3. METABOLISM AND EXCRETION

3.1. Clearance

- 'Clearance' describes the efficiency of irreversible elimination of a drug from the systemic circulation.
- 'Clearance' is the constant relating the concentration of drug in the plasma to the rate at which the drug is eliminated from the body.
- 'Clearance' is defined as the volume of blood cleared of drug per unit time (in L/hour).
- We can refer to clearance by a particular organ (liver, kidney, ...), by a particular metabolic pathway, or by the whole body. Total body clearance is the sum of all the different clearance processes occurring for a given drug.

elimination rate = clearance (CL) x plasma drug concentration (C)

(mg/hour) (L/hour) (mg/L)

Why is clearance important ?

Clearance is the one parameter that determines the maintenance dose rate required to achieve a target plasma concentration (and therefore effect) at steady state.

Steady state is defined as the situation at which the rate of drug administration is equal to the rate of drug elimination so that the amount of drug in the body, and therefore the plasma drug concentration, remains constant.

At steady state :

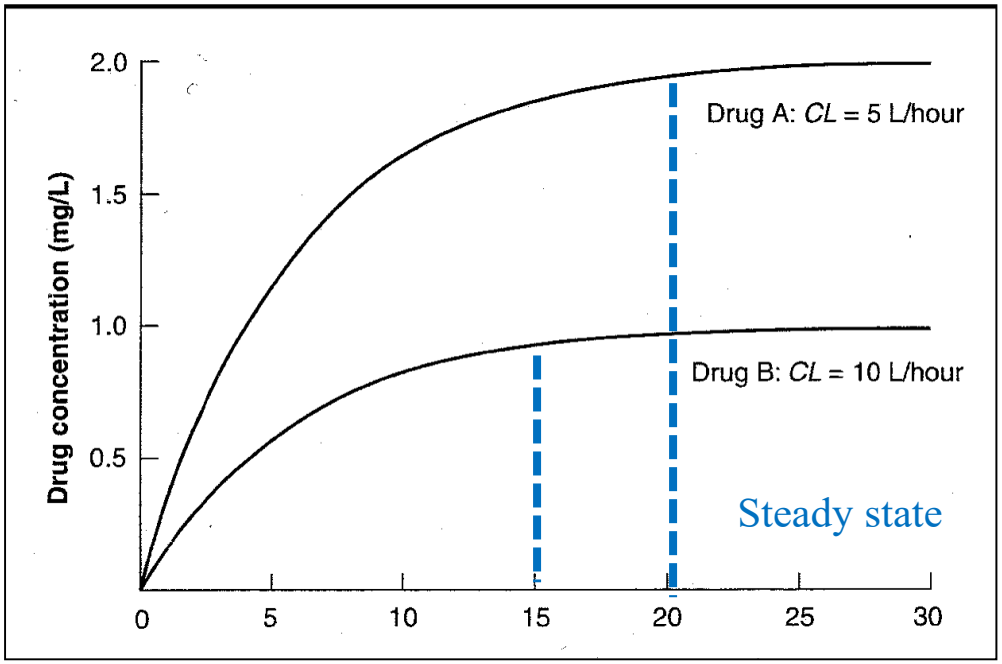
elimination rate = maintenance dose rate (DR)

DR = CL x steady state drug concentration (C_{SS})

(mg/hour) (L/hour) (mg/L)

Why is clearance important ?

Effect of clearance on steady state drug concentration



For A and B, the dose rate is 10 mg/hour.

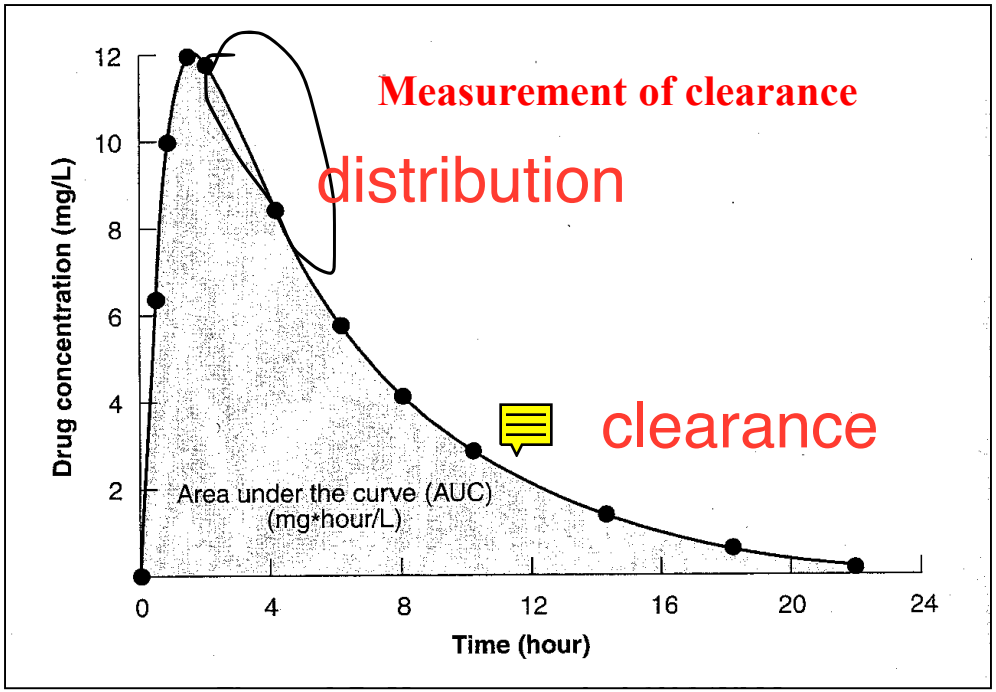
Constant infusion

How is clearance measured?

The **total body clearance** of a drug from the systemic circulation :

$$CL = \frac{DR}{C_{SS}}$$

How is clearance measured?

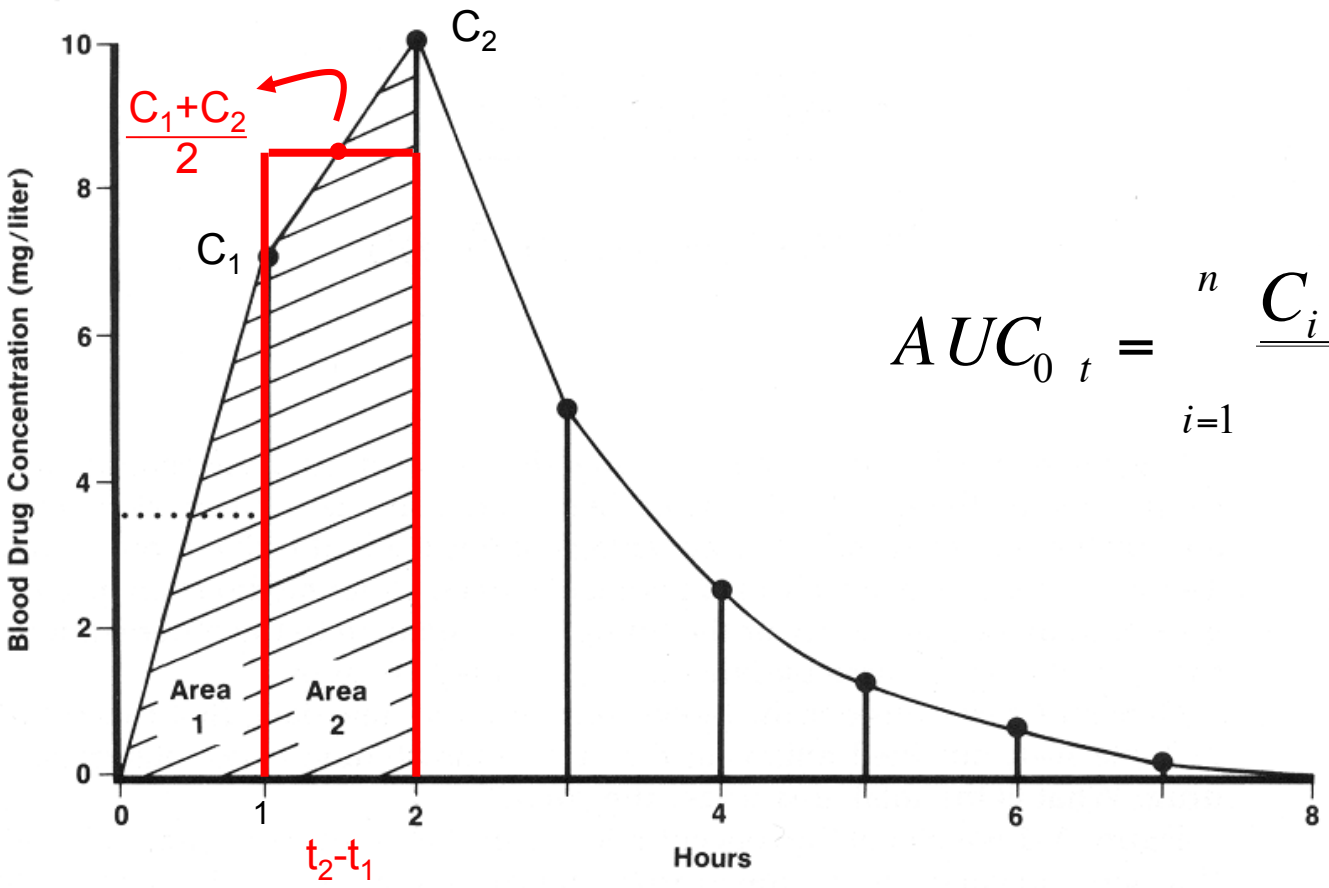


Clearance can be determined by measuring plasma drug concentrations at multiple times after a single intravenous dose.

$$\text{Clearance} = \frac{\text{dose}}{\text{AUC}}$$

$$\text{(L/hour)} \quad \frac{\text{(mg)}}{\text{(mg x hour/L)}}$$

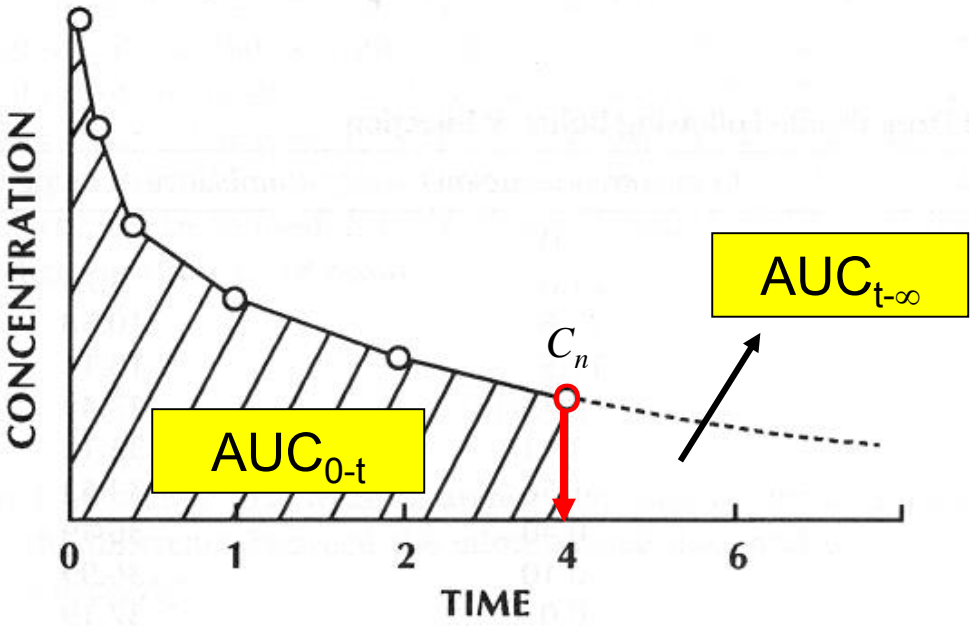
Measuring the AUC – The trapezoidal method



$$AUC_{0\ t} = \sum_{i=1}^{n} \frac{C_i + C_{i+1}}{2} \times (t_{i+1} \quad t_i)$$

$$AUC_{0\ t} = \frac{C_1 + C_2}{2} \times (t_2 \quad t_1) + \frac{C_2 + C_3}{2} \times (t_3 \quad t_2) + \infty$$

