Pharmacologie générale:
7. Pharmacocinétique et métabolisme

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Le contenu de ce cours est inspiré et reprends des parties (i) du cours "PK/PD des antibiotiques" (F. Van Bambeke, E. Ampe, P. Tulkens); (ii) du cours de Pharmacocinétique du Prof. R.K. Verbeeck

Pharmacocinétique et métabolisme:

- Concepts généraux
- Absorption
- Distribution
- Elimination
- Métabolisme
- Analyse pharmacocinétique (*)

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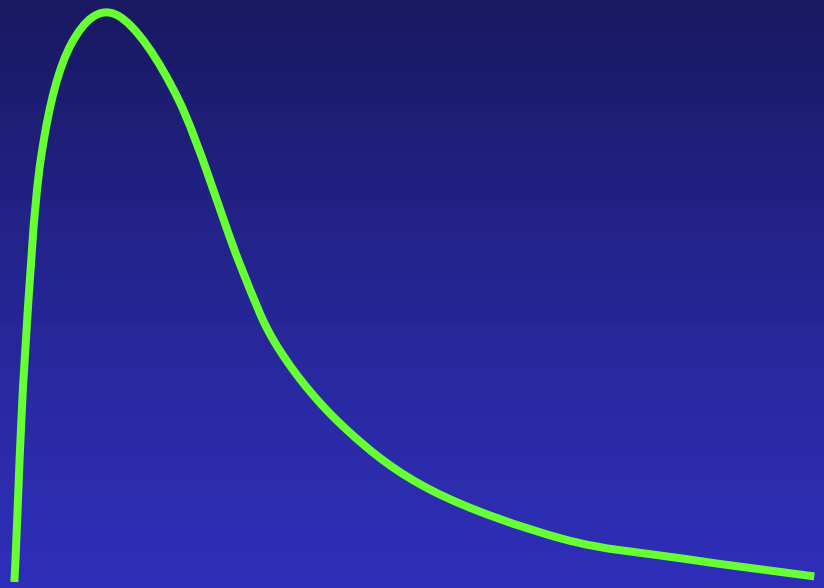
* sera donnée indépendamment

Concepts généraux de pharmacocinétique (PK)

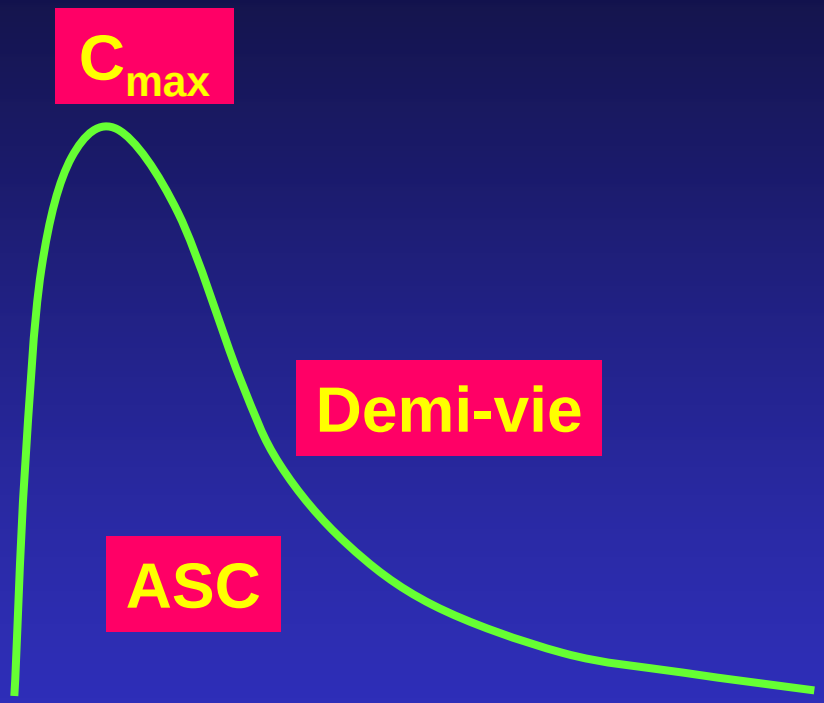


- **C_{max},**
- **clairance,**
- **V_d,**
- **Demi-vie,**
- **ASC,**
- **biodisponibilité,**
- **Liaison aux protéines**

Qu'est-ce donc que ce jargon ?

A quoi cela sert-il ?

Concepts généraux de pharmacocinétique (PK)



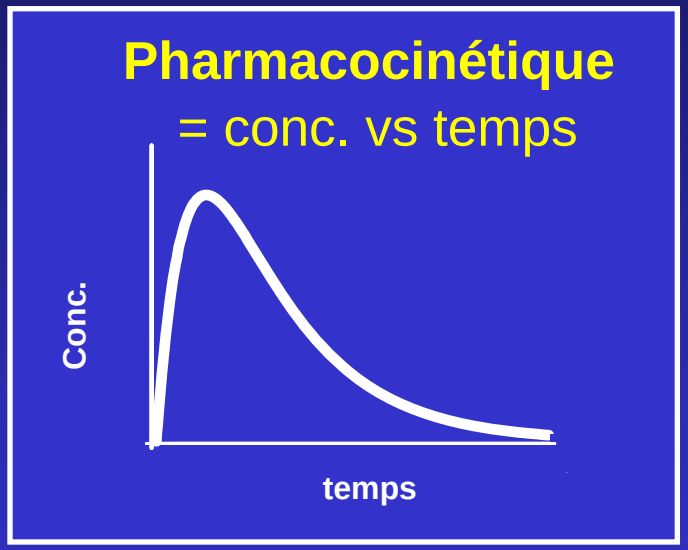
- C_{max},
- clairance,
- V_d,
- Demi-vie,
- ASC,
- biodisponibilité,
- Liaison aux protéines

ensemble ... à l'assaut !!

En quoi consiste la pharmacocinétique ?

- **" ce que le corps fait au médicament "**

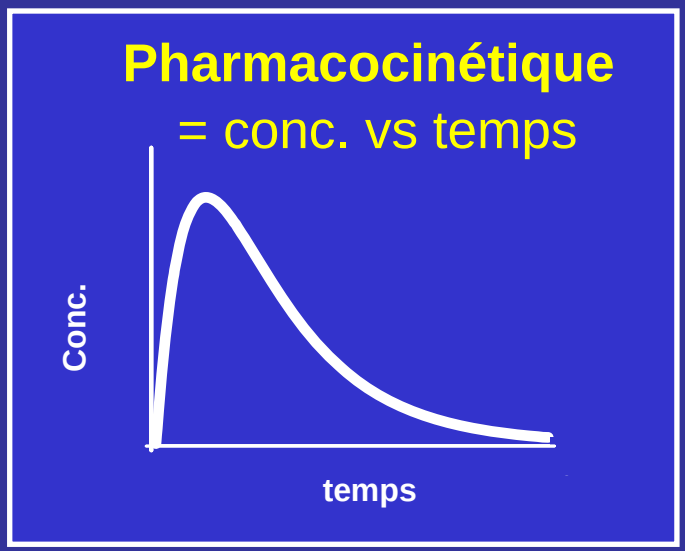
- Devenir du médicament dans l'organisme, en termes de
  - Absorption
  - Distribution
  - Métabolisme
  - Excrétion



- Variations temporelles des concentrations en médicament et en métabolites

A quoi sert la pharmacocinétique ?

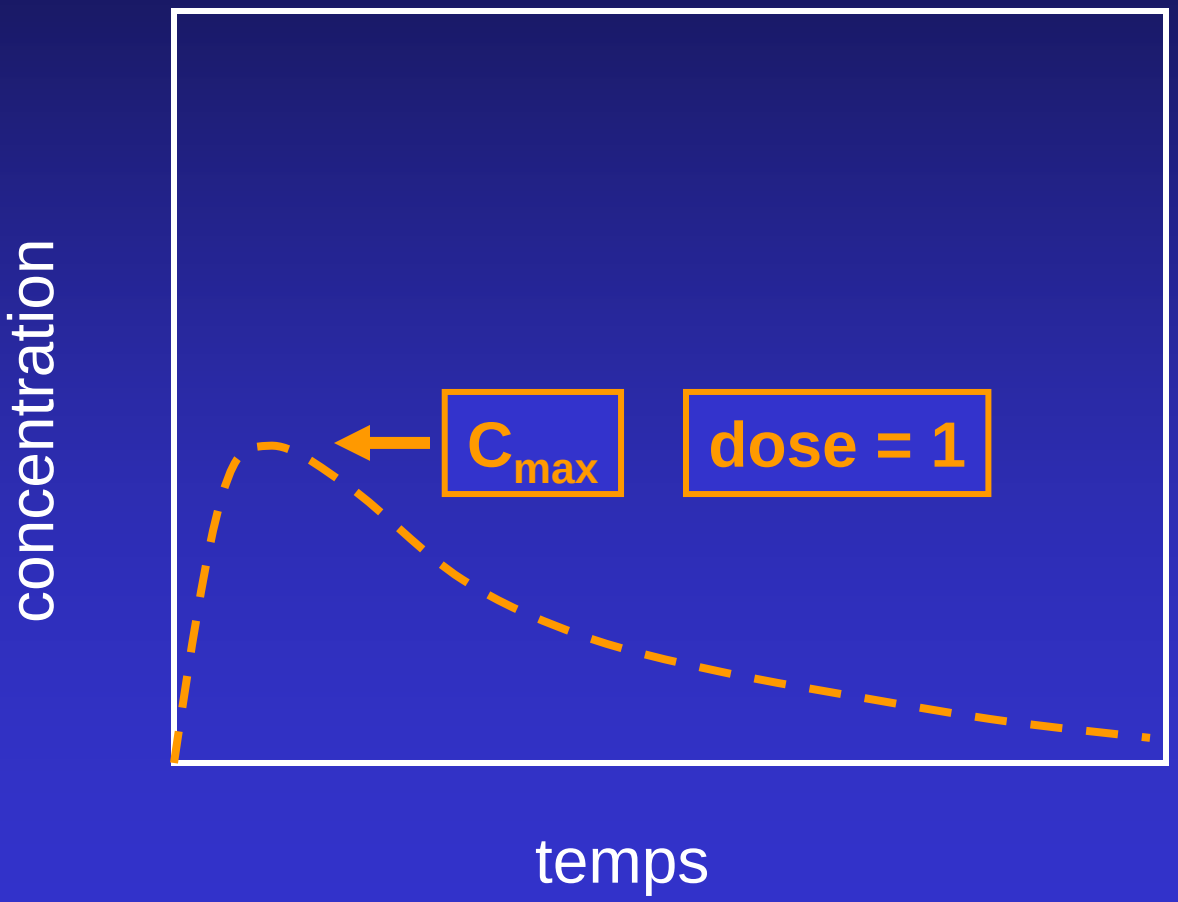
PK est un moyen de voir si le médicament peut être utilisable …



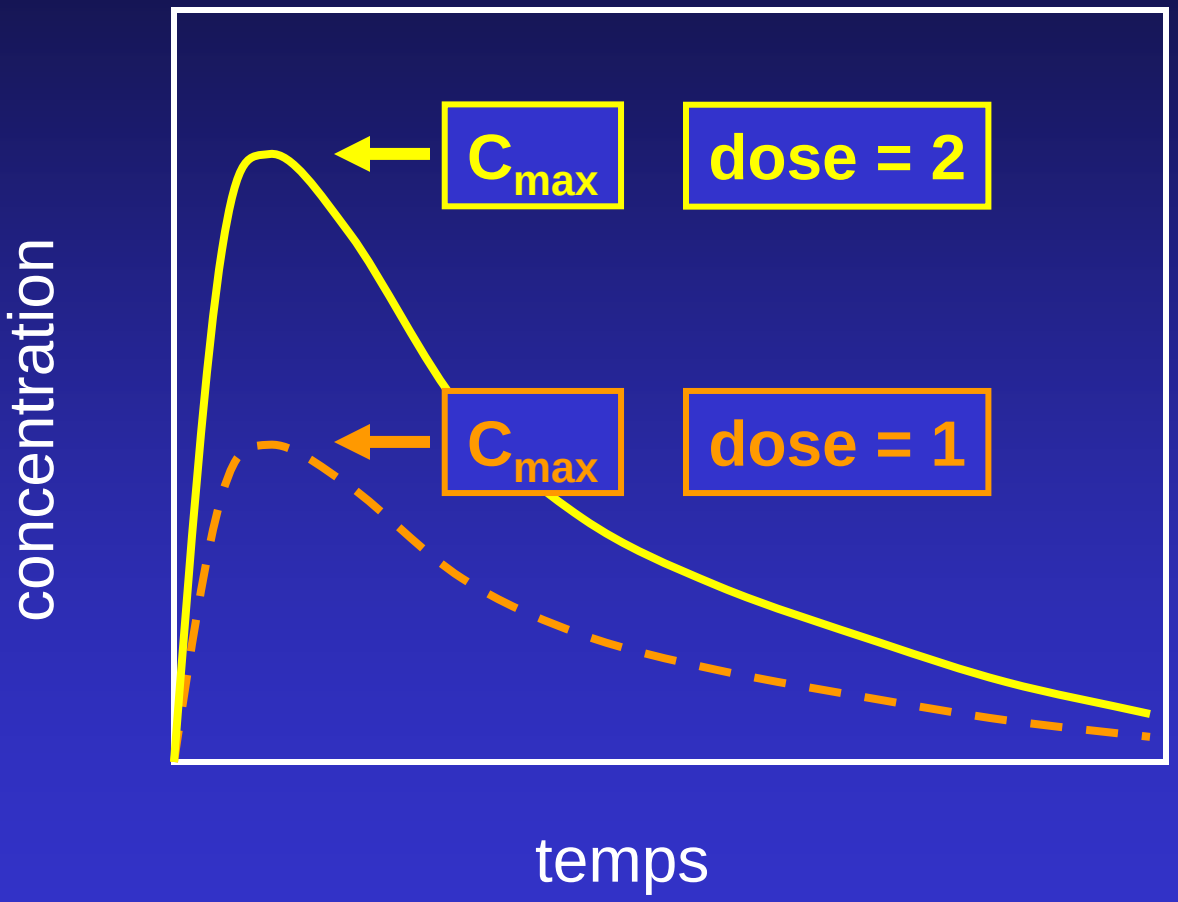
- **atteint-il sa cible en concentration suffisante ?**
- **pour un temps assez long ?**
- **atteint-il des cibles non souhaitables ?**

C_{max}

Le C_{max} est la concentration la plus élevée atteinte dans le plasma après administration du médicament ...



