Drug Distribution

Objectives

- to understand the processes by which drugs distribute throughout the body
- to understand the effect of protein binding on drug distribution
- to understand the methods used to measure protein binding

Drug Distribution

- transfer of drug between regions of the body
- distribution between blood/plasma, tissues, organ, body fluids
- drug characteristics, tissue properties and blood flow determine distribution

Distribution Patterns

- drug stays within vascular system
- drug distributes throughout body water
- drug concentrates in specific tissues
- drug distributes throughout body and tissue

Drug Stays in Vascular System

- Large molecular weight or tightly bound to plasma protein
  - e.g. plasma substitutes

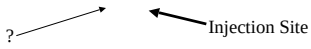
Drug Distributes in Body Water

- Low molecular weight molecules
  - e.g. ethanol, water (D_20)

Drug Concentrates in Specific Tissues

- Chloroquine in liver
  - concentration 1000 times plasma concentration
- Tetracycline to bone, teeth
- Radiopharmaceuticals
- Iodine in thyroid glands
- PCBs, highly lipid soluble compounds in fat tissue

Normal Bone Scan with ^{99m}Tc-MDP



Saha, G.B. 1984 Fundamentals of Nuclear Pharmacy, 2nd ed. P239 Fig 12-26

Drug Concentrates in Specific Tissues

- Chloroquine in liver
  - concentration 1000 times plasma concentration
- Tetracycline to bone, teeth
- Radiopharmaceuticals
- Iodine in thyroid glands
- PCBs, highly lipid soluble compounds in fat tissue

PCBs, highly lipid soluble compounds in fat tissue

- PCBs = polychlorinated biphenyls
  - Pesticide extenders … industrial uses
  - Study in growing
  - Excreted only in
  - http://www.epa.g
- DDT = dicophane
  - Banned in severa
- *Silent Spring* by R

Industrial Uses - Restricted
Adhesives
Transformers
Large, high- and low-voltage capacitors
Liquid-cooled electric motors
Hydraulic systems
Heat-transfer systems
Fluorescent light ballasts
Electromagnets
Liquid-filled cable …

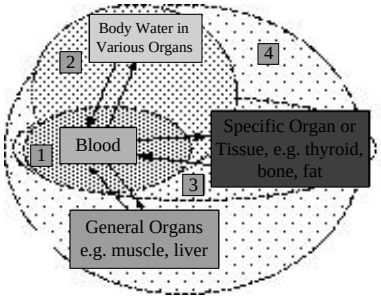
PCBs, highly lipid soluble compounds in fat tissue

- PCBs = polychlorinated biphenyls
  - Pesticide extenders … industrial uses
  - Study in growing pigs
  - Excreted only in milk
  - http://www.epa.gov/toxteam/trtpcb1.htm
- DDT = dicophane
  - Banned in several countries
- *Silent Spring* by Rachel Carson, 1962

Drug Distributes throughout Tissues and Body Fluids

- Distribution determined by ability to pass through membranes, and lipid/water partition
- A common distribution pattern
- Highest concentration often in organs of elimination
  - kidney, liver, intestine

Distribution Patterns



Apparent Volume of Distribution

Drug	Liter/Kg	Liter/70 Kg
Chloroquine	94 – 250	6600 – 17500
Nortriptyline	21	1500
Digoxin	7	500
Lidocaine	1.7	120
Theophylline	0.5	35
Tolbutamide	0.11	8

Apparent Volume

- Pattern 1 > 3-5 L
- Pattern 2 > 30 - 50 L (total body water)
- Pattern 3 > Very large V
  - Chloroquine 17,000 L
- Pattern 4 > 10 - 200 L
  - Lidocaine 120 L

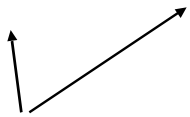
Test Values

Fluid	Volume (L)	Test Substance
Extracellular Fluid	13 – 16	Inulin, Na^{23}, Br^-, I^-
Plasma	3 – 4	Evans Blue, I^{131} Albumin, Dextrans
Interstitial Fluid	10 – 13	--
Intracellular Fluid	25 – 28	--
Total Body Water	40 – 46	Antipyrine, D_20, Ethanol