Measuring the AUC – The trapezoidal method



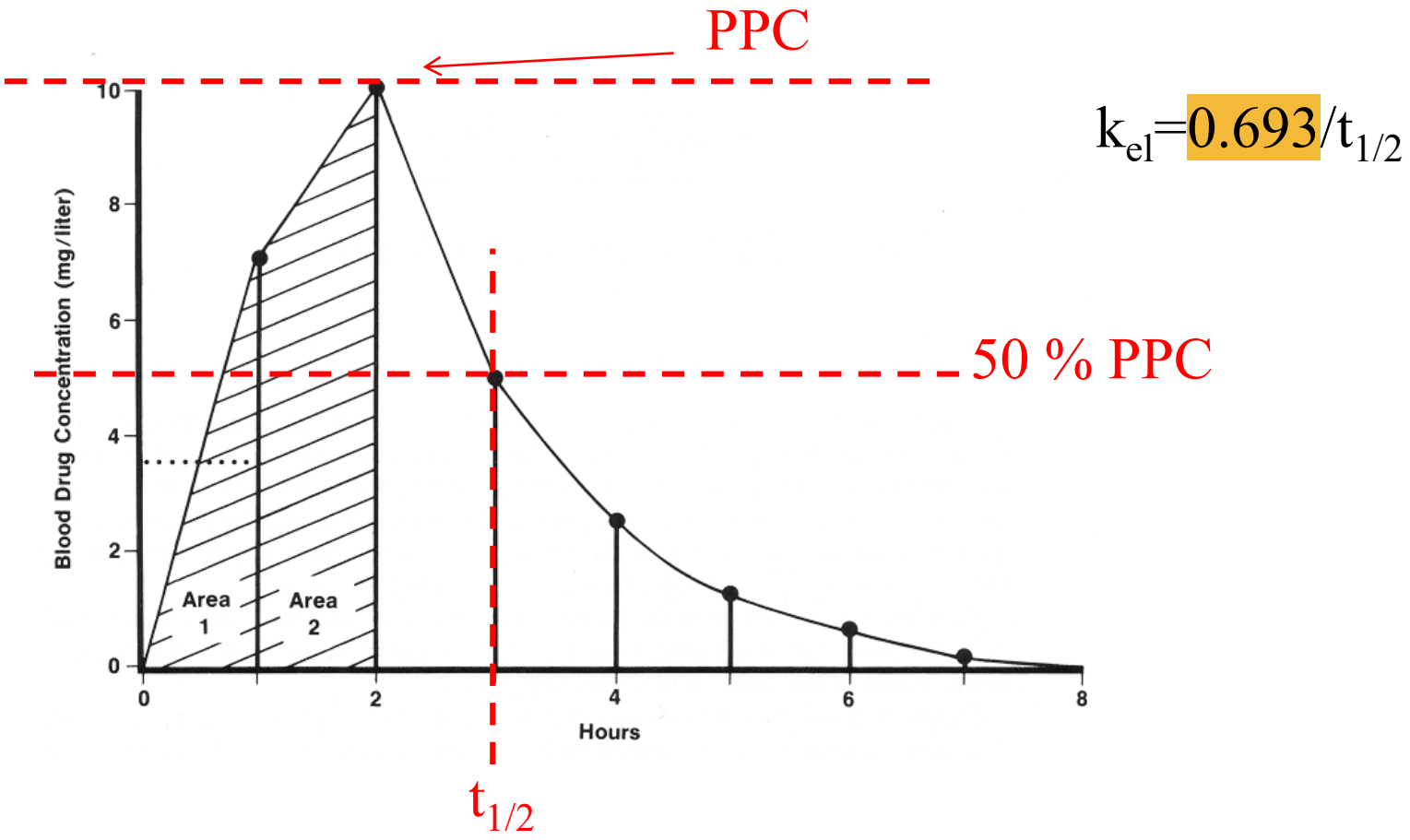
$$\mathbf{AUC_{0-\infty} = AUC_{0-t} + AUC_{t-\infty}}$$

$$AUC_{0\ t} = \sum_{i=1}^{n} \frac{C_i + C_{i+1}}{2} \times (t_{i+1} - t_i)$$

$$AUC_t = \frac{C_n}{0{,}693 / t_{1/2}} = \frac{C_n}{k_{el}}$$

What is the eliminiation half life ($t_{1/2}$)

The time to decline the plasma concentration of a drug to 50% of the peak plasma concentration (PPC).



$k_{el}=0.693/t_{1/2}$

What is the eliminiation half life ($t_{1/2}$)

Half-time is a major determinant of:

- The duration of action after a single shot
- The time required to reach steady state
- The dose frequency

Active principle	Half time
Benylpenicillin	30 min
Amoxicillin	1 hr
Paracetamol	2 hr
Atenolol	7 hr
Diazepam	40 hr

Gives an idea to estimate the total time of drug eliminiatíon

TP: Calculation of the clearance using the Trapezoidal Rule

A dose of 150 mg was administered of drug A to a healthy dog, several blood samples were collected at 0.5, 1, 2, 4, 6, 8, and 10 hours. Plasma was separated from each blood sample and analyzed for drug concentration.

Time (hr)	Cp (mg/L)
0.5	4.35
1	3.8
2	2.89
4	1.7
6	1.1
8	0.65
10	0.35

⇨ What is the Clearance?

Moving from animal to man

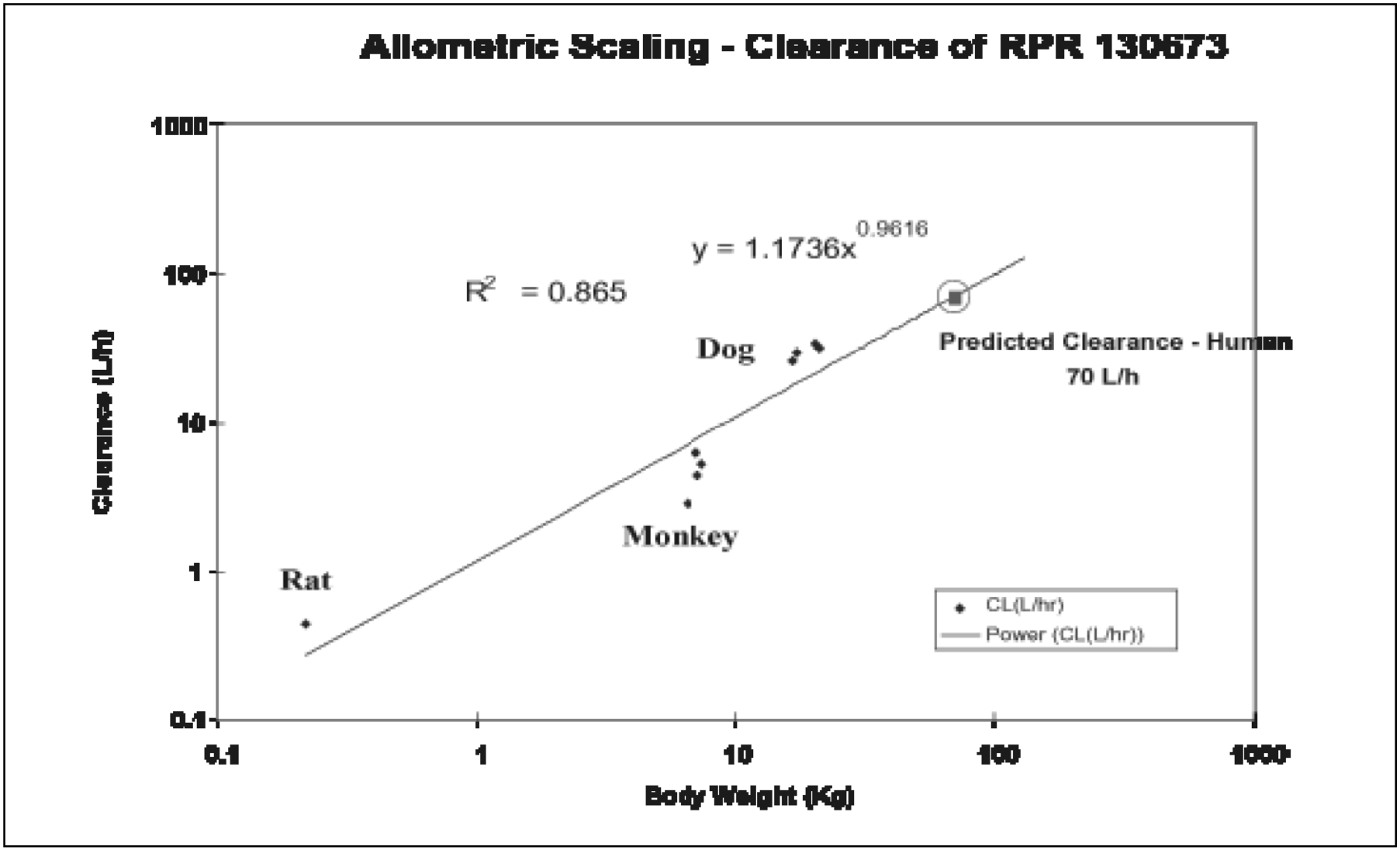
- The first tests of a new drug are done in animal study

  ⇨ how to move from animal to man?

- Human and model animals have different biochemistry, physiology and anatomy
- Predictions of a drugs PK's profiles in human much take into account these changes

  ⇨ Allometric scaling

Allometric scaling



Chaikin et al. (2000)

Allometric scaling

- The relationship of some PK parameters across species can be correlated by body weight
- For example a empirical relationship between CL and body weight exists
- The relationship is not always predictive but it can give a good estimate

45, 46). It has been noticed that when the absolute oral bioavailability in rats, dogs or primates was greater than 20%, then the corresponding absolute oral bioavailability in humans was in most cases also greater than 20% (9). However, when the absolute oral bioavailability in rats, dogs or primates was less than 20%, then there appeared to be no correlation between animals and humans. While this 20% cutoff in absolute oral bioavailability was qualitatively determined, it appears to be a good rule-of-thumb in ranking drugs into classification schemes.

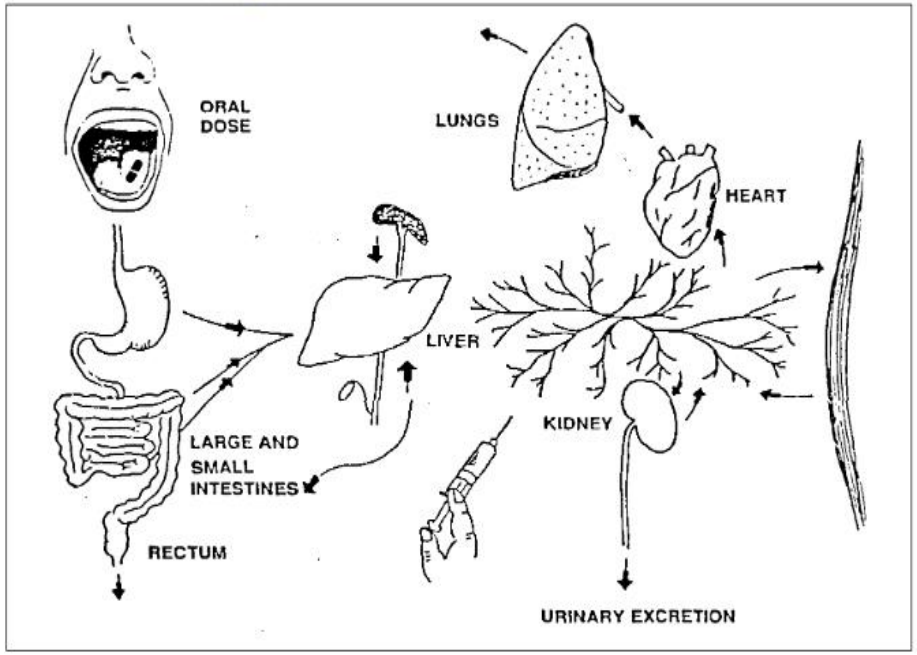
Caldwell et al. (2004)

3.2. Elimination of the drug

The two major routes of drug elimination from the body are

- elimination by **metabolism** in the liver.
- **excretion** as unchanged drug by the kidneys.

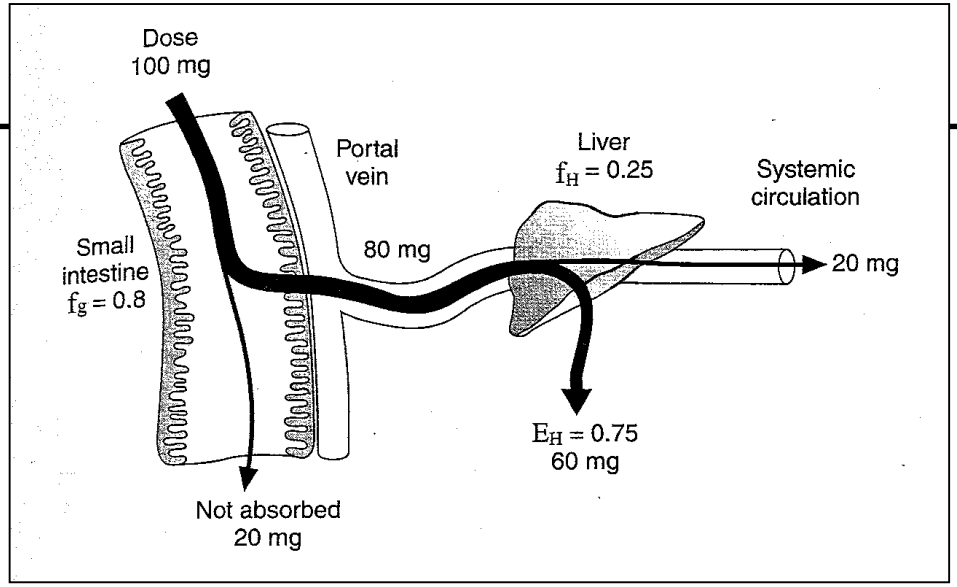
The balance between these depends on the relative efficiency of the two processes.



