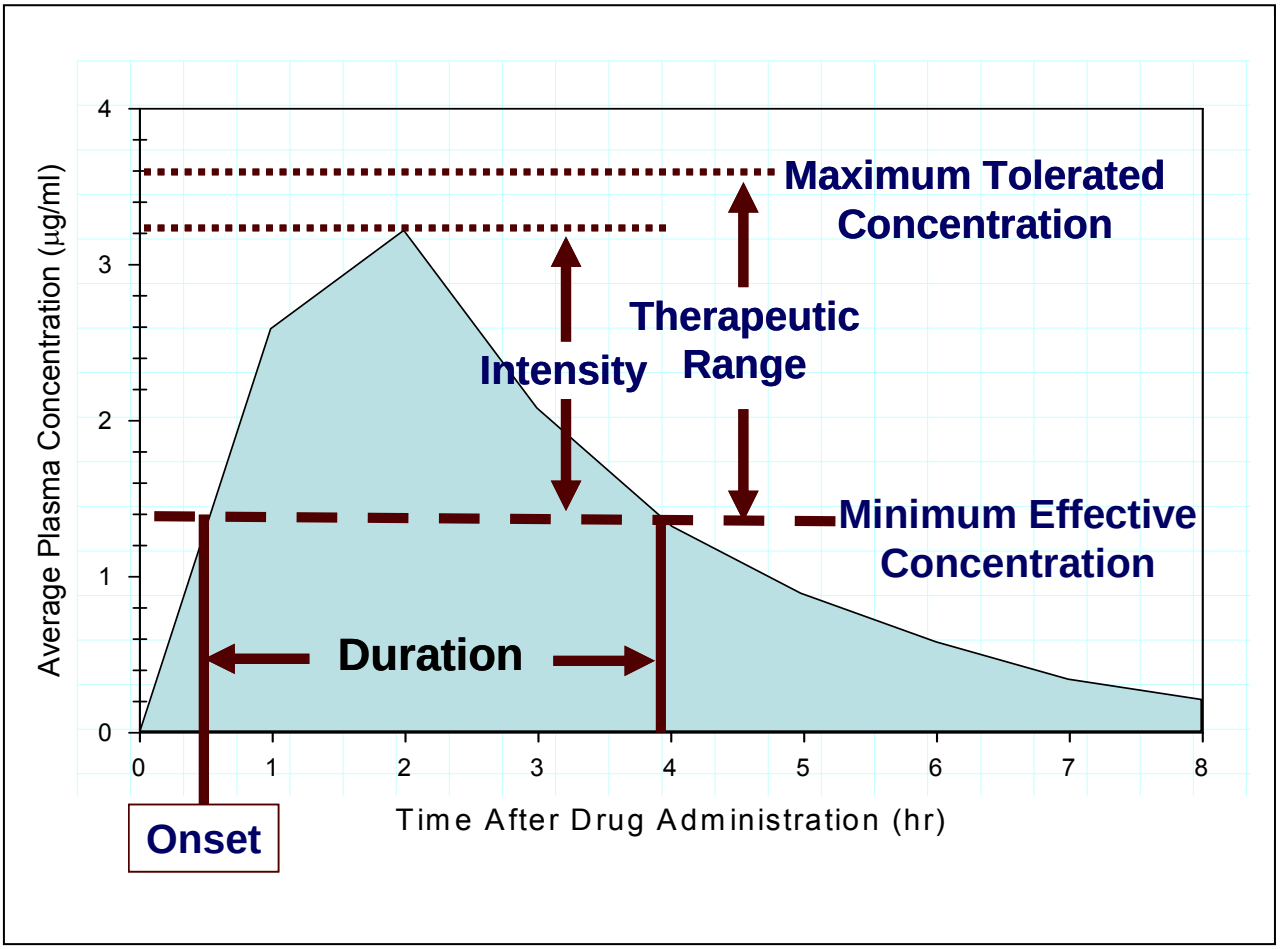
   Accumulation of drugs in tissues (e.g. fat & muscle) can prolong drug action.

DEFINITION OF PHARMACOKINETICS

Pharmacokinetics relates the time courses of a drug's absorption, distribution, and elimination (metabolism & excretion) to the intensity and time course of its pharmacological (therapeutic and/or toxic) effects.

CONSIDERATIONS FOR RATIONAL DESIGN OF A THERAPEUTIC REGIMEN:

- Dose
- Absorption
- First-pass Metabolism
- Volume of Distribution and Elimination clearance
- Area under the curve (AUC)
- Compliance



AREA UNDER THE CURVE (AUC)
Clinical Significance:

$$CL = \frac{\text{DOSE i.v.}}{\text{AUC}} \qquad CL/F = \frac{\text{DOSE p.o.}}{\text{AUC}}$$

- Used to compare amount of drug that reaches the systemic circulation by different routes of administration: determine bioavailability (F).
- Used to compare clearance (CL) of a drug in different individuals after administration of the same dose via the same route.

DRUG ABSORPTION

Definition:
The processes by which drugs move from their site of administration to the plasma.

Processes following oral drug administration:
- disintegration of solids and dissolution of drug in fluids of gastrointestinal tract
- passage of drug across or between cells to reach the systemic circulation.

Factors affecting drug absorption:
- chemical composition of drug and delivery formulation (tablet, capsule, solvent, etc)
- regional differences in blood flow
- transport mechanisms
- permeability characteristics
- ion-trapping
- nonspecific binding

I. Passage of drugs across membranes

A. Aqueous diffusion

1. small molecules (<100 kD mol. weight)
2. passive process

B. Lipid diffusion

1. passive process
2. driven by concentration gradient:
   the greater the difference across the membrane the more rapid the rate of crossing

3. lipid solubility is important

   a. the more lipid soluble the faster the rate of transport

   b. lipid solubility is affected by the degree of ionization

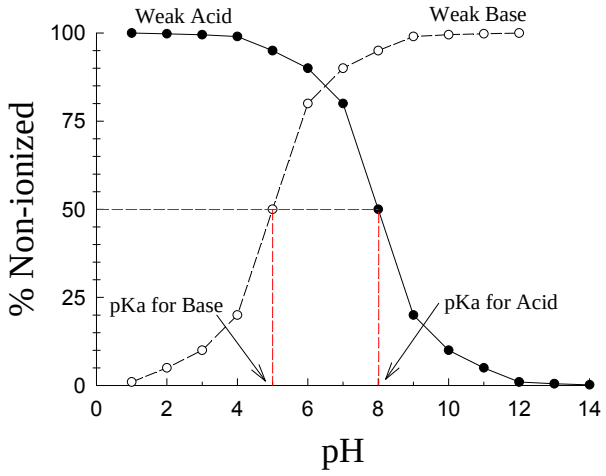
   c. degree of ionization is dependent upon pH

      i. can be determined at a given pH by using the Henderson-Hasselbalch equation

For Acids	For Bases
$pK_a = pH + \log \frac{[AH]}{[A^-]}$	$pK_a = pH + \log \frac{[BH^+]}{[B]}$

ii. this is not a linear relationship

iii. important to remember that the pH at which 50% of the compound is ionized is by definition the pK_a



KLB

Ion trapping:
The concentration of the non-ionized form of a drug will tend to equilibrate across compartments because this form can permeate lipid membranes. However, the fraction of ionized drug described in the Henderson-Hasselbalch relationship will be established within each compartment based on the difference between compartmental pH and drug pK_a. Because the ionized form cannot readily permeate lipid membranes, the drug can become trapped, resulting in a greater concentration in compartments that favor its ionized form. Weak acids become more concentrated in more alkaline compartments; weak bases tend to concentrate in more acidic compartments.

4. surface area:

the greater the surface area the faster the rate of transport

C. Active transport

1. requires expenditure of cellular energy

2. unidirectional

3. structural specificity

D. Minor mechanisms

1. facilitated diffusion

2. pinocytosis

II. Different routes of drug administration

A. Enteral

1. Oral

a. Physical form of drug can be of many types.

b. Local differences in pH affect absorption.

c. Differences in surface area can determine primary sites of absorption.

d. The fraction (F) of the orally administered dose that reaches the systemic circulation in its active form is called its oral **bioavailability**.

A drug may have less than 100% bioavailability if it is incompletely absorbed or if it undergoes metabolism, e.g. while going through the liver via the portal circulation (first-pass metabolism).

Oral bioavailability may be estimated by comparing AUC for the orally administered drug with AUC for the same dose of drug given to the same patient intravenously.

$$F_{oral} = \frac{AUC_{p.o.}}{AUC_{i.v.}}$$

First-pass effect:

Some drugs have such a high rate of metabolism that no drug ever enters the systemic circulation even though it is completely absorbed.

Oral doses may be higher than parenteral doses because of reduced bioavailability (F<1)[1]:

$$Dose_{p.o.} = \frac{Dose_{i.v.}}{F_{oral}}$$

e. Enterohepatic circulation:

Some drugs are absorbed, transported to the liver, and secreted into the bile. They are then deposited back into the intestine and can be reabsorbed.

f. Alterations in gastric emptying time can delay or speed up absorption.

Prolonged times to gastric emptying time will generally result in delayed absorption.

Some drugs can directly affect emptying time.

[1]A similar dosage adjustment is required when a drug is prepared in a formulation that provides a fraction of the total weight of drug as active drug and the remainder as an inactive salt. The fraction of total drug that will be delivered as active drug to the systemic circulation is called the "salt factor" (S). The appropriate dose is determined by dividing the desired dose of active drug by the salt factor.

2. Sublingual/buccal

a. advantages

will not be absorbed into the portal system

a higher pH than found in the stomach

b. disadvantages

drug taste

3. Rectal

a. advantages

50-60% will by-pass the portal vein & avoid first-pass hepatic metabolism

useful in cases of nausea and vomiting

b. disadvantages

discomfort, inconvenience, etc.

B. Inhalation

1. passive diffusion

2. large surface area

3. volatile gases

driven by differences in partial pressures

4. aerosol preparations

site of absorption dependent on particle size

5. drug absorption varies with depth and duration of inspiration

may be necessary to titrate to desired effect or use metered inhaler

C. Topical

1. mostly for non-systemic use

2. highly lipid soluble compounds will reach general circulation

3. common forms include creams, lotions, gels, ointments, shampoos

D. Transdermal

1. passive diffusion of drugs across the skin—driven by concentration gradient

2. potential benefits:

a. controlled release of the drug into the patient—enables a steady blood-level profile

b. user-friendly, convenient, painless, multi-day dosing—improved patient compliance

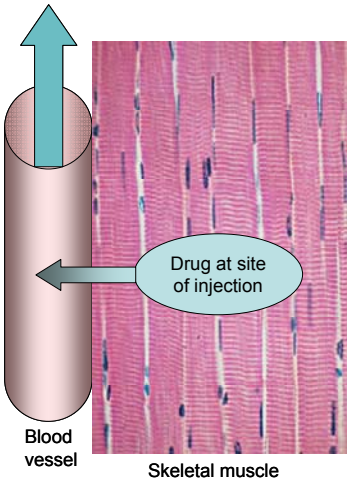
c. bypassing the gastrointestinal (GI) tract obviates GI irritation that occurs with some drugs and avoids partial first-pass inactivation by the liver

3. limitations/risks:

a. skin barrier limits the number of drugs that can be delivered by passive diffusion from an adhesive patch

b. potential skin irritation, discomfort

E. "Parenteral" (not via the digestive tract), often used to describe administration of drugs by injection



importance of blood flow:

Blood flow to the area maintains the concentration gradient (the drug is removed by the circulating blood, so its concentration will remain lower in the local blood vessels than on the tissue side at the site of injection). This helps maintain a steady rate of absorption until the local reservoir at the site of injection becomes depleted.

<u>advantages</u>

greater degree of reliability and precision of administered dose

fewer problems with absorption

do not have to worry about presence or absence of food in the stomach

do not have to worry about "first-pass effect"

disadvantages

sight of the needle

pain

tissue damage and irritation

drug must be in solution form

1. subcutaneous (sc)

a. advantages

i. a slow even absorption

ii. may be used as a depot

iii. rate of absorption can be modified by altering blood flow

b. disadvantages

i. *is of little value in peripheral circulatory failure (shock)*
ii. *only small volumes can be accommodated*

2. intramuscular (im)

a. advantages

i. a more rapid absorption than seen with sc

ii. as with sc administration, rate of absorption can be modified by altering blood flow

b. disadvantages

i. potential infection and/or nerve damage

ii. danger of inadvertent iv administration

3. intravenous (iv)

a. advantages

fastest and most reliable way of achieving a specific blood level

b. disadvantages

to avoid a bolus effect (an excessively high plasma concentration achieved by rapid i.v. drug administration) it may be necessary to administer the dose over a longer period of time

F. Other parenteral:

1. intrasynovial (within the synovial sac of a joint, or the synovial sheath of a tendon)
2. intrathecal (through the theca of the spinal cord into the subarachnoid space)
3. vaginal
4. urethral
5. ocular
6. nasal
7. aural
8. intraperitoneal
9. epidural (into the epidural space of the spinal column)

III. Distribution of absorbed drug

A. Factors influencing distribution

1. regional differences in blood flow

2. tissue mass

3. transport mechanisms

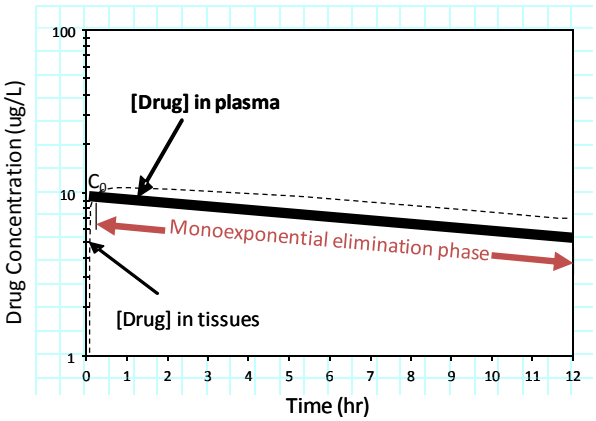
4. permeability characteristics

   some membranes are more resistant to drug passage than others, e.g. blood-brain barrier, blood-testis barrier, and placental barrier

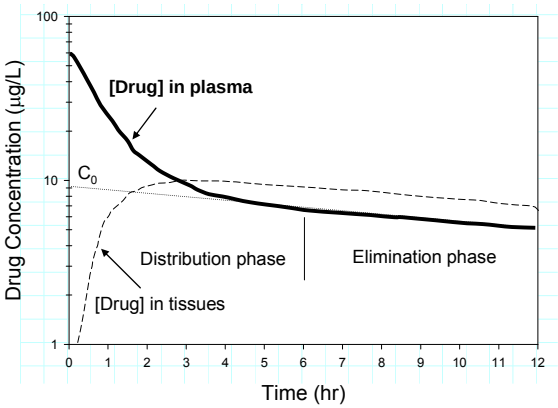
5. ion-trapping

   drug can be trapped in a body compartment due to a local pH differences

6. protein-binding
   - many drugs bind <u>reversibly</u> to plasma proteins.
     - *albumin binds acidic drugs*
     - *α1 acid glycoprotein binds basic drugs*
   - protein-bound drugs are retained in the plasma.



