2. DISTRIBUTION

After absorption of the PA into the central circulation, the drug behavior is independent of the chosen administration pathway. The PA will be distributed in the circulation and within the body.

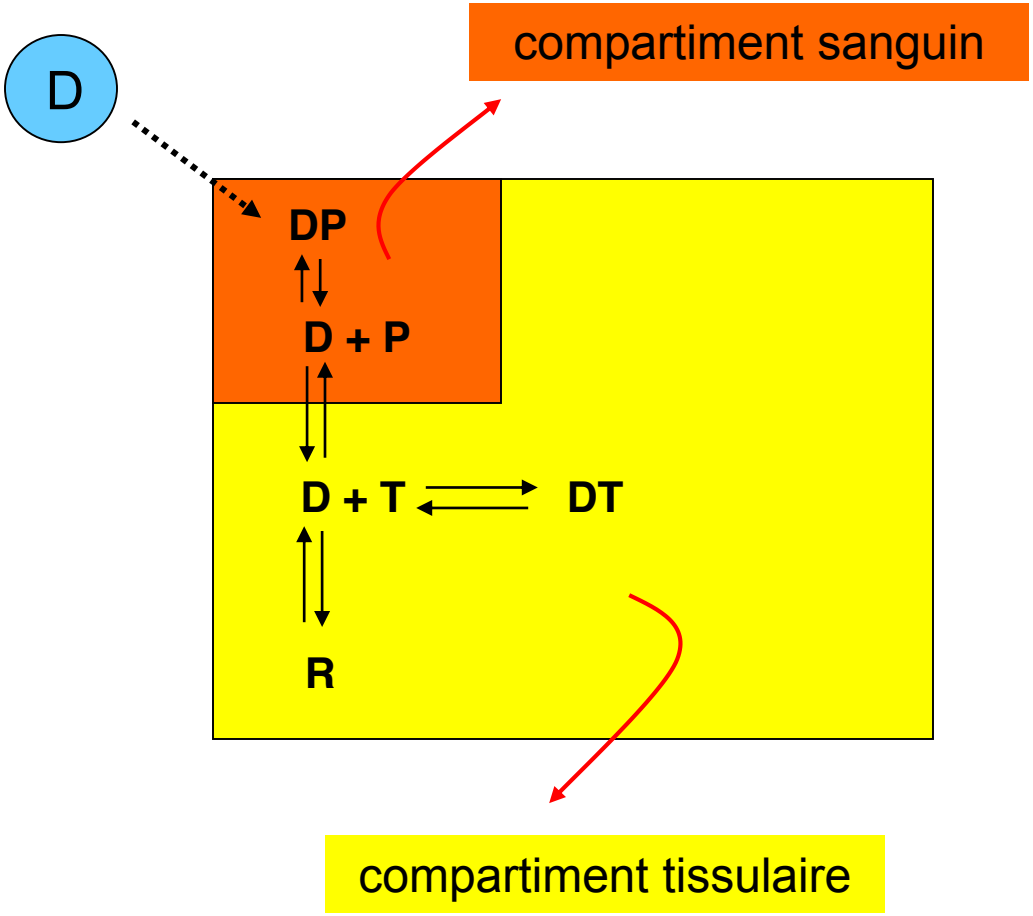
Distribution describes the reversal transfer of a PA from one location to another within the body.

As there are differences in pH, lipid content, cell membrane function and other factors between different tissues most PA are not equally distributed in the body.

Distribution

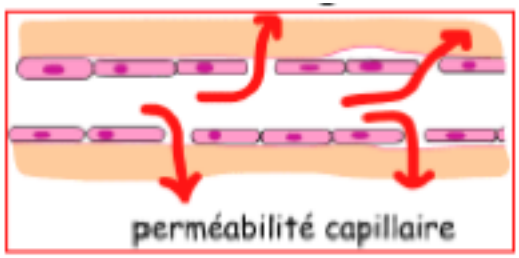
= forme pharmaceutique

D = principe actif forme libre
P = protéines plasmatiques
T = macromolécules tissulaires
R = récepteurs



The tissue distribution

La distribution tissulaire correspond au processus de répartition du médicament dans l'ensemble des tissus ou organes.



Facteurs influençant cette distribution :

- **Fixation protéique de la molécule**
- **Caractéristiques physicochimiques du composé (pKa, coeff. de partage)**
- **Irrigation des organes**
- **Affinité particulière des tissus**

2.1. Drug binding in the central circulation

• **Drug binding in the plasma** is the reversible interaction of drugs with proteins, with red blood cell and tissue membranes and other blood and tissue constituents.