3.2.1 Elimination by the liver

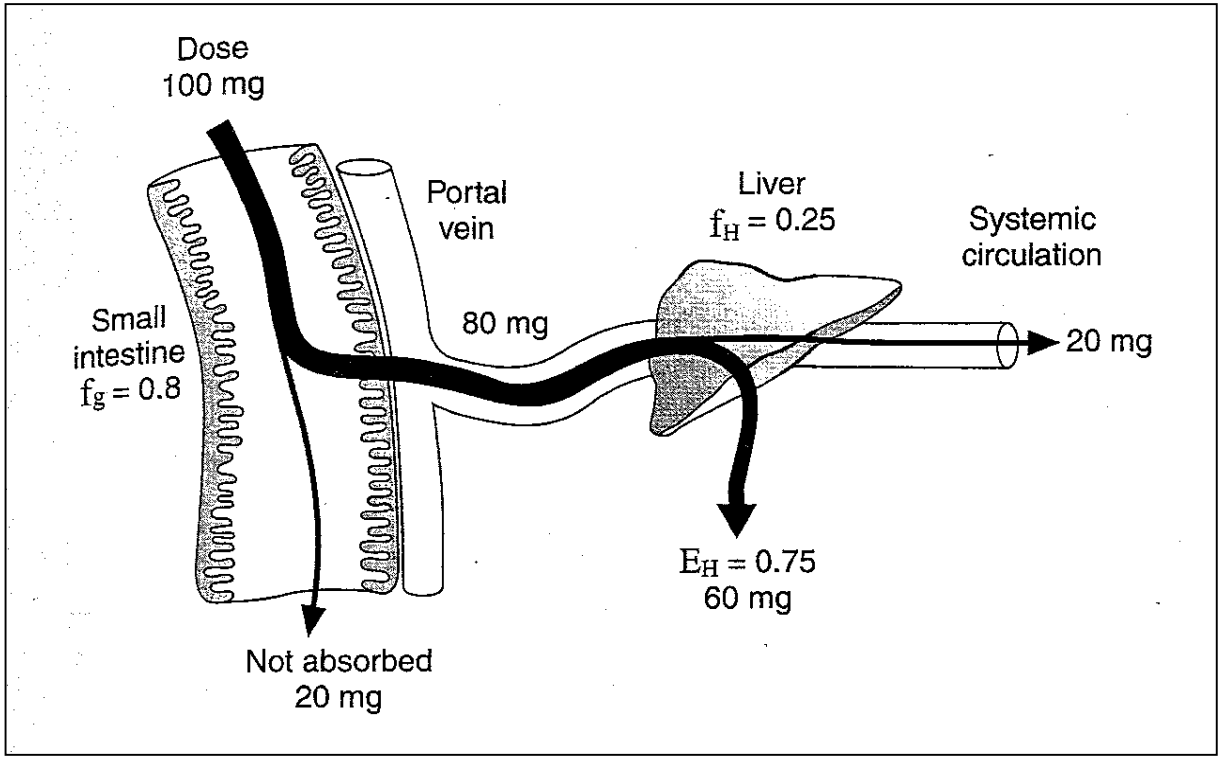
The liver is the chemical processing factory of the body (the major metabolizing organ in the body)

- Function: To get rid of toxins, to regulate blood sugar levels and to produce bile (substance needed to digest fats), to convert ammonia to urea, to destroy old red blood cells
- Location: sits between gut and the rest of the circulation
- The portal vein carries nutrient-rich blood from your small intestine directly to the liver



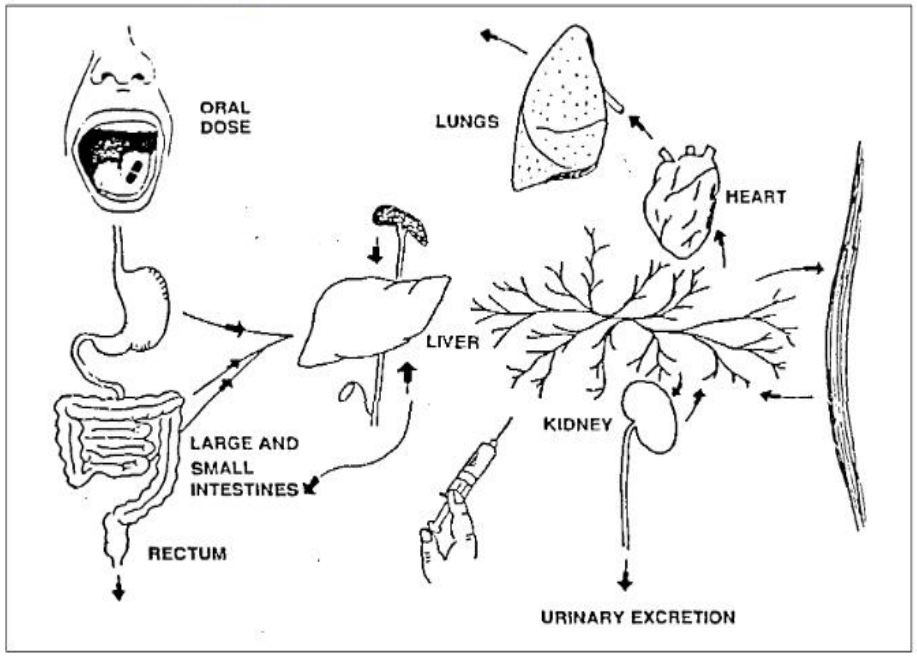
Systemic clearance and pre-systemic or first-pass extraction

The direct link between the gut and the liver leads to a first passage of drugs absorbed in the gastro-intestinal system before reaching the central circulation = pre-systemic or first-pass extraction



Systemic clearance and pre-systemic or first-pass extraction

Pre-systemic extraction is avoided by the other administration pathways.



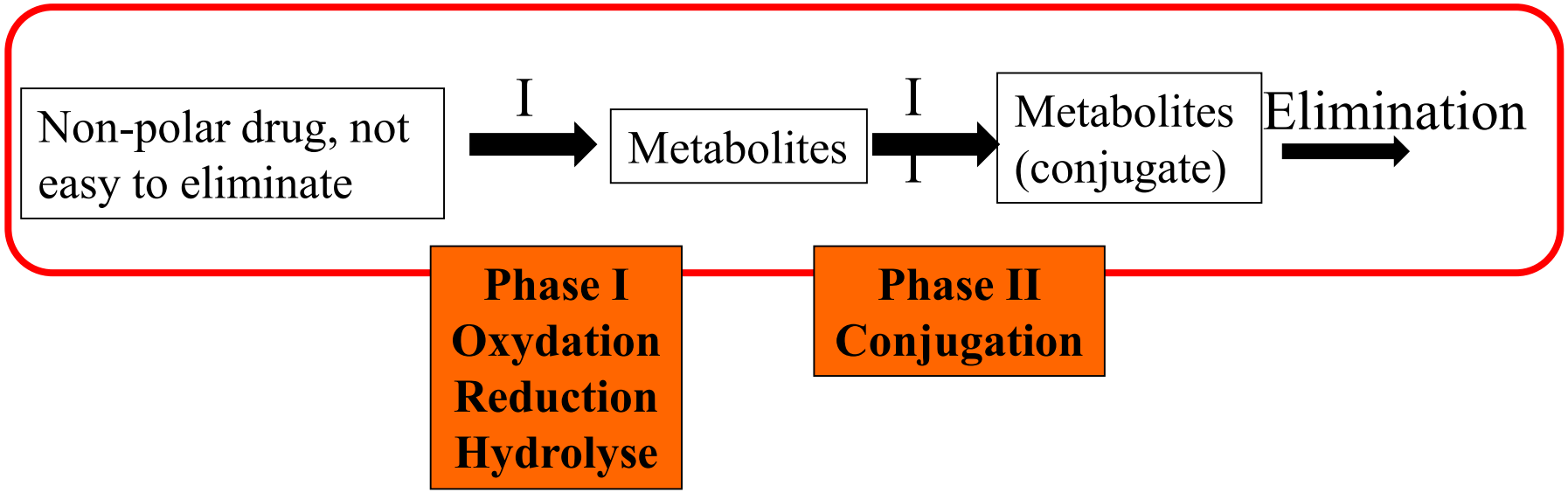
Systemic clearance and pre-systemic or first-pass extraction

- Drugs with a high extraction rate will have a reduced bioavailability due to the pre-systemic extraction.
- Examples: Lidocaine (high extraction rate) or Warfarin (low extraction rate)
- Using other than orally administration pathways, drugs will also enter the liver or the kidney after having passed the central circulation once.
- Systemic clearance = clearance of drugs from the systemic circulation

How drugs are cleared by the liver ?

-No medicament is directly eliminated in the urine or in the feces.
-Prior to elimination it has to be metabolized either
- **simply** : by a single chemical reaction and a single elimination pathways
- **complexly** : by several reactions and several pathways

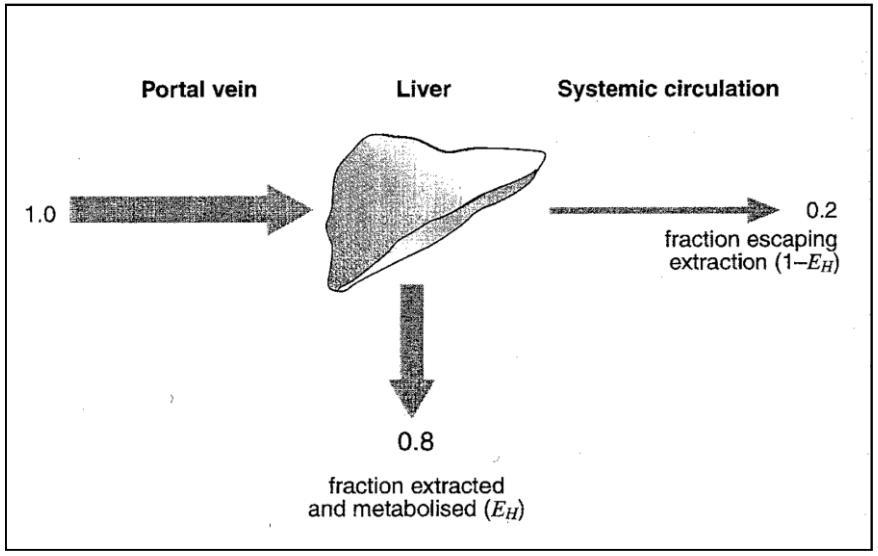
Biochemical reactions



How hepatic extraction ratio and systemic clearance are related ?

The 'hepatic extration ratio' is the fraction of the drug which is irreversibly removed (extracted) during one pass of the blood through the liver. It range from 0 (no drug at all is extracted) to 1 (all the drug entering the liver is extracted in one pass).

Hepatic extraction ratio



hepatic clearance (CL_H) = hepatic blood flow (Q_H) hepatic extration ratio (E_H)

How hepatic extraction ratio and systemic clearance are related ?

$$\text{hepatic clearance}(CL_H) = \text{hepatic blood flow}\,(Q_H) * \text{hepatic extration ratio}\,(E_H)$$

Example : In the case of propranolol, 80% of the drug in the blood entering the liver is extracted in each pass (E_H=0.8) and **liver blood flow is 90 L/hour**. Then 0.8 of 90 L of blood is cleared of propranolol each hour and the hepatic clearance is 72 L/hour.

$$\text{system clearance}(CL) = \text{hepatic clearance}(CL_H) + \text{renal clearance}(CL_R) + ...$$

What determines hepatic extraction ratio?

$$\text{extraction ratio} = \frac{\text{unbound fraction} \quad \text{intrinsic clearance}}{\text{blood flow} + \text{unbound fraction} \quad \text{intrinsic clearance}}$$

$$E_H = \frac{fu \quad CL_{int}}{Q_H + fu \quad CL_{int}}$$

$$CL_{int} = \frac{V_{max}}{K_m}$$

- *Fu* the unbound fraction of the drug in the plasma
- *CL int* Intrinsic Clearance ; the ability of the liver to remove the drug in absence of restrictions
- *QH* the hepatic blood flow
- V_{max} : maximal velocity of the reaction at saturating substrate concentration
- K_m : Michaelis constant. – the lower the K_m, the tighter the binding.

