SEMINAR ON
VOLUME OF DISTRIBUTION

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CONTENTS:

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OBJECTIVE:

- To understand and describe the processes by which drugs are distributed throughout the body
- To differentiate between apparent volume of distribution & true physiological volume
- To understand the effect of protein and tissue binding on volume of drug distribution.
**DEFINITION:**

- The **volume of distribution** \( (V_D) \), also known as **apparent volume of distribution**, is a **pharmacological** term used to quantify the **distribution** of a **medication** between **plasma** and the rest of the body after **oral** or **parenteral** dosing.

- It is defined as the volume in which the amount of drug would need to be uniformly distributed to produce the observed blood concentration.

- The volume of distribution is a hypothetical volume of fluid into which a drug is distributed, it’s a useful in predicting amount of drug in the body.
Dose = Cp \times V_D

Total amount of drug in the body at equilibrium

V_D = \dfrac{X_0}{KE \cdot AUC}
<table>
<thead>
<tr>
<th>Fluid substances</th>
<th>Volume (liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra cellular Fluid</td>
<td>14</td>
</tr>
<tr>
<td>a) Plasma</td>
<td>3-4</td>
</tr>
<tr>
<td>b) Interstitial fluid</td>
<td>10</td>
</tr>
<tr>
<td>Intracellular fluids</td>
<td>28</td>
</tr>
<tr>
<td>Total body water</td>
<td>42</td>
</tr>
</tbody>
</table>
Water compartments of the body:
Once absorbed into the plasma a drug can be distributed to one of three (or all three) distinct fluid compartments. Plasma compartment (6% body mass). Extracellular fluid (20% body mass). Total body water (60% body mass).
Drug Distribution:

- Distribution is the reversible transfer of a drug between the blood & the extravascular tissues.

- Drug distribution is the process by which a drug reversibly leaves the plasma and enters the extracellular fluid to reach cells and tissues.

- This process depends on blood flow, capillary permeability, the degree of drug binding to plasma and tissue proteins and drug solubility.
Disposition of Drugs
PROTEIN BINDING OF DRUGS:

- Extensive plasma protein binding will cause more drug to stay in the central blood compartment.

- Therefore drugs which bind strongly to plasma protein tend to have lower volumes of distribution. 
  \( \uparrow \text{Protein binding} = \downarrow V_D \)

- Although drugs are bound to many macromolecules, binding to plasma protein is the most common. Of these plasma proteins, albumin, which comprises 50% of the total proteins binds the widest range of drugs.
Contd...

- Drugs bound to plasma proteins are unable to diffuse to active sites. Irreversibly bound drugs are lost, reversibly bound drugs will respond to the concentration gradient in plasma as free drug is sequestered. It is the free drug that is active.

- This binding tends to be non-specific, drugs and endogenous substances can compete for binding sites. Albumin is the major drug binding entity and acts as a reservoir of drug.
<table>
<thead>
<tr>
<th>Binding Sites</th>
<th>Acidic Drugs</th>
<th>Basic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumins/HSA</td>
<td>Globulins, $\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$, $\gamma$</td>
<td></td>
</tr>
<tr>
<td>Bilirubin, Bile acids, Fatty Acids, Vitamin C, Salicylates, Sulfonamides, Barbiturates, Phenylbutazone, Penicillins, Tetracyclines, Probenecid</td>
<td>Adenine, Quinacrine, Quinine, Streptomycin, Chloramphenicol, Digitoxin, Ouabain, Coumarin</td>
<td></td>
</tr>
</tbody>
</table>
Acidic drugs commonly bind to \textit{albumin}, while basic drugs often bind to \textit{\textit{\alpha}_1\text{-acid glycoproteins}} and \textit{lipoproteins}. Many endogenous substances, steroids, vitamins, and metal ions are bound to globulins.

\textbf{PROTEIN BINDING DETERMINATION:}

- \textit{Spectral changes}
- \textit{Gel filtration}
- \textit{Equilibrium dialysis}
- \textit{Ultra filtration}
The one compartment model assumption is that there is a rapid equilibration in drug concentrations throughout the body, however, this does not mean that the concentration is the same throughout the body. This is illustrated in Figure below....
In the first beaker the concentration throughout the beaker is the same and the apparent volume of distribution is the same as the size of the beaker. In the second beaker after a rapid equilibrium, distribution between the solution (representing plasma) and the charcoal (representing various tissues of the body) may be complete.