Drug + Protein $\rightleftharpoons$ Protein-Drug complex

•A proportion of the drug will become bound in the plasma, but it is the unbound form which exhibits pharmacological effects

•The bound portion may act as a depot of the drug which is later released after the unbound portion is metabolized / excreted

•Alkalotic, acid and neutral drugs mainly bind to **albumin** and after saturation to **lipoprotein**

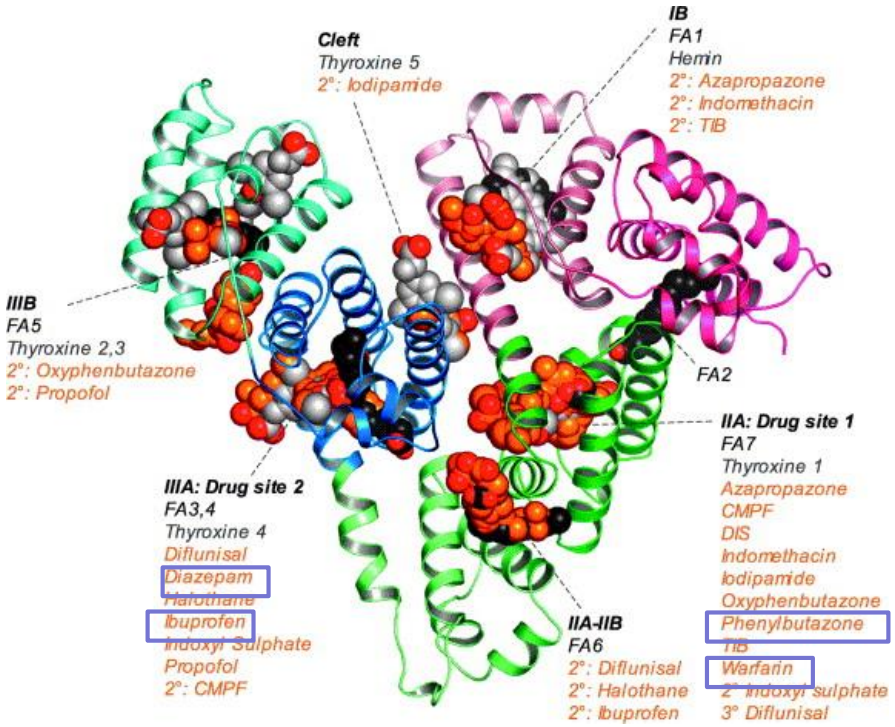
•Basic drugs will bind to **alpha-1 acid glycoprotein** (AAG)

•Various medical conditions will affect the levels of albumin, lipoprotein and AAG in the blood.

What are the binding proteins in plasma ?

A. Albumin

- Most abundant protein in human blood plasma
- transports hormones, fatty acids, and other compounds, buffers pH and maintains the osmotic pressure of the blood vessel, etc.
- has at least **six distinct binding sites** for drugs and endogenous compounds.
- There are **two major drug binding sites** called site I and site.
- Binds a wide range of different drug, thereby restricting their free, active concentration.
- Overcoming the binding affinity of a lead compound for Albumin is often a major challenge in drug development

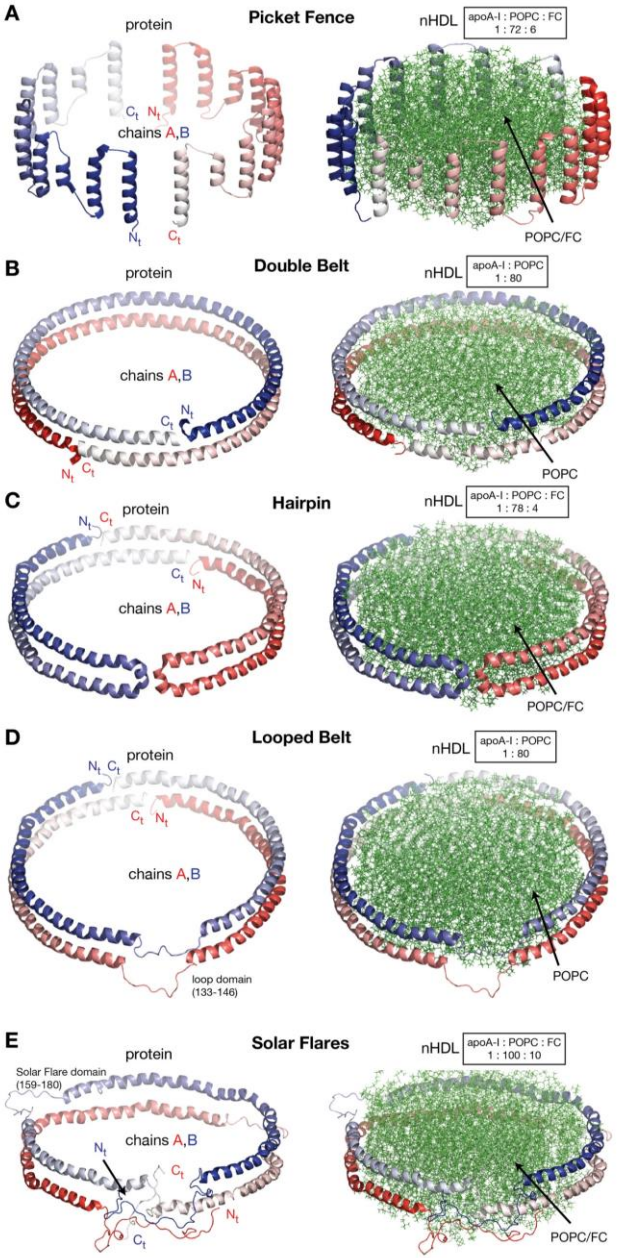


Taken from Ghuman, JBC, 2005

What are the binding proteins in plasma ?