One-compartment Distribution. Plasma (solid line) and tissue (broken line) concentrations after i.v. administration of a loading dose of drug.

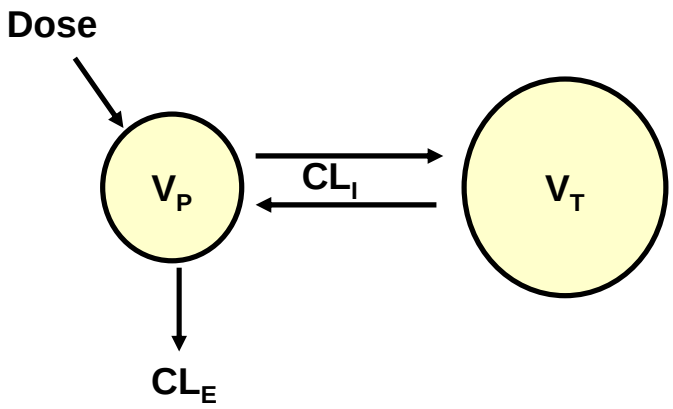


Two-compartment Distribution. Plasma (solid line) and tissue (broken line) concentrations after i.v. administration of a loading dose of drug. C_0 is estimated by back extrapolation (dotted line) of the elimination phase plasma concentrations.

B. One- vs. Two-compartment Distribution

1. One-compartment: a rapid equilibrium is achieved between plasma and tissue distribution following drug administration. Plasma concentration-time profile declines mono-exponentially.

2. Two-compartment: rapid distribution to a volume represented by a central compartment (usually plasma, V_P) is followed by slow distribution to tissues/peripheral binding sites (second compartment; V_T). This results in a bi-exponential plasma concentration-time profile. With repetitive administration, steady-state concentrations are achieved only after 5-6 elimination half-lives ($t_{½}$). Digoxin, lidocaine, and phenytoin are examples of drugs that display two-compartment pharmacokinetics.



SCHEMATIC ILLUSTRATION OF TWO-COMPARTMENT DISTRIBUTION
CL_I = inter-compartmental clearance; CL_E = clearance of elimination. During the distribution phase, the drug is cleared from the plasma by both inter-compartmental distribution (bi-directional) and by elimination (uni-directional). As the plasma concentration decreases and the tissue concentration increases, the net inter-compartmental clearance approaches zero. When net inter-compartmental clearance is zero, this marks the end of the distribution phase, but the plasma concentration continues to decrease because of clearance of elimination (a mono-exponential process for most drugs—a linear concentration time course when plotted on a logarithmic y-axis scale).

C. Volume of distribution

1. When a drug is administered it distributes to various body compartments.

2. Volume of distribution (V_d) is a measure of how much of the administered dose distributes outside of the plasma.

3. V_d describes how large a blood volume would be required to contain the entire administered dose at the concentration of drug in the plasma at time t=0 (C_0).

$$V_d = \frac{\text{Dose}}{C_0}$$

If you administer a dose D of a drug, the initial

plasma concentration (C_0) of the drug depends on the volume into which the drug distributes:

$$C_0 = \frac{D}{V_d}$$

The volume of distribution (V_d) quantifies that by specifying how large a volume would be needed in order to observe the plasma concentration actually measured.

For example, consider a case in which D = 6 mg/kg. A human has a plasma volume (V_{plasma}) of around 0.06 l/kg. This gives a C_0 = 100 mg/liter if the drug stays in the blood stream only, and thus its volume of distribution is the same as V_{plasma}, that is V_d = 0.06 l/kg. If the drug distributes into total body water, the volume of distribution would increase tenfold, to approximately 0.6 l/kg.

If the drug readily diffuses into the body fat the volume of distribution may increase dramatically. An example is chloroquine, which has a V_d = 200-300 l/kg.

In the case of one-compartment distribution, the volume of distribution is defined as: $V_d = D/C_0$, where C_0 is the measured plasma concentration immediately after the drug is administered. In the two-compartment case, C_0 is an extrapolated concentration at time = 0, extrapolated from the linear portion of the log plasma concentration vs. time plot.

Drug	V_d	Comments
Heparin	0.05-0.1 l/kg	Reflects a high degree of plasma protein binding.
Theophylline, Ethanol	0.4-0.9 l/kg	Reflects distribution in total body water.
Chloroquine	200-300 l/kg	Highly lipophilic drug that distributes into total body fat.

NOTE: The apparent Volume of Distribution is a theoretical number that may not correspond to an actual physiological space. Actual physiological volumes into which drugs distribute are often much smaller.

A drug which passes through cell membranes, is not bound to any tissue constituent or taken up into any particular cells (i.e. it is evenly distributed in total body water) would have a V_d = 0.6 L/kg (42 L/70 kg).

A drug which passes through capillary endothelium but not through cell membranes, and is not protein-bound or extremely lipid soluble may only be distributed in extracellular fluid and have a V_d = 0.14-0.2 L/kg (10-15 L/70 kg).

A drug which is tightly bound to plasma protein, would have a V_d equivalent to that of plasma water, V_d = 0.06 L/Kg (4 L/70 kg).

Protein binding affects the apparent Volume of Distribution

An increase in the unbound fraction of total [drug] (e.g. in hypoalbuminemia) will result in an increase in the apparent volume of distribution (V_d).

$$V_d = V_P + \left[V_T \times \frac{\text{fraction unbound in plasma}}{\text{fraction unbound in tissues}} \right]$$

where V_d = volume of distribution, V_P and V_T are plasma and tissue volumes, respectively. Note: V_T and fraction unbound in tissues (fu_T) cannot be determined easily. A reasonable approximation of V_T can be made by estimating tissue water volume (V_{TW}). For a 70 kg man, V_{TW} = total body water- plasma water ≈ 42L - 4L = 38L

For example, consider a drug that is 90% bound to plasma albumin (10% unbound in the plasma). If the volume of distribution under these conditions is **14L**, the value of V_T divided by fu_T will be 100L (assume V_P = 4L). Assuming no other parameters change, a drop in plasma [albumin] that decreases the fraction of bound drug to 80% (20% unbound in plasma) will increase V_d to **≈24L**:

$V_d = V_P + [(V_T/fu_T) \times fu]$

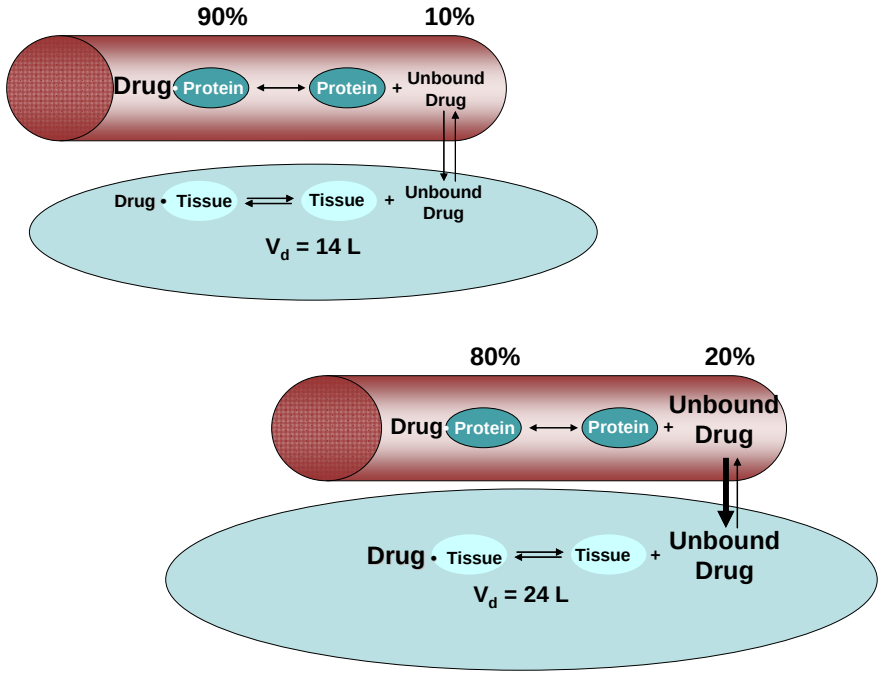
14L = 4L + $[(V_T/fu_T) \times 0.1)]$

10L = $[(V_T/fu_T) \times 0.1)]$

(V_T/fu_T) = 100L

$V_d = V_P + [(V_T/fu_T) \times fu]$

= 4L + (100L x 0.2) = 24L



D. Drug Reservoirs

- Following absorption, drugs in the systemic circulation are distributed to peripheral tissues.
- Distribution is bi-phasic: an initial distribution to organs with rich blood supply (kidney, liver, heart, lungs, brain), followed by distribution to other tissues with less rich blood supply (fat, muscles, bone, bladder).
- Different drugs distribute differently. For example, the anesthetic thiopental, a highly fat-soluble drug, rapidly enters the brain, but the antibiotic penicillin, a water-soluble drug, does not. Fat-soluble drugs such as thiopental tend to concentrate in adipose tissue. Bone can accumulate environmental toxins such as lead or drugs such as tetracycline antibiotics. Some drugs have a very narrow distribution profile, because specific tissues have a particularly high affinity for the drug (for example, iodine concentrates mainly in the thyroid gland).
- Fat and muscle in particular can act as **drug reservoirs**. Ultimately large amounts of a drug can accumulate in these tissue reservoirs, especially in obese patients. In some cases more drug may be stored in these tissues than remains in the systemic circulation.
- Deposition into any reservoir limits the fraction of the drug available for diffusion from the plasma to site of action as well as to sites of excretion (or metabolism).
- When plasma levels of the drug decline due to metabolism or excretion, they are replenished by diffusion from the reservoir. Gradual release of drug from these sites can prolong the therapeutic effect or result in toxicity if drug administration is continued.
- A reservoir may need to be saturated with the drug before a therapeutic effect is manifest. In this case a large dose may be needed to provide an effective concentration at the site of action of the drug.
- Plasma proteins can also serve as a drug reservoir. For a highly protein-bound drug, a large fraction of administered drug may be retained in the plasma because only the unbound drug molecules can cross cell membranes. In its protein-bound state the drug may not be distributed to its site of action. When the drug dissociates from plasma protein (the dissociation rate will depend primarily on its affinity for the protein) it will then be free to distribute to exert its effects.
- Many different drugs bind to sites on plasma albumin, so competition can occur between them. Theoretically, administration of drug B can reduce the protein binding, and hence increase the free plasma concentration of drug A. To do this, drug B needs to occupy an appreciable fraction of the protein binding sites. Few therapeutic drugs affect the binding of other drugs to albumin because they occupy, at therapeutic plasma concentrations, only a tiny fraction of the available sites. Sulfonamides are an exception because they occupy about 50% of the binding sites at therapeutic concentrations and so can cause unexpected effects by displacing other drugs.

PHARMACOKINETICS II: DRUG ELIMINATION & MULTIPLE DOSING

Learning Objectives

By the end of the lecture, you should be able to:

1. Explain the difference between first-order, zero-order and dose-dependent kinetics of drug elimination.
2. List examples of commonly used drugs that follow zero-order, first-order and dose-dependent kinetics.
3. Recognize the importance of steady-state plasma drug concentrations for maintenance therapy and describe the time course for achieving steady state with intermittent dosing or continuous infusion.
4. List the primary pharmacokinetic parameters and describe how they are used to determine appropriate loading dose and maintenance dose.
5. Interpret the effects of altered distribution or clearance of drugs on plasma drug concentrations and formulate an appropriately adjusted dosing strategy.
6. Discuss the roles of the kidney and liver in the elimination of drugs from the body.

Recommended Reading:

The Merck Manual Online
http://www.merck.com/mmpe/sec20/ch303/ch303a.html

Goodman & Gilman's Manual of Pharmacology and Therapeutics, Chapter 2
Randa Hilal-Dandan, PhD, Laurence Brunton, PhD, Editors

An Outline of Topics for Review

1. Review the plasma concentration versus time curve.
   a. Distribution phase.
   b. Elimination phase.

2. Review the apparent volume of distribution (V_d).
   a. The dilution principle
   b. Why is V_d larger than anatomically possible (for some drugs)?

3. The loading dose.
   a. Definition
   b. Rationale
   c. Dependence on V_d

4. The maintenance dose.
   a. Definition
   b. Rationale
   c. Dependence on CL_E

5. The concept of steady-state.
   a. The plateau principle.
   b. Dependence of eventual steady-state levels on the maintenance dose and not on the loading dose.

6. Drug administration by continuous infusion.
   Estimation of clearance from the infusion rate and the steady-state plasma concentration ($CL = I / C_{ss}$).

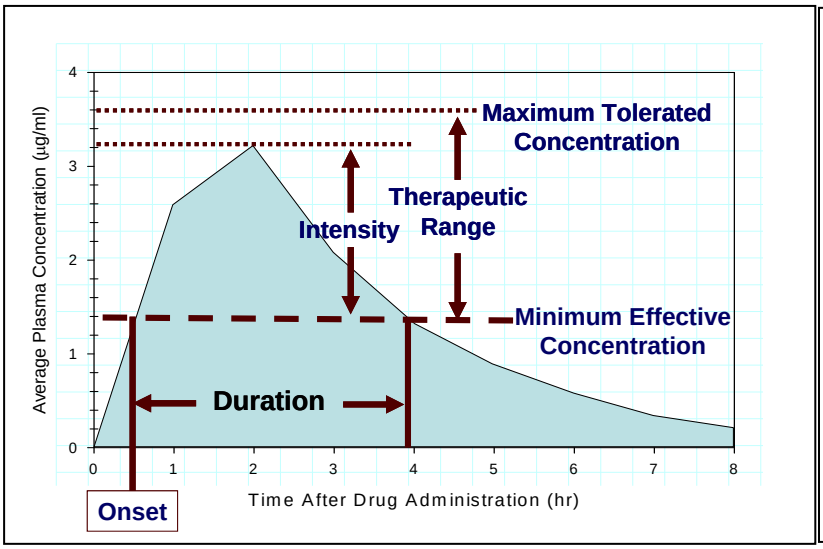
7. Kinetics of drug elimination.
   a. First-order kinetics.
   b. Zero-order kinetics.
   c. Dose-dependent kinetics.
   d. Examples of drugs that are eliminated by these types of kinetics.