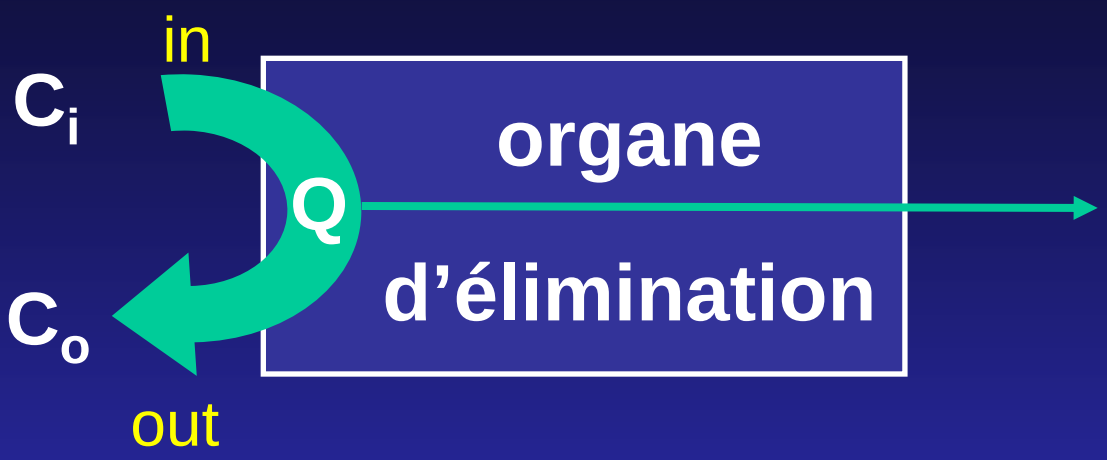
Le C_{max} ... est proportionnel à la dose ...



Quelle est la signification du C_{max} ?

- un médicament avec un C_{max} (trop) faible peut être inefficace si son activité est concentration-dépendante
- Un médicament avec un C_{max} (trop) élevé peut devenir toxique si sa toxicité est liée au C_{max} (ce qui n'est PAS toujours le cas.... !)
- Il faut donc ajuster la dose pour atteindre le C_{max} adéquat!

Clairance (Cl)



Quantité éliminée par unité de temps

➔ $C_o < C_i$

la <u>vitesse</u> à laquelle le médicament est éliminé est proportionnelle
- au flux sanguin dans l'organe d'élimination (Q)
- à la capacité d'extraction de cet organe (E)

la clairance est donc Q x E (= L/h or ml/min)

Quelle est la signification de la clairance ?

- Un médicament à clairance rapide ne reste pas longtemps dans l'organisme… et peut donc nécessiter des administrations répétées...

- Mais un médicament peut montrer une clairance lente à cause de sa liaison aux protéines, qui empêche son élimination
  (voir plus loin …)

- Si la clairance diminue pendant le traitement (ou est anormale dès le début du traitement), le patient sera "surdosé" !!

Volume de distribution (V_d)

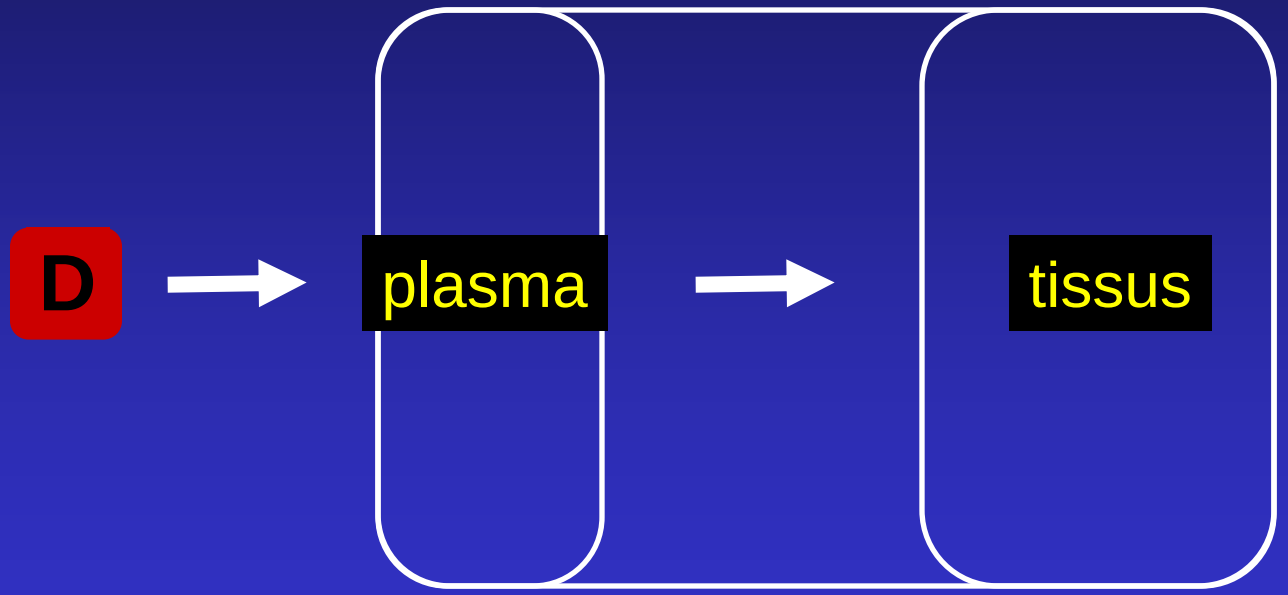
- Quantifie l'accès du médicament aux différents compartiments de l'organisme

- Relie la concentration sérique (C) à la quantité de médicament introduite dans l'organisme (= Dose)

V_d = Dose / Concentration sérique

Qu’est-ce que le V_d ?

Considérons le corps comme un grand “récipient”
à multiples compartiments
dans lequel on déverse un médicament (D) ...

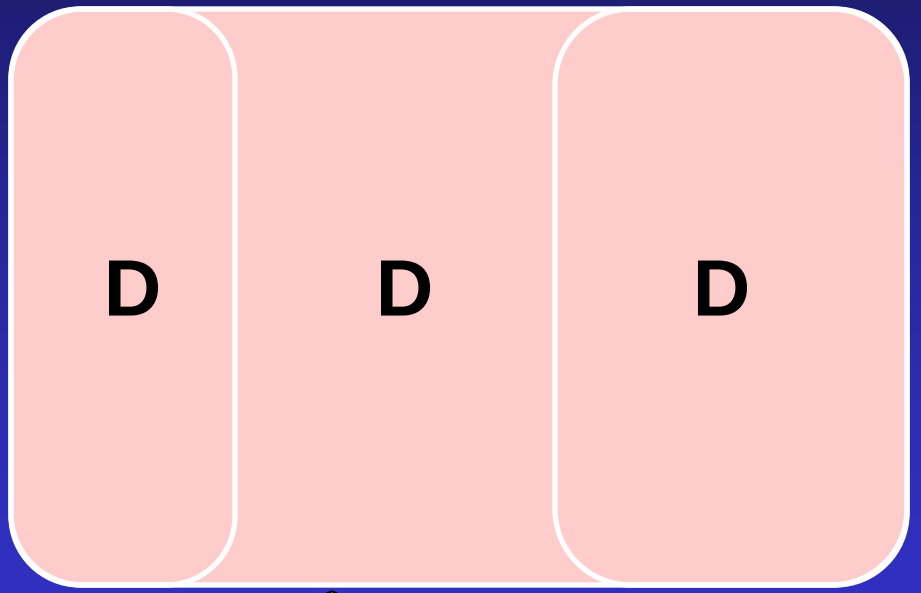


Qu'est-ce que le V_d ?

Si le médicament diffuse et se répartit **uniformément** dans l'organisme ...

Vd = 1 L/kg

C_{max} = dose / poids



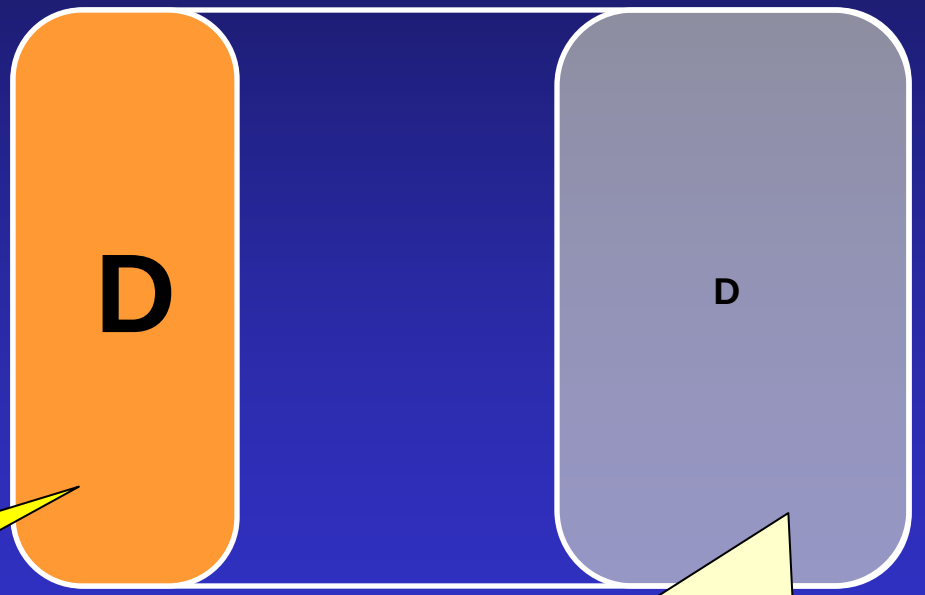
concentration sérique = concentration tissulaire

Qu'est-ce que le V_d ?

Si le médicament n'atteint que le plasma
et les liquides extracellulaires ...

Vd < 1 L/kg

C_{max} > dose / poids



Concentration sérique élevée

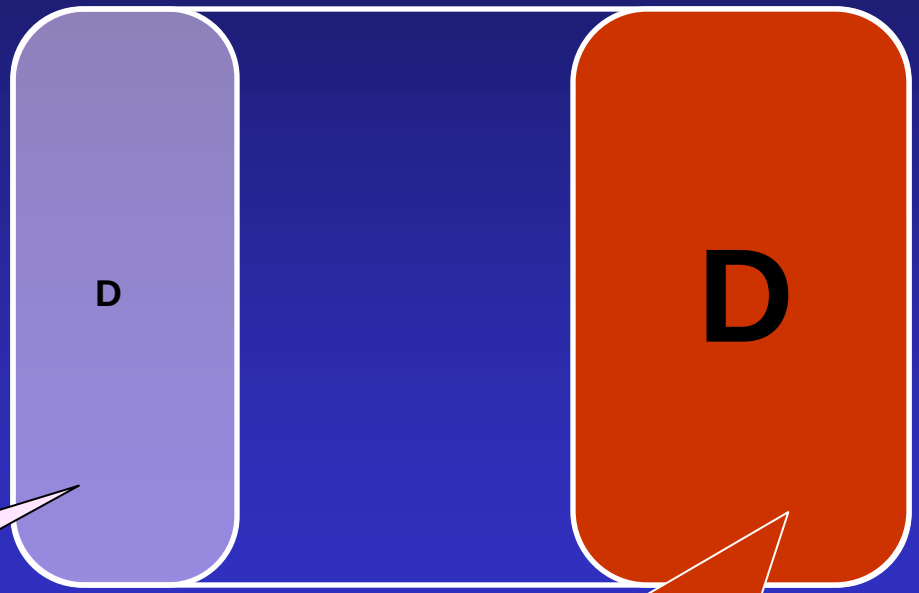
Concentration tissulaire faible ou nulle

Qu'est-ce que le V_d ?

Si le médicament **s'accumule** dans les tissus...

Vd > 1 L/kg

C_{max} < dose / poids



Concentration sérique faible

Concentration tissulaire élevée

Quelques valeurs de V_d typiques pour les antibiotiques

	L/kg
• dicloxacilline (sérum uniquement)	0.1
• gentamicine (serum +liquides extracell.)	0.25
• ciprofloxacine (fluides extracell. + accumul.tissulaire modérée)	1.8
• azithromycine (accumulation tissulaire marquée)	**31**

Quelle est la signification clinique du Vd ?

- Un médicament à faible V_d aura une concentration sérique initiale élevée mais n'atteindra pas les tissus...

- Un médicament à V_d élevé aura des taux sériques initiaux faibles …
  - Si le V_d élevé est lié à des **facteurs propres au patient** (par ex, patient brûlé), il faut augmenter la dose de médicament
  - Si le V_d élevé est une **propriété du médicament**, les taux sériques peuvent devenir infra-thérapeutiques

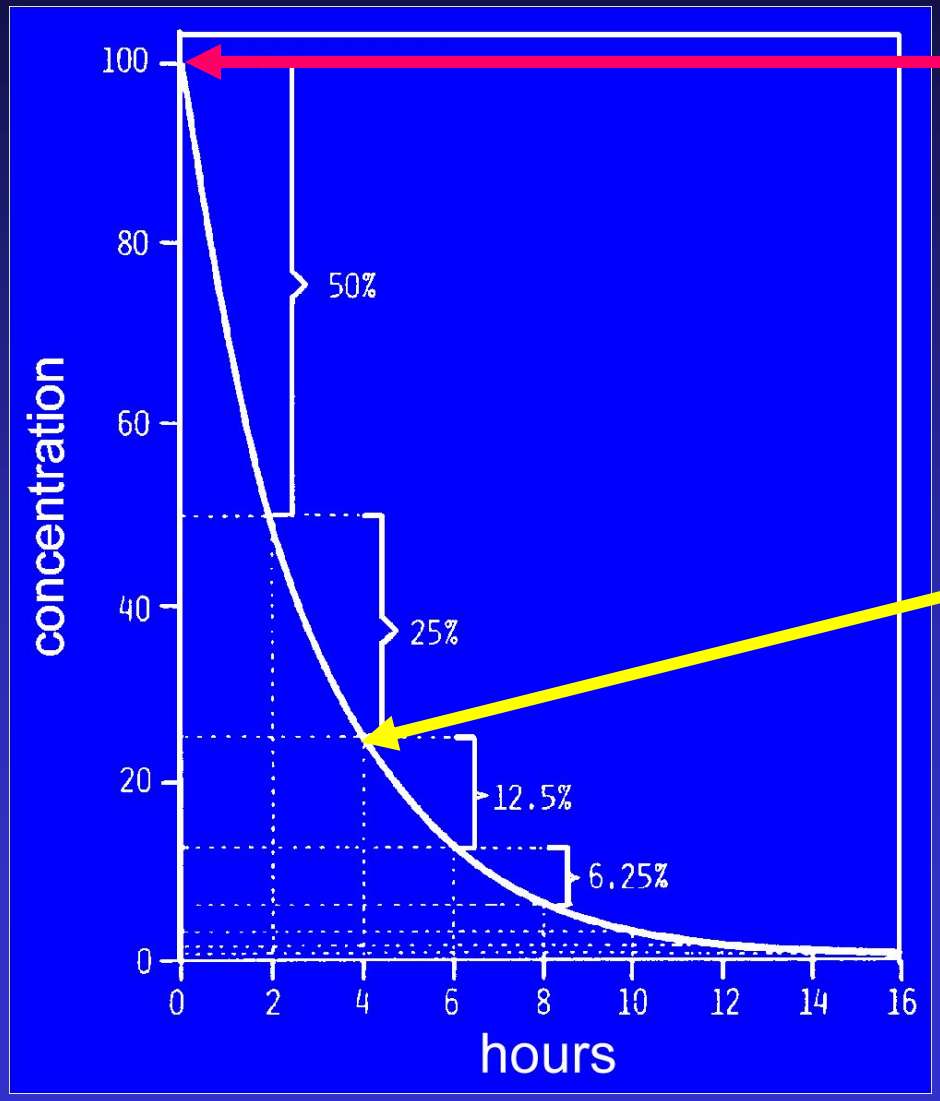
Demi-vie ($t_{1/2}$)

- La demi-vie est le temps nécessaire pour que la concentration du médicament diminue de moitié
- C'est un paramètre facile à mesurer
  (il suffit de quelques échantillons sanguins…)

  MAIS ...