B. Lipoproteins

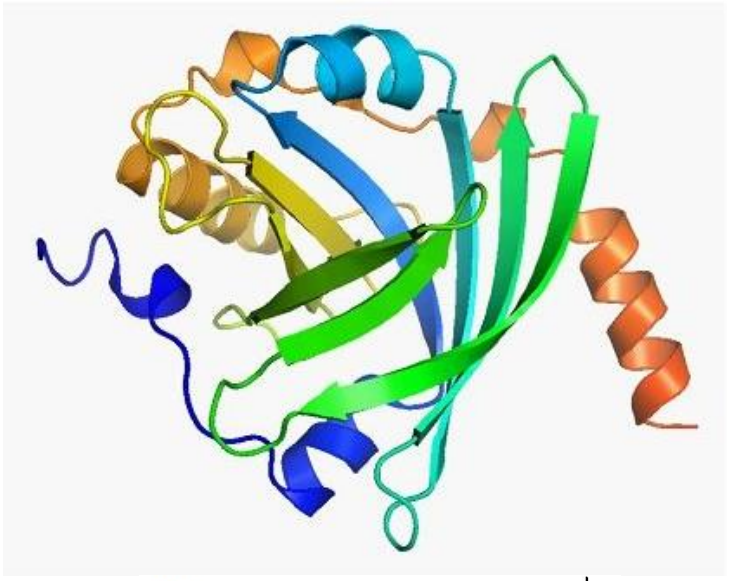
- A lipoprotein is an assembly that contains both lipids and proteins
- Enables lipids and fatty acids, transmembrane proteins of the mitochondria to be transported through the central circulation
- 'Binding' of drugs to **lipoproteins** is **more a dissolving of the drugs in the lipids of the membrane rather than a true binding reaction**.



Taken from Gogonea, Fron. Pharm. 2016

What are the binding proteins in plasma ?

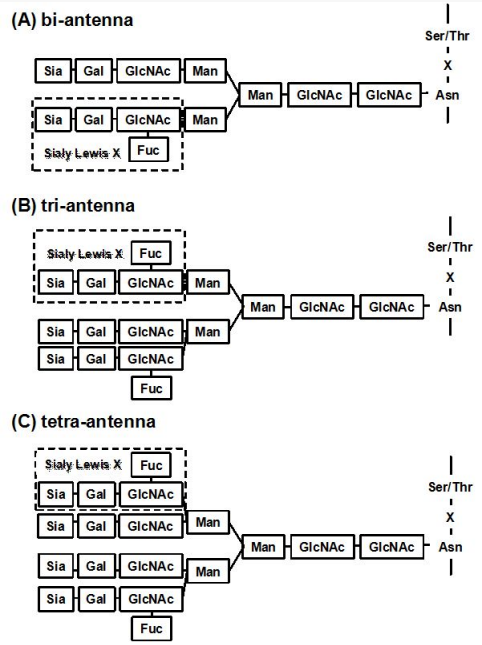
C. Alpha$_1$-acid glycoprotein



- highly solulable; immunomodulary activities dependent on its glycosylation
- **one binding site** selective for **basic drugs** such as disopyramide and lignocaine
- In healthy persons only a low plasma concentration

  ⟶ drug binding effects displaceable
- Acute phase protein ⟶ plasma concentration increases significantly due to certain diseases (cancer, inflammation, HIV) or following trauma (burns, surgery)

  ⟶ significant drug binding effect



Taken from Taguchi, „Acute Phase Proteins“ Book chapter 6, 2013

What determines extent of binding to plasma protein ?

The binding of a drug to a protein binding site is a saturable process governed by the same mass action expression that describes the interaction of a substrate with an enzyme binding site. The extent to which a drug is bound in plasma or blood is usually expressed as the fraction unbound (fu).

$$\text{fraction unbound (fu)} = \frac{\text{unbound drug concentration}}{\text{total drug concentration}}$$

The tighter the binding, the lower is the fraction unbound. The fraction unbound of a drug is determined by :

- **the affinity of the drug for the protein**
- **the concentration of the binding protein**
- **the concentration of drug relative to that of the binding protein**
- **the concentration of other compounds competiting for the same binding site.**

Unbound fraction in blood/plasma

principe actif	% lié	fu
glyburide	99.8	0.002
naproxène	99.7	0.003
félodipine	99.6	0.004
warfarin	99.0	0.01
sildénafil	96.0	0.04
oméprazole	95.0	0.05
fluoxétine	94.0	0.06
vérapamil	90.0	0.10
fentanyl	84.0	0.16
carbamazépine	74.0	0.26
indinavir	61.0	0.39
méthotrexate	46.0	0.54
ofloxacine	25.0	0.75
ranitidine	15.0	0.85
amikacine	4.0	0.96