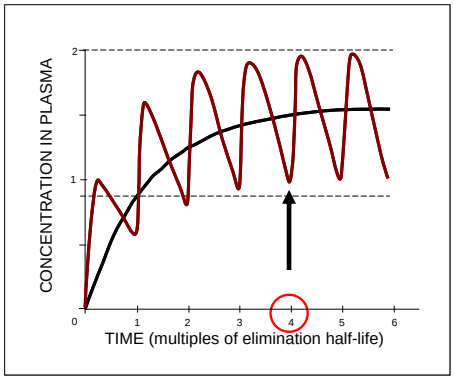
8. Elimination clearance (CL_E).
   a. Definition.
   b. The relationship of k and $t_{½}$ to clearance.

9. Elimination half-life: Clearance and Volume of Distribution as primary pharmacokinetic parameters
   a. k a dependent parameter ($k = Cl/V_d$)
   b. $t_{½}$ a dependent parameter ($t_{½} = 0.69\ V_d/CL$)

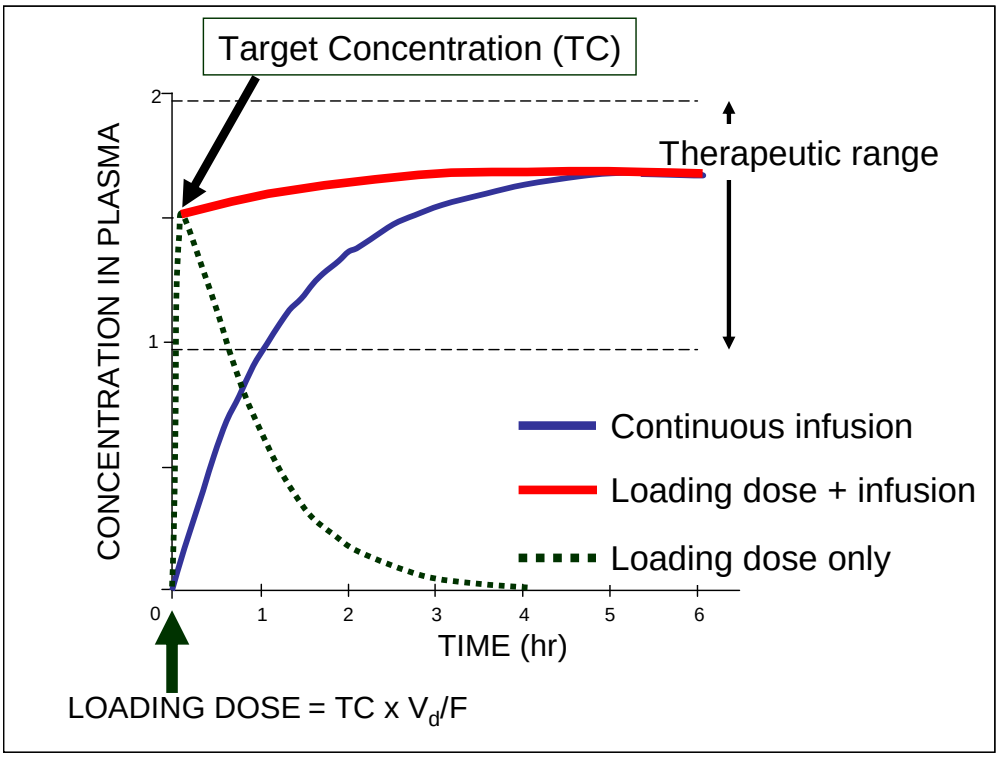
10. Renal Insufficiency.
    a. Affects on Clearance
    b. Adjustment of dosing rate.

11. Hepatic Clearance.
    a. Determinants: hepatic blood flow, protein binding, intrinsic clearance.
    b. Restrictive hepatic clearance ($CL_H = f \bullet CL_{int}$).
    c. Non-restrictive hepatic clearance ($CL_H = Q$).





REPETITIVE DOSING: IT TAKES ~4 ELIMINATION HALF-LIVES TO REACH STEADY-STATE.



A LOADING DOSE MORE RAPIDLY ACHIEVES A THERAPEUTIC DRUG LEVEL. Loading dose is dependent on the Volume of Distribution.

$LD = TC \times V_d/F$
LD = Loading Dose (e.g. in mg)
V_d = Volume of Distribution (e.g. in L)
TC = Target Concentration (e.g. in mg/L)
F = Bioavailability

MAINTENANCE DOSING

- Dosing strategy to maintain a steady-state concentration of drug in the body.
- Dose is based on replacing the amount of drug cleared from the body since the previous drug administration.

$MD = CL \times TC \times T/F$
MD = Maintenance Dose (e.g. in mg)
CL = Clearance (e.g. in L/hr)
TC = Target Concentration (e.g. in mg/L)
T = Dosing interval (e.g. in hr)
F = Bioavailability

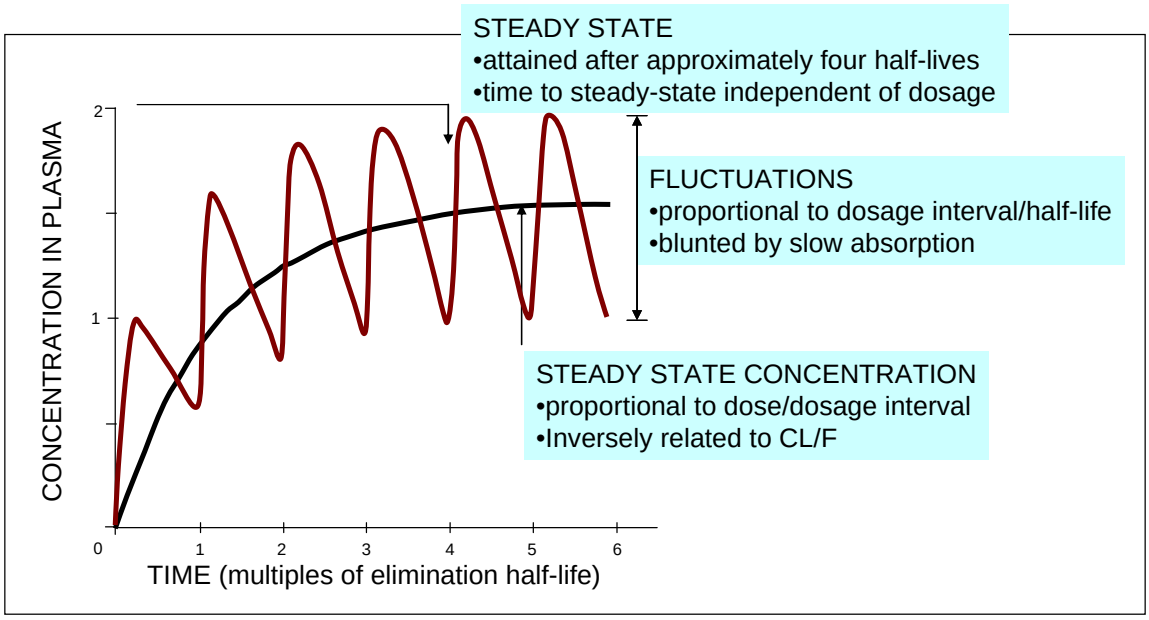
- Clearance is the primary determinant for calculating the maintenance dose.

STEADY-STATE CONCENTRATION

- A function of dosing rate and elimination clearance
- Rate of drug administration = rate of drug elimination
- Continuous I-V infusion:
  - Steady-state attained after approximately four elimination half-lives

$$C_{ss} = \frac{\text{Dosing Rate}}{\text{Clearance}} \cdot F$$

Infusion rate = $CL \times C_{ss}$

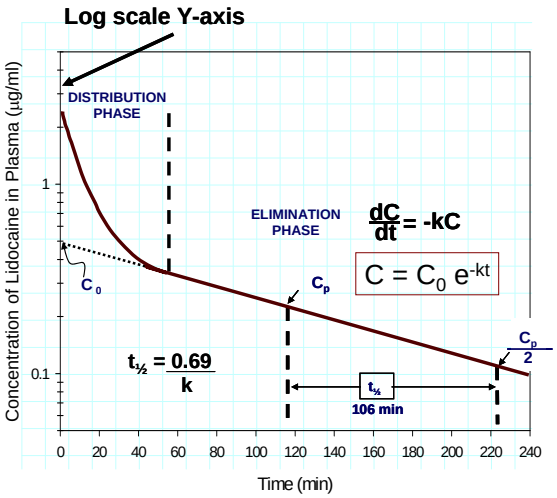


- Time to steady-state independent of dosage

KINETICS OF DRUG ELIMINATION

FIRST-ORDER KINETICS OF DRUG ELIMINATION

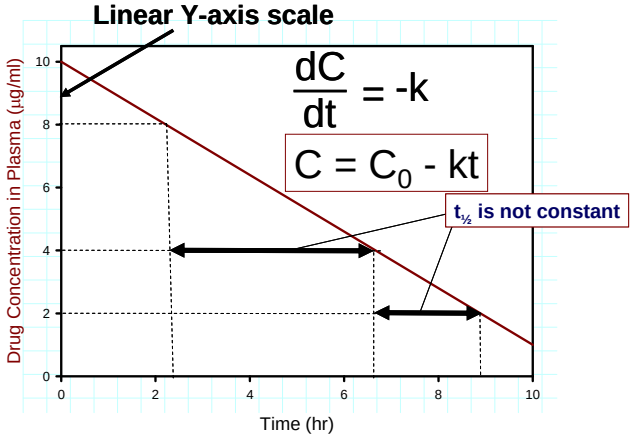
- 1st-order elimination (or kinetics): the elimination rate of the drug is a constant fraction of the drug remaining in the body per unit of time (rather than a constant amount of drug per unit of time).
- Elimination half-life ($t_{½}$) is constant.
- Most drugs used clinically obey 1st order kinetics.



First-order Elimination of Lidocaine

ZERO-ORDER KINETICS OF DRUG ELIMINATION

- Drugs that are eliminated primarily by metabolism may display zero-order kinetics of elimination.
- When metabolic pathways are saturated, metabolism occurs at a fixed rate, i.e. it does not change in proportion to drug concentration.



ZERO-ORDER ELIMINATION

- A fixed amount of drug is metabolized per unit time (zero-order kinetics).

DOSE-DEPENDENT KINETICS OF DRUG ELIMINATION

- When a drug's elimination is mediated predominantly by metabolism, its elimination will tend to follow first-order kinetics when concentrations are well below the K_M of the metabolic enzymes, but will follow zero-order kinetics at doses that greatly exceed the K_M of the metabolic enzymes.
- Common examples include phenytoin, ethanol, and aspirin.

DOSE-DEPENDENT ELIMINATION RATE

$$\frac{dC}{dt} = -\frac{V_{MAX} \cdot C}{K_M + C}$$

ELIMINATION CLEARANCE

- Volume of plasma cleared of drug per unit time. Units are ml/min or L/hr ("flow").
- Drug elimination may occur through the kidneys, the liver, the lung, and other organs.
- Total Clearance is equal to the sum of all these individual and simultaneously occurring organ clearances:

  $CL_{total} = CL_{renal} + CL_{hepatic} + CL_{other}$

ELIMINATION HALF-LIFE

Time to eliminate 50% of the body content of the drug—it is dependent on both Clearance and Volume of Distribution.

$$t_{1/2} = \frac{0.69\ V_d}{CL} = \frac{0.69}{k}$$

RENAL FAILURE

- Impaired renal function often results in reduced clearance of drugs that are eliminated primarily by the kidneys.

$$\text{Dosing Rate}_{RF} = \text{Dosing Rate}_{Normal} \times \frac{CL_{RF}}{CL_N}$$

- Dosing rate must be reduced by the ratio of measured clearance in renal failure (CL_{RF}) to expected normal, average clearance (CL_N).
- The dosing rate may be reduced by decreasing the dose, increasing the dosing interval, or both.
- Creatinine clearance (CrCL), estimated using the Cockcoft & Gault equation, can provide an assessment of renal function. The ratio of CrCL in renal failure to CrCL in a patient with normal renal function* can also be used to adjust the dosing rate. **Creatinine clearance is not the same as clearance of a drug.**

Cockcroft & Gault Eq:

$$\text{CrCL (ml/min)} = \frac{(140 - \text{age}) \times \text{wt (kg)}}{72 \times [\text{serum Cr}]\ (\text{mg/dL})} \times \underbrace{\text{if female}}_{0.85}$$

*Ranges are approximately 88–128 mL/min for healthy women and 97–137 ml/min for healthy men.

HEPATIC CLEARANCE

Determined by:

1. Hepatic Blood Flow (rate of drug delivery to the eliminating organ).
2. Plasma Protein Binding (fraction of drug available for clearance).
3. Intrinsic Clearance (hepatocellular metabolism and/or biliary excretion).

1. RESTRICTIVE HEPATIC CLEARANCE

- Drugs with low hepatic extraction ($Q >> f \cdot CL_{int}$)
- Little "first pass metabolism" when given orally.
- A change in binding or drug metabolism/excretion activity will have a greater effect on hepatic clearance than changes in liver blood flow. Capacity-limited clearance.
- Examples: warfarin, phenytoin

The Rowland's Equation:

$$CL_H = Q \left[\frac{f \cdot CL_{int}}{Q + f \cdot CL_{int}} \right]$$

Q = Liver blood flow
f = Free Fraction (unbound)
CL_{int} = Intrinsic Clearance

$$\boxed{CL_H = f \cdot CL_{int}}$$

2. NON-RESTRICTIVE HEPATIC CLEARANCE

- Drugs with high hepatic extraction ($Q << f \cdot CL_{int}$)—extensive first pass metabolism.
- Hepatic clearance is sensitive to changes in liver blood flow and less sensitive to alterations in binding or intrinsic clearance. Flow-dependent clearance: conditions that reduce hepatic blood flow (CHF, hypotension) will reduce hepatic clearance.
- Examples: lidocaine, propranolol

$$\boxed{CL_H = Q}$$

BASIC CONCEPTS IN PHARMACOKINETICS

Pharmacodynamics: A major subdivision of pharmacology dealing with the actions and the mechanisms of action of drugs (i.e., the concepts of drug-receptor interactions and the dose-response relationship are studied under pharmacodynamics).

