

Drug Distribution

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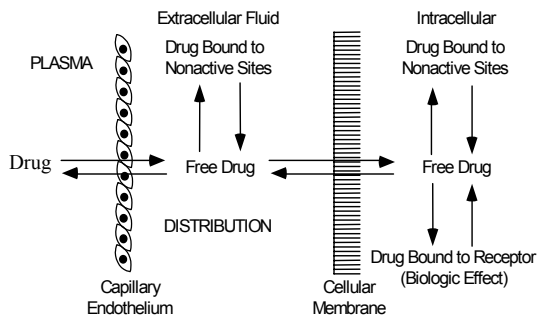
Distribution & Volume of Distribution

Distribution: the passage of drugs from blood to tissues.

Volume of Distribution (Vd): apparent volume of body water that drug appears to distribute into to produce a drug concentration equal to that in the blood.

Key factor in the onset of drug action.

Distribution of Drugs



Body Water Compartments

BODY WATER COMPARTMENTS:		50Kg	&	100Kg
		(110 lb)		(220 lb)
Total body water	(60% body weight) = 0.6 L/Kg,	30 L	&	60 L
Extracellular	(20% body weight) = 0.2L/Kg,	10 L	&	20 L
Plasma	(4% body weight) = 0.04L/Kg,	2 L	&	4 L
Interstitial	(16% body weight) = 0.16L/Kg,	8 L	&	16 L
Intracellular	(40% body weight) = 0.4 L/Kg,	20 L	&	40 L

Volume of Distribution (L)

Expressed as liters of body water in a 70 (154 lb) Kg man.

$$Vd = Q/C$$

Q = amount of drug in body (g)

C = unbound plasma drug concentration (g/liter)

Calculate Vd when 1 g is administered iv and the plasma drug level is 0.024 g/L.

$$Vd = 1 \text{ g} / 0.024 \text{ g/L} = 42 \text{ L} \quad (\text{Total Body Water})$$

Volume of Distribution (% BW)

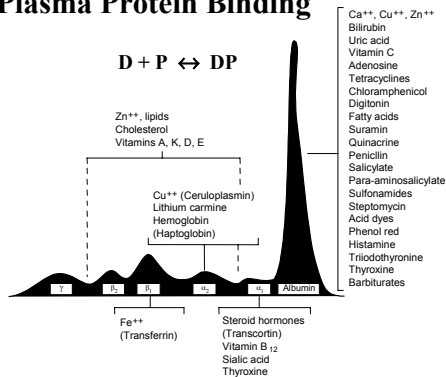
Expressed as % of body weight in a 70 Kg man.

$$Vd = (Q)(100)/(C) \quad (\text{body weight in Kg})$$

Q = drug dose **C** = plasma drug level

$$Vd = (1 \text{ g})(100)/(0.024 \text{ g/L})(70) = 60\% \quad (\text{Total Body Water})$$

Plasma Protein Binding



Plasma Protein Binding of Drugs

$D + P \leftrightarrow DP$ (reversible binding)

Bound drug is in equilibrium with free drug.

Free drug is **active** and bound drug is **inactive**.

More free drug when binding sites are saturated.

Competition between drugs for binding sites.

Percent of Protein Bound Drug [I]

Drug is 90% bound to plasma protein.

Patient is a 30 year old male weighing 70 Kg.

What % of total drug is bound if drug's Vd is:

Vd = 3 L (PLASMA)

90% PD \times 3 L = 270 PD; 10% D \times 3 L = 30 D

Total Drug = PD + D = 300; % PD = 270/300 = 90%

% of total drug bound (90%) is equal to plasma PD %.

Percent of Protein Bound Drug [II]

What % of total drug is bound if drug's Vd is:

Vd = 14 L (EXTRACELLULAR BODY WATER)

90% PD \times 3 L = 270 PD; 10% D \times 14 L = 140 D

Total Drug = PD + D = 410; % PD = 270/410 = 66%

% of total drug bound (66%) is less than blood PD %.

Percent of Protein Bound Drug [III]

What % of total drug is bound if drug's Vd is:

Vd = 42 L (TOTAL BODY WATER) [70 Kg]

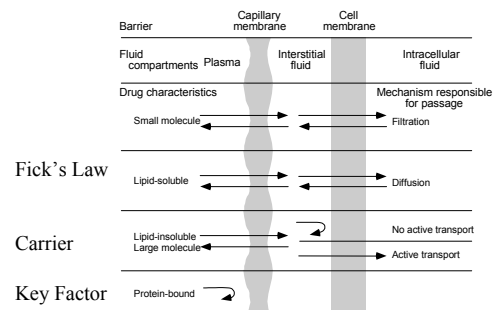
90% PD \times 3 L = 270 PD; 10% D \times 42 L = 420 D

Total Drug = PD + D = 690; % PD = 270/690 = 39.1%

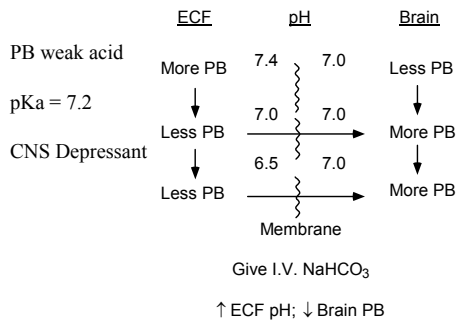
% total drug bound (39.1) is less than plasma PD % .

As Vd increases the % of total drug bound decreases.

Passage of Drugs Across Membranes



Phenobarbital [PB] Poisoning



Blood Flow to Various Tissues

Rapidly perfused (ml/100 g/min) tissues respond quickly

- Brain (55)
- Liver (20)
- Kidney (450)

Less rapidly perfused tissues respond to drug more slowly

- Muscle (3)
- Skin (5)

Poorly perfused tissues respond very slowly to drug

- Fat (1)

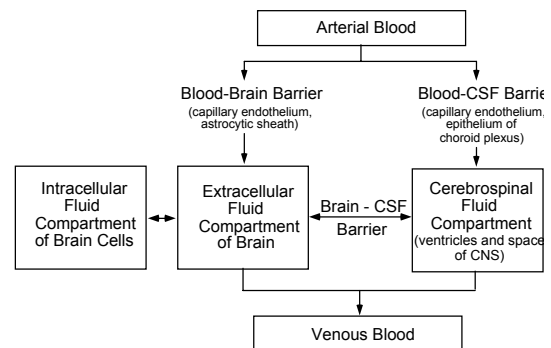
Aging Effect on Drug Distribution

Increased fat and decreased lean body mass (higher Vd of some drugs)

Decreased total and % body water (lower Vd of some drugs)

Decrease in serum albumin (more free drug)

Drug Distribution in CNS



Fetal Drug Distribution

Most drugs readily distribute by passive diffusion

Epithelium of villi is the only major barrier

Endothelium of capillaries

Risks

Abortion and abnormal development [**Cocaine, Tamoxifen**]
 Malformation [**Thalidomide, Methotrexate, Organic Solvents**]
 Alter behavior and intelligence [**Alcohol, Cocaine, Amphetamines**]
 Produce cancer later in life [**Diethylstilbesterol**]
 Dependence/Withdrawal [**Heroin, Morphine and Cocaine**]
 Intrauterine growth retardation, prematurity, SIDS [**Smoking**]

Drug Reservoirs

Stomach ionizes basic drugs and traps them (pH effect)

Albumin binds various drugs and limits distribution

Tissues such as the liver can avidly bind drugs (**chloroquine**)

Lipid soluble compounds can localize in fat tissue (**thiopental**)

Redistribution of Thiopental