- C'est un paramètre pharmacocinétique **secondaire** car il dépend de la clairance ET du volume de distribution

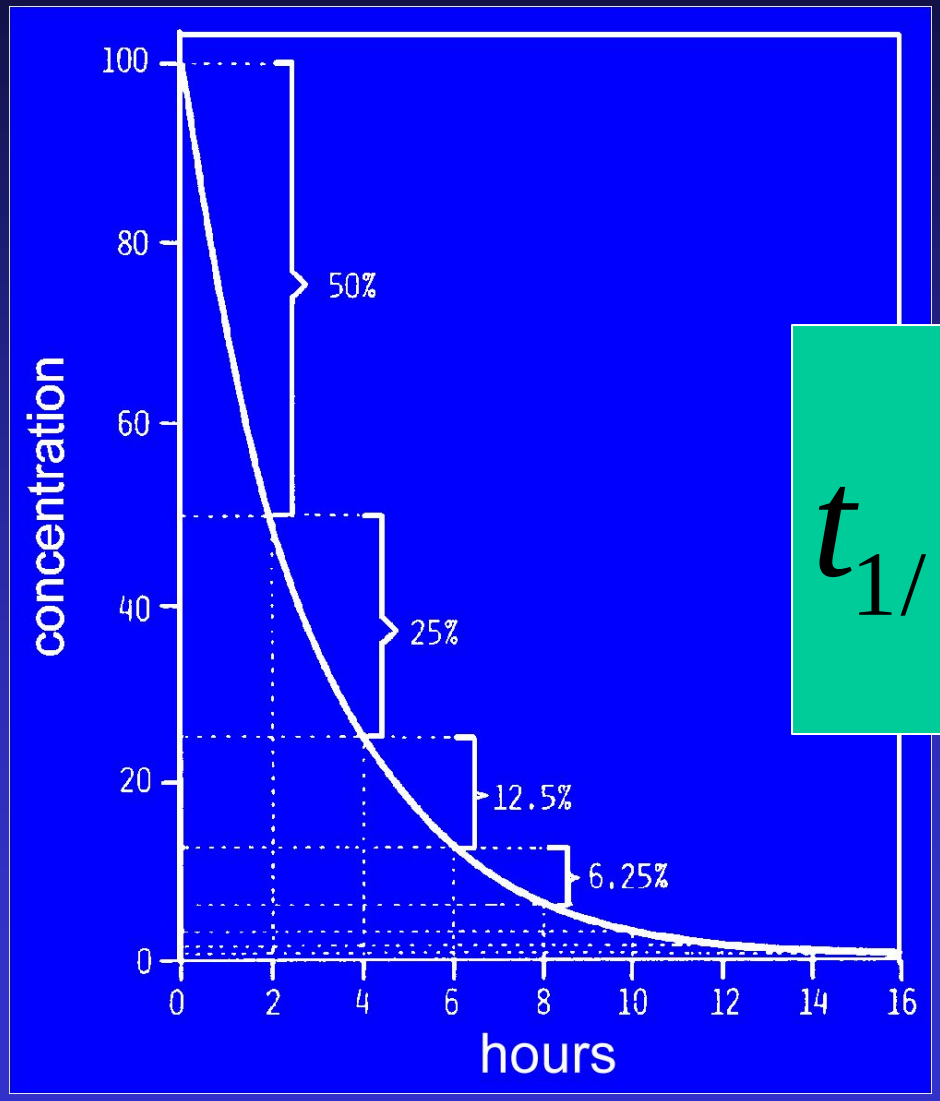
Pourquoi $t_{1/2}$ est-elle un paramètre secondaire ?



Vous partez d'ici …
C'est le C_{max},
c.à.d Dose / Vd

Et vous suivez une courbe définie par la vitesse d'élimination du produit,
càd sa clairance totale

Pourquoi $t_{1/2}$ est-elle un paramètre secondaire ?



$$t_{1/2} = \frac{0.693 \cdot Vd}{CL}$$

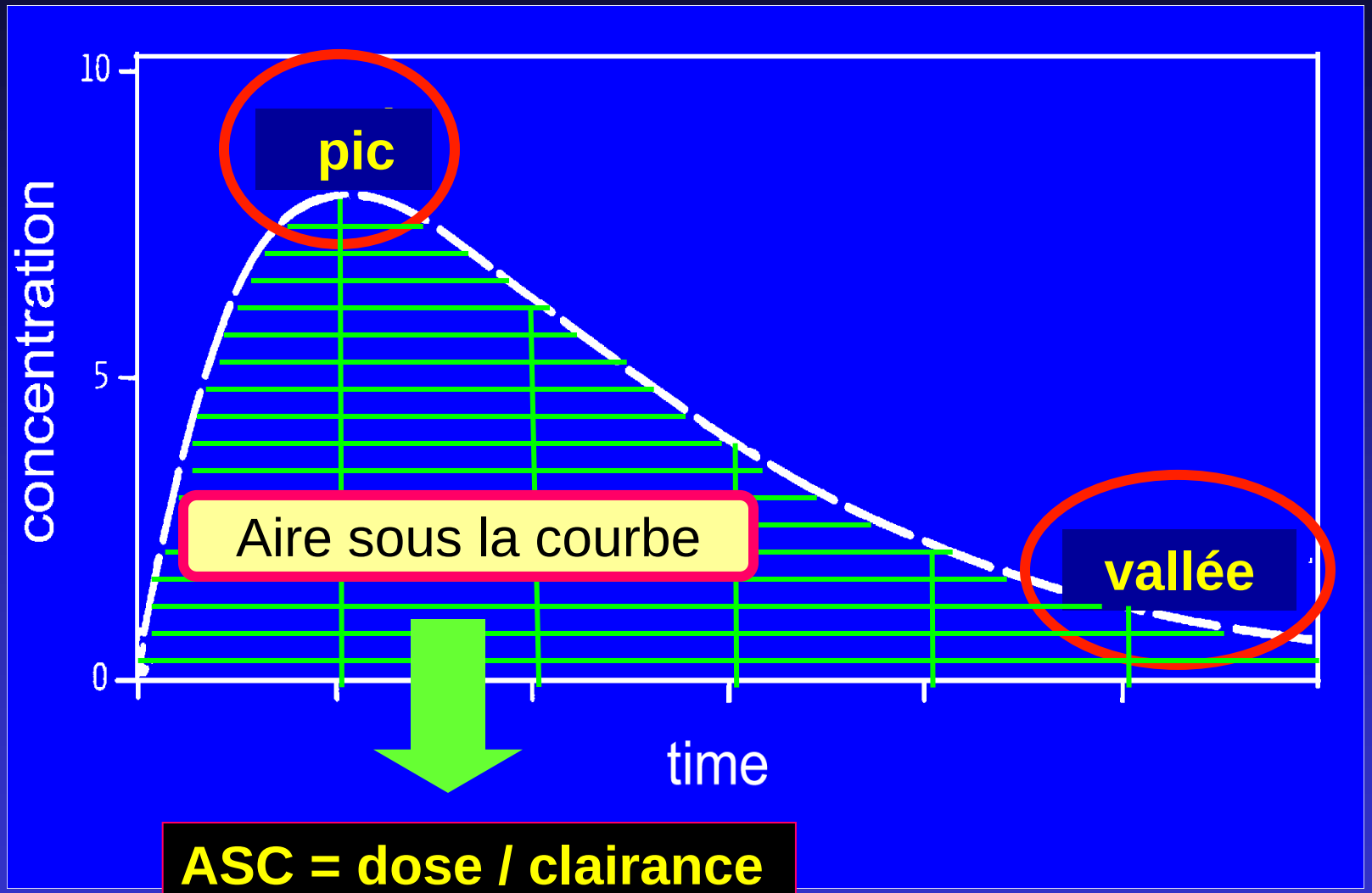
Pourquoi $t_{1/2}$ est un paramètre utile au clinicien?

- information directe sur la vitesse à laquelle la concentration diminue dans le temps … et atteint un seuil défini ... Si vous connaissez le C_{max} (càd votre point de départ)

- Comparaison directe de médicaments … s'ils ont un V_d similaire ...

Vous pouvez comparer entre elles les demi-vies des β-lactames, ...
MAIS vous ne pouvez PAS comparer directement les β-lactames (faible V_d) à l'azithromycine (V_d élevé), par exemple.

Surface sous la courbe (ASC ou AUC*)



* Area Under the Curve

Surface sous la courbe (ASC)

- combine
  - Un paramètre directement lié à la décision médicale: **la dose du médicament** !
  - Un paramètre lié au médicament ET au patient: la **clairance** ...
- Sa valeur est indépendante du schéma d'administration ...
- Ce paramètre est utile pour évaluer l'exposition totale au médicament

24h-ASC des fluoroquinolones (p.o.)

médicament	Dose (mg/24h)	24h-ASC (mg/L x h)
norfloxacine	800	14 *, #
ciprofloxacine	500	12 *
ofloxacine	400	31 to 66 *, +
levofloxacine	500	47 *
moxifloxacine	400	48 *

Peu si CMI ↑

Bien mieux !!

* notice américaine (adulte 60 kg) de NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, et AVELOX®

\# données de la littérature

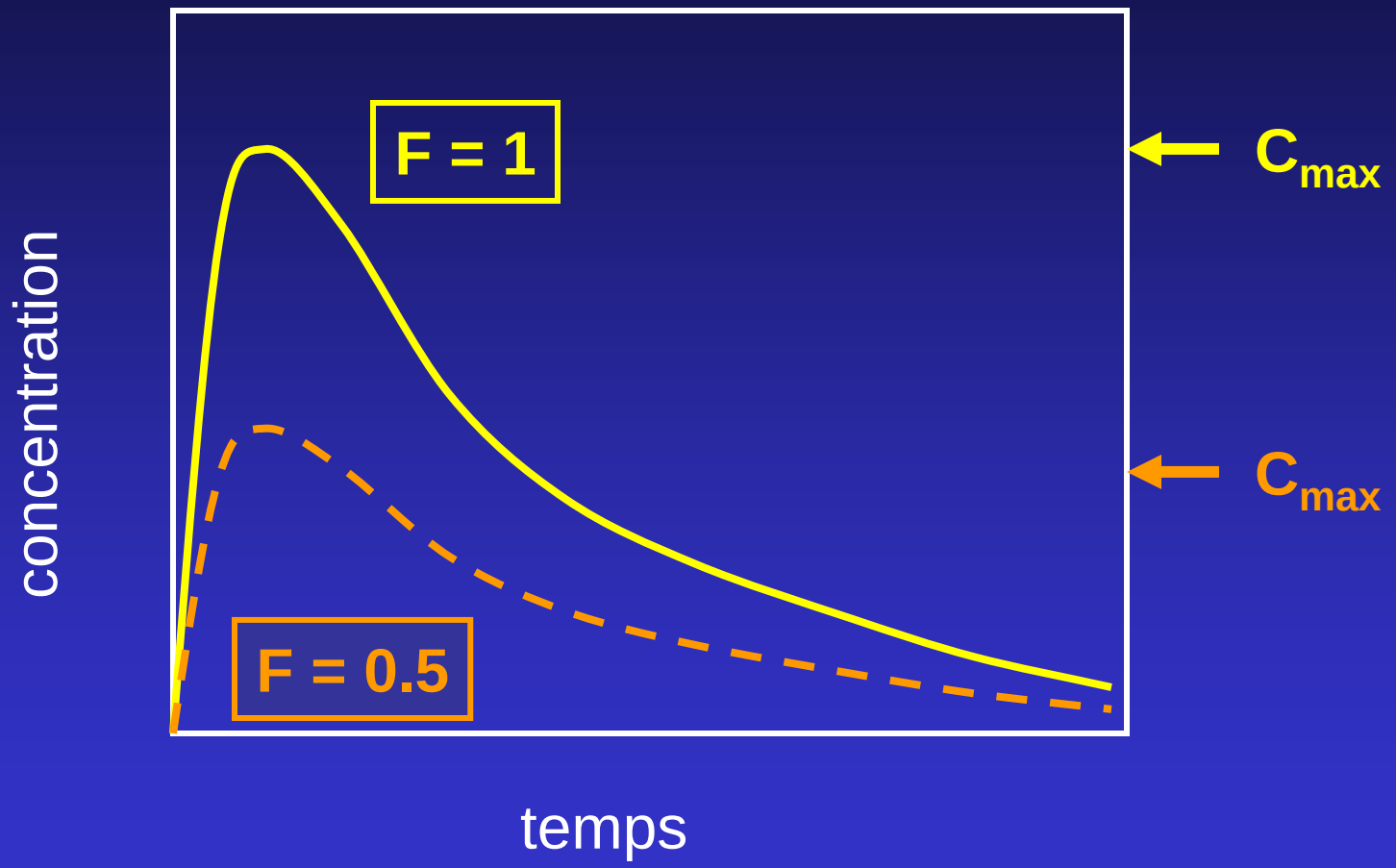
\+ première dose à l'équilibre

Biodisponibilité

- quantifie l'**ABSORPTION** depuis le site d'administration jusqu'au **sang**
- est mesurée en comparant la voie orale (ou autre) à la voie intra-veineuse

Une biodisponibilité faible réduit à la fois le C_{max} et l'ASC ... et conduit donc à une diminution de l'efficacité !!!