Simplifying the situation

$$CL_H = Q_H * E_H$$

$$CL_H = Q_H \frac{fu \; CL_{int}}{Q_H + fu \; CL_{int}}$$

1.The very low enzyme activity case : when the intrinsic clearance (enzyme activity) is much, much less than liver blood flow => $Q_H >> fu*CL_{int}$

$$CL_H = fu \; CL_{int}$$

low hepatic extraction ratio drugs

2. ***The very high enzyme activity case*** : when the intrinsic clearance (enzyme activity) is much, much higher than liver blood flow => $Q_H << fu*CL_{int}$

$$CL_H = Q_H$$

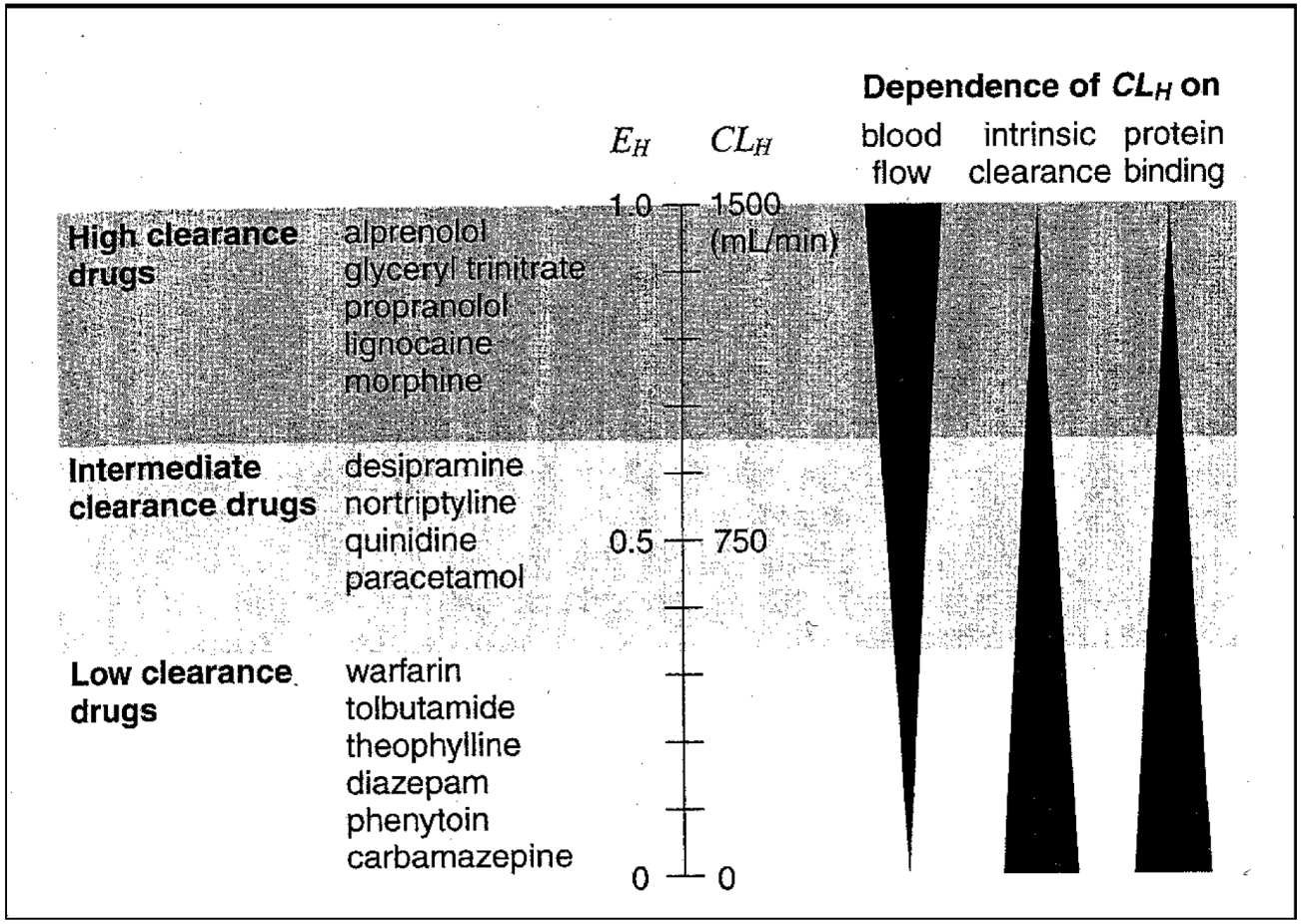
high hepatic extraction ratio drugs

low or high hepatic extraction ratio (clearance) determines the hepatic clearance of the PA and thus its plasma concentrations and maintenance dosing.

Practical application of these concepts

Determinants of E_H and CL

$$CL_H = Q_H * E_H$$



Practical application of these concepts

Effects of changes in Q_H and CL_{int}

$$CL_H = Q_H \frac{fu \; CL_{int}}{Q_H + fu \; CL_{int}}$$

	Hepatic Extraction Ratio			
	Low		High	
	Initial	Changed	Initial	Changed
Halving $fu*CL_{int}$				
$fu*CL_{int}$ (L/hour)	5	2.5	1800	900
E_H	0.053	0.027	0.95	0.91
CL_H (L/hour)	4.7	2.4	86	82
Change in CL_H	49%		5%	
Halving Q_H				
Q_H (L/hour)	90	45	90	45
E_H	0.053	0.1	0.95	0.98
CL_H (L/hour)	4.7	4.5	86	44
Change in CL_H	4%		49%	

Reminder of the Absorption

• ***Absorption*** is the extent to which intact drug is absorbed from the gut lumen into the portal circulation. This is expressed as the fraction of the dose which is absorbed from the gut, f_g.

Determinants of drug absorption from the gut

Dissolution
- physico-chemical properties of drug
- crystal size and form
- excipients
- special dosage forms (sustained release, enteric coated)
- pH (stomach and small intestine)

Gastric emptying rate
- stability of drug at acid pH
- solution or solid dosage forms (liquids and small particles empty more quickly)
- affected by: food; antacids; drugs (opiates, anticholinergics, metoclopramide); disease (autonomic neuropathy)

Intestinal motility
- dissolution of slowly soluble drugs (digoxin, sustained release formulations)
- chemical degradation or metabolism by microflora

Drug interactions in the gut lumen
- complexation (tetracyclines with divalent metal ions)
- adsorption (anion exchange resins)
- food interactions (many antibiotics)

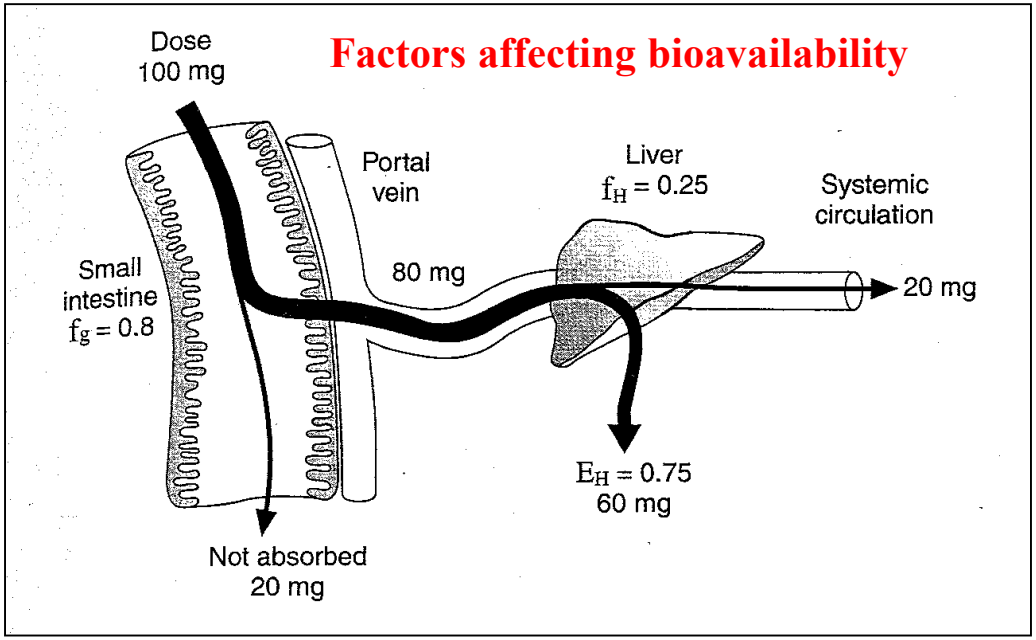
Passage through the gut wall
- physico-chemical characteristics of the drug (quaternary ammonium compounds)
- metabolism by enzymes in the intestinal endothelium

Bioavailability and first-pass clearance

• ***First-pass clearance*** is the extent to which a drug is removed by the liver during its first passage in the portal blood through the liver to the systemic circulation. The fraction of drug which escapes first-pass clearance from the portal blood is expressed as f_H.

• ***Bioavailability*** is the fraction of the dose which reaches the *systemic* circulation as intact drug. This is expressed as F.

$$F = f_g \quad f_H$$



The bioavailability F is 0.8*0.25 = 0.20 (20%).

• ***Bioequivalence*** is a clinical definition referring to two formulations of a drug if the extents and rates of absorption of drug from them are so similar that there is likely to be no clinically important difference between their effects, either therapeutic or adverse.

How is bioavailability measured ?

Absolute bioavailability is measured against an intravenous reference dose (100% by definition). The areas under the plasma drug concentration versus time curves (AUC), after two doses, are used to calculate the bioavailability of the oral formulation by simple proportion.

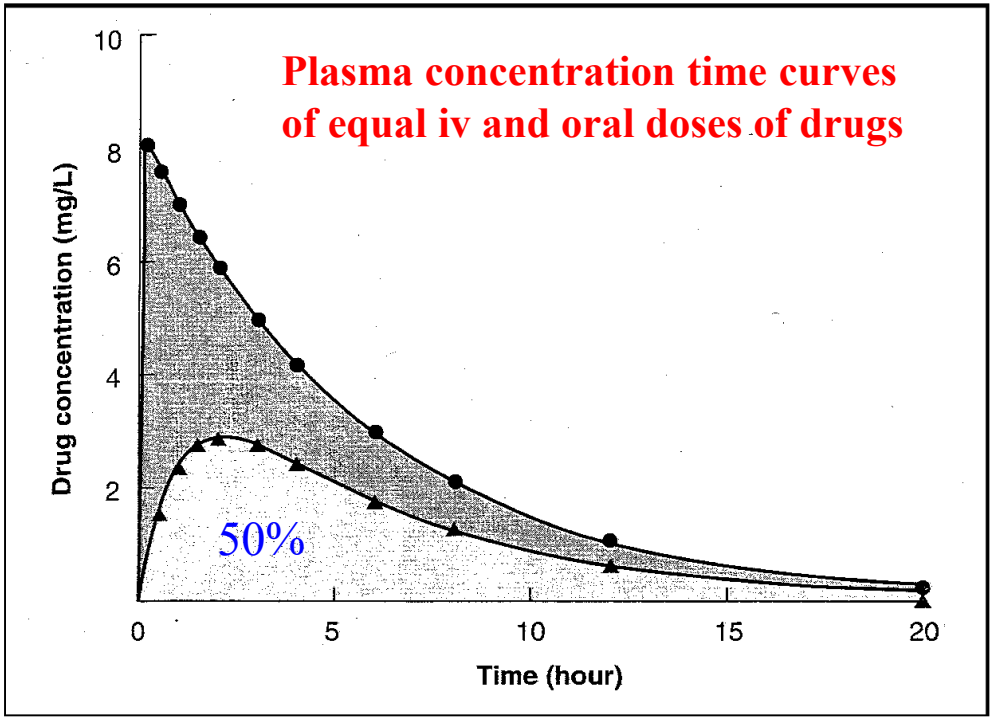
$$AUC_{iv} = \frac{dose_{iv}}{clearance}$$

$$AUC_{oral} = \frac{F \quad dose_{oral}}{clearance}$$

$$\frac{AUC_{oral}}{AUC_{iv}} = \frac{F \quad dose_{oral}}{dose_{iv}}$$

If the oral and iv doses are the same

$$F = \frac{AUC_{oral}}{AUC_{iv}}$$

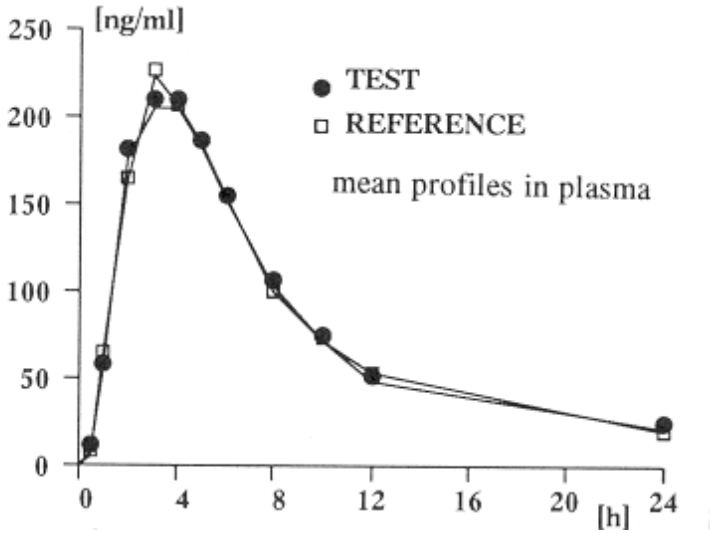


How is bioavailability measured ?

