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Sheet ○Slides

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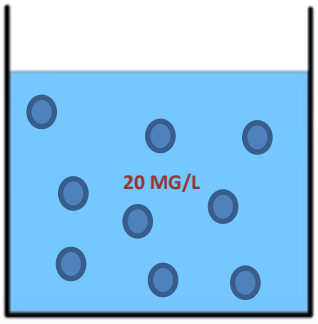
Volume of Distribution (Vd)

Understand the concept

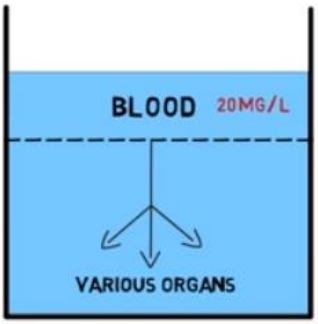
Imagine having a container with an unknown volume of water in it. Then **1000mg** of a drug is added and dissolved completely in the water.



A **sample** is then taken from the container and the concentration of the drug is for example, **50mg/L**. Now, to estimate the **total volume** of the water the drug distributed in, we apply the following formula:

$$\text{Volume of Distribution} = \frac{\text{Drug amount (mg)}}{\text{Concentration (mg/L)}} = \frac{1000}{50} = 20\text{L}$$

So if we apply that concept on **the human body**, we can estimate the **volume a drug** distributes through. However, a human body is a little different from that container; the drug injected into the blood, may distribute into **other tissues**, which explains why the volume of distribution, in a particular compartment in the body, is sometimes way larger than its **original capacity**. That's why the Vd is **not real** but rather a **theoretical measure** that can tell us how a drug is distributed.



Taking the formula into consideration, we realize that:

1) The **higher the Vd**, the **lower** the concertation of the drug **in the plasma**, indicating that drug got **distributed** into other tissues.
2) The **lower the Vd**, the **higher** the concertation of the drug **in the plasma**, indicating that drug **didn't** distribute into other tissues, which maybe because of the fact that:
   - **a-** The drug has **high affinity** towards plasma protein, thus **binding** to them and **not** leaving the plasma.
   - **b-** The drug is **too large** to leave the plasma membrane.

Examine the following drugs and their Volume of distribution

Warfarin	**7**	**Small Vd** indicating that the drug mainly stays in the **plasma** and **less** in other tissues.
Gentamicin	**16**	
Theophylline	**35**	**Medium Vd** indicating that **similar** concentrations of the drug in the **plasma** and **tissues**.
Cimetidine	**140**	
Digoxin	**520**	**Large Vd** indicating that the drug **mainly** distributes into the **tissues** and **less** remains in the **plasma**.
Mianserin	**910**	
Quinacrine	**50,000**	

Note: *Warfarin Reflects a high degree of* ***plasma protein binding****, thus having* ***a low Vd.***

To sum up

Volume of Distribution is a **theoretical measure** of the **apparent space** in the body needed to **contain a drug.**

Its importance lies in the fact that it will **predict** whether a drug will reside in the **plasma** or in the **tissue.**

Formula: $$\boldsymbol{Volume\ of\ Distribution = \frac{Drug\ amount\ injected\ (mg)}{Drug\ concentration\ in\ the\ plasma\ (mg/L)}}$$

Example 1: 50mg of a drug was injected into a patient. A sample of the blood was taken and the concentration of the drug appeared to be **2.5mg/L**. Find the volume of distribution.

$$Volume\ of\ Distribution = \frac{50\ mg}{2.5\ mg/L} = 20\ L$$

Example 2: The same amount **(50mg)** of another drug was injected. However, this drug has a **high binding affinity to proteins**, thus more amount of the drug remaining in the blood. The concentration of the drug in a sample taken was **5mg/L**. Find the volume of distribution.