Factors Affecting Drug Distribution

- Rate of Distribution
  - Membrane Permeability
  - Blood Perfusion
- Extent of Distribution
  - Lipid Solubility
  - pH - pKa
  - Plasma Protein Binding
  - Intracellular Binding

Membrane Permeability



The walls of capillaries are very thin, consisting of only a single layer of endothelial cells, making them highly permeable

Capillary Walls

- quite permeable
- lipid material passes through quickly
- water soluble material more slowly
- pH and pKa influence transfer
  - renal capillaries and hepatic sinusoids allow extensive transfer
  - 'blood-brain' barrier restrict transfer to lipid soluble drugs

Blood Perfusion Rate

Organ	Perfusion Rate (ml/min/ml)	% of Cardiac Output
Bone	0.02	5
Brain	**0.5**	**14**
Fat	0.03	4
Heart	0.6	4
Kidney	**4.0**	**22**
Liver	**0.8**	**27**
Muscle	0.025	**15**
Skin	0.024	**6**

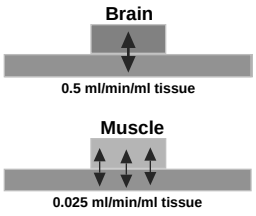
Blood Perfusion…

- % of C.O. highest for brain, kidney, liver, muscle
- Perfusion rate highest for brain, kidney, liver, heart
- Concentration should change rapidly in these organs
  - other organs: adrenals (1.2/0.2%) and thyroid (2.4/1%)

Relative Perfusion…

- thiopental gets into brain faster than into muscle
  - thiopental gets across brain or muscle quickly: perfusion limited - brain has higher perfusion [perfusion limited]
- penicillin gets into muscle more quickly than into brain
  - penicillin more polar, only slowly perfused into brain [transfer limited]

Relative Perfusion



Extent of Distribution

- Plasma protein binding
  - proteins involved
  - forces involved
  - protein binding determination
  - protein binding equilibria
- Tissue localization

Plasma Protein Binding

- Proteins involved
- Albumin
- α_1-acid glycoprotein
- lipoprotein
- globulins

Binding Sites

Drugs	**Binding Sites**
• Bilirubin, Bile acids, Fatty Acids, Vitamin C, Salicylates, Sulfonamides, Barbiturates, Phenylbutazone, Tetracyclines, Probenecid	Acidic Agents Albumin
• Adenisone, Quinacrine, Quinine, Streptomycin, Chloramphenicol, Digitoxin, Ouabain, Coumarin	Basic Agents Globulins, α_1, β_1, β_2, γ

Forces Involved

- Electrostatic Interactions
  - $-NH_3^+$ of lysine and N-terminal amino acids
  - $-NH_2^+$ of histidine and $-S^-$ of cysteine
  - $-COO^-$ of aspartic and glutamic acid
- van der Waal's forces
  - dipole - dipole, dipole - induced, induced dipole - induced dipole
- hydrogen bonding

Binding Forces

- short range forces distorted by altered protein configuration
- binding may be competitive resulting in displacement

Percent Unbound

Drug	Percent Unbound
Caffeine	90
Digoxin	77
Gentamicin	50
Theophylline	85
Phenytoin	13
Diazepam	4
Warfarin	0.8
Phenylbutazone	5
Dicumarol	3

Changes in Binding

- Slight changes in binding of tightly bound drugs can be significant
  - 99 to 98% leads to double the free concentrations
  - increased activity
  - increased elimination
- e.g. phenylbutazone displacing tolbutamide

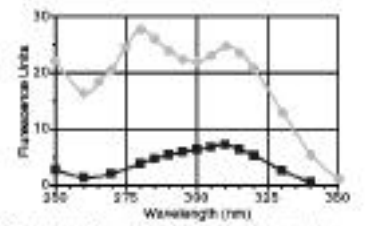
Protein Binding Determination

- Spectral changes
- Gel filtration
- Equilibrium dialysis
- Ultrafiltration

Spectral Changes

- Drug have distinct UV or visible spectra
  - absorbance versus wavelength
- Free and bound drug may have different spectra
- Fraction bound can be quantitated
- Fluorescence spectra could be used - warfarin