The bioavailability of one oral formulation (the test formulation) is often assessed against a second oral (reference) formulation. This is referred to as measuring relative bioavailability, and is **commonly done for new generic products** where the reference formulation is the innovator's brand or the the market leader formulation for that drug. It is called relative bioavailibility **as the absolute bioavailibility of both formulations might be quite low due to poor absorption and/or first-pass clearance, and this would not be detected**.

$$\text{relative bioavailibility} = \frac{AUC_{test}}{AUC_{reference}}$$

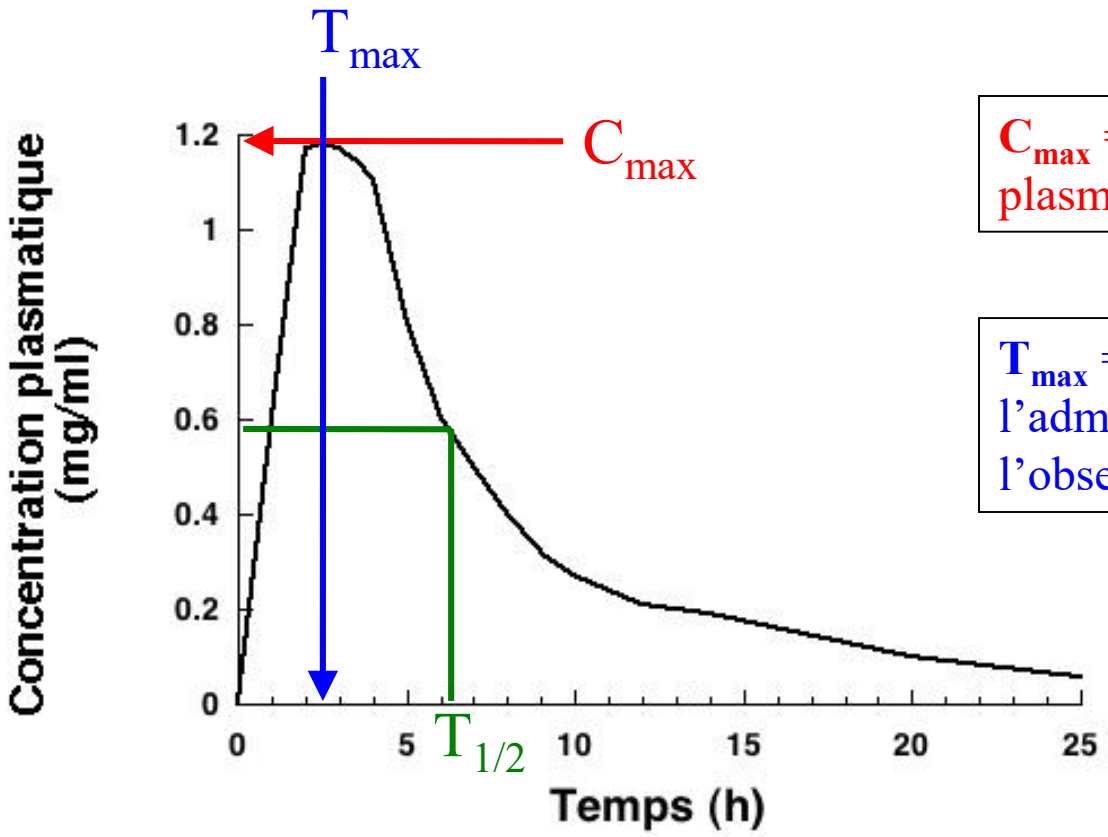
Bioequivalence



Deux formes pharmaceutiques seront considéreées comme bioéquivalentes si, à dose molaire identique, elles présentes des biodisponibilités similaires, engendrant ainsi des effets, aussi bien en terme d'efficacité que de sécurité, similaires.

Biodisponibilité équivalente (=bioéquivalence) veut dire que AUC, Tmax et Cmax du PA sont très similaires pour les deux formes pharmaceutiques.

Parameters for Bioequivalence



C_{max} = Pic de concentration plasmatique d'un PA donné

T_{max} = Temps qui s'écoule entre l'administration de ce PA et l'observation de sa **C_{max}**

$T_{1/2}$ = La demi-vie plasmatique d'un médicament est le temps nécessaire pour que sa concentration plasmatique diminue de moitié

Bioavailability - first-pass clearance

bioavailibility = (1 – hepatic extraction ratio)

Effect of increase or decrease in hepatic drug metabolising enzymes activity on bioavailability:

Hepatic enzyme activity	% extracted first pass	Bioavailability (% escaping first-pass clearance)	
Low extraction ratio drug			
Normal	2	98	
Doubled (induced)	4	96	Minor effect
Halved (inhibited)	1	99	
High extraction ratio drug			
Normal	90	10	
Doubled (induced)	95	5	Major effect
Halved (inhibited)	83	17	

1. Low hepatic extraction ratio drugs nearly all the dose gets through the liver first pass and bioavailibility is essentially complete as long as they are well absorbed from the gut.

2. High hepatic extraction ratio drugs : most of the dose is extracted on the first pass through the liver so that only a minor proportion reaches the systemic circulation intact.

Why is first-pass clearance important ?

• ***Variability in drug response***. Small changes in the hepatic extraction ratio can cause **large changes in bioavailibility**.

• ***Relationship between oral and intravenous doses***. With the high extraction ratio drugs, **only 10% of the oral dose reaches** the systemic circulation as against 100 % of an iv dose.

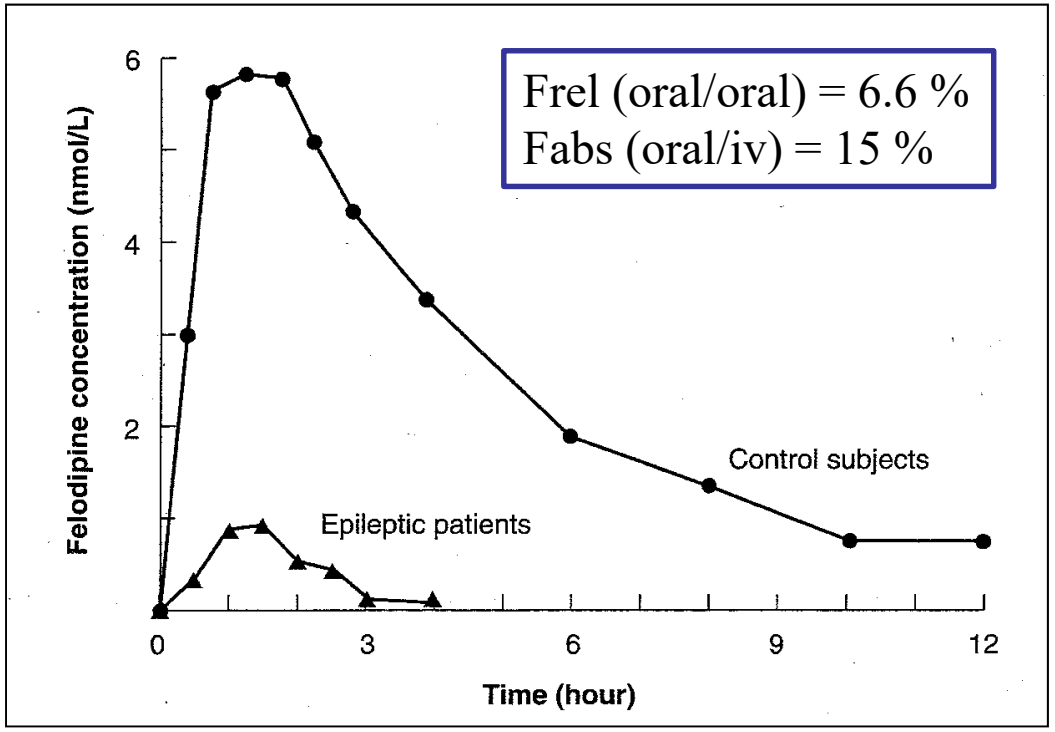
• ***Alternative routes of administration***. Some drugs are so **highly extracted by the liver** that their oral bioavailability is negligible (glyceryl trinitrate and ergotamine have first-pass clearances of 99% or more). It is thus necessary to choose other routes of administration : sublingual, transdermal administration, rectal administration, inhalation.

• ***Liver disease***. In chronic liver disease, a **substantial part of the portal circulation does not perfuse functional liver cells**, that will increase the bioavailability significantly. High hepatic extraction drugs given to patients with liver disease are particularly liable to cause an increased incidence of adverse effects.

Why is first-pass clearance important ?

•***Drug interactions***. Induction or inhibition of drug metabolising enzymes in the liver by other drugs or environmental agents (cigarettes) can cause large changes in the oral bioavailability of high (but not low) clearance drugs.

Effect on felodipine bioavailability due to a drug interaction with anticonvulsants



In four of the 10 epileptic patients, felodipine could not be detected in plasma. (Adapted from *Lancet* 1988;2:481)

Some examples …

	Molécule A	Molécule B	Molécule C	Molécule D
Quantité administrée (mg)	100	100	100	100
Coefficient d'absorption (f)	1	1	0.8	0.3
Quantité absorbée (mg)	100	100	80	30

quantité absorbée = quantité administrée x f_G

Définition of the absorption coefficient f_G:
C'est la fraction ou le % de la dose administrée qui est absorbée au niveau de la muqueuse gastro-intestinale.

Les molécules non absorbées sont évacuées avec les fèces.

Some examples …

	Molécule A	Molécule B	Molécule C	Molécule D
Quantité administrée (mg)	100	100	100	100
Coefficient d'absorption (f)	1	1	0.8	0.3
Quantité absorbée (mg)	100	100	80	30
EI	0	0.2	0.2	0
Fraction échappant au métabolisme intestinal (fI	1	0.8	0.8	1

EI = 1 moins la fraction échappant au métabolisme intestinal
EI = 1 - fI

<u>Définition of intestinal extraction coefficient (EI)</u>:
The quantity of the drug with is altered by the metablism of the intestin.

Some examples …

	Molécule A	Molécule B	Molécule C	Molécule D
Quantité administrée (mg)	100	100	100	100
Coefficient d'absorption (f)	1	1	0.8	0.3
Quantité absorbée (mg)	100	100	80	30
EI	0	0.2	0.2	0
Fraction échappant au métabolisme intestinal (fI)	1	0.8	0.8	1
Fraction de dose administrée active Arrivant dans la veine porte	1	0.8	0.64	0.3

La fraction de dose administrée arrivant dans la veine porte = fG x fI

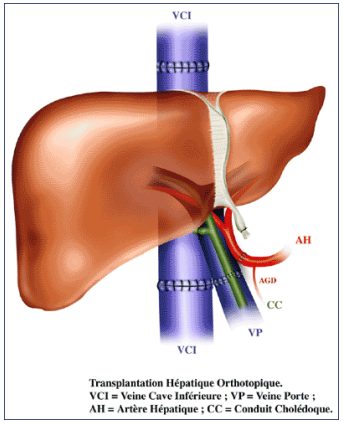
Some examples …

	Molécule A	Molécule B	Molécule C	Molécule D
Quantité administrée (mg)	100	100	100	100
Coefficient d'absorption (fG)	1	1	0.8	0.3
Quantité absorbée (mg)	100	100	80	30
EI	0	0.2	0.2	0
Fraction échappant au métabolisme intestinal (fI)	1	0.8	0.8	1
Fraction de dose administrée Arrivant dans la veine porte (f.fI)	1	0.8	0.64	0.3
Fraction de dose administrée Arrivant dans la veine porte (mg)	100	80	64	30

La quantité en mg de dose administrée arrivant dans la veine porte = quantité administrée x fG x fI

Some examples …

	Molécule A	Molécule B	Molécule C	Molécule D
Quantité administrée (mg)	100	100	100	100
Frac. échap. intest. (fI)	1	0.8	0.8	1
Coef. extract. intest. (EI)	0	0.2	0.2	0
Quantité dans la veine porte (mg)	100	80	64	30
Fraction dans la veine porte	1	0.8	0.64	0.3
Frac. échap. hépat. (fH)	1	0.2	0.8	0.4
Coef. extract. hépat. (EH)	0	0.8	0.2	0.6



Transplantation Hépatique Orthotopique.
VCI = Veine Cave Inférieure ; VP = Veine Porte ;
AH = Artère Hépatique ; CC = Conduit Cholédoque.

EH = 1 moins la fraction échappant au métabolisme hépatique

EH = 1 - fH

Some examples …

	Molécule A	Molécule B	Molécule C	Molécule D
Quantité administrée (mg)	100	100	100	100
Frac. échap. intest. (fIG)	1	0.8	0.8	1
Coef. extract. intest. (EI)	0	0.2	0.2	0
Quantité dans la veine porte (mg)	100	80	64	30
Fraction dans la veine porte	1	0.8	0.64	0.3
Frac. échap. hépat. (fH)	1	0.2	0.8	0.6
Coef. extract. hépat. (EH)	0	0.8	0.2	0.4
Fraction de dose administrée atteignant les veines sus-hépatiques	1	0.16	0.51	0.18

La fraction de dose administrée arrivant dans les veines sus-hépatiques = fG x fI x fH

Some examples …

	Molécule A	Molécule B	Molécule C	Molécule D
Quantité administrée (mg)	100	100	100	100
Frac. échap. intest. (fI)	1	0.8	0.8	1
Coef. extract. intest. (EI)	0	0.2	0.2	0
Quantité dans la veine porte (mg)	100	80	64	30
Fraction dans la veine porte	1	0.8	0.64	0.3
Frac. échap. hépat. (fH)	1	0.2	0.8	0.6
Coef. extract. hépat. (EH)	0	0.8	0.2	0.4
Fraction de dose admin. (f.fI.fH)	1	0.16	0.51	0.18
Quantité arrivant dans 1es veines sus-hépatiques (mg)	100	16	51	18

La quantité en mg de dose administrée arrivant dans les veines sus-hépatiques = quantité administrée x f x fI x fH

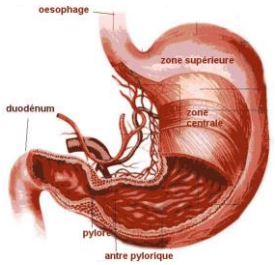
Some examples …

	Molécule A	Molécule B	Molécule C	Molécule D
Quantité administrée (mg)	100	100	100	100
Quantité arrivant dans la veine porte (mg)	100	80	64	30
Extraction hépatique (EH)	0	0.8	0.2	0.4
Quantité arrivant dans les Veines sus-hépatiques (mg)	100	16	51	18

Quelle molécule est faiblement/moyennement/fortement/complètement extraite ?