Pharmacokinetics: The other major subdivision of pharmacology, dealing with the quantitative description of absorption, distribution, metabolism and elimination of drugs (i.e., pharmacokinetics provides the scientific basis for dose selection and also deals with the time-course of drug action).

Bioavailability: For drugs given orally, it is defined as the fraction of the administered dose that reaches the systemic circulation unchanged. A drug may have incomplete bioavailability (less than 100%) if it is incompletely absorbed or if it undergoes metabolism while going through the liver via the portal circulation (first-pass metabolism). Some drugs have high bioavailability (e.g., 90-100% of a dose of warfarin, phenytoin, theophylline or digitoxin will reach the systemic circulation unchanged after oral administration). Other drugs will undergo extensive first-pass metabolism in the liver and will have a low bioavailability when given orally (e.g., about 30-35% of a dose of lidocaine or propranolol will reach the systemic circulation unchanged after oral administration).

Apparent Volume of Distribution: A primary pharmacokinetic parameter used to relate the dose administered to the resulting plasma concentration of drug. This parameter is calculated in reference to plasma concentration of drug, and may be large or small (sometimes much larger than anatomically possible), depending on the tissue:plasma partition ratio for the drug in question (e.g. the apparent volume of distribution for digoxin is of the order of 9.8 liters/kg body weight, which in a 70 kg individual would amount to a total apparent volume of distribution of 686 liters, reflecting the much higher affinity of digoxin for tissues than for plasma). Knowledge of the apparent volume of distribution is important for the appropriate calculation of loading doses. The apparent volume of distribution is also a primary determinant of the drug's elimination half-life ($t_{½}$).

Apparent Volume of Distribution (V_d) = Loading Dose/C_o (initial concentration)

When given intravenously, drugs distribute at different rates from the intravascular compartment to the peripheral target tissues. For example, plasma lidocaine is in equilibrium with tissue lidocaine in 30-60 minutes, whereas other drugs distribute more slowly (e.g. plasma digoxin does not reach equilibrium with tissue digoxin for at least 6-8 hours after an i.v. dose). This is relevant to the proper interpretation of plasma concentrations of drugs. For drugs that distribute slowly, the elimination phase of the plasma concentration vs. time plot should be extrapolated back to the zero time axis to determine C_0 for V_d calculations.

Clearance: The other primary pharmacokinetic parameter, clearance determines the rate of drug elimination. Just as, for example, creatinine clearance, the clearance of a drug may be defined as the volume of plasma that is cleared of drug per unit time. Some drugs undergo only renal clearance (e.g. gentamicin, tobramycin, vancomycin), some are eliminated only via hepatic clearance (e.g. theophylline, warfarin, phenytoin, lidocaine), and others undergo both renal and hepatic clearance (e.g. digoxin, procainamide, penicillin G). The term nonrenal clearance is often used to include hepatic clearance and any other extrarenal route of clearance for a drug. Renal and nonrenal clearances are additive, such that:

Clearance of elimination = Renal clearance + Nonrenal clearance

Clearance of elimination is another major determinant of a drug's elimination half-life ($t_{½}$).

Elimination Half-Life ($t_{½}$): This concept is applicable to drugs that follow first-order kinetics of elimination. It is defined as the time required to eliminate one-half (50%) of the body content of a drug. It is important to note that elimination half-life is dependent on both the apparent volume of distribution and the clearance of elimination, according to the following relationship:

$$t_{½} = \frac{0.69 \times \text{Apparent Volume of Distribution}}{\text{Clearance of Elimination}}$$

Volume of distribution and clearance are the primary parameters and are biologically independent of each other. Thus, half-life could change if either or both volume of distribution and clearance change. Consequently, $t_{½}$ reflects rate of drug clearance only when volume of distribution is constant (congestive heart failure appears to reduce both the apparent volume of distribution and the clearance of lidocaine, so that the $t_{½}$ of this drug may appear normal and may be misleading in the choice of the proper infusion rate; the reduced volume of distribution also requires a reduction in the loading doses).

Steady-State Concentrations: With continuous drug administration (maintenance therapy) by either constant rate i.v. infusion or constant oral dosing rate (e.g., lidocaine infused at a rate of 2 mg/min i.v., or digoxin given orally at a dosing rate of 0.25 mg/day), most drugs will accumulate exponentially until a plateau or steady-state concentration is reached. With dosing at a constant interval, concentrations will fluctuate above and below the steady-state concentration. Once steady-state has been achieved (the rate of drug administration is equal to the rate of drug elimination), the following relationship applies:

$$\text{Steady-State Concentration} = \frac{\text{Dosing Rate}}{\text{Elimination Clearance}}$$

Thus, there is a directly proportional relationship between the dosing rate and the steady-state plasma concentration. This is true for most drugs used in clinical medicine, since most drugs follow **first-order kinetics** of elimination (the rate of drug elimination is proportional to the amount of drug present in the body).

Some drugs like phenytoin, aspirin and ethyl alcohol are exceptions to the rule in that they follow **dose-dependent kinetics** of elimination. At low doses and plasma concentrations, they follow apparent first-order kinetics, but at higher doses and plasma concentrations the metabolic

pathways become saturated and the drugs exhibit zero-order kinetics of elimination (a constant amount of drug is eliminated per unit time; drug metabolism is capacity-limited and is not proportional to the amount of drug present in the body). Thus, changes in the dosing rate may result in disproportionate, non-linear changes in drug concentrations, and toxicity may develop.

With first-order kinetics, if the dosing rate is doubled, the steady-state concentration will double. With dose-dependent kinetics, doubling the dose may result in tripling or quadrupling the steady-state concentration, with the attendant risk of toxicity.

Maintenance Dosing: Maintenance dosing is a regimen whereby a drug is administered at regular intervals (or continuously infused) to achieve a steady-state plasma concentration. Once steady-state is achieved, the maintenance dose matches the amount of drug cleared since the previous dose was administered (or the infusion rate matches the rate of elimination). Maintenance dosing is therefore dependent on the clearance of elimination according to the formula:

$MD = CL \times TC \times T/F$

where MD = maintenance dose (e.g. in mg), CL = clearance of elimination (units of flow, e.g. L/hr), TC = target concentration (at steady-state; units of concentration, e.g. mg/L), T = interval (units of time, e.g. hr), and F = bioavailability.

An alternative representation of this relationship is that the maintenance dosing rate (dose/interval) equals the product of clearance and target concentration:

F x MD rate (mg/hr) = CL x TC = infusion rate (for continuous i.v. administration)

The time to reach the steady-state target concentration is approximately 4-6 elimination half-lives. At steady-state the plasma concentration can be adjusted by a proportional change in maintenance dose (if the clearance and interval are constant and assuming first-order kinetics of elimination). For example, doubling the maintenance dose would double the plasma concentration (but it would take 4-6 elimination half-lives to achieve the new steady-state).

When the drug is administered at regularly spaced intervals, the plasma concentrations will fluctuate above and below the steady-state concentration. The magnitude of the fluctuations will be directly proportional to the ratio of interval to the elimination half-life.

In some cases, a **loading dose** may be given to more rapidly achieve a therapeutic plasma concentration. The loading dose is dependent on volume of distribution rather than clearance and is intended to rapidly achieve a specific concentration of drug:

$LD = V_d \times TC/F$

where LD = loading dose (e.g. in mg), V_d = volume of distribution (e.g. in L), TC = target concentration (e.g. in mg/L), and F = bioavailability.

If drug levels are measured and found to be inadequate, a new target concentration can be rapidly achieved using an adjusted loading dose formula:

$LD = V_d \times (TC - C_{measured})/F$

There is no interval specified in the loading dose formula because it does not take into account the clearance of elimination. Therefore the loading dose formula cannot strictly be used to specify a maintenance dosing regimen—the time it takes for the concentration to decline from the calculated target concentration is not figured into the equation. A maintenance dosing regimen, based on the clearance of elimination, is normally initiated at its specified dosing interval (T) after the loading dose.

Time to Reach Steady-State: With continuous or repetitive drug administration, it is useful to know that 90% of the eventual steady-state concentrations will be achieved in a time equal to 3.3 elimination half-lives ($t_{0.90} = 3.3\ t_{½}$). The longer the $t_{½}$, the longer it will take to reach steady-state.

If the clearance of a drug is decreased and the $t_{½}$ prolonged, for example, due to renal or hepatic disease, it will take longer to achieve steady-state concentrations, in proportion to the increase in $t_{½}$. Note that we are talking about the time required to reach steady-state, not the actual steady-state concentration that will be reached. The actual steady-state concentration will be a function of the dosing rate (i.e. mg/min, mg/day, etc.) and the elimination clearance (see above).

Drug	Use	Some pharmacokinetic characteristics
aspirin	Analgesic, antipyretic, anti-inflammatory.	Approximates zero order kinetics of elimination at high concentrations.
digoxin	Atrial fibrillation, atrial flutter and congestive heart failure	Narrow therapeutic index, large Volume of Distribution (V_d), high bioavailability, two-compartment distribution profile.
ethyl alcohol	Makes you drunk.	Concentration-dependent kinetics of elimination; zero-order at high concentrations.
gentamicin tobramycin	Aminoglycoside antibiotics, used to treat many types of bacterial infections, particularly Gram-negative bacterial infections	Cleared exclusively by the kidney, both can be highly nephrotoxic, particularly if multiple doses accumulate over a course of treatment—usually dosed by body weight and serum levels are monitored during treatment. Tobramycin does not pass the gastro-intestinal tract, so for systemic use it can only be given intravenously or intramuscularly.
lidocaine	Local anesthetic and antiarrhythmic	Low bioavailability (extensive first-pass metabolism in the liver). Lidocaine hydrochloride is available in various forms including: injectable (for i.v. injection/infusion or as local anesthetic), dermal patch, nasal instillation/spray, oral (gel, liquid), topical (gel, liquid, or patch). Eliminated primarily by metabolism in the liver. Two-compartment distribution profile.
penicillin G	Antibiotic used in the prophylaxis and treatment of infections caused by Gram-positive bacteria.	Elimination rate is dependent on renal function and is greatly reduced in renal failure: $t_{½}$ can increase as much as 20-fold.
phenytoin	Antiepileptic—acts by stabilizing the inactive state of voltage gated sodium channels.	Approximates zero-order kinetics of elimination at therapeutic concentrations. High bioavailability. Eliminated primarily by metabolism in the liver. Highly protein-bound.
propranolol	β-blocker, mainly used in the treatment of hypertension.	Extensive first-pass metabolism (low bioavailability), lipid soluble, large V_d.
theophylline	A methylxanthine drug used in therapy for respiratory diseases such as COPD or asthma	Theophylline has a narrow therapeutic index. It approaches zero-order kinetics of elimination at high concentrations. High bioavailability. Eliminated primarily by metabolism in the liver.
vancomycin	A glycopeptide antibiotic used in the prophylaxis and treatment of infections caused by Gram-positive bacteria.	Vancomycin must be given intravenously, because it is not absorbed orally (it is a large hydrophilic molecule which partitions poorly across the gastrointestinal mucosa). It is eliminated by the kidney.
warfarin	Anticoagulant	Warfarin has a long half life. It may be given orally once per day, but it is highly protein-bound and often takes several days to reach therapeutic effect. High bioavailability. Eliminated primarily by metabolism in the liver.

#5 - Clinical Pharmacokinetics: Individualizing Therapy

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Learning Objectives:

Upon completion of this lecture, the student should be able to:

1. Describe how patients' characteristics can influence the four basic pharmacokinetic parameters of medications (Absorption, Distribution, Metabolism, and Elimination).
2. List factors involved in individualizing a dosing regimen and describe how deviations from standards can be anticipated.
3. Describe how drug interactions can be associated with pharmacokinetics and pharmacodynamics.
4. Apply the information presented in lecture to describe which pharmacokinetic parameter is impacted when given a medication nonspecific drug interaction scenario.

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Definitions:
Pharmacokinetics: How the body affects a drug.
Pharmacodynamics: How the drug affects the body.

I. Pharmacokinetic Principles

A Four main principles are associated with every pharmacological agent (see section I C).
- a. Familiarity with these principles for each medication is essential to ensure accurate patient dosing (HINT: memorize general rules with *exceptions* for specific drugs).
- b. Assess your patient (use your eyes!) and use available information.
  - (i) Physical
  - (ii) Laboratory
  - (iii) Radiological
  - (iv) Overall clinical response

B These principles provide a basis for "usual" doses but deviations occur within patients.

C Four pharmacokinetic principles:
- a. Absorption (A)
  - (i) How the drug gets into the body from the site of administration
    - (a) Bioavailability (F): Fraction of administered drug that reaches the systemic circulation
      - (i) Intravenous: F = 100%
    - (b) PKa and PKb
      - (i) Ionized versus nonionized form
      - (ii) Nonionized (non protonated) forms distribute more readily
      - (iii) pH of environment
        1. Certain drugs require and acidic or basic environment for absorption
        2. Itraconazole (azole antifungal) requires an acidic environment
        3. Didanosine (nucleoside reverse transcriptase inhibitor) requires a basic environment
    - (c) Site of administration
      - (i) Oral / Enteral
        1. Bioavailability generally < 100% (some exceptions do occur)
        2. Function of GI tract
           a. Ileus (lazy or sluggish bowel tract)
           b. Bowel obstruction
           c. Intact versus impaired GI tract
           d. Most drugs are absorbed in stomach or first part of duodenum
        3. Tube feeds – where is the tip of the feeding tube located
           a. Gastrostomy tube
           b. Duodenal
           c. Jejunal tube (hint: not great for enteral absorption)
           d. Can the medication be given via a feeding tube?
              i. Liquid formulations preferred
              ii. Not all tablets may be crushed OR opened.

iii. Do not crush sustained release/controlled release drugs (sometimes formulations can be dissolved in water)

(ii) Parenteral
1. Intravenous
   a. 100% bioavailability
   b. Avoids first pass effect
2. Intramuscular
   a. Bioavailability ≤ 100%
   b. Avoids first pass effect
3. Less common parenteral routes
   a. Intrathecal, intraventricular
   b. Intraocular
   c. Intra-articular
4. Topical/Transdermal/ Subcutaneous
   a. Bioavailability ≤ 100%
   b. Avoids first pass effect
   c. Thick skin versus thin skin impacts topical absorption
   d. Intact versus non-intact skin impacts topical absorption
   e. Skin temperature will affect absorption (e.g. fentanyl transdermal patches)

b. Distribution Vd (L/kg) (D)

(i) Theoretical fluid volume needed to maintain the total absorbed drug amount in the plasma.