Une faible biodisponibilité (F) réduit à la fois le C_{max} et l'ASC



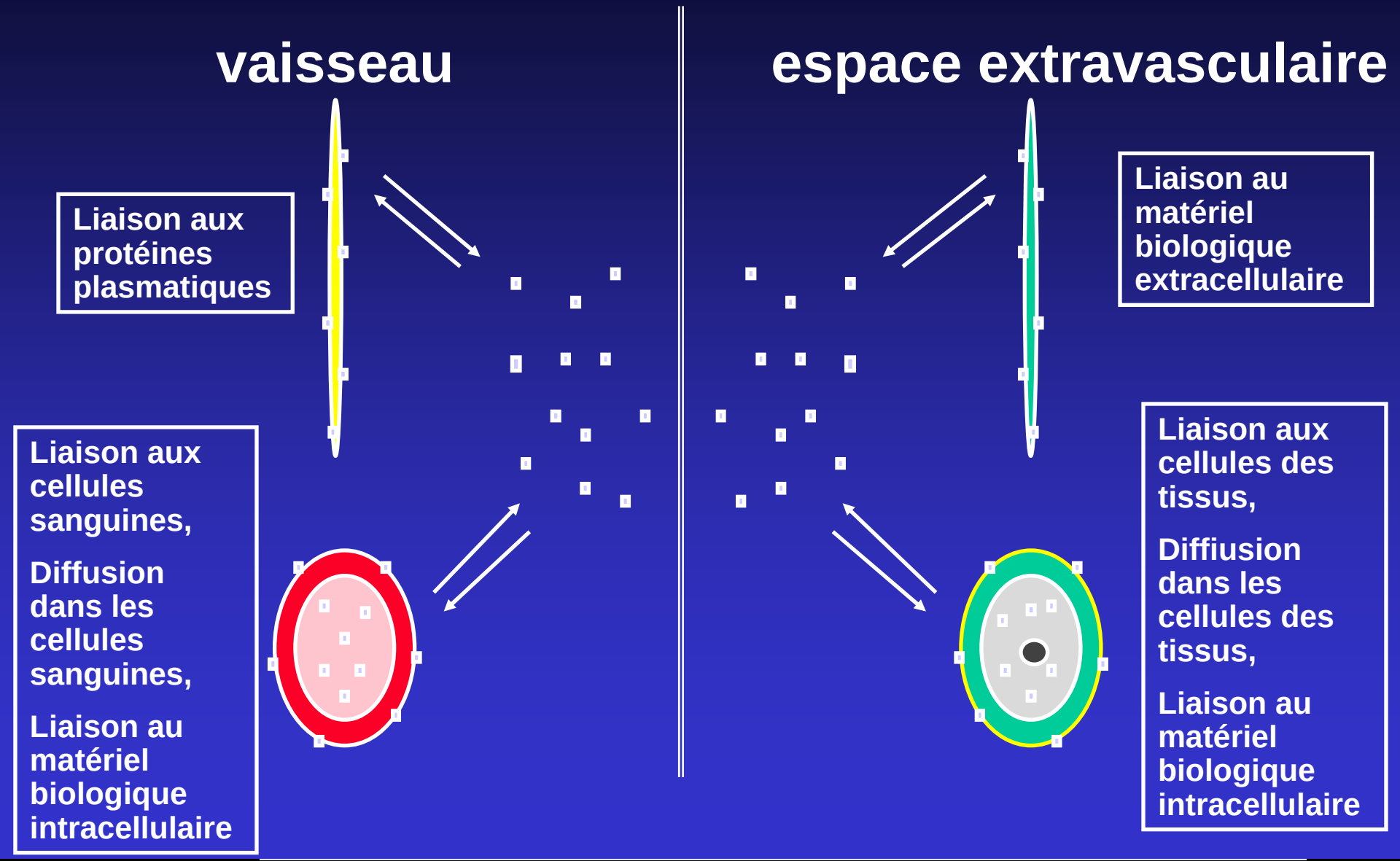
Fluoroquinolones : biodisponibilité (p.o.) et C_{max}

médicament	Dose (mg/24h)	Biodisp. (%)	C_{max} (mg/L)
norfloxacine	800	~ 35	2.4 *
ciprofloxacine	500	~ 70	2.4 *
ofloxacine	400	~ 95	3-4.5 *, +
levofloxacine	500	~ 99	5-6 *, +
moxifloxacine	400	~ 90	4.5 *

* notice américaine (adulte 60 kg) de NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, et AVELOX®

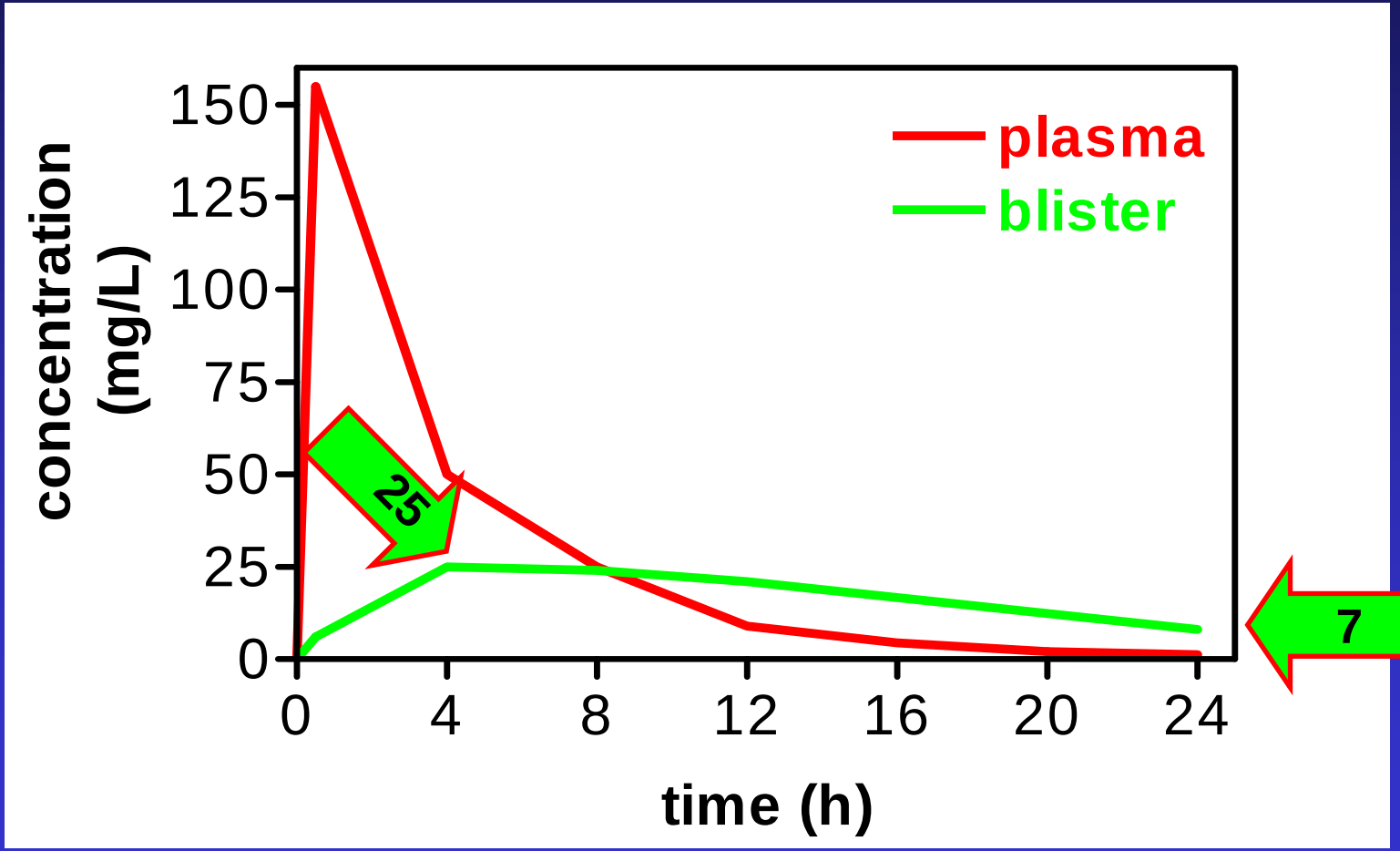
\+ première dose à l'équilibre

Liaison aux protéines: c'est (quasi toujours) la forme du libre du médicament qui agit ...

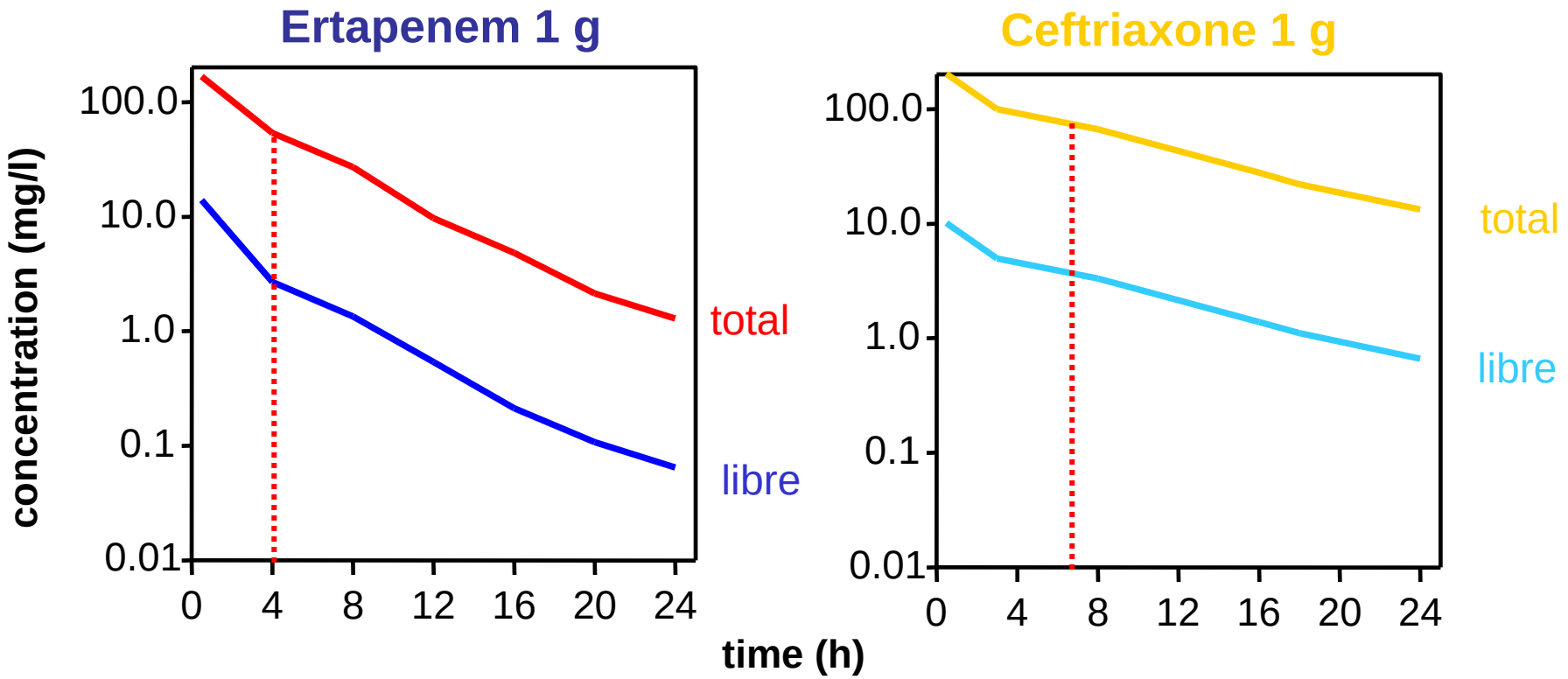


La liaison aux protéines empèche et ralentit la diffusion tissulaire...

Concentration TOTALE de l'ertapenem
(une β-lactame fortement liée aux protéines plasmatiques)
dans le plasma et le liquide d'exsudat après 3 jours de traitement

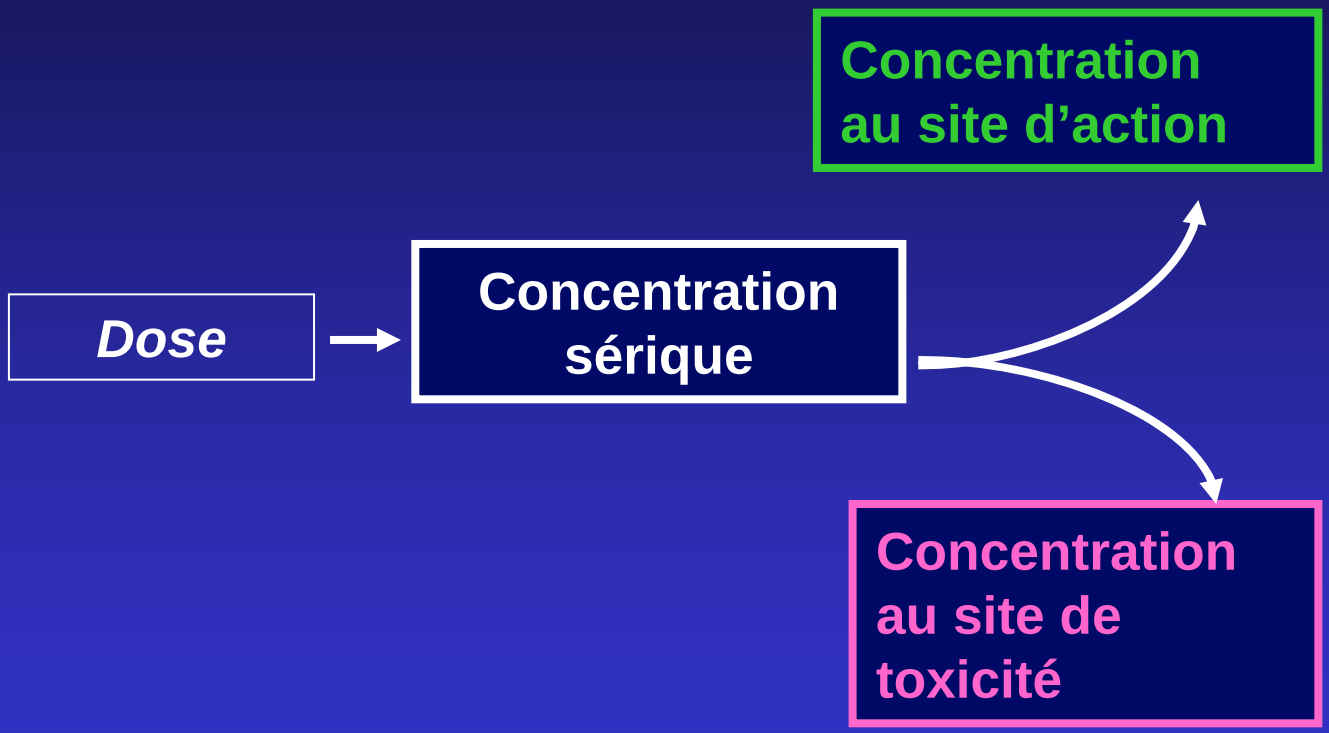


Mais la liaison aux protéines prolonge la demi-vie



ceftriaxone data: Paradis *et al*, AAC 1992, 36: 2085-2092
Perry & Schentag, Clin Pharmacokinet. 2001, 40: 685-694

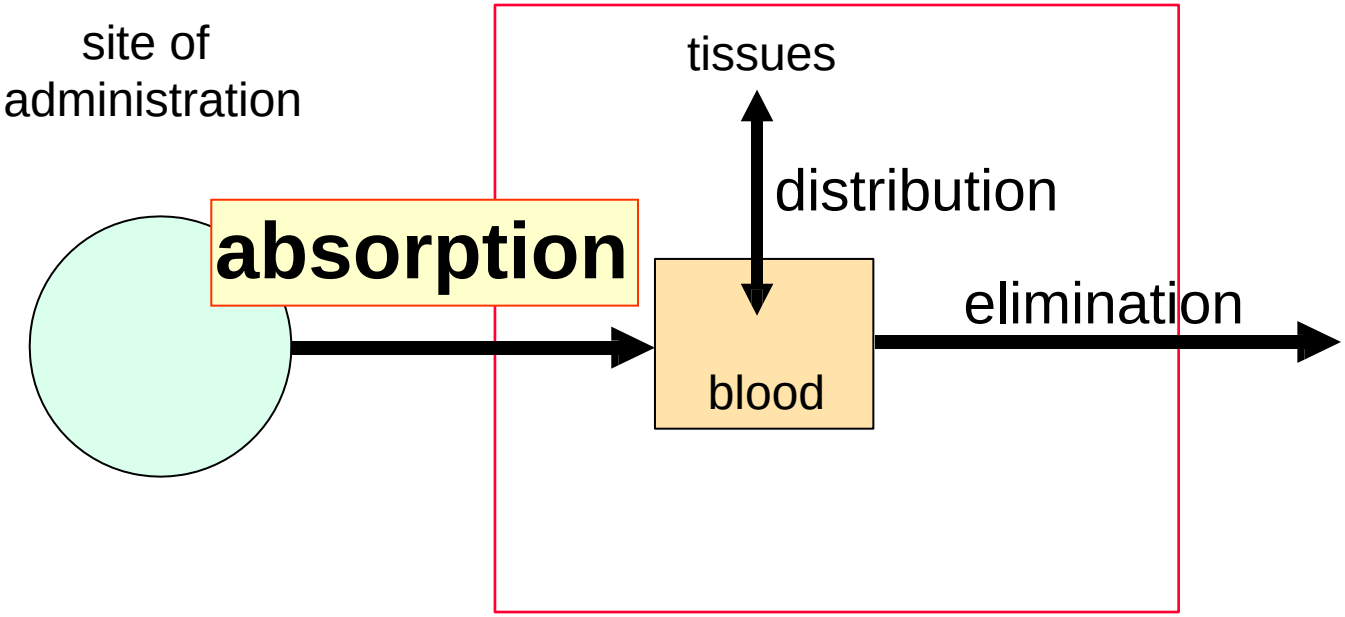
Voilà où nous en sommes ...