However, drug concentrations within the beaker (representing the patient) are not uniform. Much of the drug is held with the charcoal leaving much smaller concentrations in the solution. After measuring the drug concentration in the solution the apparent volume of the patient is much larger.
**Figure:**

**Drug concentration in beaker:**
- **Dose:** 10 mg
- **Cp₀:** 20 mg/L
- **Apparent Volume:** 500 ml

**With charcoal in beaker:**
- **Dose:** 10 mg
- **Cp₀:** 2 mg/L
- **Apparent Volume:** 5000 ml
Examples of apparent $V_D$ for some drugs:

<table>
<thead>
<tr>
<th>Drug</th>
<th>L/Kg</th>
<th>L/70 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfisoxazole</td>
<td>0.16</td>
<td>11.2</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0.63</td>
<td>44.1</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>0.55</td>
<td>38.5</td>
</tr>
<tr>
<td>Diazepam</td>
<td>2.4</td>
<td>168</td>
</tr>
<tr>
<td>Digoxin</td>
<td>7</td>
<td>490</td>
</tr>
</tbody>
</table>
### FACTORS AFFECTING $V_D$

<table>
<thead>
<tr>
<th>A - Rate of distribution</th>
<th>B - Extent of Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Membrane permeability</td>
<td>1. Lipid Solubility</td>
</tr>
<tr>
<td>2. Blood perfusion</td>
<td>2. pH - pKa</td>
</tr>
<tr>
<td></td>
<td>3. Plasma protein binding</td>
</tr>
<tr>
<td></td>
<td>4. Tissue drug binding</td>
</tr>
<tr>
<td>Organ</td>
<td>Perfusion Rate (mL/min/mL of tissue)</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Bone</td>
<td>0.02</td>
</tr>
<tr>
<td>Brain</td>
<td>0.5 - 0.55</td>
</tr>
<tr>
<td>Fat</td>
<td>0.01 - 0.03</td>
</tr>
<tr>
<td>Heart</td>
<td>0.6 - 0.7</td>
</tr>
<tr>
<td>Kidneys</td>
<td>4.0 - 4.5</td>
</tr>
<tr>
<td>Liver</td>
<td>0.8 - 0.95</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.025 - 0.030</td>
</tr>
<tr>
<td>Skin</td>
<td>0.04 - 0.05</td>
</tr>
<tr>
<td>Lungs</td>
<td>10-10.2</td>
</tr>
</tbody>
</table>
CAPILLARY / MEMBRANE PERMEABILITY:
- Capillary permeability is determined by capillary structure.
- In the liver & spleen large openings between the discontinuous endothelial cells allows even large plasma proteins to pass easily.
- Most capillaries allows large molecules to pass with little impedance, permeability is responsive to both local & systemic factors (inflammation).

- The CNS blood brain barrier is created by tight junctions between endothelial cells and a basement membrane supported by astrocytic foot processes; this presents a formidable barrier to drug penetration. Lipid soluble agents or drugs with specific transport mechanisms can penetrate rapidly.
A  Structure of endothelial cells in the liver

Large fenestrations allow drugs to exchange freely between blood and interstitium in the liver.

B  Structure of a brain capillary

Astrocyte foot processes

At tight junctions, two adjoining cells merge so that the cells are physically joined and form a continuous wall that prevents many substances from entering the brain.

C  Permeability of a brain capillary

Charged drug

Lipid-soluble drugs

Carrier-mediated transport
Blood Perfusion/flow:

- Tissue distribution of a drug is dependent on transport in the bloodstream. High flow tissues (brain, liver, & kidney) receive drugs in large volumes prior to muscle & adipose tissue. Some tissues have such low blood flow that drug delivery is a major concern (cartilage, connective tissue, abscess).

Lipid Solubility:

C. Drug structure has a major influence on a drug's ability to penetrate membranes. **Hydrophobic, nonpolar drugs with uniform electron distribution and no net charge** (but still soluble in an aqueous state) move directly through endothelial membranes to reach targets. Polar, hydrophilic, charged molecules must pass through endothelial slit junctions.
Tissue binding of drugs:

- Certain drugs may bind to specific tissues proteins in addition to plasma proteins. They may also bind to other macromolecules such as melanin or DNA.

- The higher the binding of a drug to the tissue/macromolecule, the decrease in plasma conc. Results in increase in apparent $V_D$.