$$fu = \frac{Cu}{Cp}$$

fu: fraction (*unbound*) libre dans le plasma

C*u*: conc. libre dans le plasma

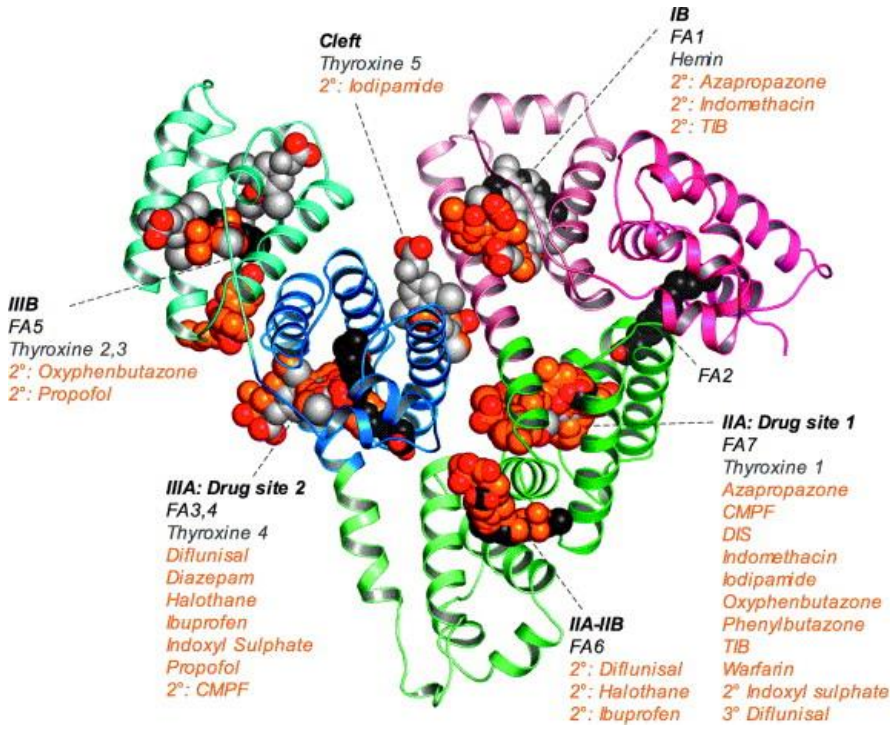
C*p*: conc. totale dans le plasma

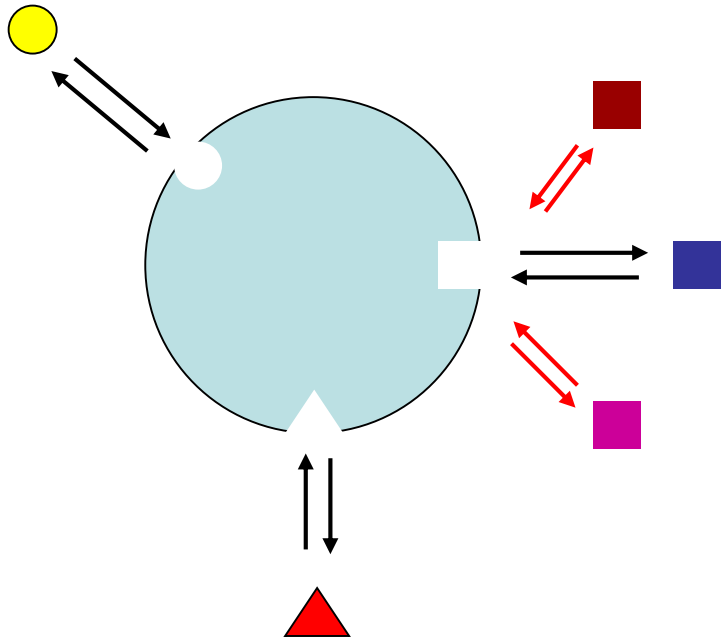
- Notably, it is the **unbound fraction** which exhibits **pharmacologic effects**.

- If the amount of plasma protein is decreased (such as in malnutrition, liver/renal **disease**), there would also be a **higher fraction unbound** !!!

Binding to the plasmatic proteins : Competition

Un PA (ou une substance endogène) peut entrer en compétition pour les mêmes sites de liaison à la protéine $\Rightarrow$ **compétition**





Taken from Ghuman, JBC, 2005

Drug Competitive Displacement

• Displacement of Drug A (highly protein bound) by competing Drug B

Drug A	Alone	Displaced by Drug B	% increase in unbound fraction
%bound	95	90	
%unbound	5	10	+ 100

•Displacement of Drug C (less protein bound)

Drug C	Alone	Displaced by Drug B	% increase in unbound fraction
%bound	50	45	
%unbound	50	55	+ 10

•Problematic for highly protein bound drugs with a low therapeutic index (for example Warfarin)?

Except in rare circumstances, protein binding displacement in vivo does not result in increased drug effect.

Protein binding & therapeutic drug monitoring

Drug assays for therapeutic drug monitoring nearly always measure total drug. **As it is the unbound drug which is active**, a false impression can be gained if fu is changed substantially.

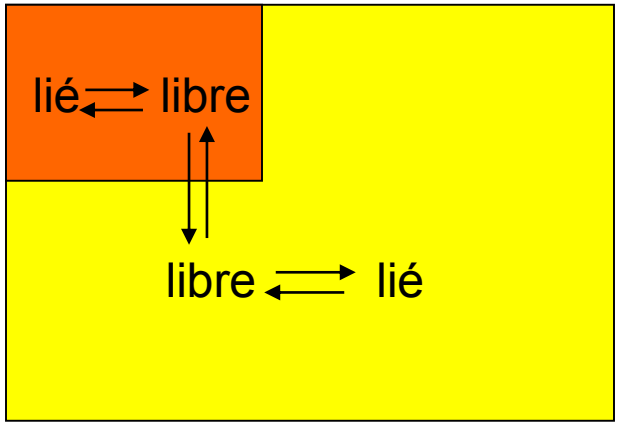
Example : Phenytoin binding to albumin is reduced particularly in renal failure patients, but also in some other situations such as liver disease or the presence of competitive drugs. In such cases, total concentration measurements are misleading and control of therapy needs to be based on measurements of unbound phenytoin concentration. Such measurements are available in specialised centres, but are expensive and currently are carried out only in special circumstances such as those mentioned above.