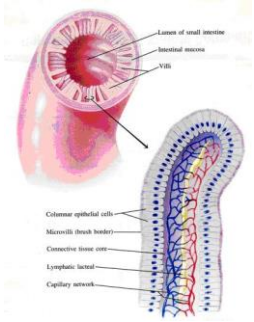
From oral administration to the systemic circulation

Oral administration



Stomach

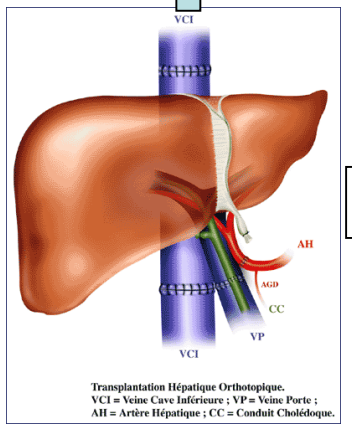
Gut lumen



Gut mucosa

fG, fI

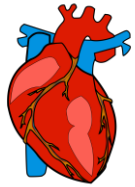
Portal vein



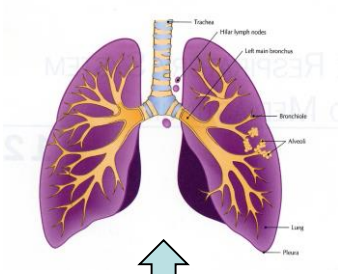
Transplantation Hépatique Orthotopique.
VCI = Veine Cave Inférieure ; VP = Veine Porte ;
AH = Artère Hépatique ; CC = Conduit Cholédoque.

Liver

fH



Heart

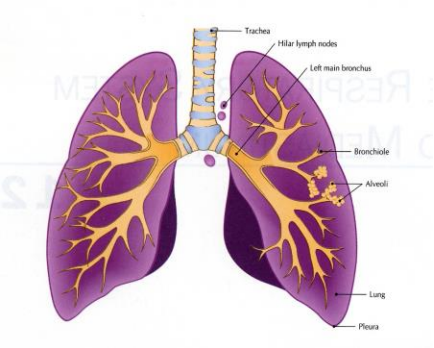


Lung

fP

Central Circulation

Pulmonary Elimination



Au niveau des poumons, on aura une éventuelle nouvelle perte partielle du produit initial et donc de l'effet thérapeutique.

First pass clearance

On parlera de l'extraction pulmonaire (EP) et de la fraction pulmonaire ayant échappée au métabolisme pulmonaire (fP).

$EP = 1 - fP$

! L'extraction pulmonaire ne s'exerce que sur la fraction atteignant les poumons !

Some examples …

	Molécule A	Molécule B	Molécule C	Molécule D
Fraction dans la veine porte (f.fl)	1	0.8	0.64	0.3
Frac. échap. hépat. (fH)	1	0.2	0.8	0.6
Coef. extract. hépat. (EH)	0	0.8	0.2	0.4
Fraction dans les veines s-h (f.fl.fH)	1	0.16	0.51	0.18
Frac. échap. pulm. (fP)	1	0.7	0.8	0.9
Coef. extract. pulm. (EP)	0	0.3	0.2	0.1

EP = 1 moins la fraction échappant au métabolisme pulmonaire
EP = 1 - fP

Some examples …

	Molécule A	Molécule B	Molécule C	Molécule D
Fraction dans la veine porte (f.fl)	1	0.8	0.64	0.3
Frac. échap. hépat. (fH)	1	0.2	0.8	0.6
Coef. extract. hépat. (EH)	0	0.8	0.2	0.4
Fraction dans les veines s-h (f.fl.fH)	1	0.16	0.51	0.18
Frac. échap. hépat. (fP)	1	0.7	0.8	0.9
Coef. extract. pulm. (EP)	0	0.3	0.2	0.1
Fraction de dose administrée atteignant la circulation générale	1	0.11	0.41	0.16

La fraction de dose administrée arrivant dans la circulation générale = f x fI x fH x fP

Some examples …

	Molécule A	Molécule B	Molécule C	Molécule D
Fraction dans la veine porte (f.fl)	1	0.8	0.64	0.3
Frac. échap. hépat. (fH)	1	0.2	0.8	0.6
Coef. extract. hépat. (EH)	0	0.8	0.2	0.4
Fraction dans les veines s-h (f.fl.fH)	1	0.16	0.51	0.18
Frac. échap. hépat. (fP)	1	0.7	0.8	0.9
Coef. extract. pulm. (EP)	0	0.3	0.2	0.1
Fraction dans la c.g. (f.fI.fH.fP)	1	0.11	0.41	0.16
Quantité arrivant dans la Circulation générale (mg)	100	11	41	16

La quantité en mg de dose administrée arrivant dans la circulation générale = quantité administrée x f x fI x fH x FP

Some examples …

	Molécule A	Molécule B	Molécule C	Molécule D
Quantité administrée (mg)	100	100	100	100
Quantité arrivant dans la veine porte (mg)	100	80	64	30
Quantité arrivant dans les veines sus-hépatiques (mg)	100	16	51	18
Quantité arrivant dans la circulation générale (mg)	100	11	41	16

Which drugs can be adminstered orally?

What determines steady state drug concentrations during chronic dosing ?

For intravenous dosing

Total concentration

$$\text{maintenance dose rate} = CL \times C_{SS} \Rightarrow C_{SS} = \frac{\text{dose rate}}{CL}$$

For low hepatic extraction ratio drug ($CL \approx fu \times CL_{int}$)

$$C_{SS} = \frac{\text{dose rate}}{fu \times CL_{int}}$$

For high hepatic extraction ratio drug ($CL \approx Q_H$)

$$C_{SS} = \frac{\text{dose rate}}{Q_H}$$

Unbound concentration

$$Cu_{SS} = fu \times C_{SS}$$

For low hepatic extraction ratio drug

$$Cu_{SS} = \frac{\text{dose rate}}{CL_{int}}$$

For high hepatic extraction ratio drug

$$Cu_{SS} = \frac{fu \times \text{dose rate}}{Q_H}$$

What determines steady state drug concentrations during chronic dosing ?

For oral dosing

Total concentration

$$C_{SS} = \frac{F \quad \text{dose rate}}{CL} \Rightarrow C_{SS} = \frac{f_g * f_H * \text{dose rate}}{CL} \Rightarrow C_{SS} = \frac{F * \text{dose rate}}{fu * CL_{int}}$$

$$C_{SS} = \frac{F * \text{dose rate}}{Q_H}$$

Unbound concentration

$$Cu_{SS} = fu \quad C_{SS}$$

$$Cu_{SS} = \frac{F * \text{dose rate}}{CL_{int}} \qquad Cu_{SS} = \frac{F * f_u * \text{dose rate}}{Q_H}$$

3.2.2 Elimination by the kidneys

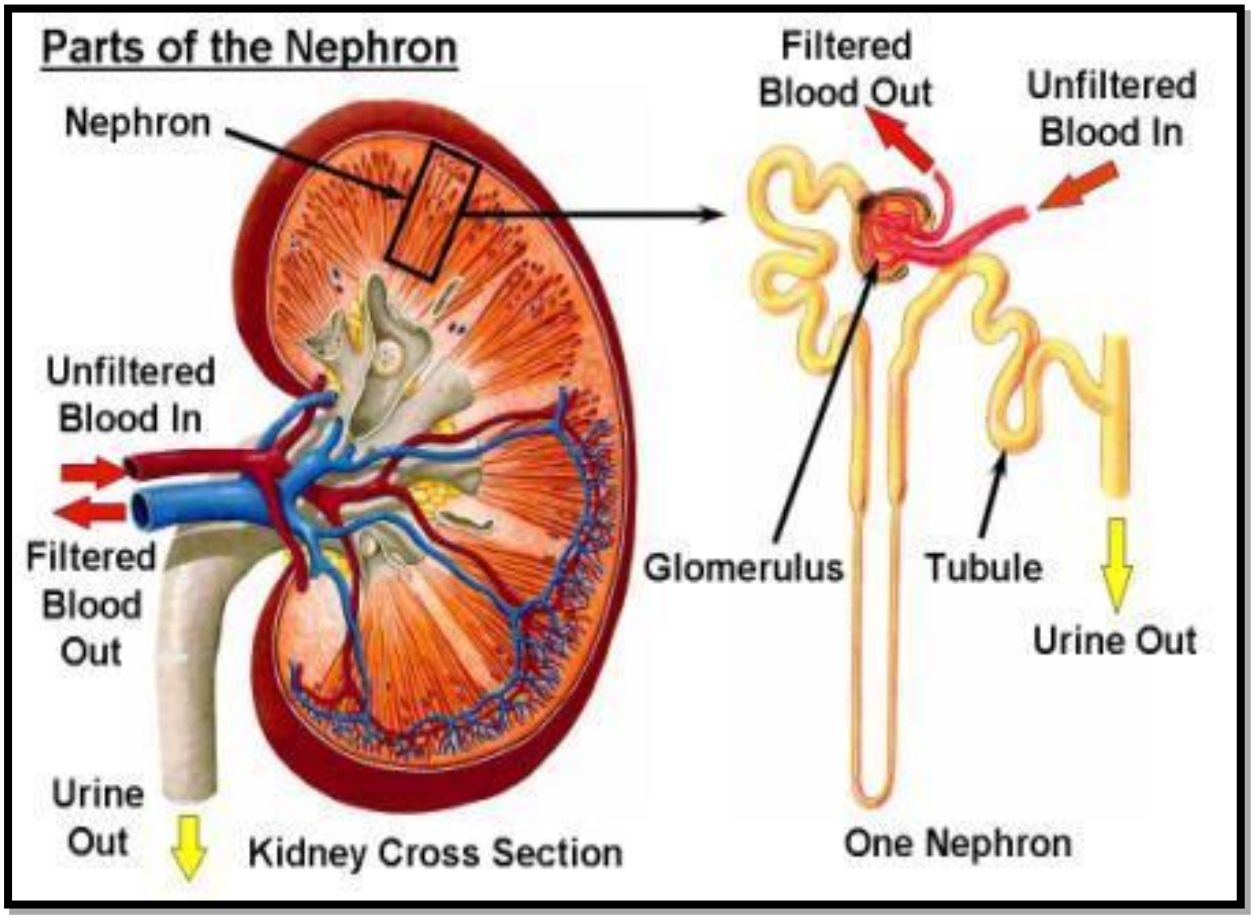
The kidneys

Function:

