DRUG DISTRIBUTION

Katzung' s Basic & Clinical Pharmacology, 16th Edition
Goodman and Gilmans The Pharmacological Basis of Therapeutics, 13th Edition

Pre-Lecture Assessment

1. Drugs that dissolve in water (water-soluble drugs), such as such as the antihypertensive drug atenolol, tend to stay where in the body?

A. Ones
B. Blood
C. Muscle
D. Nerves
E. Fat

Pre-Lecture Assessment

4. The Initial distribution of drug into the tissue is determined chiefly by

A. Rate of blood flow to tissue
B. Plasma protein binding of drug
C. Affinity for tissue
D. Gastric emptying time
E. pH of the medium

MOTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Pre-Lecture Assessment

2. Drugs that dissolve in fat (fat-soluble drugs), such as the antianxiety drug clorazepate, tend to concentrate in fatty tissues, which act as a reservoir of extra drug. How does this affect the distribution of a fat-soluble drug?

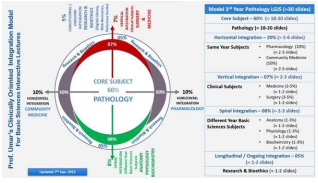
A. The drug's effects do not last long
B. It is more potent.
C. It must be taken more often.
D. Its effects are prolonged.
E. It has short t1/2

Pre-Lecture Assessment

5. The distribution of drugs into the central nervous system (brain) usually depends on:

A. Aqueous diffusion
B. Lipid diffusion
C. Active transport
D. Facilitated transport
E. Endocytosis

UMAR' S MODEL OF INTEGRATION



Pre-Lecture Assessment

3. Distribution of a drug may vary from person to person. Distribution of a fat soluble drug in older people may be similar to distribution in which other people?

A. Young people
B. Obese people
C. Thin people
D. Very thin people
E. Children

Pre-Lecture Assessment

6. Which of the following is most likely to be associated with a high apparent volume of distribution

a. High hepatic extraction ratio
b. Penetration across the blood:brain and blood:testes barriers
c. Extensive binding to plasma protein
d. Extensive binding to tissue constituents
e. High clearance

Pre-Lecture Assessment

7. If the plasma concentration immediately after an IV bolus injection of 100 mg of drug is 8 ug/mL, what is the volume of distribution?

A) 12.5 mL
B) 800 mL
C) 80 L
D) 12.5 L
E) 125 L

Pre-Lecture Assessment

10. Following intravenous administration, drugs are distributed fastest to:

(a) the skin, kidney, and brain
(b) the liver, kidney, and brain
(c) the liver, adipose, and brain
(d) the liver, kidney, and adipose
(e) the lung , liver and bone

FACTORS AFFECTING DISTRIBUTION

- Regional blood flow (perfusion rate)
- Capillary permeability
- Binding to plasma and tissue proteins
- Tissue permeability of drugs
- Miscellaneous factors

Core-Pharmacology

Pre-Lecture Assessment

8. A 70 kg man with severe burns arrives in the Emergency Department and requires i.v. morphine to treat his pain. The Vd for morphine is 200 L. What i.v. loading dose do you need to give to rapidly achieve a therapeutic level of 60 ng/ml and relieve his pain?

A. 3 ug
B. 30 ug
C. 120 ug
D. 12 mg
E. 30 mg

LEARNING OBJECTIVES

- Recall drug distribution
- Discuss the factors affecting drug distribution
- Describe plasma protein binding and its effect on drug distribution
- Recognize the importance of drug distribution
- Define volume of distribution
- Express volume of distribution mathematically

FACTORS AFFECTING DISTRIBUTION

Regional Blood Flow/ Perfusion Rate

- Greater the blood flow, faster is the rate of distribution
- There are two phase of distribution based on perfusion rate:
  - Rapid initial phase
  - Slow second phase

Organs/tissue	*% of Body Volume*	*Blood Flow (ml/min)*	*% of Cardiac Output*	*Perfusion Rate (ml/min/ml)*
I. Highly Perfused				
1. Lungs	0.7	5000	100.0	10.2
2. Kidneys	0.4	1250	25.0	4.5
3. Adrenals	0.03	25	0.5	1.2
4. Liver	2.3	1350	27.0	0.8
5. Heart	0.5	200	4.0	0.6
6. Brain	2.0	700	14.0	0.5
II. Moderately Perfused				
7. Muscles	42.0	1000	20.0	0.034
8. Skin	15.0	350	7.0	0.033
III. Poorly Perfused				
9 Fat (adipose)	10.0	200	4.0	0.03
10.Bone (skeleton)	16.0	250	5.0	0.02