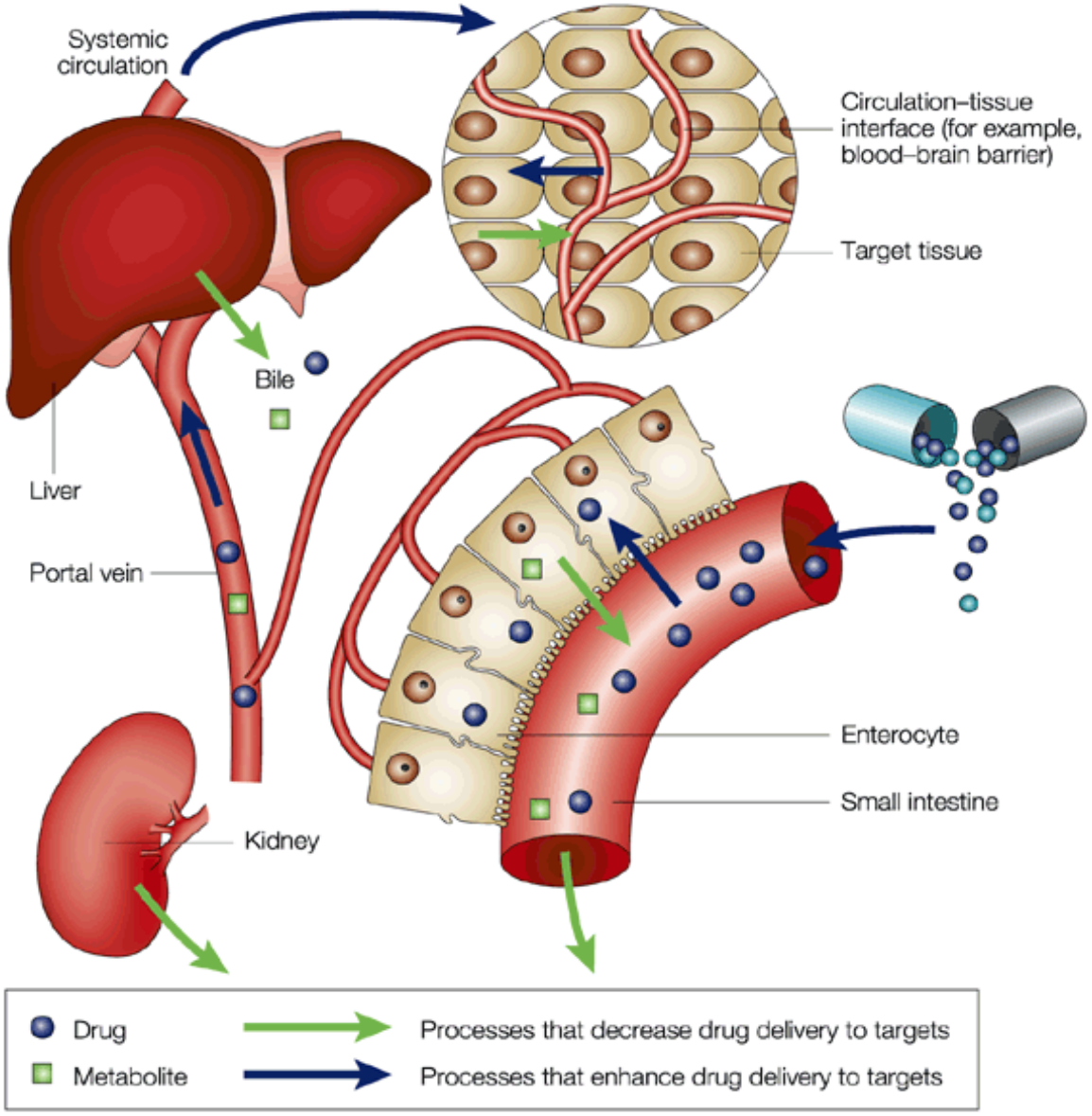
Mais maintenant …

Voyons les étapes…

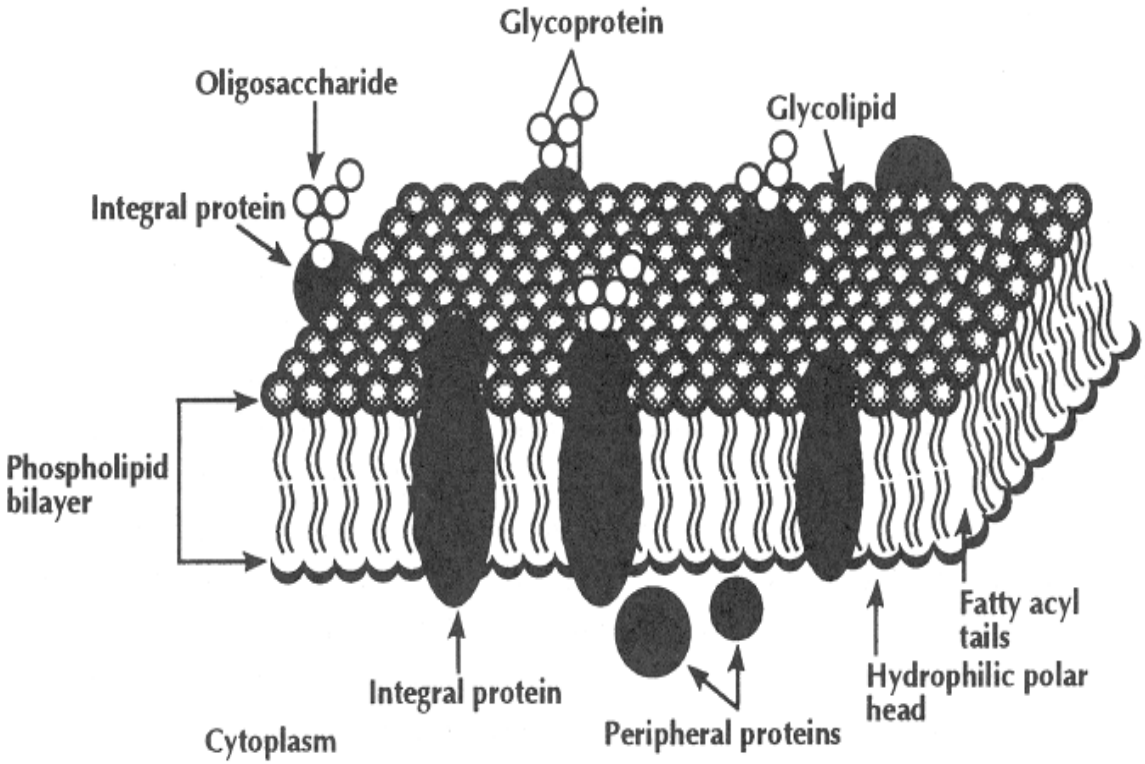
Absorption


site of
administration
tissues
distribution
absorption
elimination
blood

Le parcours du médicament



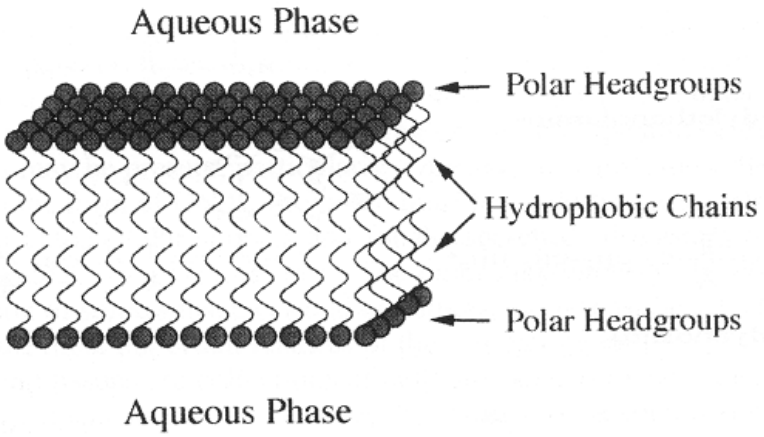
MOVEMENT ACROSS MEMBRANES

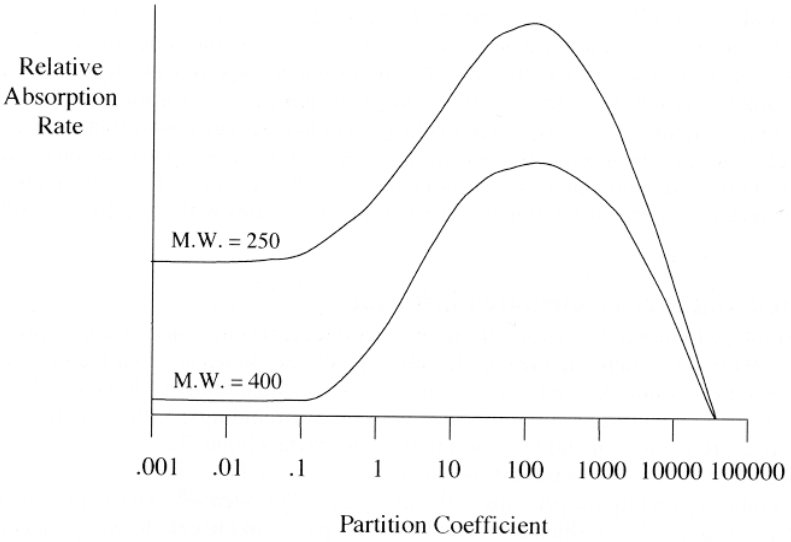


- passive diffusion
- facilitated diffusion
- active transport
- cotransporters/antiporters
- efflux pumps
- pinocytosis/endocytosis

MOVEMENT ACROSS MEMBRANES

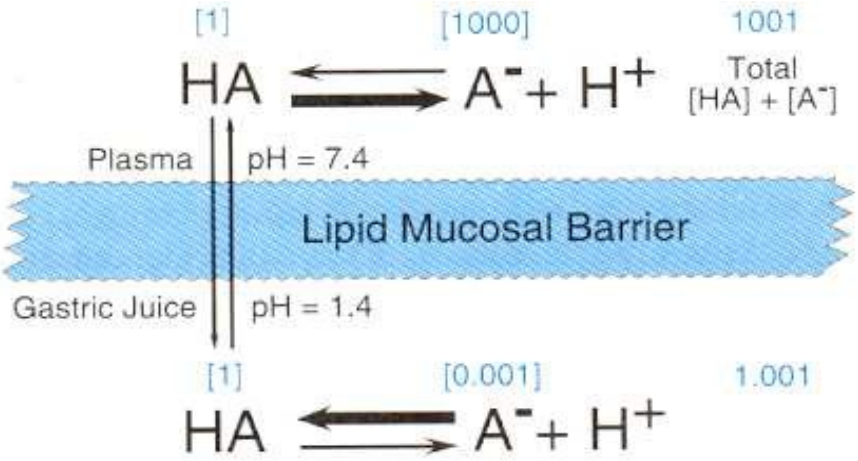
1. lipophilicity





Lipophilicity and **molecular weight** are two factors influencing passive diffusion across biological membranes

MOVEMENT ACROSS MEMBRANES
2. ionization



Henderson-Hasselbalch equation

$$pH = pK_a + \log \frac{[ionized]}{[non-ionized]}$$

$$pH = pK_a + \log \frac{[non-ionized]}{[ionized]}$$

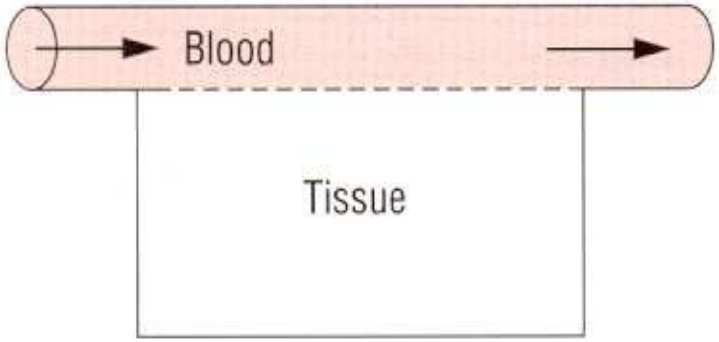
The weak acid will tend to accumulate by ion trapping in the compartment where its ionization is favored.