$$Volume\ of\ Distribution = \frac{50\ mg}{5\ mg/L} = 10\ L$$

Note how drugs that are **highly bound to proteins** have **low Vd.**

Volume of Distribution and body weight

Vd **depends** on the weight of the human body. If a certain drug for example **Theophylline**, has a distribution value of **0.48 L/Kg**, then in a human with **60kgs** Theophylline would distribute through:

$$Vd = \frac{0.48\ L/Kg}{60\ Kg} = 28.8\ L$$

Practice Calculation:

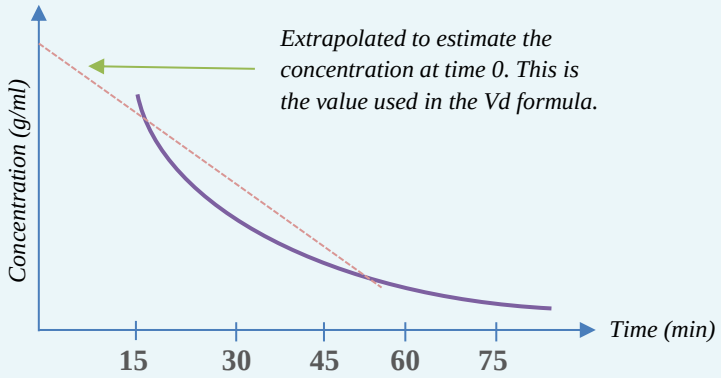
A dose of analgesic **(50mg)** is administered through IV and a blood sample is taken shortly afterwards. The initial concentration of the analgesic in the blood sample was **0.85 µg/ml.** Calculate the volume of distribution of the analgesic in **Liters**. (pay attention to the units)

$$Vd = \frac{50 * 10^{-3} g}{0.85 * 10^{-6} g/ml} = 58{,}824\ mL = 59\ L$$

This is only an addition for understanding purposes.

When should a sample be taken from the blood in order to measure the concentration after the injection?

A plot is drawn in in order to find the volume of distribution of various drugs, where on ***the x-axis*** *we have the* ***time intervals*** *in which a sample is taken (e.g. each 15min), and on* ***the y-axis*** *is the* ***concentration of the drug*** *in the sample. Since we cant know the concentration at time 0 because the drug didn't take time to distribute yet, we* ***extrapolate*** *the curve (which is the extension of a curve of values to conclude* ***unknown*** *values from trends of known data) to estimate the concentration at time 0 which is* ***used in the Vd formula****.*



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Metabolism

It is the process of transformation of a drug within the body to make it **more hydrophilic** so that it can be **excreted out from the body** by the kidneys. If the drug stayed in the **lipophilic state**, it is going to be **reabsorbed** by the kidney and **accumulate** in the body for prolonged periods.

The liver is the **major** site of metabolism for many drugs, but other organs, such as **lungs**, **plasma**, **GI tract** and the **kidneys** can also metabolize drugs.

Metabolism results in:

1) Activation the drug
2) Inactivate the drug
3) Produce other active metabolites

> ***Note****: Metabolism* ***mostly****, but* ***not always****, results in* ***inactivation*** *of the drug.*

Metabolism can be affected by:

1) **Disease state:** For example if a liver disease is present **disrupting the liver's enzymatic activity**, then the liver won't work **as effectively** in **metabolism** as when it was healthy.

2) **Blood Flow**: **Less blood flow** to a certain site means that **less amount of the** drug is delivered to it, therefore the **metabolism rate** is **reduced** *(and vice versa)*.

3) **Inducers and Inhibitors**. *discussed later in this sheet*

4) **Genetic background** of the patient. *discussed in the next lecture :)*

5) **Tolerance**: Repeated administration of a drug results in a quantitate **increase** of the SER in the liver cells. Which leads to the **increase** of drug-metabolizing enzymes *(Increased rate of metabolism)*. So when the body metabolizes the drug **faster t**han it normally would, the **period of time** in which a drug is in its **minimum effective dose** is less, requiring a **higher** dose to reach the **same effect** it would cause normally (Known as Tolerance).