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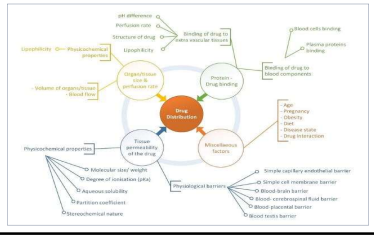
Pre-Lecture Assessment

9. Which one of the following has very low perfusion rate?

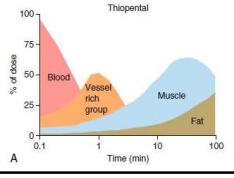
a) Fat and bone
b) Muscle and skin
c) Lungs and kidney
d) Liver and Heart
e) Brain and kidney

FACTORS AFFECTING DISTRIBUTION



FACTORS AFFECTING DISTRIBUTION

Regional Blood Flow/ Perfusion Rate



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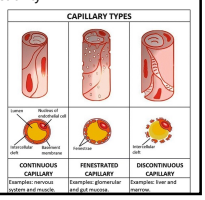
FACTORS AFFECTING DISTRIBUTION
Capillary permeability

- Capillary permeability is tissue dependent
- It determines the ease with which the drug crosses the blood tissue barrier



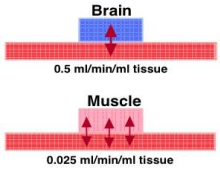
FACTORS AFFECTING DISTRIBUTION
Plasma Protein Binding

- **Albumin**
  Most abundant plasma protein
  Multiple drug binding sites
  Binds acidic drugs (one or two molecule/albumin)
  Subject to change in different diseases
- **α1 glycoprotein**
  Binds basic drugs
  Levels vary in certain conditions(stress, trauma, injury)
- **Lipoproteins**
  Drugs dissolve in the lipid portion of lipoprotein core
  Binding capacity depends upon the lipid content
- **Globulins (α1,α2-globulins)**
- Binds to endogenous substances

FACTORS AFFECTING DISTRIBUTION
Extravascular/ Tissue Binding

- **Liver :** Paracetamol, chloroquine, digoxin
- **Skin** : Chloroquine
- **Eye** : Ephedrine, atropine
- **Bones & teeth** : Tetracycline, phenytoin
- **Fat :** DDT, thiopental, minocycline
- **Skeletal muscle**, **heart** : digoxin, emetine
- **Brain** : acetazolamide, chlorpromazine
- **Kidney, vestibular apparatus** : gentamicin

FACTORS AFFECTING DISTRIBUTION



FACTORS AFFECTING DISTRIBUTION
Plasma Protein Binding

Protein	*Molecular Weight*	*Concentration (g%)*	*Drugs that bind*
Human Serum Albumin	65,000	3.5-5.0	Large variety of all types of drugs
α1-Acid Glycoprotein	44,000	0.04-0.1	Basic drugs such as imipramine, lidocaine, quinidine, etc.
Lipoproteins	200,000 to 3,400,000	Variable	Basic, lipophilic drugs like chlorpromazine
α1-Globulin	59,000	0.003-0.007	Steroids like corticosterone, and thyroxine and cyanocobalamin
α2-Globulin	1,34,000	0.015-0.06	Vitamins A, D, E and K and cupric ions
Haemoglobin	64,500	11-16	Phenytoin, pentobarbital, and phenothiazines

FACTORS AFFECTING DISTRIBUTION
Tissue Permeability of Drugs

- ❖ Physiochemical properties of drugs
  - Molecular size
  - Molecular charge
  - pKa-Degree of ionization
  - Lipid/ water solubility
- ❖ Physiological barriers to drug distribution
  - Blood brain barrier
  - Placental barrier
  - Blood testis barrier

FACTORS AFFECTING DISTRIBUTION
Protein Binding of Drugs

- Formation of reversible complexes between drugs and blood components and extravascular tissues
- Protein-binding data are frequently expressed in terms of per cent bound. (90% bound are called highly bound drugs)
- Binding of drugs to proteins falls into 2 categories:

i. Blood components
- ❖ Plasma proteins
- ❖ Blood cells (barbiturates, chlorpromazine, imipramine, and phenytoin)

ii. Extravascular tissue proteins

FACTORS AFFECTING DISTRIBUTION
Plasma Protein Binding

- Binding between the drug and plasma proteins is reversible
- The unbound concentration of drug in plasma and tissues will be the same at equilibrium
- Unbound fraction is pharmacological and toxicological active (drug design)
- Binding affects the duration and intensity of drug action
- Endogenous substances and co-administered drugs compete for binding sites
- Bound drugs can act as drug reservoir
- Determinants of plasma protein binding are :

i. Concentration of the drug
ii. Number of available binding sites
iii. Affinity for binding sites (association constant)