Protein binding and the therapeutic range of phenytoin

Patient	fu	Therapeutic range based on total drug mg/L	Therapeutic range based on unbound drug mg/L
Normal	0.1	10–20	1–2
Renal failure	0.2	5–10	1–2

Phenytoin fu averages 0.1 in normal patients, but increases up to a twofold in renal failure patients (GFR < 20 mL/min) due to low albumin concentration and accumulation of competing endogenous compounds.

Binding to tissue macromolecules or to erythrocytes



Contrairement à la liaison aux protéines plasmatiques, il est impossible de mesurer directement la liaison des PA aux macromolécules tissulaires sans endommager les tissus.

Un PA peut avoir une grande affinité pour les protéines plasmatiques, mais s'accumuler malgré tout dans les tissus si l'affinité pour les sites de liaison tissulaires est plus élévée.

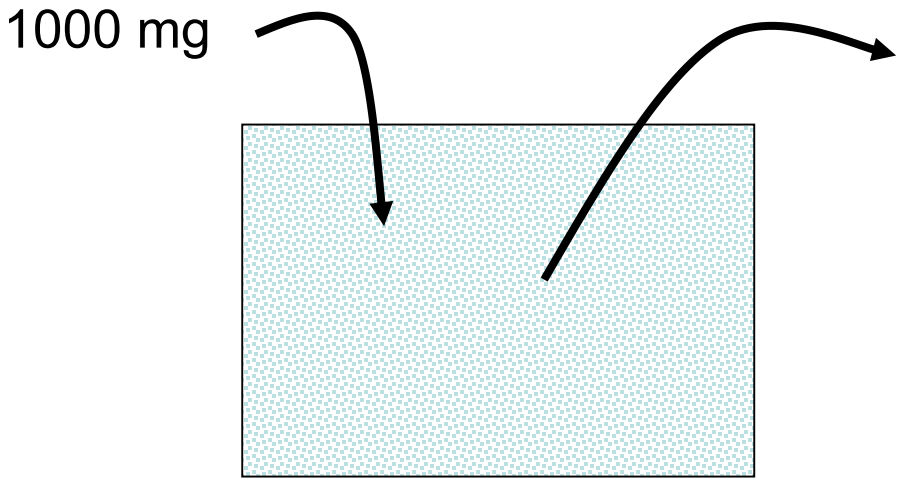
2.2. Volume of distribution

Definition: Fluid volume that would be required to contain the amount of drug present in the body at the same concentration as in the plasma under equilibrium conditions.

Quantity needed to determine how much drug must be given to the patient

The volume of distribution

Le calcul du volume de distribution d'un PA dans notre corps est analogue à la détermination du volume d'un réservoir qu'on obtient en divisant la quantité totale d'une substance ajoutée dans ce dernier par la concentration de la substance obtenue après vérification de l'homogénéité du mélange.

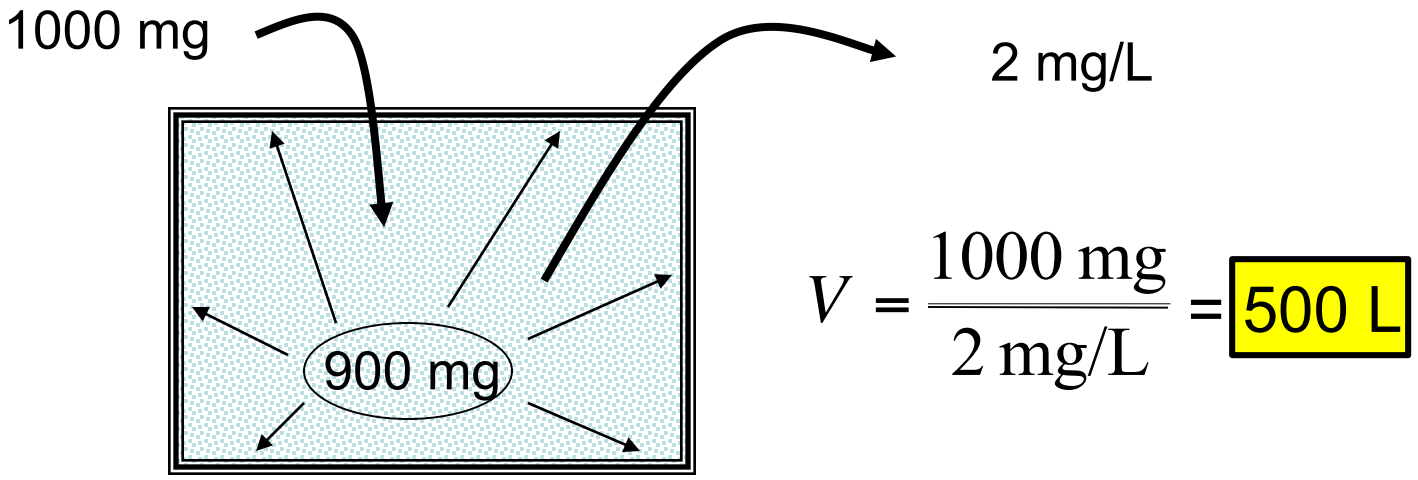


$$V = \frac{1000\ \text{mg}}{20\ \text{mg/L}} = 50\ \text{L}$$

Le volume ainsi mesuré représente un espace de dilution ou de distribution.