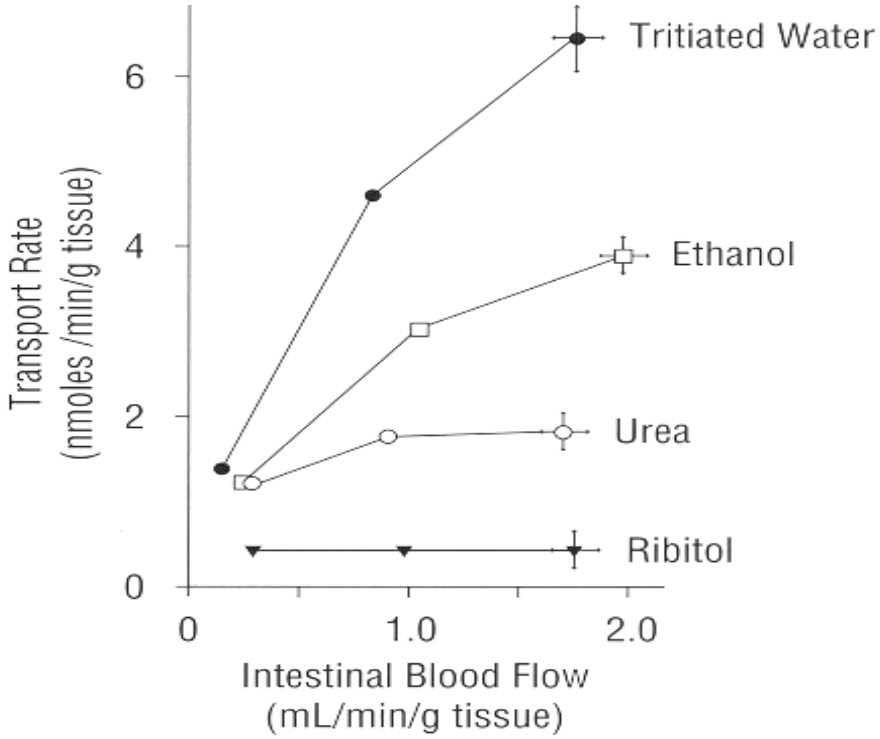
Exercice: faites le même raisonnement pour une base faible

MOVEMENT ACROSS MEMBRANES

3. blood flow

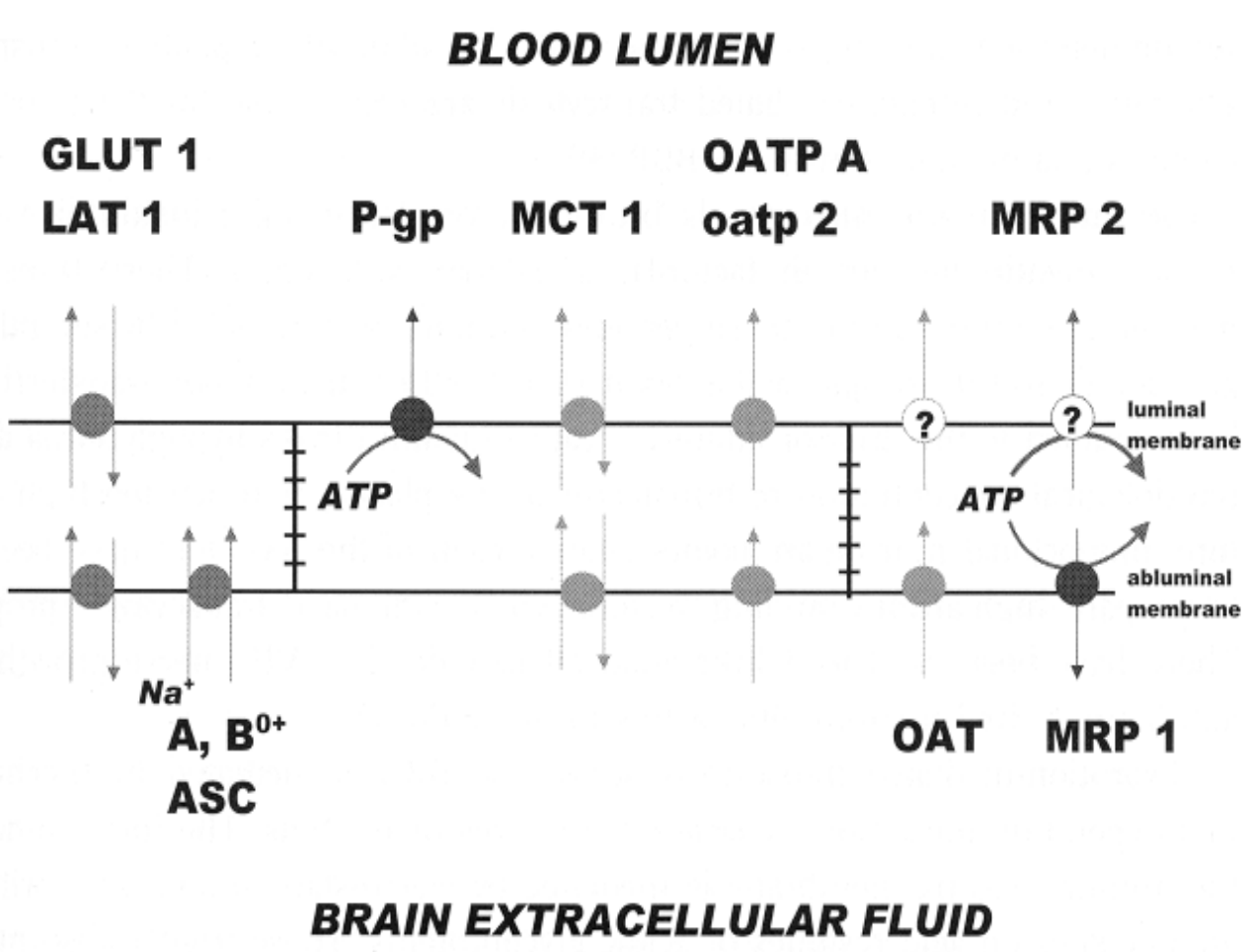
A. Perfusion-Rate Limitation



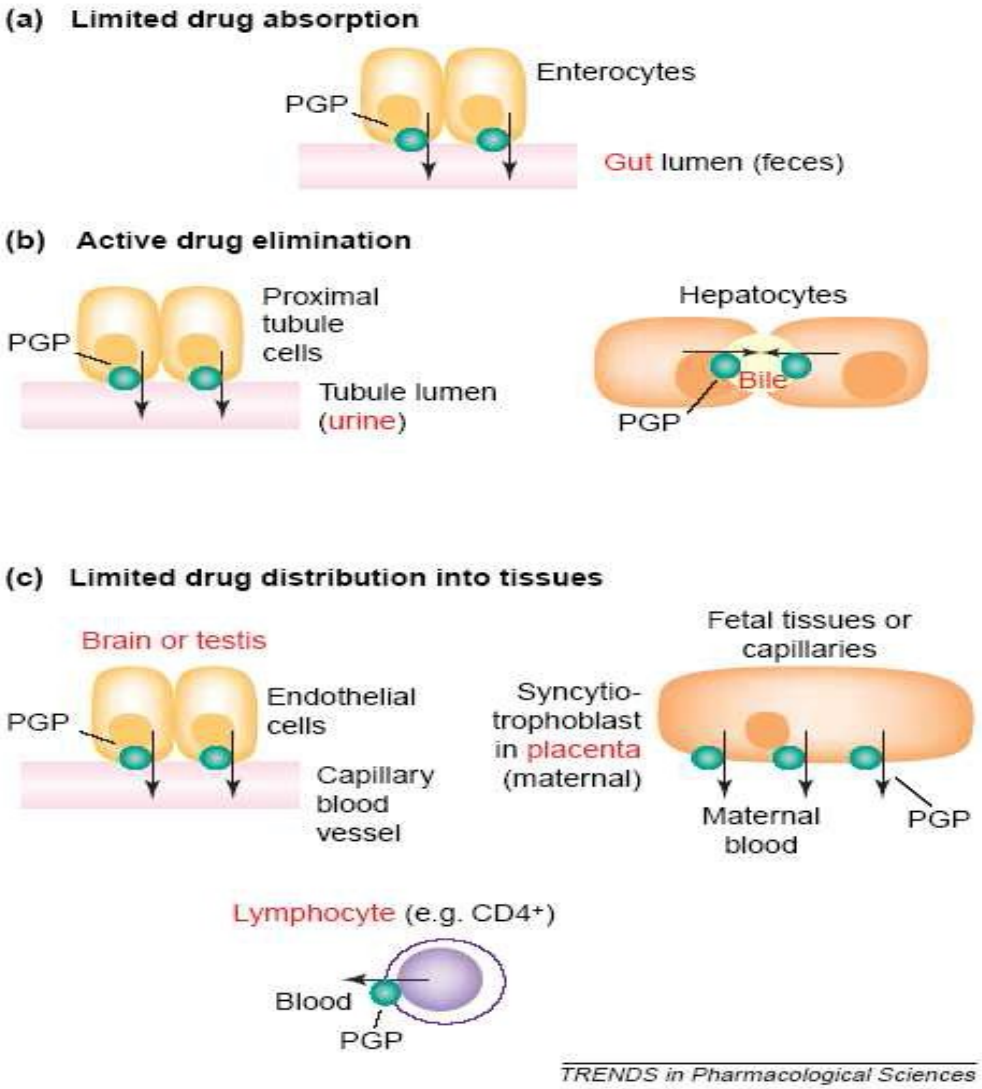


MOVEMENT ACROSS MEMBRANES

4. drug transport processes



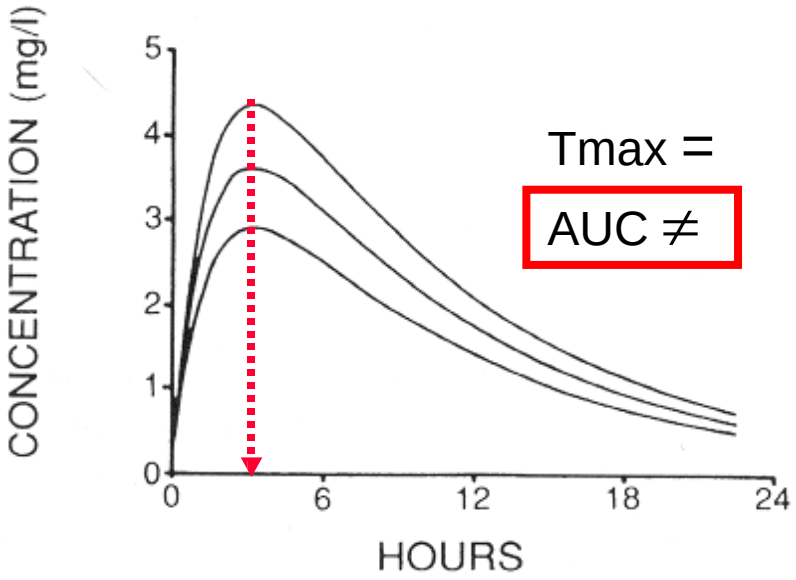
IMPORTANCE OF P-GLYCOPROTEIN

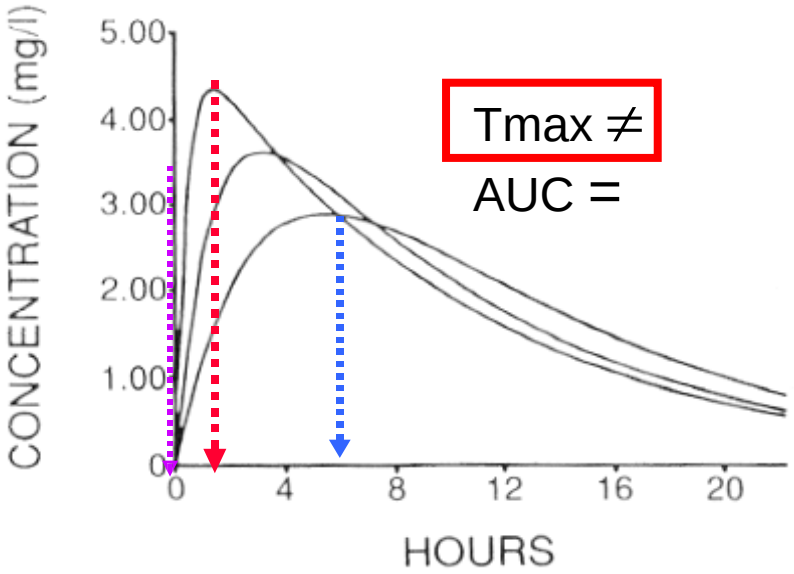


P-glycoprotein (P-gp) is the product of the MDR1 gene. It translocatesa broad variety of xenobiotics out of cells. P-gp was first described in tumor cells that were resistant to various anticancer agents as a result of P-gp overexpression.

P-gp is not only expressed in tumor cells but also in a broad variety of normal tissues with excretory function (small intestine, liver and kidney) and at blood–tissue barriers (blood–brain barrier, blood–testis barrier and placenta).

ORAL ABSORPTION

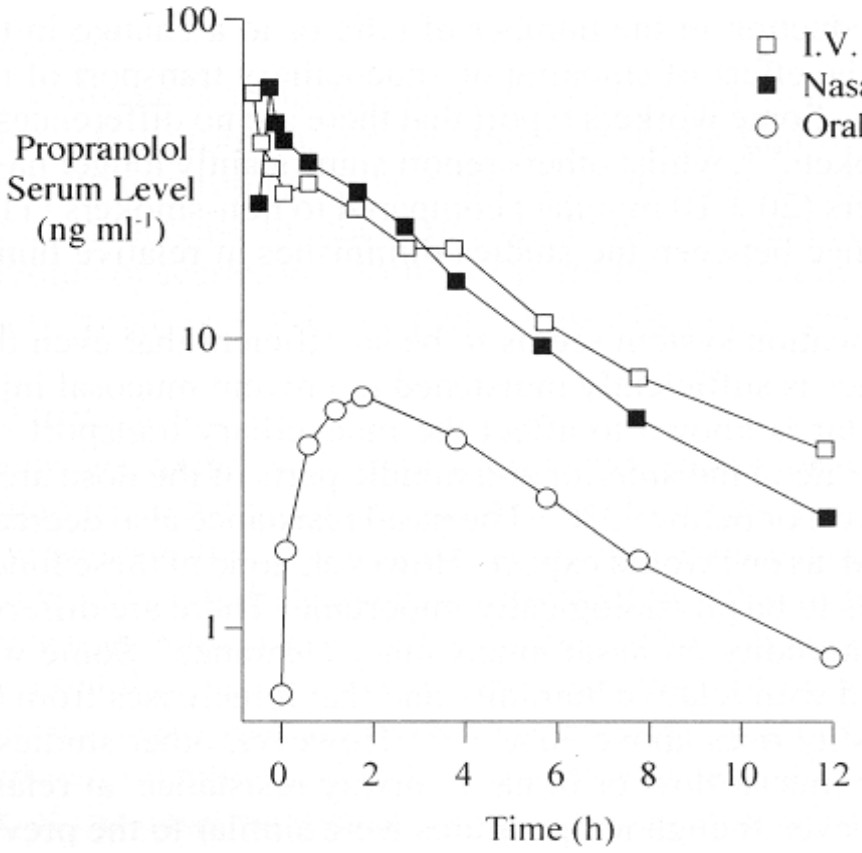




both extent (AUC) and rate (Tmax) of absorption influence the plasma concentration-time profile of a drug and hence therapeutic efficacv and safety