(ii) Factors to consider if the drug will get where it needs to go?

(a) Perfusion rate

(i) Normal perfusion allows for organs such as the liver, kidney, heart, brain etc. to be exposed to the medication

(ii) Impaired perfusion limits exposure
1. Ischemia (physiologic versus pharmacologic)
2. Higher doses may be required

(b) Properties of the medication

(i) Lipophilic - Adipose (i.e. vancomycin – an antibiotic)

(ii) Hydrophilic - Extracellular fluid (i.e. aminoglycosides – antibiotic class)

(iii)Other areas – Bone, eye

(c) Physiologic barriers

(i) Protein binding
1. Low protein binding → generally large Vd
2. High protein binding → Vd may be challenged
3. Changes can potentially affect clinical response & drug disposition
4. Albumin is often used as a clinical marker

(ii) Blood Brain Barrier (BBB)
1. Noninflamed meninges: tight web, minimal penetration
2. Inflamed meninges: increased spaces, possibly better penetration
3. Medications with decreased protein binding cross BBB easier
4. Maximize dosing or consider alternate routes of administration (i.e. intraventricular)

(iii)Bone, Eye, Placenta

c. Metabolism (M): How a drug is broken down
   (i) Many drugs undergo some form of hepatic metabolism with breakdown into active or inactive metabolites.
      (a) Phase I: reduction oxidation, hydrolysis with Cytochrome P450
      (b) Phase II: Conjugation (glucuronidation, acetylation, sulfation)
   (ii) Interactions often present due to competition for metabolic pathway with Cytochrome P450 system being the most common pathway
d. Elimination (E)
   (i) Clearance relates the rate of elimination to the plasma concentration
   (ii) Clearance affects half-life (t ½)
   (iii)Clearance may be impaired with hepatic or renal dysfunction
      (a) Most drugs are renally eliminated.
         (i) Renal function deteriorates with age.
         (ii) Estimate of renal function made via Creatinine Clearance (CrCl)
            1. Cockroft & Gault most common formula (mL/min)
            2. Most drug references list renal dose adjustment per CrCl (mL/min) as defined above, however some drugs are now adjusted per estimated glomerular filtration rate (eGFR).
               a. eGFR is used as a marker for chronic kidney disease (CKD)
               b. reports as mL/min/1.73m^2
            3. CrCl will be different for healthy 30yo and healthy 80yo.
            4. Creatinine also comes from muscle.
            5. Calculation using actual serum creatinine in elderly patients <u>may</u> overestimate true renal function.
         (iii)Acute versus chronic renal insufficiency
         (iv)Hemodialysis and hemofiltration
            1. <u>May</u> filter out drug
               a. Hydrophilic
               b. Small molecular size
            2. CrCl <10ml/min generally equates to end stage renal disease
         (v) Anticipate dose adjustment with deviations from ‘normal’ renal function (CrCl < 70-100 ml/min-clinically) due to prolonged t ½
      (b) Assess the patient in addition to the laboratory result
         (i) Serum creatinine may look normal after a dialysis session
         (ii) Serum creatinine may not be that elevated but patient may be anuric
      (c) Some medications will require dosing changes for hepatic dysfunction
   (iv)Biliary and fecal elimination
      (a) Less common
      (b) Ceftriaxone (antibiotic)– primarily biliary elimination
      (c) Linezolid (antibiotic) – primarily fecal elimination
      (d) Dose adjustments are generally not needed
   (v) Useful equations
      (a) t ½ = 0.693 / K (hr-1)
      (b) Cl (L/hr) = K(hr-1) x Vd (L)

II Population pharmacokinetics

A "Textbook" pharmacokinetics
- a. General pharmacokinetic parameters based on clinical trials.
- b. Basis for recommended dosing
- c. Provide standard pharmacokinetic information with ranges
  - (i) Gentamicin (antibiotic)
    - (a) Vd 0.25L/kg (0.2-0.3L/kg); t ½ 2h; <30% protein binding
    - (b) Interpatient variability: renal function, hydration status
    - (c) Intrapatient variability: clinical status
  - (ii) Phenytoin (Dilantin®) (antiseizure medication)
    - (a) Vd varies with age
    - (b) Protein binding 90% - binds to albumin (variances with neonates/infants)
    - (c) Interpatient variability: protein binding, metabolism

B Patients do not always behave like textbooks!!
- a. You must assess patient's individual pharmacokinetic parameters.
  - (i) What is the best route? Will the patient absorb the medication?
  - (ii) Will the drug get to where I want it to go? Is my patient dehydrated, edematous, cachectic or obese?
  - (iii) How is his/her renal or liver function? Do I need to adjust the dose?
  - (iv) How many doses did the patient receive?
- b. Reference books / Internet health care information sites to serve as guides
  - (i) Clinical pharmacology®
  - (ii) Epocrates®, Rxlist®
  - (iii) Lexicomp Drug Information®
  - (iv) Micromedex®,Medscape®
  - (v) Other reputable sources

C Examples of variations in pharmacokinetic parameters per age group
- a. Neonates (<30 days of life)
  - (i) Immature skin, increased skin hydration → increased absorption of topical products
  - (ii) Increased extracellular fluid → higher volume of distribution of water soluble drugs (i.e. aminoglycosides)
  - (iii) Metabolic pathways mature at different times
  - (iv) Glomerular filtration, tubular secretion and reabsorption immature at birth
- b. Elderly
  - (i) Skin thinning → increased topical absorption
  - (ii) Increased adipose tissue → increase in volume of distribution of fat soluble drugs
  - (iii) Decreased extracellular fluid → decrease in volume of distribution of water soluble drugs
  - (iv) Age related decrease in renal function

III Therapeutic Drug Monitoring (TDM)

A Starting dose for drugs requiring TDM are designed based on population pharmacokinetics. Adjustments are made utilizing patient specific pharmacokinetic parameters calculated from patient specific drug levels.

B Depending on the drug, a Loading Dose (LD) may be given to help achieve an immediate therapeutic response by reaching levels that are seen at steady state quickly. However, steady state is not reached any faster—3 to 5 half-lives are still needed.

C Dose adjustments are best made when the patient is at steady state
- a. Steady state is dependent only on half life (t ½)
- b. Pharmacokinetic parameters must remain stable for accurate dosing.
  - (a) Renal function for renally eliminated drugs
  - (b) Hepatic function for hepatically eliminated drugs
- c. Why is being at steady state important?
  - (i) Minimizes potential for over/under dose adjustment
  - (ii) Assumes maximum and stable distribution
- d. Level interpretation
  - (i) The adjustment is only as good as the drug level assessment
  - (ii) Was the level drawn appropriately in relation to the dose and from the appropriate IV line?
    - (a) False levels may lead in inappropriate dose changes

D Dose adjustment may be needed when a patient is not at steady state
- a. Adjust based on the pharmacokinetic information available and the patient's clinical condition.
- b. Frequent monitoring is essential.

E Dosing is not always "one stop shopping"
- a. Different doses may be needed to treat the same indication for different patients
- b. Patients with similar age, height, weight may still require different dosing

F Examples of drugs that require TDM
- a. Select antibiotics (Aminoglycosides, Vancomycin)
- b. Select antiepileptic agents (i.e. carbamazepime, phenytoin)
- c. Select anticoagulants (warfarin, heparin---monitor coagulation times not drug levels per se)

G Clinical Scenario

LC is a 41yo female who is being treated for E. Coli urosepsis. She has multiple true drug allergies and her only treatment option at this time is tobramycin.

Vital signs: stable
Height 64inches
Admission weight 60kg
Usual weight 57kg (IBW 55kg)
Bun 10 Cr 0.8
2+ pitting edema

You notice that she has not yet received any diuretic. You estimate her CrCl to be 78.3mL/min based on her admission weight and labs.
Your desired peak is 6mcg/mL and trough is <2mcg/mL.

Using population PK parameters of Vd of 0.25L/kg and a dosing interval of 8h you start the following:

Tobramycin 120mg x 1
Then tobramycin 90mg Q8h starting 8hours after the first dose

Tobramycin levels are drawn at steady state (4th dose) along with other labs:

Peak: 4mcg/mL (desired peak is 6mcg/mL)
Trough: 0.5mcg/mL (desired trough is <2mcg/mL)
Serum creatinine remains stable at 0.8mg/dL
Weight 64kg
3+ pitting edema

What is your assessment?

Answer: Aminoglycosides readily distribute into extracellular fluid. When dosing was initiated in this patient, she was dosed based on a euvolemic status or normal hydration state. However, she was fluid overloaded at the time of medication initiation and is even more fluid loaded at present. The tobramycin readily distributes into the extracellular fluid and in an edematous patient may result in lower serum levels if not dose adjusted. Slightly increasing the milligram amount of the dose would have accounted for some of the extracellular shifting. However, if the patient were to have been given a diuretic to help remove the extra water, the levels would have been right on target.

IV. Drug Interactions

A. Approximately 3-5% of inpatients are reported to have a preventable adverse drug reaction (ADE). (FDA)
B. Drug interactions are the leading cause of ER visits and hospital admissions. (FDA)
C. Drug interactions can occur before or after administration. (FDA)
D. Causes of drug interactions
    a. Drug incompatibility
    b. Pharmacokinetic interactions
        i. Absorption
        ii. Distribution
        iii. Metabolism
        iv. Elimination
    c. Pharmacodynamic interactions
E. Types of drug interactions
    a. Drug-Drug
    b. Drug- Nutrient
    c. Drug-Disease State
    d. Level of drug action or organ system
    e. Examples

i. Drug incompatibility
    1. At time of preparation or during administration set up
    2. Precipitation
        a. IV calcium and IV ceftriaxone (antibiotic)
    3. Amphotericin B (antifungal) and 0.9% sodium chloride
ii. Pharmacokinetic
    1. Absorption
        a. Will drug A affect absorption of drug B
        b. Chelation
            i. Levofloxacin (quinolone antibiotic) + ferrous sulfate
            ii. Ciprofloxacin (quinolone antibiotic) + yogurt
        c. Changes in stomach pH
            i. Iitraconazole (antifungal) + cola soft drink
    2. Distribution
        a. Competition for binding sites
            i. Aspirin (NSAID) + warfarin (blood thinner)
        b. Changes in protein binding due to disease states
            i. Phenytoin (anti-seizure) + extensive burn patient
        c. Changes in extracellular fluid or adipose
            i. Vancomycin (antibiotic) + obese
                1. Gentamicin (aminoglycoside antibiotic) + edema
    3. Metabolism
        a. Hepatic
            i. Inducer of CYP_{450}
                1. Increased metabolism
                    a. Carbamazepine (anti-seizure) + oral contraceptives
                    b. Rifampin (antibiotic) + protease inhibitors (HIV medication)
            ii. Inhibitor of CYP_{450}
                1. Decreased metabolism
                    a. Atorvastatin (cholesterol medication) + grapefruit juice
                    b. Disulfiram + alcohol
                    c. Disulfiram-like reaction
                        i. Metronidazole + alcohol
            iii. Major enzymes: 1A2, 2C9, 2C19, 2D6, 3A4
        b. Other metabolic pathways
            i. Plasma esterases
    4. Elimination
        a. Competition for elimination pathways
        b. Renal elimination is the most common
        c. Decreased or increased elimination

iii. Pharmacodynamic interactions
    1. Warfarin + green leafy vegetables (vitamin K rich foods)
        a. Warfarin inhibits vitamin K dependent clotting factors
        b. Most green leafy vegetables have vitamin K
        c. End result is decreased anticoagulant effect
    2. Dronedarone (antiarrhythmic) and NYHA class IV heart failure
        a. Dronedarone can worsen heart failure
    3. Medications that can prolong QTc interval
        a. Combination can increase risk of Torsades de Pointes
        b. E.g. amiodarone, haloperidol, levofloxacin, ondansetron
    4. Tobramycin (aminoglycoside antibiotic) + cyclosporine (immunosuppressant)
        a. Both drugs undergo renal elimination
        b. Both can cause nephrotoxicity
        c. Increased risk of nephrotoxicity if used in combination
    5. Methylprednisolone and glucose control
        a. Steroids can increase blood sugar
iv. Intentional vs. unintentional interaction
    1. Often, interactive properties of drugs may be used to enhance dosing regimen
        a. Amoxicillin + probenecid
            i. Probenecid decreased the renal elimination of amoxicillin
        b. Ritonavir + lopinavir (HIV protease inhibitors)
            i. Ritonavir is a CYP450 inhibitor
            ii. Increased lopinavir concentrations
            iii. Resulting in decreased dose
            iv. Decreased frequency of administration
v. Steps to minimize drug interactions
    1. Know your most commonly prescribed drugs
    2. Know your reputable references
    3. Education patients to use only one pharmacy and maintain accurate written medication histories
    4. Accurate and detailed medication reconciliation at each clinic visit, upon hospital admission, transfer and discharge