- Tissue binding of a drug cannot be determined directly. Binding studies are important in understanding the distribution of drugs.

- Order of binding:
  - liver > kidney > lungs > muscles.
Factors affecting protein binding

- **Drug related factors:**
  1. physicochemical characteristics of the drug
  2. Conc. Of the drug in the body
  3. Affinity of the drug for binding component

- **Protein related factors:**
  1. physicochemical characteristics of the protein
  2. Conc. Of the protein/binding component
  3. No. of binding sites on the binding agent
Drug interactions:
1. Competition between drugs for binding site
2. Competition between drugs & normal body constituents
3. Allosteric changes in protein molecule

Patient related factors:
1. Age
2. Inter subject variation
3. Disease states
Steady state $V_D$:

- It's an estimate of drug distribution independent of elimination process.
- Amount of drug in the body during steady state is given by:

\[ A^{ss} = C^{ss} \cdot V_{ss} \]

$C^{ss} =$ steady state plasma concentration, which is obtained when drug is introduced into blood at a constant rate (i.e. iv-infusion)

$V_{ss} =$ steady state volume of distribution.
Relation ship between apparent $V_D$ & tissue binding of drugs:

$$V_D = V_P + V_T \frac{f_u}{f_u_t}$$

**Hence** $V_D$ is directly proportional to the free/unbound concentration of the drug in plasma.

$V_P = \text{volume of plasma}$

$V_T = \text{volume of extravascular tissues}.$
Relation between clearance & $V_D$ & elimination $t_{1/2}$:

- **Clearance** is defined as the hypothetical volume of body fluids containing drug from which the drug is removed or cleared in a specific period of time.
- It is expressed in “ml/min”

\[
\text{Cl}_t = K_E \cdot V_D = 0.693 \cdot V_D / t_{1/2}
\]

$K_E$ = apparent elimination rate constant

$\text{Cl}_t$ = total body clearance
Significance:

- Most of the drugs have an apparent volume of distribution smaller than or equal to, the body mass.
- For some drugs apparent $V_D$ will be several times the body mass.
- In i.v administration

$$V_D = \frac{\text{Dose}_{iv}}{C_p}$$

- For a given dose, a very small $C_p$ may occur in the body due to conc. of drug in peripheral tissues and organs, for this dose small $C_p \rightarrow$ large $V_D$
Drugs with large apparent $V_D$ more concentrated in extravascular tissues & less concentrated intravascularly.

If a drug is highly bound to plasma proteins or remains in vascular region then $C_p$ will be higher resulting in a smaller apparent $V_D$

$V_D$ is a volume term can be expressed in

- simple volume in liters
- % body weight
If $V_D$ is a large number i.e. $> 100\%$ of body weight then it may be assumed that the drug is more concentrated in certain tissue compartments. Thus the apparent $V_D$ is a useful parameter in considering the relative amounts of drug in the vascular & in the extravascular tissues.

If apparent $V_D$ for a particular drug is known, the total amount of drugs in the body at any time after administration of the drug may be determined by measurement of drug conc. in the plasma.
Apparent $V_D$ is a constant, for each drug. But in certain *pathologic cases*, the apparent $V_D$ for the drug may be altered, if the distribution of the drug is changed.

Example: In *edematous condition*, total body water + total extracellular water increases, this is reflected in a large apparent $V_D$ for a drug that is *highly water soluble*.

Similarly changes in *total body weight*, *lean body mass* may also affect the apparent $V_D$.
Vd is useful in determining an appropriate dose to obtain a particular plasma level, therapeutic levels are measured and referenced to plasma levels.

A large Vd has an important influence on the half-life of a drug because elimination usually depends on the amount of free drug delivered to the liver or kidney, with a large volume of distribution much/most of a drug will be extravascular or protein bound and not readily available to excretory organs.

\[
\text{Cl}_t = K_E \cdot V_D = 0.693 \cdot V_D / t_{1/2}
\]
Conclusion:

- Apparent $V_D$ is simply a proportionality constant relating the plasma concentration to the total amount of drug in the body.

- Depending on the degree of binding to plasma proteins & tissues, the apparent $V_D$ of a drug may vary in man from $0.04L/kg$ – $20L/kg$ or more.

- Actual distribution volume of a drug is related to body water, it never exceeds TBW. i.e. about 60% body weight or 42L in a normal 70 kg adult.
• **References:**

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Thank u..