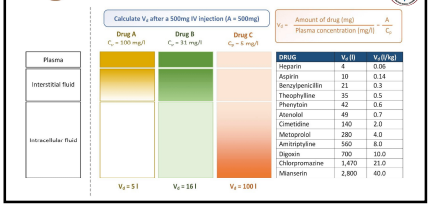
FACTORS AFFECTING DISTRIBUTION
Miscellaneous

- ❖ Age
- ❖ Gender
- ❖ Pregnancy
- ❖ Obesity
- ❖ Oedema
- ❖ Ascites

CLINICAL CONSEQUENCE OF DIFFERENT DIFFUSION PATTERN

- Slow onset of pharmacologic effect of some drugs (e.g., Digoxin)
- Termination of pharmacologic effect after bolus intravenous injection of others (e.g., Thiopental and lidocaine).
- Predict effectiveness of dialysis in removal of drugs in overdose

VOLUME OF DISTRIBUTION



DRUG	V_d (l)	V_d (l/kg)
Heparin	4	0.06
Aspirin	10	0.14
Benzylpenicillin	21	0.3
Theophylline	35	0.5
Phenytoin	42	0.6
Atenolol	49	0.7
Cimetidine	140	2.0
Metoprolol	280	4.0
Amitriptyline	560	8.0
Digoxin	700	10.0
Chlorpromazine	1,470	21.0
Mianserin	2,800	40.0

VOLUME OF DISTRIBUTION

Clinical Significance

- Vd is used to determine the loading dose needed to achieve a certain concentration.

Loading dose= Vd x desired concentration

- Predict effectiveness of dialysis in removal of drugs in overdose

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VOLUME OF DISTRIBUTION

- Volume of distribution is the volume of fluid "apparently" required to contain the total-body amount of drug homogeneously at a concentration equal to that in plasma (or blood)
- Vd is a *proportionality constant* that relates the total amount of drug in the body to the plasma concentration of the drug at a given time.

$$Vd = \frac{\text{Amount of drug administered (D)}}{\text{Plasma concentration ©}}$$

Core-Pharmacology

VOLUME OF DISTRIBUTION

- Volume of distribution provides a reference for the plasma concentration expected for a given dose
- Vd is a pharmacokinetic parameter representing an individual drug's propensity to either remain in the plasma or redistribute to other tissue compartments
- Vd is a characteristic property of the drug rather than the patient, although disease states may influence Vd

Core-Pharmacology

RESEARCH

Wang Y, Chen L. Lung tissue distribution of drugs as a key factor for COVID-19 treatment. British Journal of Pharmacology. 2020 Nov;177(21):4995.

VOLUME OF DISTRIBUTION

Table 1: Examples of volume of distribution estimates

Drug	% plasma protein binding	Lipid solubility/ tissue binding	Volume of distribution (L/kg)
Warfarin	99	low	0.14
Gentamicin	< 10	low	0.25
Amoxicillin	18	low	0.30
Theophylline	40	low/medium	0.48
Phenytoin	90	medium	0.70
Diazepam	99	high	1.10
Digoxin	25	high	7.00
Amitriptyline	95	high	15.00
Chloroquine	61	high	115.00

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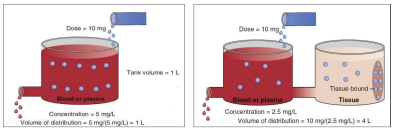
Assessment of the Extent of Drug Distribution

Consider two beakers, each filled with 1 L of water



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BIOETHICS

- Extensively bound drugs (phenytoin, diazepam etc) should be prescribed cautiously in patients with co –morbidities (chronic renal failure, chronic liver disease)

ARTIFICIAL INTELLIGENCE

Yuan Y, Chang S, Zhang Z, Li Z, Li S, Xie P, Yau WP, Lin H, Cai W, Zhang Y, Xiang X. A novel strategy for prediction of human plasma protein binding using machine learning techniques. Chemometrics and Intelligent Laboratory Systems. 2020 Apr 15;199:103962.