-Filtration

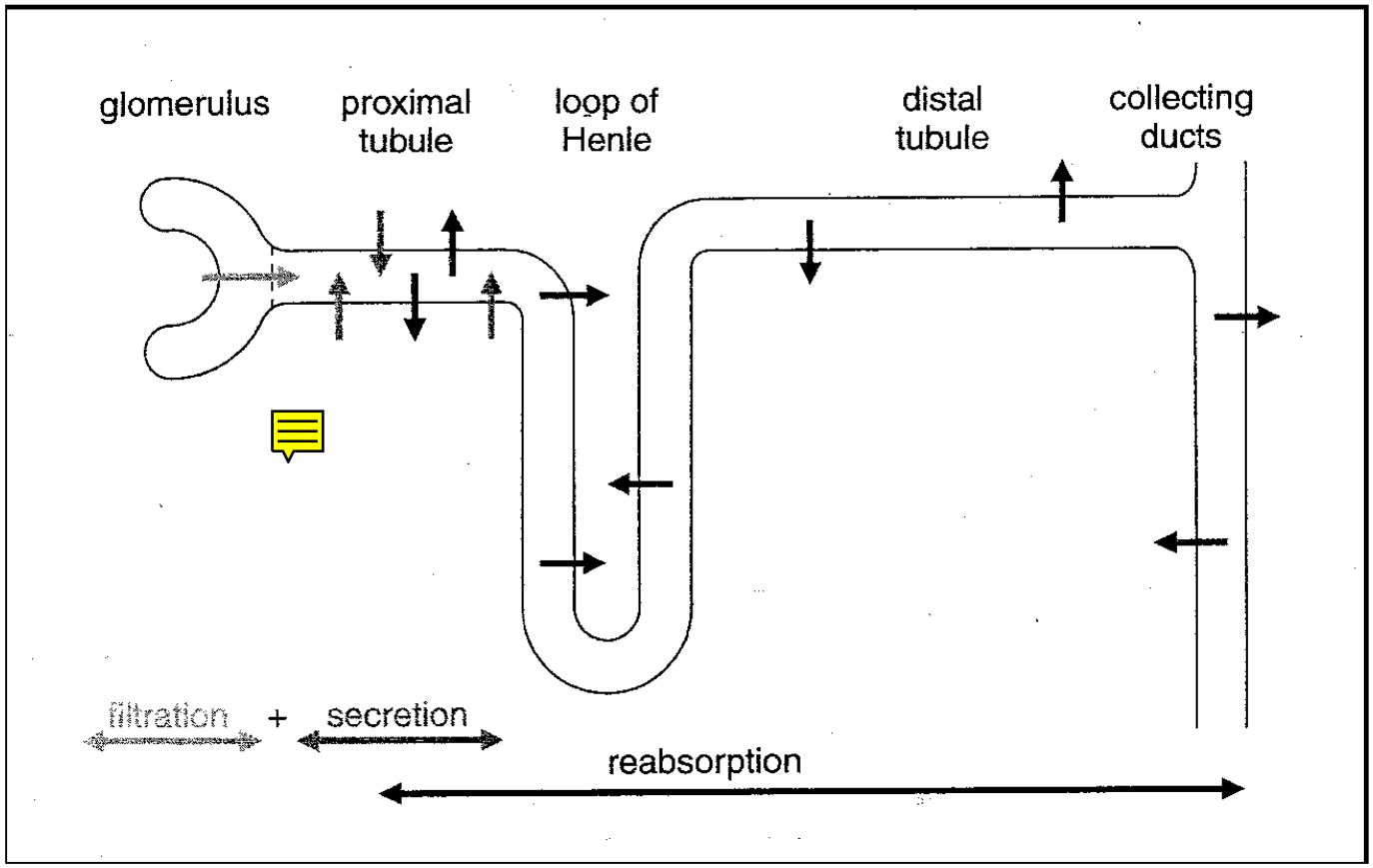
-Reabsorption

-Secretion

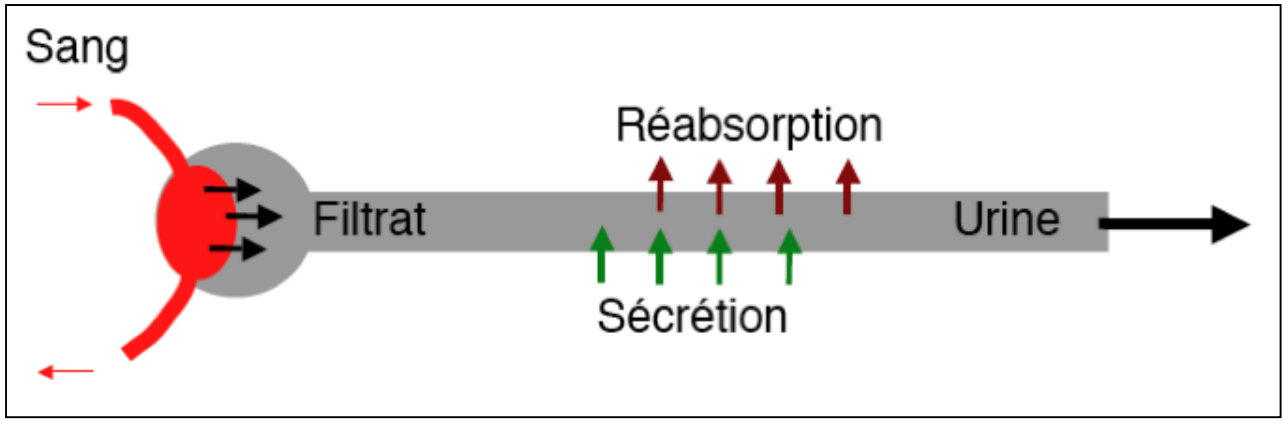


How are drugs cleared by the kidneys ?

renal clearance = filtration + secretion - reabsorption



Renal clearance : Mechanisms



Mécanisme de la clairance rénale :

La formation de l'urine se fait par la mise en œuvre de trois mécanismes:

- La **filtration glomérulaire** ne laissant diffuser que des composés de faible PM, excluant les protéines en particulier l'albumine.
- La **sécrétion tubulaire** permettant le passage direct de substances des cellules vers le tube où se forme l'urine.
- La **réabsorption tubulaire** permettant aux substances ayant filtrées de repasser dans les cellules et de disparaître de l'urine.

1. The glomerular filtration

1. **Glomerular filtration** : As blood passes (1200 mL/minute), about 10% is filtered as plasma water into the renal tubule (that is, **glomerular filtration rate** (**GFR**) is about 120 mL/minute), and drug in plasma water (unbound drug) goes with it. Drug bound to plasma proteins is not filtered.

$$CL_{GF} = fu \quad GFR$$

fu= fraction of unbound protein

Creatinine and insulin are not bound to plasma proteins (fraction unbound is 1), are not secreted and are not reabsorbed. This allows their renal clearances to be used as measures of GFR.

Dose adjustment in renal dysfunction

•the renal clearance of drugs is reduced in proportion with the reduction in creatinine clearance (glomerular filtration rate). = *intact tubule hypothesis*.

•**creatine clearance** provides a **simple guide** to the reduction of dose rate in **renal dysfunction**.

$$\text{creatine clearance} = \frac{(140 - \text{age}) * (\text{weight in kg}) * 0.85\{\text{for females}\}}{814 * \text{serum creatine concentration (mmol/L)}}$$

•More than 50 % of a drug cleared by renal elimination ($f_e > 0.5$) and renal function is reduced to half of normal or less.

⇨ Dose rate is reduced proportionately to the reduction in creatinine clearance

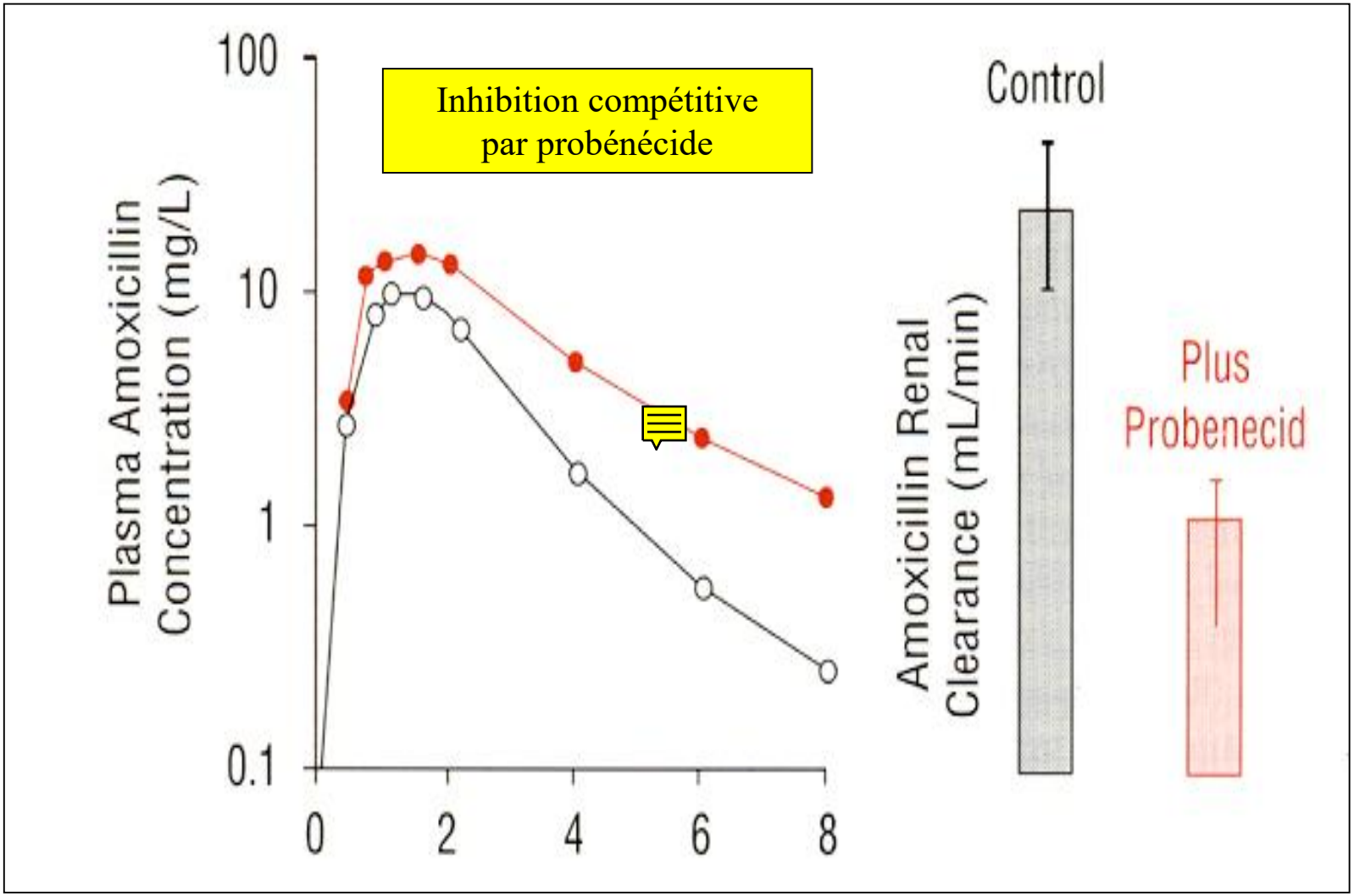
2. Active tubular secretion

(La **sécrétion tubulaire** permettant le passage direct de substances des cellules vers le tube où se forme l'urine.)

- Mécanisme : **Transport actif** (nécessite de l'énergie, saturable)
- Lieu : Tube contourné proximal
- Produits concernés : Fractions ionisées hydrosolubles des médicaments (par sécrétion des acides faibles ou par transport des bases faibles)
-Two major active transport systems: for acidic and basic compounds
-Competitive drug interaction

$$\text{Secretion clearance} = \text{fu} * CLs$$

2. Active tubular secretion



3. Passive tubular reabsorption

120 mL/minute of plasma water filtered but 1-2 mL/minute finally appears as urine.

⇒ passive tubular reabsorption

- For drugs which are **reabsorbed**, renal clearance **varies with urine flow rate**. The higher the flow, the greater the clearance.

- For ionizable drugs which are lipid soluble enough to be **reabsorbed**, renal clearance **varies with urine pH**.