Drugs listed throughout this lecture.			
Drug	**Class**	**Context**	**Page #**
Amiodarone	Calcium Channel Blocker	Drug Interaction	9
Amoxicillin	Beta lactam Antibiotic Aminopenicillin	Drug Interaction	9
Aspirin	Salicylate	Drug Interaction	8
Atorvastatin	Drug interaction	Drug Interaction	8
Calcium Carbonate	Calcium Salt, antacid	Drug Interaction	8
Carbamazepine	Antiepileptic agent	Drug Interaction	6,8
Ceftriaxone	Beta lactam antibiotic 3rd generation cephalosporin	Biliary elimination	4,8
Ciprofloxacin	Quinolone antibiotic	Drug Interaction	8, 10
Cyclosporine	Immunosuppressant, IL II inhibitor	Drug Interaction	9
Didanosine	HIV. NRTI	Requires basic environment for absorption	2
Disulfiram	Aldehyde dehydrogenase inhibitor	Drug Interaction	8
Dronedarone	Antiarrhythmic	Drug interaction	8,9
Fentanyl Patches	Opioid analgesic	Absorption and skin temp	3
Gentamicin	Aminoglycoside antibiotic	Population PK example, Vd changes with increased ECF, TDM	5, 8
Haloperidol	Atypical Antipsychotic	Drug Interaction	9
Heparin	Anticoagulant	TDM	6
Iron Sulfate	Mineral	Case	8
Itraconazole	Azole antifungal	Requires acidic environment for absorption, Drug Interaction	2, 8
Levofloxacin	Quinolone antibiotic	Drug interaction	8,9
Linezolid	Oxazolidanone antibiotic	Fecal elimination	4
Lopinavir/Ritonavir	HIV Protease Inhibitors	Drug Interaction	9
Methylprednisolone	Corticosteroid	Drug Interaction	9
Metronidazole	Amebicide/antiprotozoal antibiotic	Drug Interaction	9
Oral Contraceptives (OCP)	Contraceptive	Drug Interaction	8
Phenytoin	Antiepileptic agent	Population PK example, Drug interaction	5, 6,8
Probenecid	Anti-gout	Drug Interaction,	9
Tobramycin	Aminoglycoside antibiotic	TDM	6,7, 9
Vancomycin	Glycopeptide antibiotic	Drug reservoir (adipose) TDM	3, 6, 8
Warfarin	Anticoagulant	TDM, Drug Interaction	6, 8, 9,

Drug Metabolism

Date: Friday, August 4th, 2017 – 9:30 am

Relevant Reading:
Basic and Clinical Pharmacology- B.G. Katzung, 13th Edition, Chapter 4 p57-73

KEY CONCEPTS & LEARNING OBJECTIVES

At the end of the lecture the learner will be able to:

1. Describe the principal consequences of drug metabolism
2. List the major anatomical and subcellular locations involved in drug metabolism
3. Describe the first pass effect and how it contributes towards determining drug bioavailability
4. Describe the major features of Phase I and Phase II metabolic reactions and how they each contribute towards the modification of drug activity and drug elimination
5. List the major types of enzymatic reactions and enzymes involved in Phase I and Phase II metabolism
6. Describe the major features of CYP450 enzymes and the types of chemical reactions they perform
7. Describe the principal differences between the metabolism of a typical drug and a prodrug
8. Describe how enterohepatic drug recirculation influences the elimination and pharmacokinetic parameters of drugs that are excreted in the bile
9. Describe the two principal mechanisms underlying metabolic drug-drug interactions and predict how each mechanism affects the efficacy and toxicity of drugs and prodrugs
10. Describe how grapefruit juice consumption can affect the metabolism of certain drugs
11. Identify well-known inhibitors and inducers of the CYP3A4 enzyme and explain their potential effects on drug efficacy and toxicity
12. Describe the principal factors known to influence drug metabolism
13. Apply knowledge of drug metabolism processes to explain mechanisms underlying specific drug-drug interactions

The Pharmacology of Drug Transporters

Date: Friday, August 4th, 2017 – 10:30 am-11:30am

KEY CONCEPTS & LEARNING OBJECTIVES

At the end of the lecture the learner will be able to:

1. Describe the mechanisms by which drug transporter proteins contribute towards the transport of drugs across biological membranes

2. Describe the mechanisms by which drug transporter proteins can influence drug pharmacokinetics

3. Describe the mechanisms by which drug transporters can contribute towards drug-induced adverse effects

4. Describe the mechanisms by which drug transporters can contribute towards drug-drug interactions

5. Distinguish between the seven major families of drug transporter proteins based upon their mode of transport (influx/efflux), patterns of expression and broad substrate specificity.

6. Describe the mechanism by which probenecid contributes towards interactions with drugs transported by the OAT class of drug transporters

7. Describe the role of the OATP1B1 transporter in influencing the pharmacokinetics of the STATIN class of drugs

8. Describe the mechanism by which cimetidine contributes towards interactions with drugs transported by the OCT class of drug transporters

9. Describe the role of the ATP-binding class of transporters in contributing towards the integrity of the Blood Brain Barrier

10. Describe the effects of cyclosporin, rifampicin and St. John's Wort on the pharmacokinetics of drugs that are substrates for the P-glycoprotein/MDR1 drug transporter and discuss the underlying mechanisms

11. Describe the role of P-gp/MDR1 in determining the responsiveness of tumor cells to chemotherapeutic drugs

Pharmacogenetics/Pharmacogenomics

Date: Monday, August 7th, 2017 – 10:30 am

Relevant Reading:
Basic and Clinical Pharmacology- B.G. Katzung, 13th Edition, Chapter 5 p74-86

KEY CONCEPTS & LEARNING OBJECTIVES

At the end of the lecture the learner will be able to:

1. Define pharmacogenetics and describe how it can be used to enhance patient care
2. List the main factors that can affect the genetic variability of the drug response
3. Describe how genetic polymorphisms in drug metabolizing enzymes can affect the metabolism of drugs and the effects that this has on serum drug concentration, drug efficacy and the risk of toxicity
4. Describe how polymorphisms in drug transporter proteins can contribute towards the variability in drug responses
5. Describe how polymorphisms in drug target proteins and related pharmacodynamics genes can contribute towards the variability in drug responses
6. Describe how polymorphisms in CYP2C9 and VKORC1 can each contribute towards the variability in the clinical response to warfarin
7. Discuss the different mechanisms by which genetic polymorphisms can contribute towards drug-induced adverse effects
8. Predict the clinical impact of pharmacogenetic differences in drug metabolizing enzymes, drug transporter proteins and drug targets on the clinical efficacy and potential toxicity of a given drug
9. Describe how pharmacogentic testing can be used in translational research studies to influence the identification of drug targets, diagnostic biomarkers and biomarkers to guide therapeutic decisions
10. Define targeted therapy and explain how pharmacogenetic data is used in the therapeutic decision making process
11. List some of the current barriers to the full implementation of pharmacogenetics into clinical practice

PHARMACODYNAMICS I: DRUG - RECEPTOR INTERACTIONS

Date: August 8, 2017 – 9:30 a.m.
Reading Assignment: Katzung 11th Edition, Chapter 1, pp. 1-8 & Chapter 2.

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Identify the characteristic that differentiates a biological receptor from a binding site and describe the concepts of drug stereospecificity and receptor saturability.

2. Explain why increasing drug concentration (or dose) results in non-linear increases in receptor occupation and non-linear increases in response.

3. Identify the only two parameters that dictate receptor fractional occupancy for any drug and the equation that relates these two parameters to receptor fractional occupancy.

4. Understand the difference between the terms K_D and EC50 and explain why the values of both terms would be identical for an agonist in a system without spare receptors.

5. Explain why the clinical effectiveness of a drug is dependent on its maximal efficacy and not potency.

6. Be able to construct and compare dose response curves for a full agonists, a partial agonists, a neutral antagonists and a negative antagonists (inverse agonists).

7. Explain why the response produced by any full agonist would not be increased by subsequent administration of a partial agonist acting on the same receptor.

8. Describe the different pharmacological and non-pharmacological mechanisms by which the effects of a drug can be antagonized.

9. Describe the concept of spare receptors (aka receptor reserve) and the effect that increases in receptor reserve have on the shape of the graded dose-response curve.

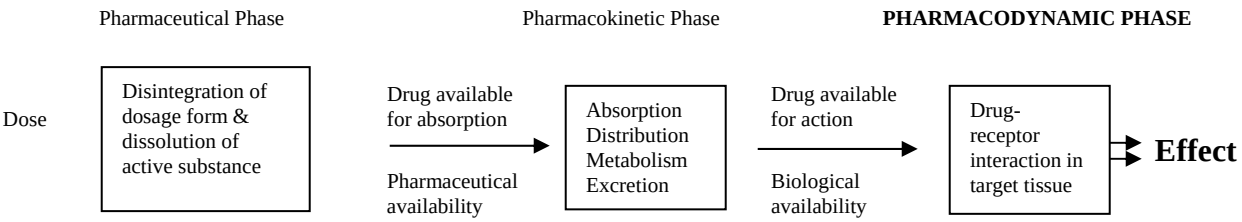
10. Compare the effects of increasing concentrations of a non-competitive antagonist on an agonist dose response curve in system without spare receptors versus systems with spare receptors.

11. Compare the effects of increasing concentrations of a competitive antagonist on an agonist dose response curve in system without spare receptors versus systems with spare receptors.

PHARMACODYNAMICS I: DRUG-RECEPTOR INTERACTIONS

I. INTRODUCTION

Overview of Main Phases in Drug Action



Adapted from: T.P. Kenakin, Analysis of Drug Receptor Interactions, 1987

A. **DRUG** - defined as any substance that affects living processes

- most, but not all, drugs produce their effects by interacting with specific receptors
- biologic responses to drugs are graded. Increasing the dose increases the effects
- their biologic effects, which can be therapeutic or toxic, depends on the drug, dose and "selectivity"

Drug Nomenclature: A drug is often referred to by a name that reflects its most prominent site of action or clinical effect, although it may interact with many other receptors within a given dose range. This "label" attached to a drug often determines how the drug is used or sometimes misused. Remember…

Drug interactions with a receptor or receptors are dictated by the drug's chemical and structural properties, not by the name ascribed to it by humans.

Chemical forces involved in drug binding include:

1. Electrostatic forces
2. Hydrogen Bonding
3. Van der Waals Forces (at closer distances)
4. Hydrophobic bonds

****Most Drug Receptor Interactions are REVERSIBLE**

Most Drug Binding Interactions DO NOT form Covalent Bonds

The reversible interaction (i.e. binding) of a drug with a receptor can be thought of as a dynamic equilibrium process. That is, the drug is either "on" or "off" the receptor at any point in time.

Implication: ***ANY DRUG CAN INTERACT ONLY WITH UNOCCUPIED ("FREE") RECEPTORS***

- Drug "displacement" does not generally occur in drug-receptor interactions

B. RECEPTORS versus "BINDING SITES"

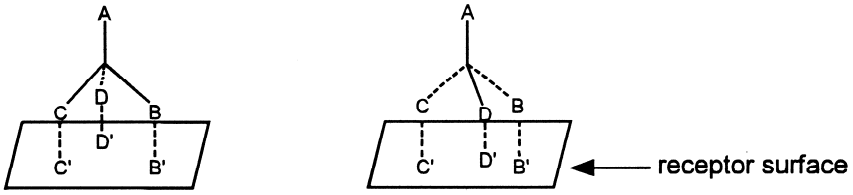
BINDING SITES- "receptive" components that can interact with (or "bind" to) substances but are not capable of initiating any subsequent response are often referred to as "acceptor" sites or "binding" sites. (e.g. albumin and α_1 acid glycoprotein).

RECEPTOR - any component that is "receptive" to interacting with drugs or endogenous substances and is **capable of initiating a subsequent response**

Some Important General Features of Receptors

1. **Structural Specificity**: Receptors exhibit some degree of specificity for the drug molecule. The component of the receptor that "recognizes" and "binds" the drug is known as the receptor recognition site or pharmacophore.

2. **Stereospecificity**: Receptors generally exhibit stereospecificity for drugs containing asymmetric carbon atoms. Isomers of a drug may exhibit differences in affinity, potency and/or efficacy.



A pair of optical enantiomers showing the different patterns of projection of three functional groups onto a receptor surface

Adapted from: Goldstein, Aronow and Kalman, Principles of Drug Action, 2nd ed., 1974.

3. **Saturability**: Receptors exist in finite numbers and as such can be saturated by high concentrations (i.e. doses) of drug. Therefore, increasing the dose after saturating (occupying) all receptors will not increase its response any further.

4. **Response**: There will be some quantitative relationship between the magnitude the pharmacological response and the number of receptors occupied.

   The response to a drug depends on:

   (1) the amount of drug reaching its site of action (pharmacokinetic consideration)

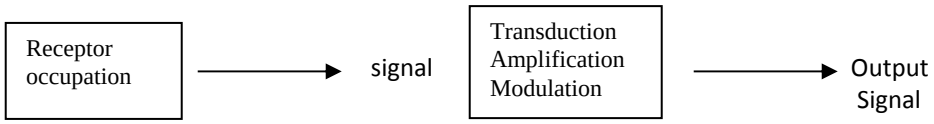
   (2) the drug-receptor interaction at that site

   (3) the functional status of the receptor and/or target cell

5. **Regulation**: Receptors are dynamic entities that can be functionally regulated by physiological, pharmacological and pathological factors.
   (e.g. pharmacodynamic tolerance, supersensitivity, etc.)

C. RECEPTOR SYSTEMS - The receptor is <u>only the first</u> step in the transfer of drug "information" to the system. This is shown in the figure below.

DRUG + RECEPTOR
(Discriminator)



Main steps in the pharmacodynamic phase of action (figure above) & visualization of signal amplification following receptor occupation by agonist (figure below).

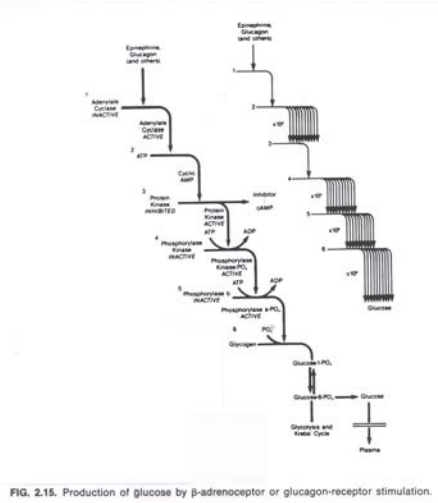


FIG. 2.15. Production of glucose by β-adrenoceptor or glucagon-receptor stimulation.

II. RELATIONSHIP BETWEEN DRUG CONCENTRATION AND RECEPTOR OCCUPATION

The principles that apply to the binding of drugs to receptors are similar to those that govern chemical reactions and are analogous to the parameters observed in enzyme kinetics. Let's see how:

Briefly: $D + R \equiv DR$

D = free drug
R = free receptors
DR = drug-receptor complex

The rate of formation of DR complex with time is:

$$d[DR]/dt = k_1 [D][R]$$

and the rate of breakdown of the DR complex with time is:

$$-d[DR]/dt = k_2 [DR]$$

At equilibrium, these two rates are equal.