The volume of distribution

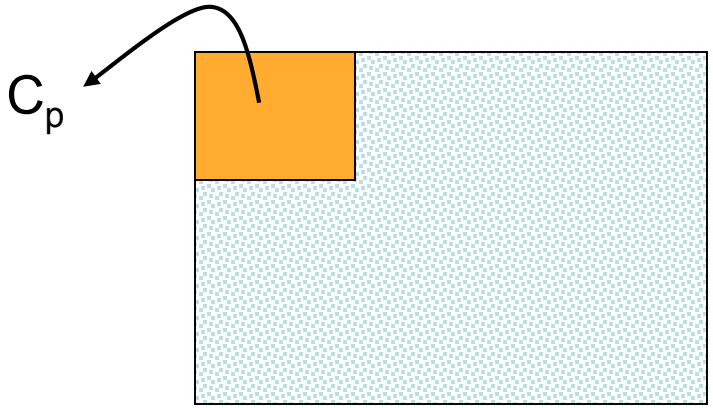
Supposons qu'on prend le même réservoir, qui a donc un volume de 50 L, mais maintenant à l'intérieur il y a une couche de charbon actif. Cette couche est tellement fine que le volume reste pratiquement 50 L mais si la substance ajoutée est adsorbée (à 90% soit 900 mg) par le charbon actif on va mesurer un volume apparent ou fictif qui ne représente plus le volume réel du réservoir.



Le volume mesuré est maintenant un volume fictif ou apparent parce que la répartition de la substance ajoutée n'est plus homogène.

The volume of distribution

Le calcul du volume apparent de distribution d'un PA dans le corps est analogue au dernier exemple. La concentration du PA est déterminée dans le plasma mais le PA n'est pas distribué d'une façon homogène dans le plasma et les autres organes/tissus du corps.



$$V_D = \frac{Q_{corps}}{C_p}$$

V_D est faible si la plupart du PA dans notre corps se trouve dans le plasma. Si, au contraire, le PA se trouve pour la plus grande partie dans les tissus le V_D sera large.

What is the volume of distribution (V) ?

Important: It is NOT a real 'volume'. It is a parameter relating the concentration of a drug in the plasma to the total amount of the drug in the body.

Example: If a drug has a plasma concentration of 10 mg/L when there is 1000 mg of the drug in the body, the volume of distribution would be 100 L.

$$V = \frac{\text{total amount of drug in body (A)}}{\text{plasma drug concentration (C)}}$$

The main determinant of V is the ratio of the fraction of drug unbound in the plasma to the fraction unbound in the tissues (fu/fu_T)

$$V = \text{plasma volume } (V_P) + \frac{\text{fraction unbound in plasma (fu)}}{\text{fraction unbound in tissue } (fu_T)} * \text{tissue volume } (V_T)$$

The volume of distribution

Drug	Vd (L)
Warfarin	8
Theophylline	35
Quinidine	150
Digoxine	420
Imipramine	2100
Chloroquine	15000

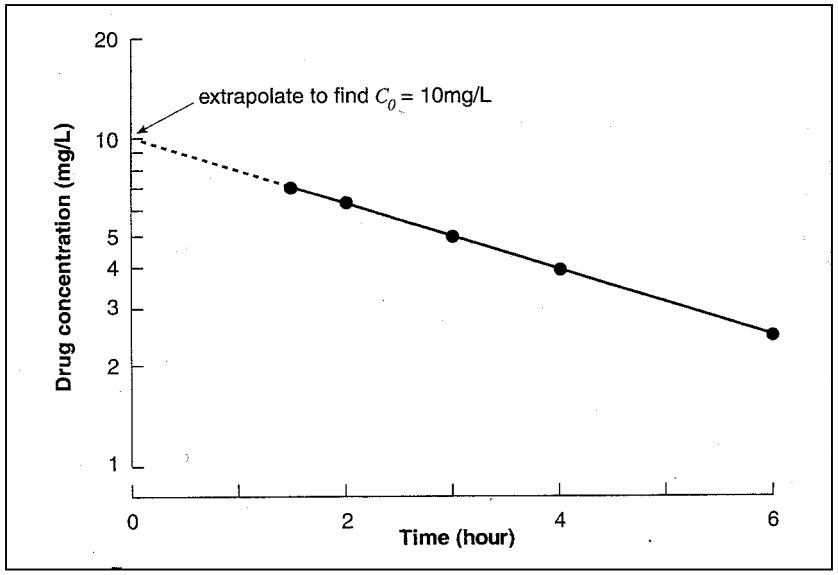
Many **acidic drugs** (eg, warfarin, aspirin) are **highly protein-bound** and thus have a **small** apparent volume of distribution. Many **basic drugs** (eg, amphetamine, meperidine) are extensively **taken up by tissues** and thus have an apparent volume of distribution **larger** than the volume of the entire body.

Factors influencing the volume of distribution

- Fixation aux protéines plasmatiques
- Caractères physico-chimiques du médicament
- Irrigation des organes
- Affinité pour les tissus
- Facteurs physiologiques : âge, grossesse, corpulence, …

How V is measured ?