   Shortly said, Tolerance causes **increased** metabolic rate

Drug metabolism occurs in two phases:

Phase I

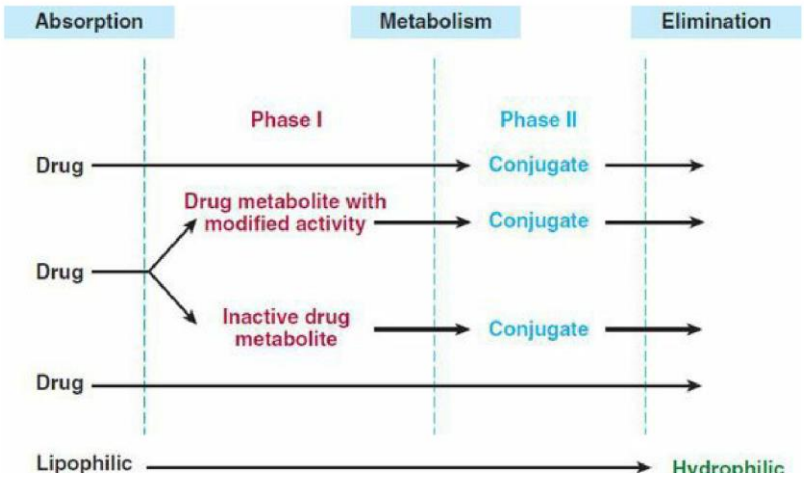
It consists of reactions such as **oxidation, reduction and hydrolysis** and is primarily catalyzed by **cytochrome P450s**. The purpose of this phase is to **decrease the lipophilicity** sufficiently *(increase water solubility)* and **alter the chemical activity** in order to **facilitate renal clearance**.

$$Drug + O^2 + NADPH + H^+ \rightarrow Drug_{modified} + H_2O + NADP+$$

If the metabolite from phase I is **polar enough**, it will **excreted by the kidney**. However, if it is **still lipophilic** to be **retained in the kidney**, Phase II metabolism will take place.

Phase II

It consist of **conjugation reactions** with **endogenous substances**, such as: **glucuronic acid, sulfuric acid, or an amino acid,** resulting in a **highly polar** and usually **more water soluble compounds**.



Cytochrome P450 system (CYP)

Most drugs are **metabolized by CYP proteins**, **decreasing** the amount of drug in the **active state.** However, CYP can be **induced or inhibited** by certain drugs altering the **rate of metabolism** of other drugs, causing **drug-drug interactions** by affecting the CYP's activity *(inducing/inhibition).*
*For this reason, taking different medications together is **strictly** controlled by doctors.*

Examples to understand the CYP's role in drug-drug interactions:

1) Cytochrome P450 enzymes **Inducers** like ***Rifampin and Carbamazepine*** induces the activity of the CYP enzymes.

   Rifampin for example, **induces CYP**, thus **decreasing the concentrations** of HIV **proteases inhibitors** in the plasma in which it won't reach the **minimum effective concentration** to produce the **therapeutic effect.**

2) Cytochrome P450 enzymes **inhibitors** like ***Omeprazole*** inhibits three CYP isoforms that are responsible for **Warfarin metabolism** (*Warfarin is used as an anti-coagulant).*

   Consequently, **elevating** the Warfarin concentration, and so **greater inhibition** of **coagulation**, leading in to more risk of **major bleeding event** and may reach to **toxic levels.**

3) Even **natural substances** found in foods can affect CYP enzymes, which in turn can alter drug responses. For example, **grapefruit juice** can inhibit a type of CYP enzyme that is important to degrade several types of drugs *(e.g. Lipitor which is used to reduce the level of bad cholesterol in the blood)*, thus **elevating** the concentrations of the drugs in the plasma and thereby increasing the risk of **toxicity with those drugs**.

Note: *Till now, **12 unique isoforms** of the CYP enzymatic system have been identified that play a role in human drug metabolism (e.g. CYP1A2, CYP 2D6, CYP3A4..). Each isoform has **various polymorphisms.** (discussed more in the next lecture)*

Good luck 😊