Therefore:

$\mathbf{k_1}[D][R] = \mathbf{k_2}[DR]$ or $\mathbf{k_2/k_1} = \frac{[D][R]}{[DR]}$

The term $\mathbf{k_2/k_1}$ is the $\mathbf{K_D}$ (i.e., the equilibrium dissociation or affinity constant)

This $\mathbf{K_D}$ value of a drug for a given receptor reflects the propensity of a drug to bind to that receptor. This propensity to interact with a receptor (i.e., form [DR]) is referred to as the drugs affinity for the receptor and it is typically expressed by the $\mathbf{K_D}$ value for a given receptor. Consequently, if a drug has a high affinity for a receptor, [DR] will be large. From the above equation, if [DR] is large, the value of K_D will be small.

Thus, for any drug, **the K_D value and affinity are inversely related**.
Also, the K_D value for any drug is the concentration of that drug that will occupy 50% of a receptor population (as per the equation below).

You (yes, I mean YOU) can determine the fraction of any receptor population that will be occupied by any concentration of any drug by using the simple **Receptor Fractional Occupancy Equation (shown below)**

$$\text{Fractional Occ.} = \frac{1}{1 + \frac{K_D}{[D]}}$$

Thus, for any drug, the FRACTION of a receptor population that it will occupy will depend ONLY on it's: (1) ***affinity*** and
(2***) concentration*** (i.e. dose).

- Note that the <u>fraction of receptors</u> occupied by any drug will be <u>independent</u> of the number of receptors present in a tissue.

- However, <u>the total number of receptors occupied</u> by a drug will depend on both:
(1***) fraction of the receptor population occupied*** &
(2) ***the number of receptors in a given tissue***, (i.e., B_{max})

The magnitude of the RESPONSE will be some function (i.e. α) of the total number of receptors occupied.

Response = α (fractional occupancy) (Receptor #)

<u>Relationship between Drug Dose (concentration) and Receptor Occupancy</u>: Increasing dose will increase receptor occupation in a non-linear fashion over most of the dose range (fig. below).

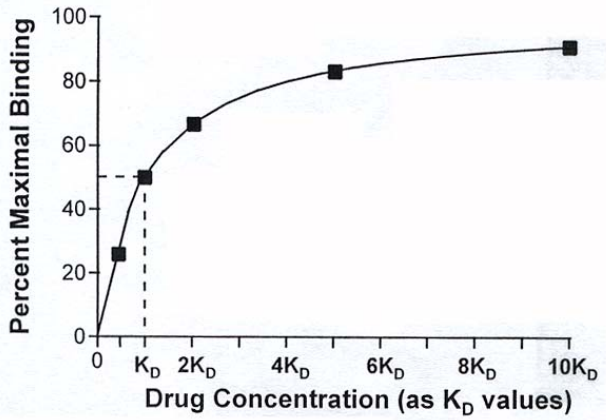
As the concentration of a drug increases, the fraction of receptors occupied by the drug will increase from 1 - 91% over approximately 3 orders of magnitude (3 log units of drug concentration) about its K_D value, as shown in the figure below.

In the figure below, drug concentration is expressed as a function of its affinity (i.e. K_D units of concentration) so that the receptor occupation curve shown applies to any drug.

For example: if the K_D for a drug is 5nM, then a 5nM concentration of the drug could be expressed as $1K_D$ unit of concentration, 10nM would be $2K_D$ units, etc.

Non-Linear Occupation of Receptors

GB



Conc. As K_D Units	Fractional Occupancy %
0.01	1
0.10	9
1.00	50
10.00	91
100.00	99

Drug Selectivity: Since most drugs have comparable affinity for a number of receptors, the selectivity of a drug refers to its ability to interact with one type of receptor versus other receptors. For any drug, ***selectivity*** will decrease as dose is increased.
This is shown in the figure below:

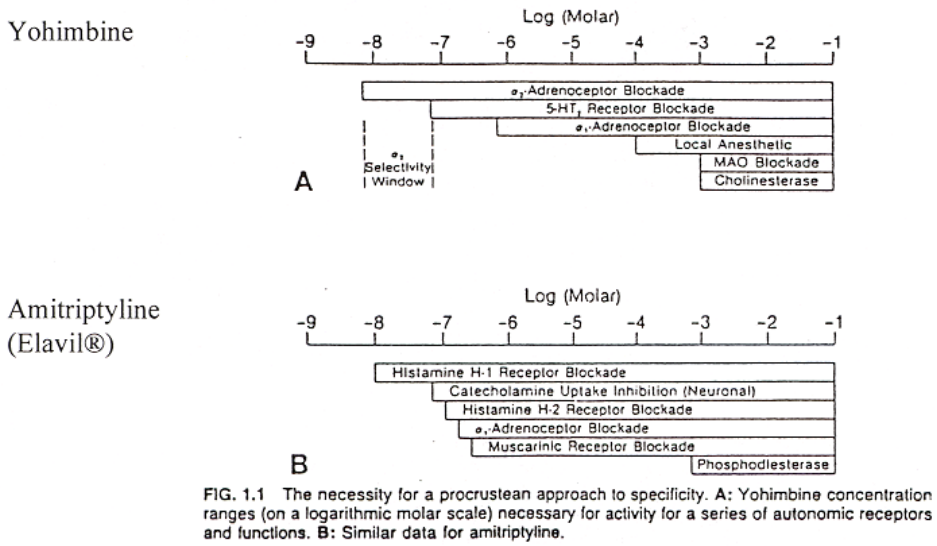


FIG. 1.1 The necessity for a procrustean approach to specificity. **A:** Yohimbine concentration ranges (on a logarithmic molar scale) necessary for activity for a series of autonomic receptors and functions. **B:** Similar data for amitriptyline.

Adapted from: T.P. Kenakin, Pharmacological Analysis of Drug Receptor Interactions, 1987

The "selectivity window" of a drug is dependent on the drug dose or concentration range employed. It can be difficult to obtain this range in vivo where numerous other factors are operative (e.g. drug distribution, metabolism, tissue receptor heterogeneity, etc.).

III. GRADED DOSE RESPONSE CURVES – The Relationship Between Drug **DOSE**, Receptor Occupation and the magnitude of the **RESPONSE**

The Dose-Response Relationship: ***This is the correspondence between the amount of a drug and the magnitude of the effect produced*.** The initial step in producing any effect is the binding (i.e. interaction) of a drug with a receptor.

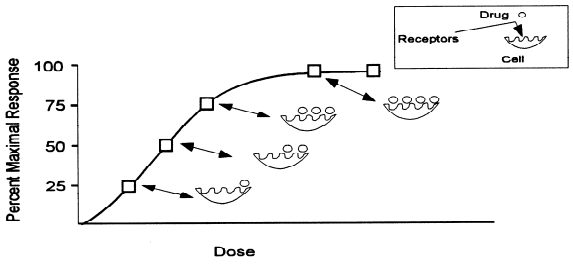
[D + R ≡ DR] -> ->-> RESPONSE

Simple Occupancy Theory – predicts that there is a one to one relationship between receptor occupation and response. Thus:

1) the magnitude of the pharmacological effect is linearly proportional to the number of receptors occupied by the drug

2) the maximum response is obtained only when all receptors are occupied**.**

Adapted From: R.A. Lehne, Pharmacology for Nursing care, 1990



The simple occupancy theory states that the intensity of response to a drug is proportional to the number of receptors occupied; maximal response is reached with 100% receptor occupancy. Since the hypothetical cell in this figure has only 4 receptors, maximal response is achieved when all 4 receptors are occupied. (It should be noted that real cells have thousands of receptors)

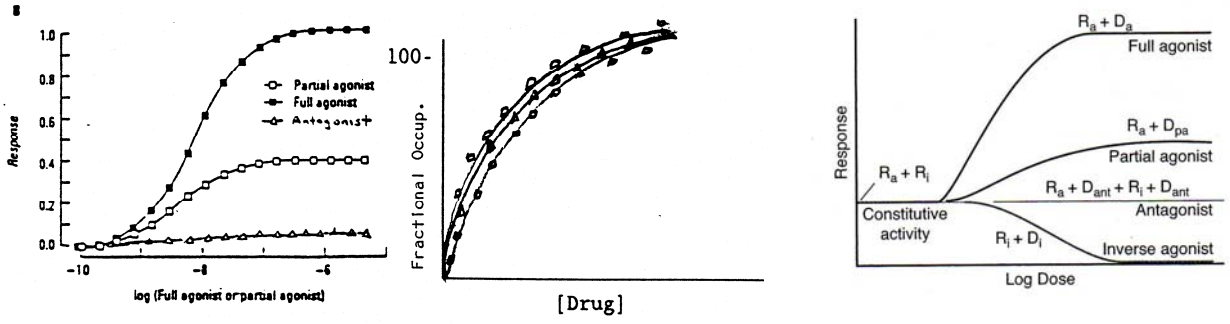
<u>Modified Occupancy Theory</u> - Expansion of simple occupancy theory to account for experimental findings that could not be explained by the original theory. Thus:

1. The response of a drug was some positive <u>function</u> of receptor occupancy (i.e., not necessarily linearly proportional to the percent of receptors occupied).
2. Maximum effects could be produced by an agonist occupying only a small proportion of receptors.
3. Different drugs may have varying capacities to initiate a response.

These findings resulted in the concepts of Drug Efficacy and Potency

<u>Efficacy</u> (a.k.a. maximal efficacy, intrinsic activity) - this can be determined directly from the graded dose-response curve and is the limit (or plateau) of the dose-response curve on the response axis

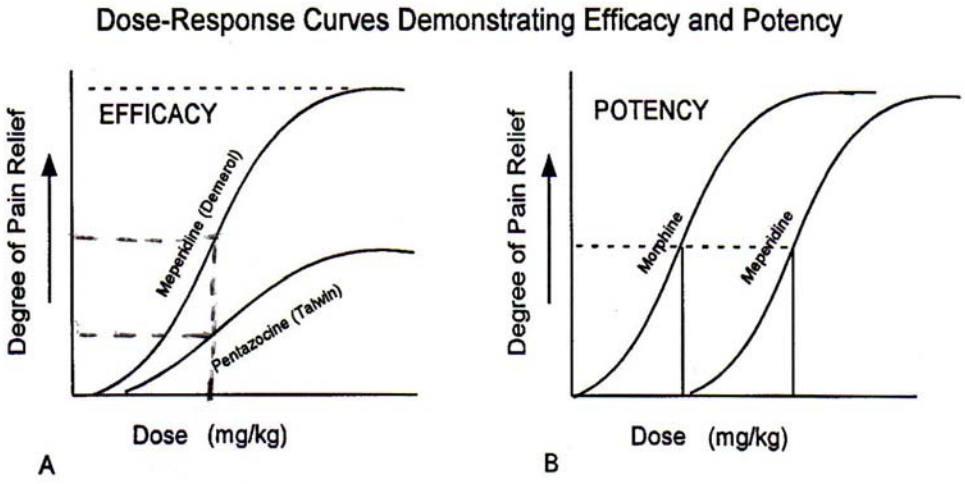
Thus: **<u>Full</u>** agonists would have an intrinsic activity = 1 **<u>Partial</u>** agonists would have an intrinsic activity < 1 and **<u>Neutral Antagonists</u>** that bind but produce no biologic effect would have an intrinsic activity of 0. **<u>Negative Antagonists</u>** (Inverse Agonists) reduce the response produced by constitutively active receptors (active in the absence of agonist) and have a negative intrinsic activity.



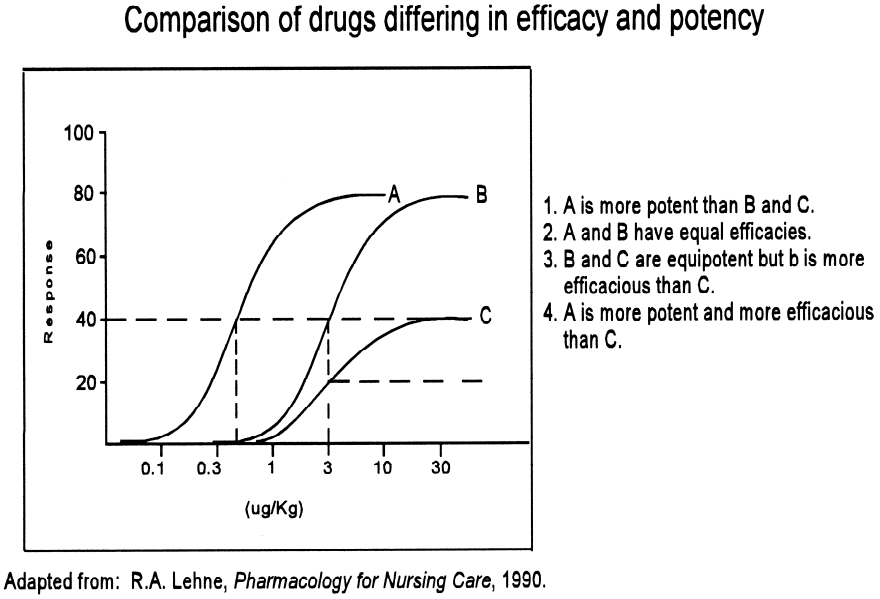
Modified from: R.R. Ruffolo, J. Auton. Modified from:, J. Auton. Pharmacol. 277-295, 1982; Katzung's Basic & Clinical Pharmacology. page 8, 11th ed, 2009.

Potency - *refers to the concentration or dose of a drug necessary to produce 50% of that drug's maximal response and is expressed as* an ED_{50} value. The potency of a drug depends in part on: (1) its affinity for the receptor (i.e., its K_D value), and (2) the efficiency with which drug-receptor interaction is coupled to response.

THE CLINICAL EFFECTIVENESS OF A DRUG DEPENDS ON ITS MAXIMAL EFFICACY (Emax) NOT ON ITS POTENCY (ED_{50}).



Adap. from: R.A. Lehne, Pharmacology for Nursing Care, 1990

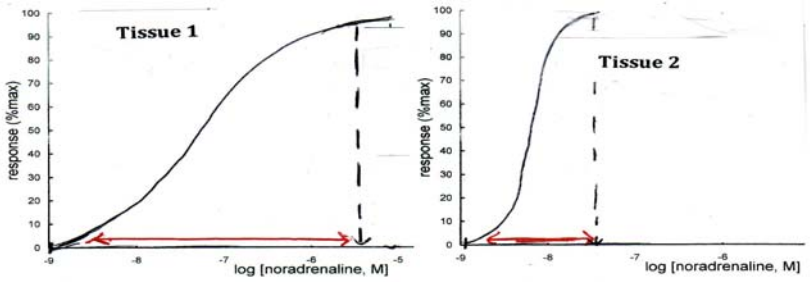


Adapted from: R.A. Lehne, *Pharmacology for Nursing Care*, 1990.