Determination of V



$$V = \frac{\text{amount of drug in body}}{\text{plasma drug concentration}}$$

At zero time

$$V = \frac{A}{C} = \frac{\text{dose}}{C_0} = \frac{200}{10} = 20\text{L}$$

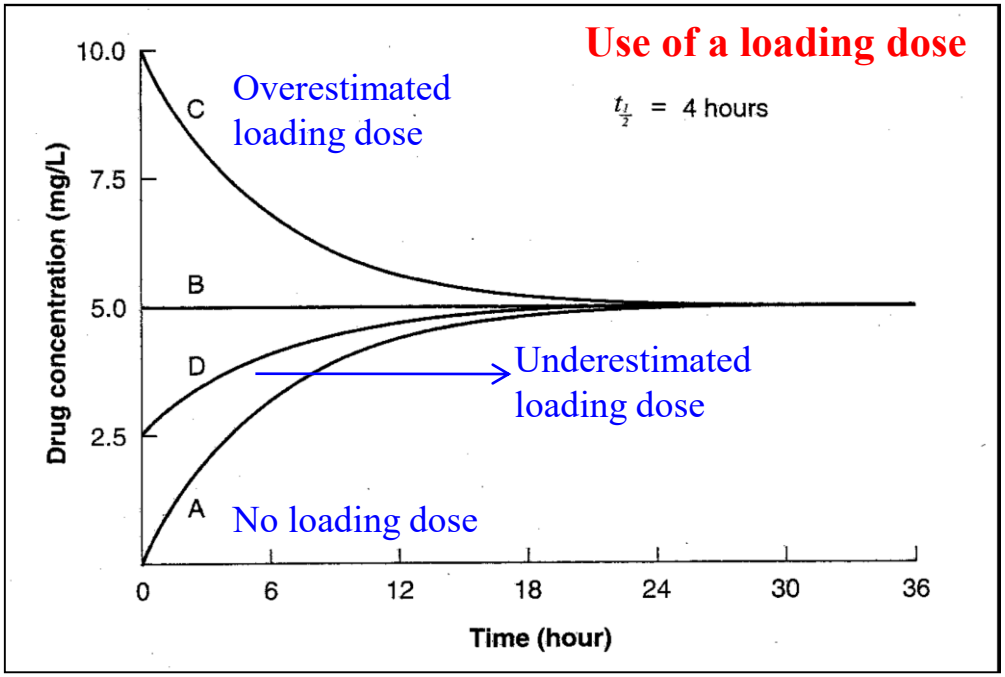
A dose of 200 mg was given and the first sample taken 1h30 later. Note that the drug concentration scale is logarithmic.

What is V used for ?

It takes some time to accumulate to steady state. To get close to steady state more quickly, a *loading dose* is often used and V is the determinant of the size of the loading dose.

loading dose = *V* target plasma concentration

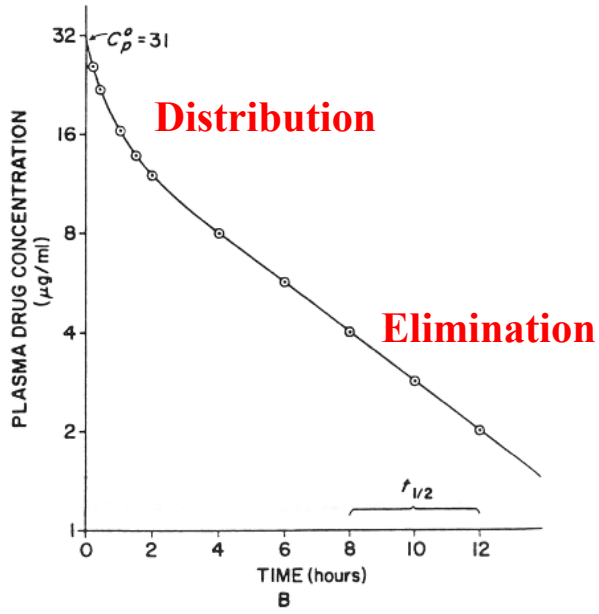
Example of Theophylline : 175 mg (for 70 kg patient) = 2.5 g/kg = 0.5 L/kg * 5 mg/L