ORAL ABSORPTION

absolute bioavailability

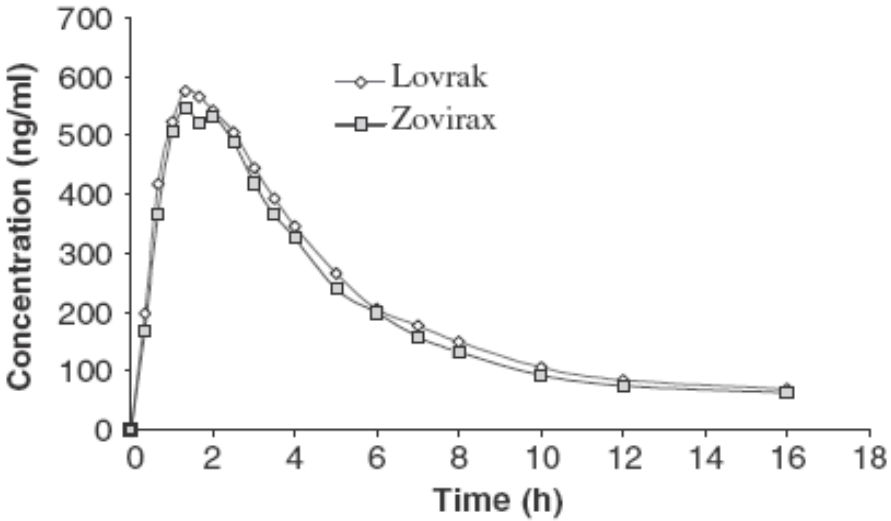


$$F = \frac{AUC_{oral}}{AUC_{iv}} \times \frac{DOSE_{iv}}{DOSE_{oral}}$$

ORAL ABSORPTION

relative bioavailability

Très important pour les génériques

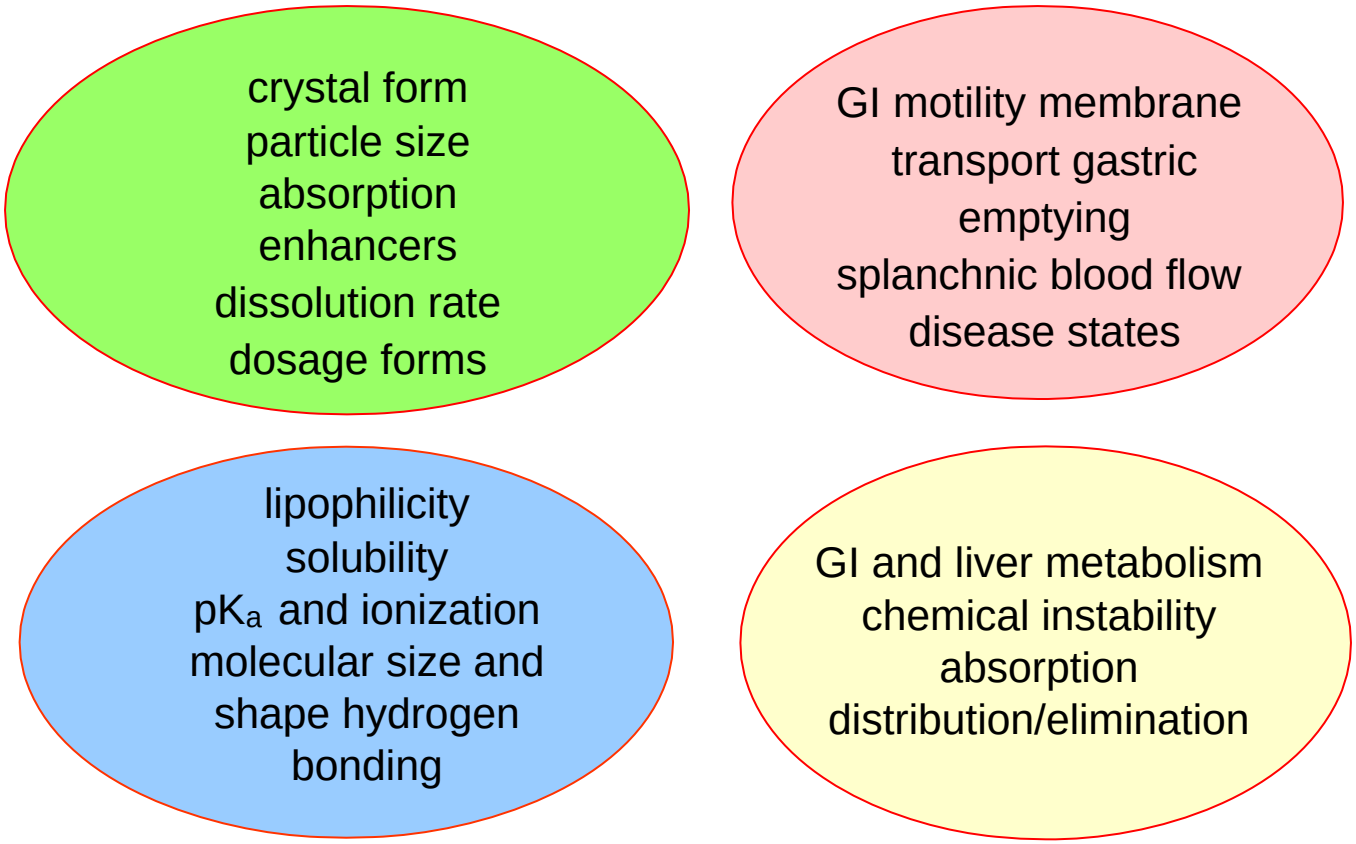


$$F_{rel} = \frac{AUC_{formA}}{AUC_{formB}}$$

In a bioequivalence (BE) study the bioavailability of a test medicinal product (e.g. LOVRAK®) is compared to the bioavailability of a reference medicinal product (ZOVIRAX®). A BE study is a relative bioavailability study.

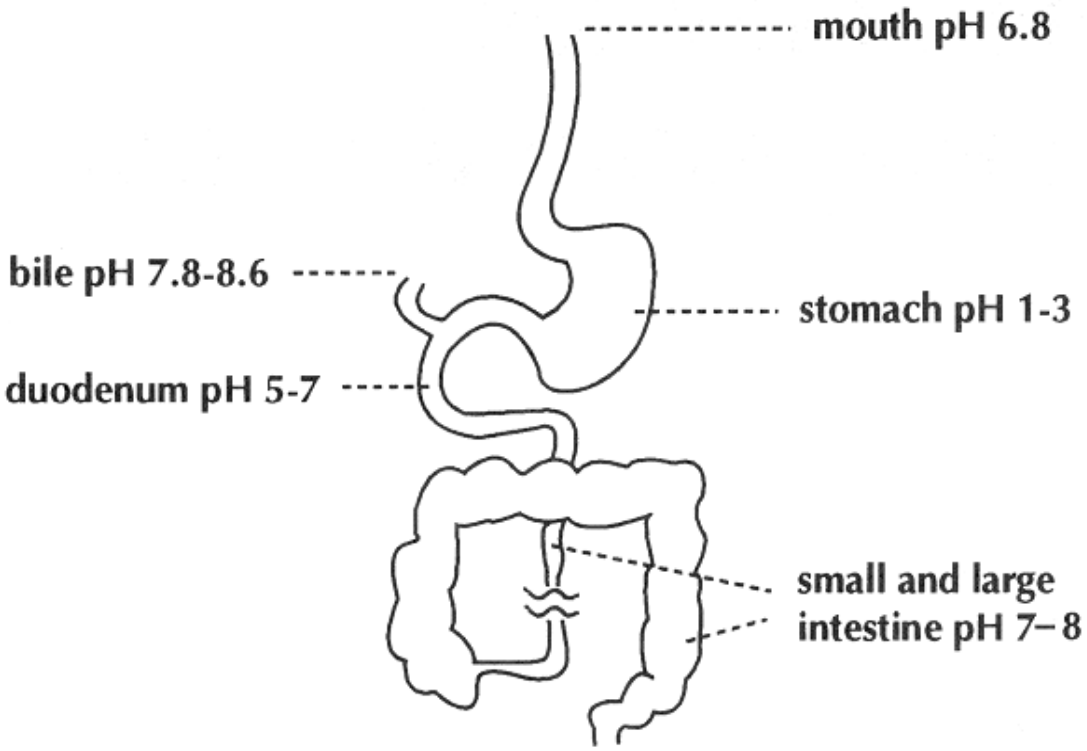
ORAL ABSORPTION

factors affecting oral bioavailability



ORAL ABSORPTION

GIT physiology

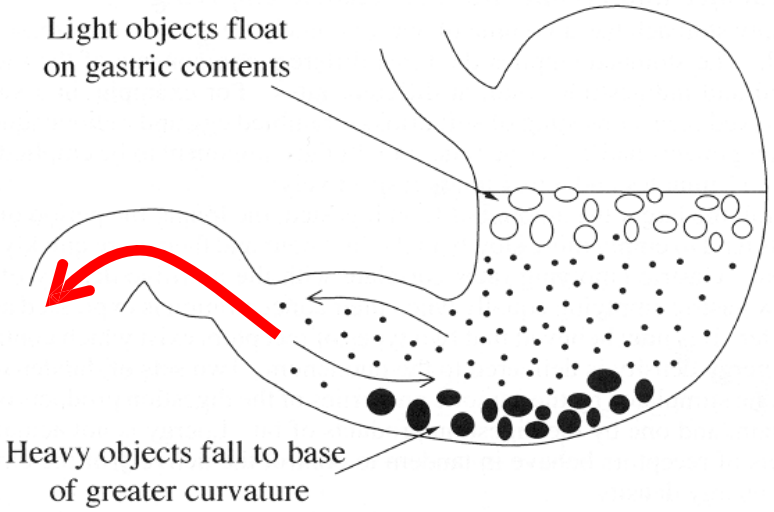


the small intestine is the most important site of drug absorption:

➔ blood flow much larger (**200 m²**, 1 L/min) compared to the stomach (**1 m²**, 0.15 L/min)

ORAL ABSORPTION

GIT physiology



the effect of particle size and density on gastric distribution

ORAL ABSORPTION

gastric emptying favors fast drug reabsorption

GE is retarded by

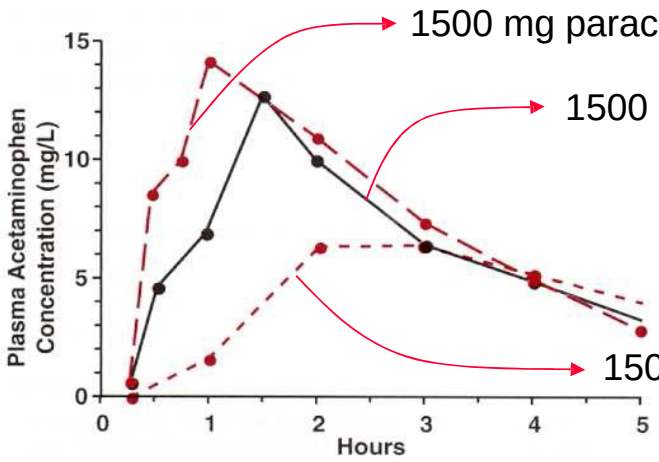
- meals
- lying on the left side
- mental depression
- psychic stress
- physical activity
- drugs that slow down gastric movements (narcotic, analgesics)

GE is promoted by

- fasting
- alkaline buffer solutions
- lying on the right side
- drugs that stimulate gastric emptying (e.g. metoclopramide)

ORAL ABSORPTION

impact of gastric emptying



1500 mg paracetamol with 10 mg metoclopramide iv

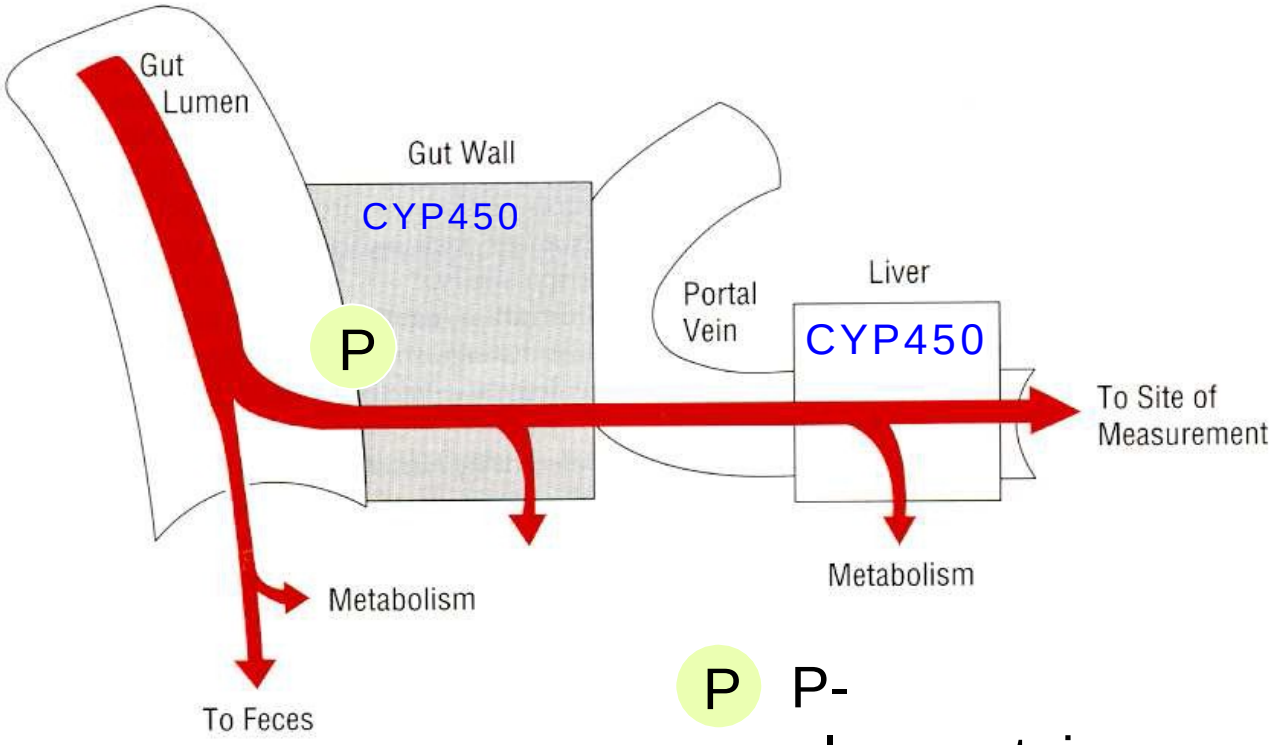
1500 mg paracetamol po alone

1500 mg paracetamol po with 30 mg propantheline iv

Slowing gastric emptying by propantheline (30 mg iv) slows the rate of absorption of paracetamol (1500 mg dose) ingested orally by a 22-year old man as seen by a decrease in Cmax and a longer Tmax compared with values when paracetamol is given alone. Metoclopramide (10 mg iv) which shortens the time for gastric emptying, increases the absorption rate of paracetamol.