Spectral Changes



Redrawn from Chignell, C.F. (1973) Recent Advances in Methodology: Spectroscopic Techniques, Acta, NY Academy of Science, 226, p55

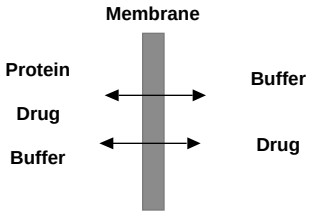
Gel Filtration

- Porous gel acts as a molecular sieve
- Components separated on the basis of molecular size
  - Bound drug moves quickly
  - Free drug held in gel pores
- Determination of free and bound drug

Equilibrium Dialysis

- Free drug passes freely through membrane
- At equilibrium free concentration on each side of membrane is the same
- Equilibrium after 12 - 24 hours
- Drugs must be stable
- Concentrations can be determined on either side of the membrane

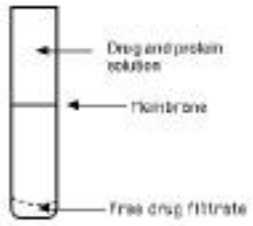
Equilibrium Dialysis…



Ultrafiltration

- Faster separation
- Free solution in solution is forced through membrane by centrifugation
- Filtrate contains free drug concentration

Ultrafiltration…



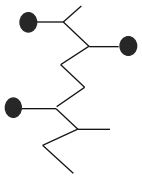
Protein Binding Equilibria

with One Type of Binding Site

$$[D] + [nP - rP] \underset{Kd}{\overset{Ka}{\rightleftharpoons}} [DP]$$

- [D] is free drug concentration
- [nP] total binding sites = n • [P]
- [rP] bound sites
- [nP - rP] is free protein binding site

Binding Sites



n = 4
r = 3

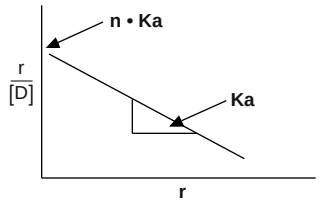
Ka = Association Constant

$$Ka = \frac{[\text{Concentration Bound}]}{[D] \bullet [\text{Protein Free}]}$$

$$= \frac{[rP]}{[D] \bullet [nP - rP]}$$

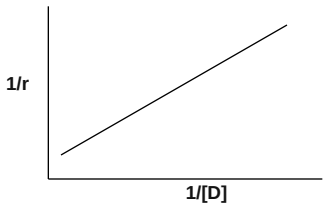
where $r = \frac{[DP]}{[P]_{total}} = \frac{[\text{Drug Bound}]}{[\text{Total Protein}]}$

Scatchard Plot



$$\frac{r}{[D]} = n \bullet Ka - Ka \bullet r$$

Double Reciprocal



$$\frac{1}{r} = \frac{1}{(n \bullet Ka \bullet [D])} + \frac{1}{n}$$

Data Analysis - Plots

- One type of binding site
  - straight line
  - use slope and intercept
- Two or more binding sites
  - curved line plot
  - curve fitting

Tissue Localization (Binding)

- Binding to intracellular molecules, drug receptor >> pharmacological effect
- Binding to tissue protein (albumin, etc.), nucleic acids, or dissolution in lipid
  - e.g. chloroquine in liver > DNA
  - barbiturates > adipose tissue
  - tetracycline > bone
- Difficult to measure - disrupt binding

Weight Consideration

- Apparent volume of distribution, V, often proportional to body weight
  - V often reported as xxx L/kg
- Appropriate if tissue proportions similar
- Very young or old could be quite different
- Overweight or underweight quite different
  - different proportions of adipose tissue
  - e.g. antipyrine 0.62 L/kg in normal weight and 0.46 L/kg in obese individuals

Protein Binding Interaction

- One drug may displace another from the same binding site
- One drug bound may alter binding of another
- Interactions can occur when one drug displaces another
- Free drug concentration usually the important factor with drug activity
- Higher free drug concentration often causes an increase in elimination

Objectives

- to understand the processes by which drugs distribute throughout the body
- to understand the effect of protein binding on drug distribution
- to understand the methods used to measure protein binding