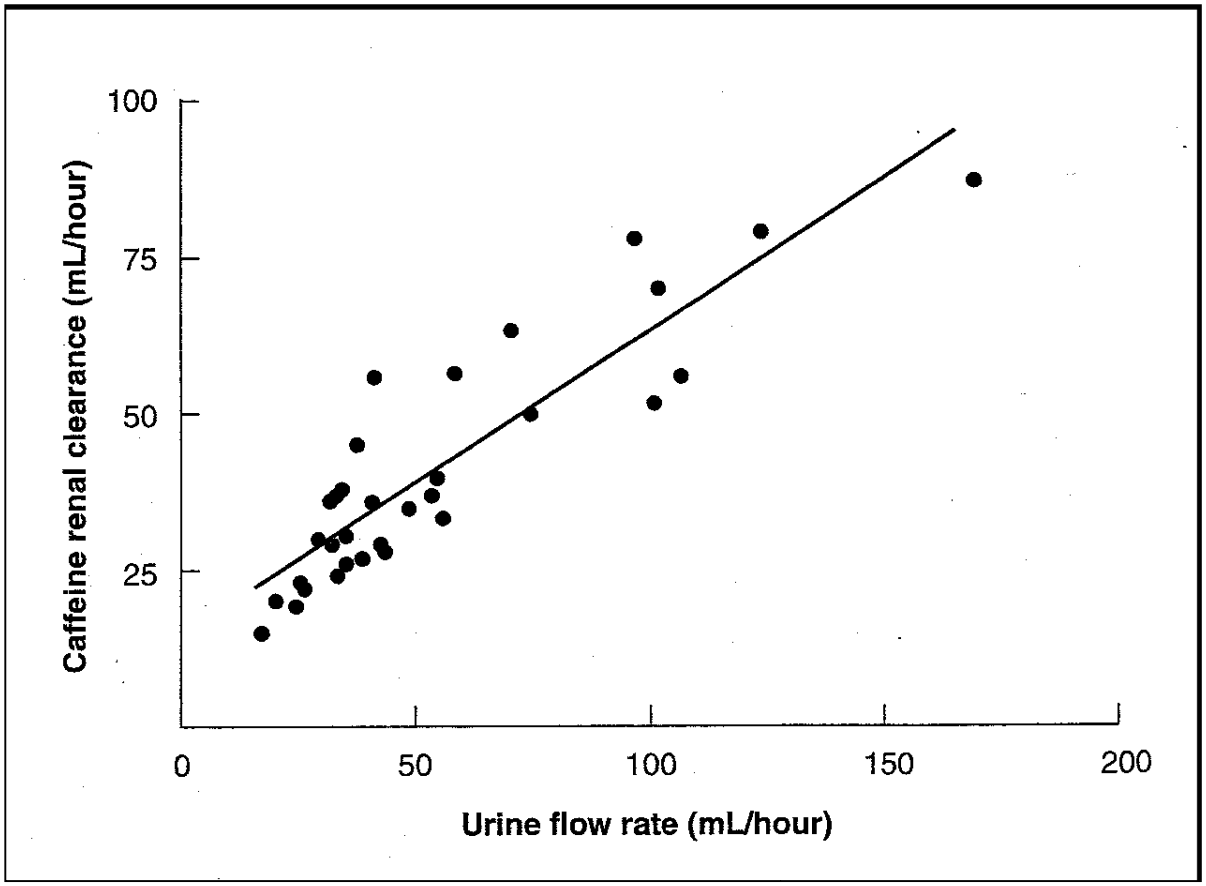
⇒ passive diffusion

$$\text{Reabsorption} = (1 - FR)$$

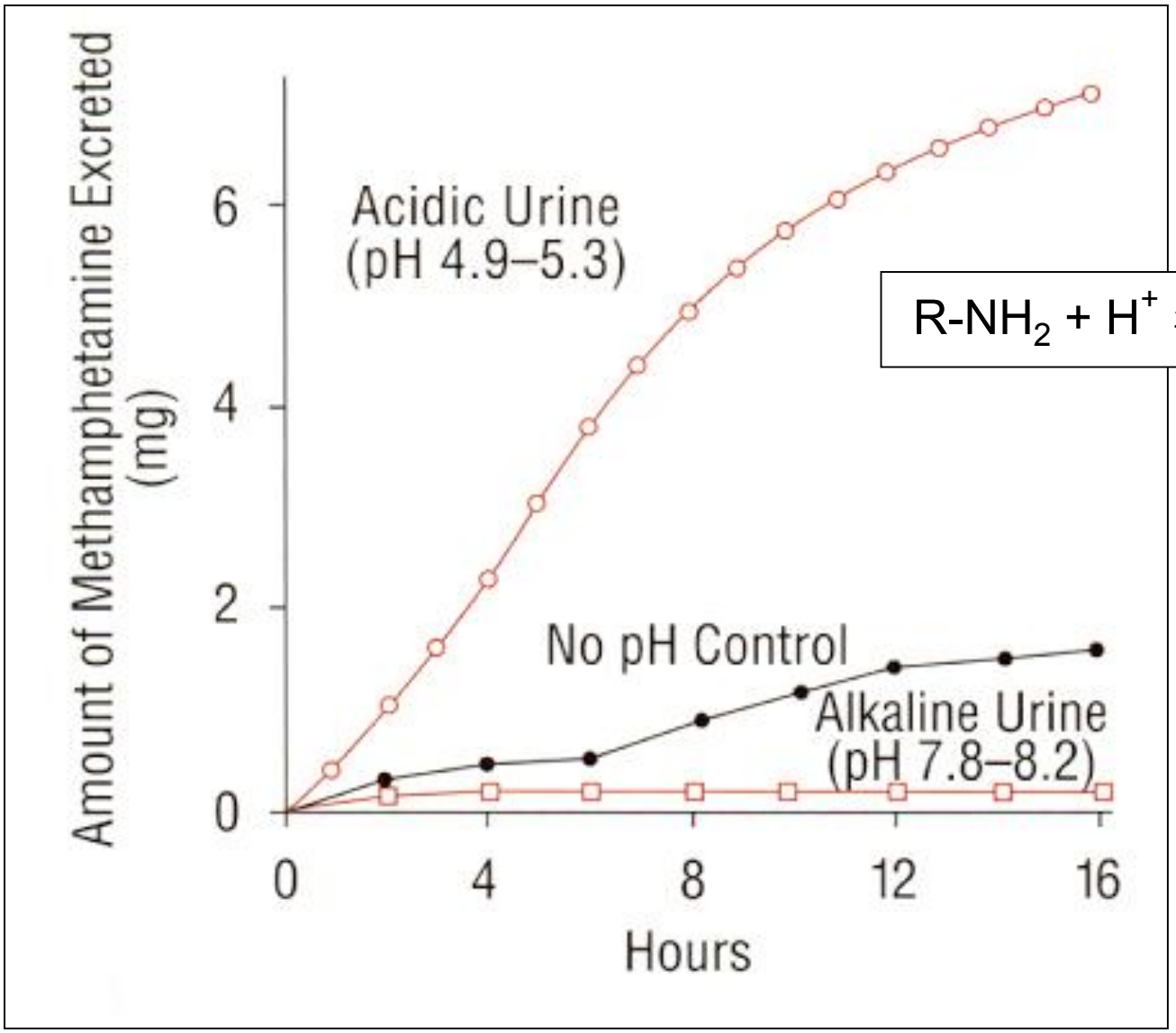
FR = fraction of the drug not being reabsorbed

Passive tubular reabsorption

Effect of urine flow rate on caffeine renal clearance



Passive tubular reabsorption

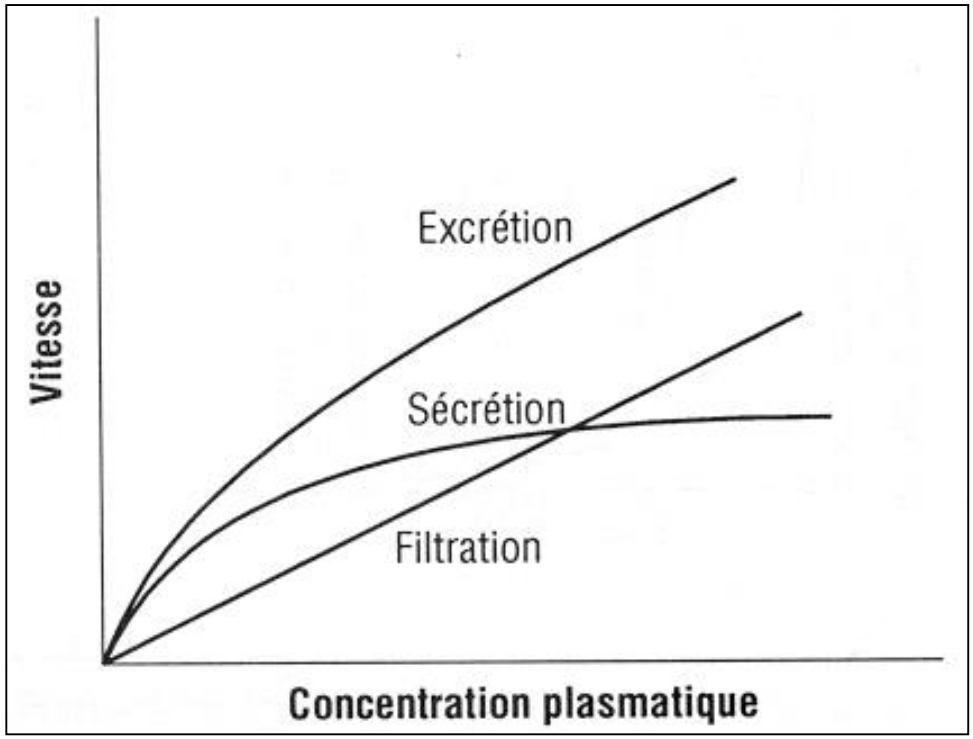


$R\text{-}NH_2 + H^+ \rightleftharpoons R\text{-}NH_3^+$

Renal clearance

La vitesse d'excrétion rénale d'un PA est le résultat d'une vitesse de **filtration** (réaction d'ordre 1), et éventuellement une vitesse de **sécrétion** saturable (cinétique Michaelis-Menten) suivie dans certains cas d'une **réabsorption** passive.

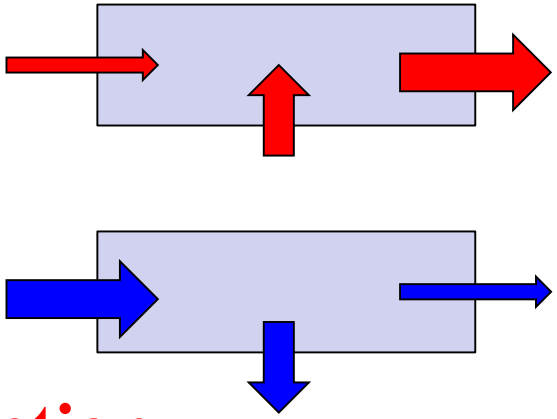
$$CL_R = fu * (GFR + CL_S)(FR)$$



How to tell if a drug is secreted or reabsorbed ?

- Baseline renal clearance: baseline = fu * GFR

  (glomerular filtration)

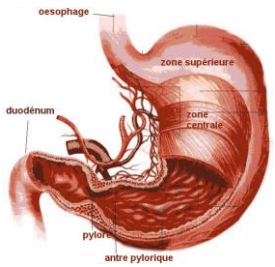


- CL_R > fu*GFR: **Secretion**
- CL_R < fu*GFR: **Reabsorption**
- known competitor reduces CL_R : **Secretion**
- Different urine flow rate and/or pH -> CL_R changes: **Reabsorption**

3.3. Different clearance processes

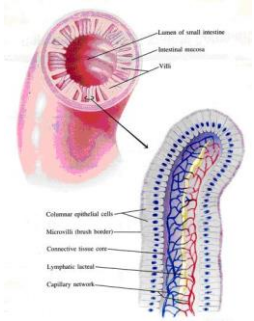
Intravenous administration

Oral administration



Stomach

Gut lumen

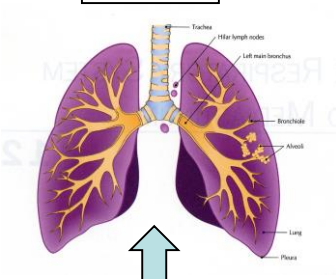


fG, fI

Gut mucosa

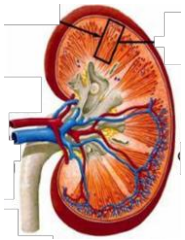
Central Circulation

Lung



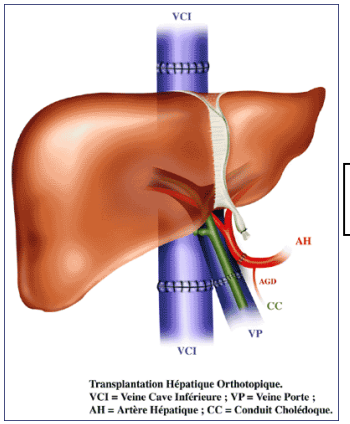
fP

Heart



Kidney

Portal vein



Transplantation Hépatique Orthotopique.
VCI = Veine Cave Inférieure ; VP = Veine Porte ;
AH = Artère Hépatique ; CC = Conduit Cholédoque.

fH

Liver

How to determine the relative importance of metabolism and renal excretion ?

- All drugs are partly metabolized by the liver
- And partly excreted unchanged by the kidney.
- Measure amount of unchanged drug in the urine
- The ***fraction excreted unchanged (fe)*** of a known doses corresponds to the kidney elimination
- The ***fraction of the dose which is metabolized*** is **(1- fe)** is the part of the doses corresponding to the liver elimination

Drugs with high and low fe

Very high fe	Very low fe
Propranolol	Penicillin
Morphine	Amoxycillin
Tolbutamide	Gentamicin
Theophylline	Digoxin

Clearances are additive – calculating hepatic and renal clearances

$$\text{total clearance} = \text{renal clearance} + \text{hepatic clearance}$$

$$\text{fraction excreted unchanged} = \frac{\text{renal clearance}}{\text{total clearance}}$$

$$\text{fraction metabolised} = \frac{\text{hepatic clearance}}{\text{total clearance}}$$

$$\text{fraction metabolised} = \frac{\text{total clearance - renal clearance}}{\text{total clearance}}$$

3.4. Predicting drug effects

What determines steady state drug concentrations during chronic dosing

Physiological parameters determining C_{SS} of highly metabolised drugs during chronic dosing

- O*rally* administered drugs, a combination of factors determining first-pass clearance and systemic clearance
- *Intravenously* administered drugs, only systemic clearance is important.
- Assumption often made is that for orally administered drugs that f_g is 1.0 (all of the drug is absorbed into the portal circulation).
- The unbound drug interacts with receptors and produces drug effect.

TP1: Predicting everything about a drug from a few simple pharmacokinetic parameters

Drug A is known to be only metabolized by the liver and extrected by the kidney and we have a few parameters known.

Known parameters	Drug A
Total clearance	80 L/hour
Volume of distribution	500 L
Fraction exrected unchanged	0.1
Liver blood flow	90 L/hour

⇨ Predict the renal clearance, the hepatic clearance, the hepatic extraction ratio and the maximum oral bioavailability (in %).

TP2: Prediction of disease and drug interaction effects

Known parameters	Ampicillin
Clearance (L/h)	13
Volume of distribution	20
Fraction eliminated unchanged	0.8
Fraction unbound in plasma	0.8
Acid or base	Acid
Predicted	
Renal clearance (L/h)	
fu*GFR	
Secreted	
Reabsorbed	
Competition (acidic)	
Competition (basic)	
Affected by urine flow/pH	
Adjust dose on renal failure	

- We assume that GFR is 7 L/h
- Competition (acidic) with propenecid
- Competition (basic) with cimetidine

TP3: Prediction of disease and drug interaction effects

Known parameters	Gentamicin	Procainamide
Clearance (L/h)	6	25
Volume of distribution	20	130
Fraction eliminated unchanged	1	0.6
Fraction unbound in plasma	1	0.85
Acid or base	Base	Base
Predicted		
Renal clearance (L/h)		
fu*GFR		
Secreted		
Reabsorbed		
Competition (acidic)		
Competition (basic)		
Affected by urine flow/pH		
Adjust dose on renal failure		

Narrow therapeutic index

GFR =7 L/h

3.4. Predicting drug effects

Using a few basic pharmacokinetic parameters we can predict the behavior of the drug in the body

Is helpful to predict
- the doses regime of the drug
- possible competitions with other drugs
- possible interactions with other diseases

⇒ allows for faster and more accurate drug trials