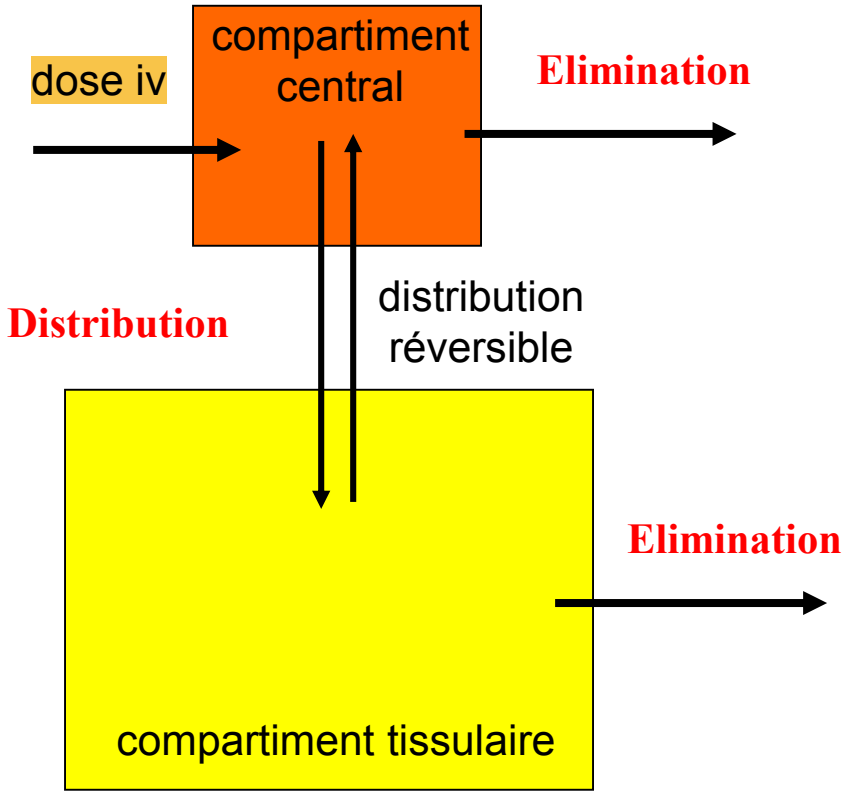


With no loading dose, drug accumulates slowly to steady state (dose A). Loading dose B happened to give an initial concentration the same as that maintained by the infusion which followed the loading dose. Loading dose C was overestimated and D underestimated. The initial concentrations in C and D are closer to the steady state concentration, but it still takes the same time (5 half-life) to reach steady state.

The compartment models

Aprés administration iv (bolus), la distribution du PA dans une série de **tissus bien perfusés** est considérée comme un **processus instantané**. La distribution dans les tissus **moins bien perfusés** est **plus lente** ce qui explique la décroissance bi-exponentielle des concentrations plasmatiques du PA.



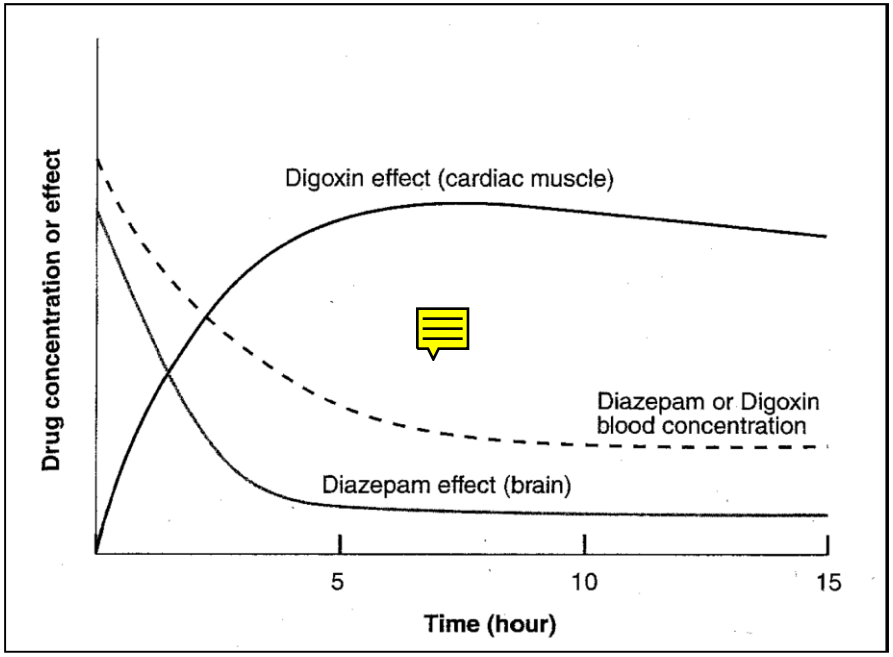


Blood flow in various organs

organ/tissue	Total blood flow (ml/min)	Blood flow per unit of mass (ml/min/100 g)	
lung	**5000**	**1000**	bien perfusé
kidney	**1100**	**400**	
adrenal gland	**25**	**120**	
liver	**1350**	**80**	
heart	**200**	**60**	
brain	**700**	**50**	
skin	**300**	**4**	peu perfusé
fat	**200**	**3**	
muscle	**750**	**2.5**	
bone	**250**	**2**	

Is the rate of distribution from blood to tissues important ?

The drug distributes from the blood into various tissues at a rate and to an extent which **depends on the perfusion of the tissue** and the ease with which the drug can pass through the lipid membranes of the cells. Some tissues such as the **brain are highly perfused** (drugs such as diazepam and thiopentone distribute very rapidly from the blood into them), while **skeletal muscle and fat are less perfused**.



Plasma drug concentrations falls rapidly initially due to redistribution and then more slowly due to elimination. The effect of diazepam is in a highly perfused tissue (brain). The site of action of digoxin is a compartment to which the drug is distributed slowly. Once the distribution phase is over, effects of both drugs are related to plasma concentration.

Plasma or blood drug concentration ?

It is the convention in pharmacokinetics to use *plasma* concentrations of drugs.

$$= \frac{\text{drug concentration in whole blood}}{\text{drug concentration in plasma}} = \frac{C_b}{C}$$

The ratio is usually close to 1.0 as the drug concentration in the cellular and plasma components of blood are usually about the same. The ratio cannot be less than about 0.5 (the haematocrit).

It can, however, be quite large **for highly lipophilic drugs** like cyclosporin and chloroquine which are relatively **concentrated in the red cells**.

In such cases, it is better to express CL and V in terms of drug concentrations in whole blood rather than in plasma.