Spare Receptors (Receptor Reserve)

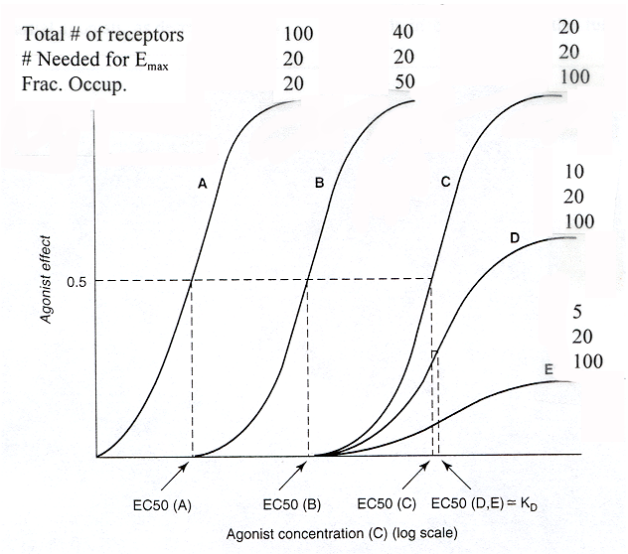
In most systems, a maximum response can be obtained using doses of agonists that occupied only a small percentage or fraction of receptors. Such a system is referred to as having "receptor reserve" or containing "***spare receptors".***

Shape of Graded Dose Response Curve – can sometime provide information about spare receptors. If it takes 3 log units of concentration (dose) for a drug to occupy 91% of any receptor population yet a maximal response occurs over a more narrow dose range (e.g. < 3 log units), not all receptors need to be occupied to produce that maximal response (i.e. there are "spare receptors").



Note the difference in range of concentrations for the same agonist, noradrenaline, to produce an Emax response in Tissue 1 (> 3 log units) versus Tissue 2 (~1.5 log units). This large difference in DR range indicates large differences in receptor reserve (or spare receptors) for the same receptor in tissue 1 versus tissue 2. Smaller differences in receptor reserve may not be revealed by such obvious visual differences in the DR curves. (figure provided by GB)

Experimentally, spare receptors can be demonstrated using increasing concentrations of a non-competitive (irreversible) antagonist to eliminate an increasing number of the available receptors. Curve A is the effect of the agonist alone. Curves B - E show the effect of the same agonist in the same system with fewer and fewer receptors.



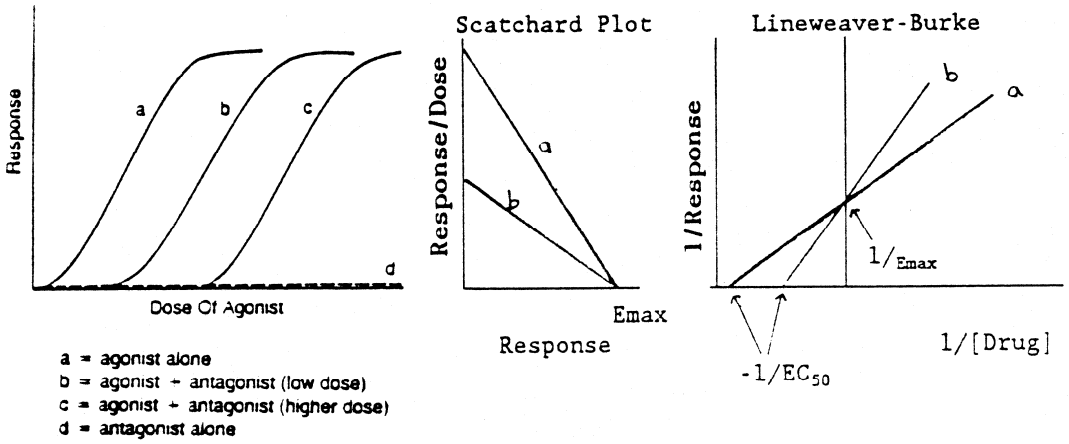
Modified from B.G. Katzung, ed. Basic and Clinical Pharmacology p14, 2004

ANTAGONISM OF DRUG EFFECTS

1. Pharmacological Antagonism

A. Competitive Antagonists: (***Surmountable*** Antagonism)

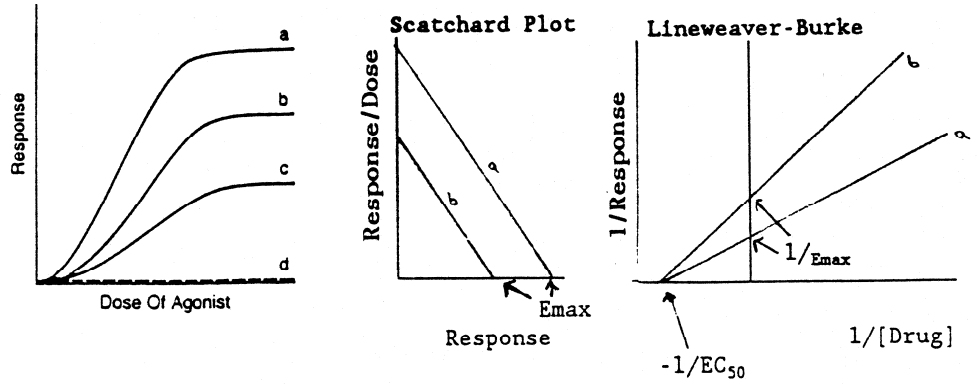
Since an antagonist will "bind" but not elicit a response, higher concentration of agonist are required to occupy the same number of receptors to produce an equivalent response to that observed at lower concentrations in the absence of antagonist. Competitive antagonists will change the ED_{50} of the agonist for the receptor rather than reduce the maximal response (Emax).



Modified from: R.A. Lehne, Pharmacology for Nursing Care, 1990

B. Non-Competitive Antagonists: (***Insurmountable*** Antagonism)

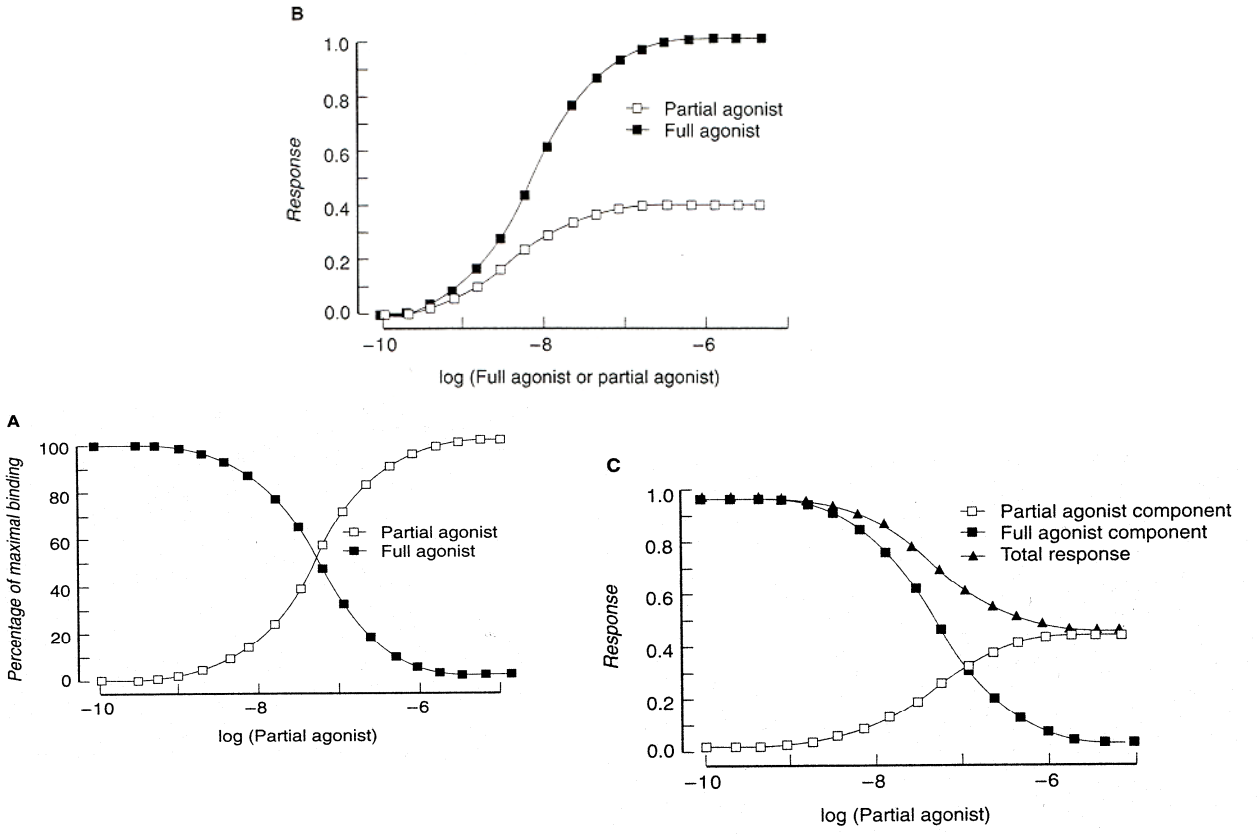
Non-competitive antagonists bind to the receptor and result in a change in the receptor that effectively removes it from the sites available to interact with the drug (this process could be reversible or irreversible). Consequently, if there is no receptor reserve, there would be a decrease in the maximal response (Emax) due to the loss of available receptors to be activated. However, the remaining receptors would exhibit the same affinity (K_D) for the drug and thus the ED_{50} would not be altered.



Modified from: R.A. Lehne, Pharmacology for Nursing Care, 1990

C. Antagonism by Partial Agonists

Since partial agonists can bind to the full complement of a receptor population but cannot produce the maximal response of full agonists, ***they can reduce the maximal response of full agonists*** when both drugs are administered together.



From: B.G. Katzung, ed., Basic and Clinical Pharmacology p 19, 2009

Other Types of Non- Pharmacological Antagonism

- Chemical antagonists- chemical inactivation of a drug
  e.g., protamine (positively charged) inactivation of heparin (negatively charged)

- Physiologic antagonism- the use of opposing regulatory pathways to antagonize the effects of a drug. These effects are less specific and less easy to control than the effects of a receptor specific antagonist.

PHARMACODYNAMICS II: DRUG-RECEPTOR INTERACTIONS

Date: August 9, 2017 – 8:30 a.m.
Reading Assignment: Katzung 11th Edition, Chapter 1, pp. 1-8 & Chapter 2.

KEY CONCEPTS AND LEARNING OBJECTIVES (what you should be able to do)

1. Describe the key aspects of the 5 major types of receptor signaling mechanisms, the conceptual similarities and differences and how they differ in response times.

2. Describe the ways that receptor function can be altered by physiological, pharmacological and pathological factors.

3. Describe the factors that can affect the magnitude of response that can be produced by an agonist.

4. Describe the ternary complex model of G-protein activation and signaling of subsequent messengers.

5. Describe the steps involved in receptor signaling via the adenylyl cyclase and Phospholipase C pathways and their respective downstream effectors.

6. Describe the different means by which drugs can produce beneficial versus toxic effects and the different strategies that may be used to maximize the beneficial effects.

7. Describe the quantal dose response relationship, how you would obtain a quantal dose response curve, what specific information can be obtained from these curves and how this differs from the graded dose-response curve.

8. Describe the different types of variations in responsiveness to drugs.

9. Compare homologous and heterologous desensitization in terms of: (a) respective mechanisms, (b) its effect on the agonist dose response curves and (c) the therapeutic consequences of the altered responsiveness to drugs.

10. Describe the phenomenon of receptor supersensitivity, the factors that can produce it, how it affects the dose response curve and the therapeutic consequence of supersensitivity.

Drug Toxicity

Date: Wednesday, August 9th, 2017– 9:30 am

KEY CONCEPTS & LEARNING OBJECTIVES

At the end of the lecture the learner will be able to:

1. Define a drug-induced adverse effect
2. List some of the factors that can influence the development of a drug-induced adverse effect
3. Explain how drug toxicity can result from the effects of a drug on its direct molecular target
4. Explain how drug toxicity can result from "off-target" effects
5. Explain how the metabolism of harmful metabolites can contribute towards drug toxicity
6. Describe the mechanisms by which an overdose of acetaminophen can cause hepatotoxicity and why timely treatment with N-acetyl Cysteine can be effective in the treatment of acetaminophen poisoning.
7. Describe how drugs can trigger the immune system to cause adverse effects
8. Define the key features of idiosyncratic drug toxicity, the influence of genetics in developing an iodiosyncratic drug reaction, and the potential mechanisms involved
9. Define the term teratogen and identify the key time windows when tetatogen exposure is most profound
10. Describe the classification of drugs used in pregnancy with particular focus on the potential risk/benefit to the mother and fetus

#11 - DRUG DISCOVERY & CLINICAL TRIALS

Date: Wednesday, August 9th, 2017 – 10:30 am

KEY CONCEPTS & LEARNING OBJECTIVES

At the end of the lecture the learner will be able to:

1. Describe the principal three stages of drug discovery and development and their specific roles in the drug development process

2. Describe the essential elements of compound-centered and target-centered drug discovery

3. Define the role of lead drug optimization in the context of the drug development process

4. Describe the principal goal of pre-clinical drug development, the major steps involved in this process and their primary function.

5. Describe the process by which a new drug candidate becomes an approved new drug.

6. Describe the functions of the Food and Drug Administration (FDA) in the drug approval process

7. Describe the composition, primary functions and role of Institutional Review boards in the drug approval process

8. Describe the primary purpose of an Investigational New Drug Application (IND) and list the major required components of the application.

9. Describe the three distinct types of Investigational New Drug Application (IND) and their specific uses.

10. Describe the basic elements and primary purpose of the four stages of clinical trial, including the typical number of participants, the setting, typical trial design, endpoints and primary objective

11. Define terms used to describe clinical trials and study design

12. Define the purpose and contents of a New Drug Application (NDA)

13. List the FDA-approved data that must be included on the approved drug packaging label

14. Define the three classes of drug recall

15. Describe the process by which generic drugs are approved including what critical pharmacological information needs to be provided to support the application

16. Describe drug repurposing/drug repositioning and its potential advantages in the drug discovery process