ORAL ABSORPTION

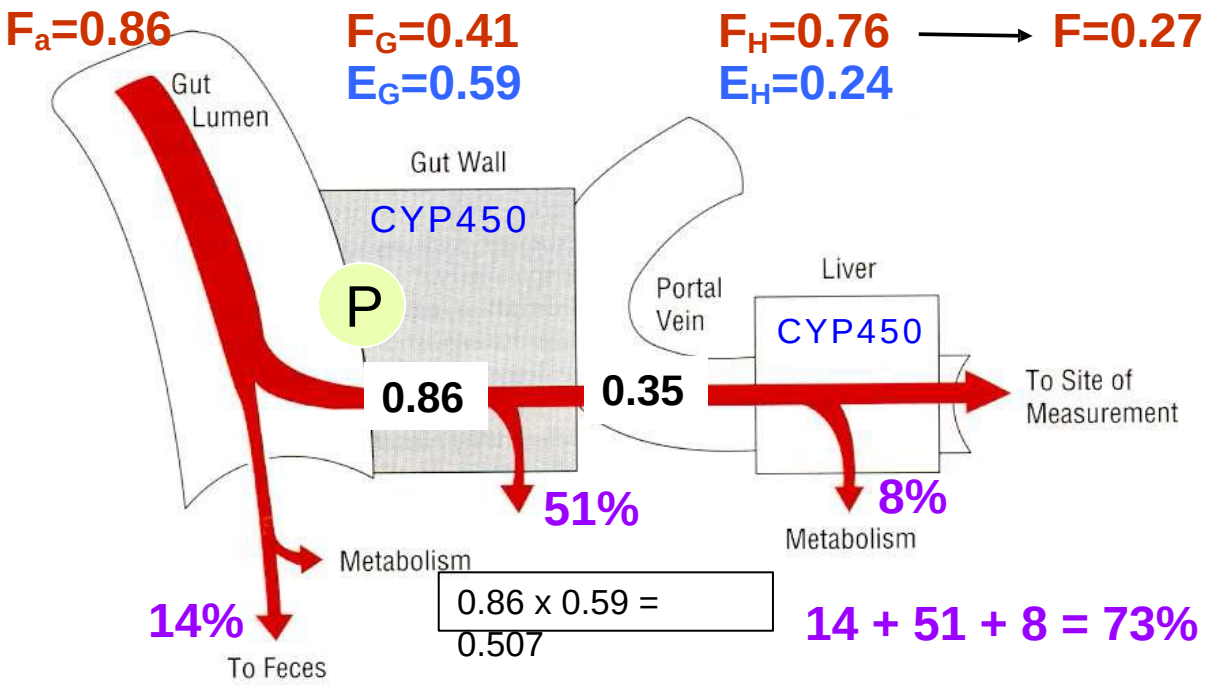
first pass effect



P P-glycoprotein

ORAL ABSORPTION

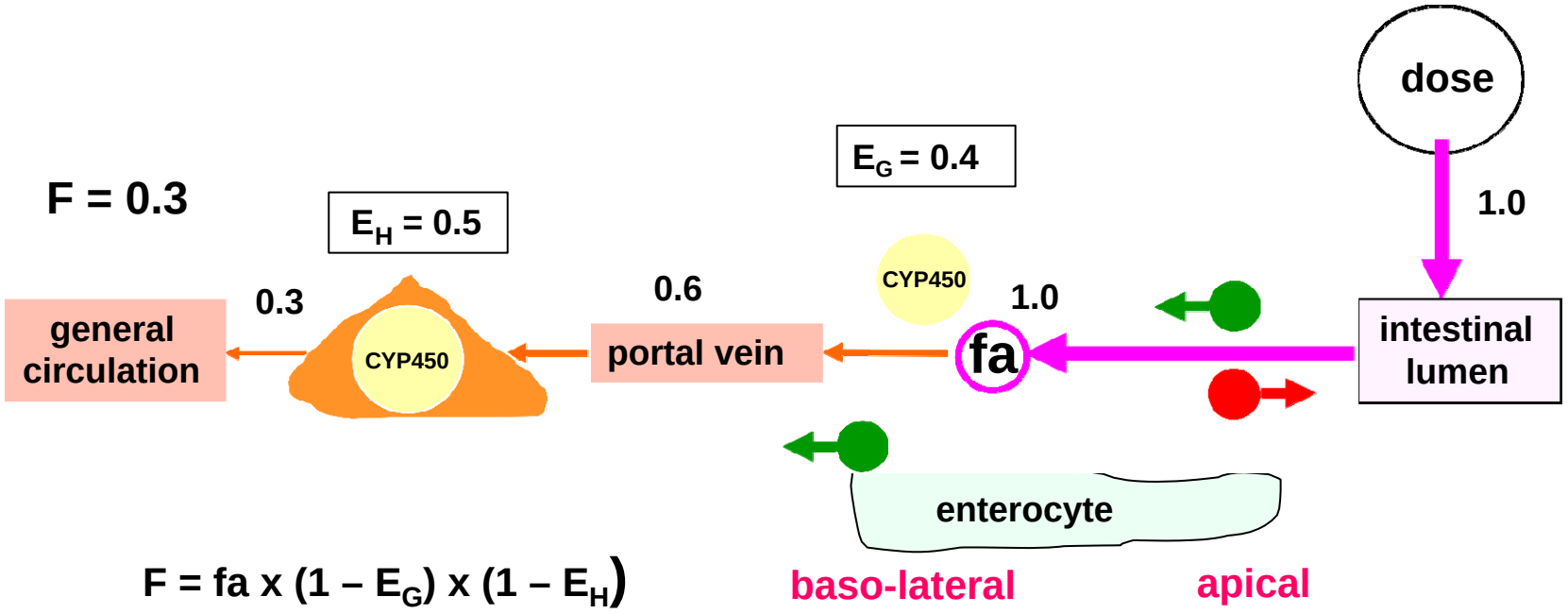
cyclosporine



P P-glycoprotein

73% of the orally administered cyclosporine dose does not reach the systemic circulation

How much drug reaches the target ?



$F = fa \times (1 - E_G) \times (1 - E_H)$

fa is the fraction of the dose transported (absorbed) across the apical cell membrane into the cellular space of the enterocyte according to scientific and regulatory definitions

ABSORPTION

example of drugs with major oral absorption problems

general mechanism	drug	specific situation
complexation	quinolones	polyvalent cations
	digitoxin	if cholestyramine
hydrolysis	penicillin G	acid hydrolysis
	erythromycin	acid hydrolysis
	insulin	peptidases
1st pass effect	cyclosporin	CYP3A4
	isoproterenol	sulfoconjugation
efflux pump	cyclosporin	P-glycoprotein

ABSORPTION

oral vs non-oral routes of administration

- oral ingestion is the most common method of drug administration: safest, most convenient, most economical
- disadvantages to the oral route include: limited absorption of some drugs, emesis, destruction of drug by digestive enzymes or low gastric pH, …
- enteral: oral, sublingual, buccal, rectal
- parenteral administration (for systemic action): intravenous (iv), intra-arterial (ia), subcutaneous (sc), intramuscular (im), pulmonary, nasal, transdermal
- topical application: skin, eye, ear, vagina, …

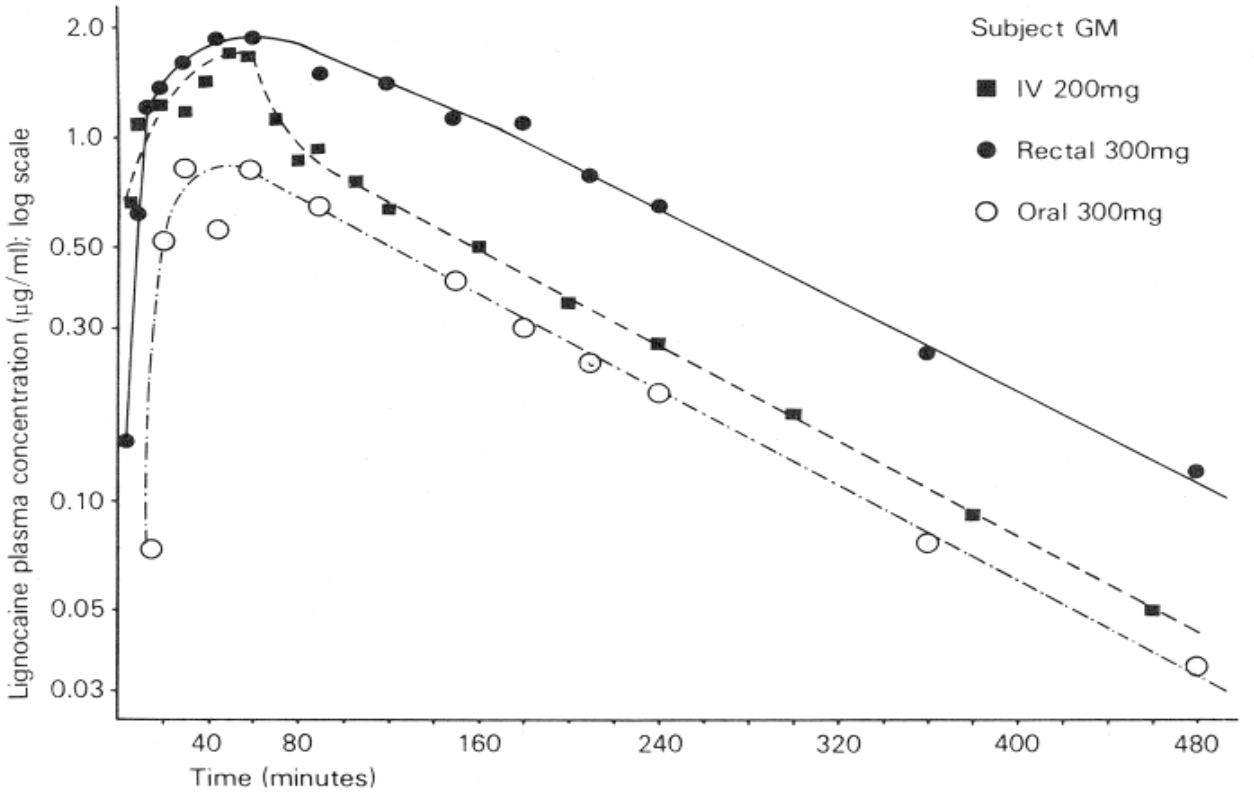
ABSORPTION
rectal

- useful route of administration when patient is unconscious or has a tendency to vomit
- $\pm$ 50% of the absorbed drug will bypass the liver

$\Rightarrow$ first pass effect is less pronounced than following oral administration

- rectal absorption is often irregular and incomplete
- many drugs cause irritation of the rectal mucosa

ABSORPTION
rectal



Plasma concentrations of lidocaine in a healthy subject following administration of lidocaine via intravenous perfusion (200 mg), oral (300 mg) and rectal (300 mg) administration.

ABSORPTION

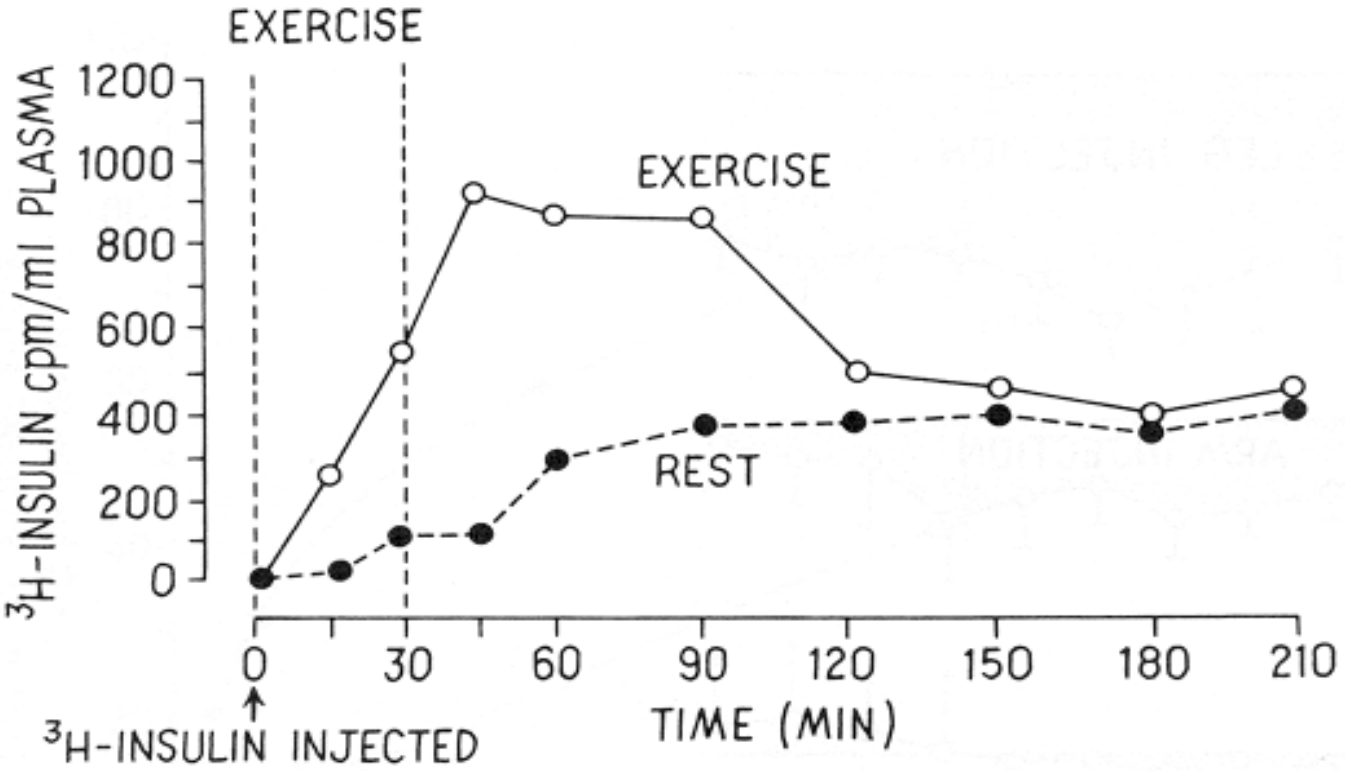
intramuscular

- drugs in aqueous solution are absorbed quite rapidly after im injection depending upon the rate of blood flow to the injection site (but can be quite variable !)
- the rate of absorption following im injection of an aqueous solution of a drug is faster from the deltoid and vastus lateralis compared to the gluteus maximus; for females the absorption rate is slower following injection into the gluteus maximus compared to males
- very slow, constant absorption can be obtained when the drug is injected in solution in oil or suspended in various other repository vehicles $\Rightarrow$ depot preparations
- avoids degradation of the drug in the GIT and hepatic FPE

ABSORPTION
subcutaneous

- injection of a drug into a sc site is often used, but only for drugs that are not irritating to tissue
- rate of absorption from the sc injection site is often sufficiently constant and slow to provide a sustained effect: e.g. the rate of absorption of a suspension of insoluble insulin is slow compared with that of a soluble preparation of the hormone
- absorption rate of a drug in solution is dependent upon the blood flow to the sc injection site
- avoids degradation of drug in GIT and hepatic FPE

ABSORPTION
subcutaneous



Exercise (cycling) increases the absorption of insulin injected subcutaneously in the leg.

ABSORPTION
transdermal

- may be used for local or systemic effects
- few drugs penetrate the intact skin: lipid solubility of the compound is very important
- systemic absorption of drugs occurs more readily through abraded, burned, denuded or inflamed skin
- controlled release transdermal delivery systems are becoming increasingly available, e.g. scopolamine, fentanyl, estradiol, nitroglycerin, …
- avoids degradation of compound in GIT and hepatic/intestinal FPE

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ABSORPTION
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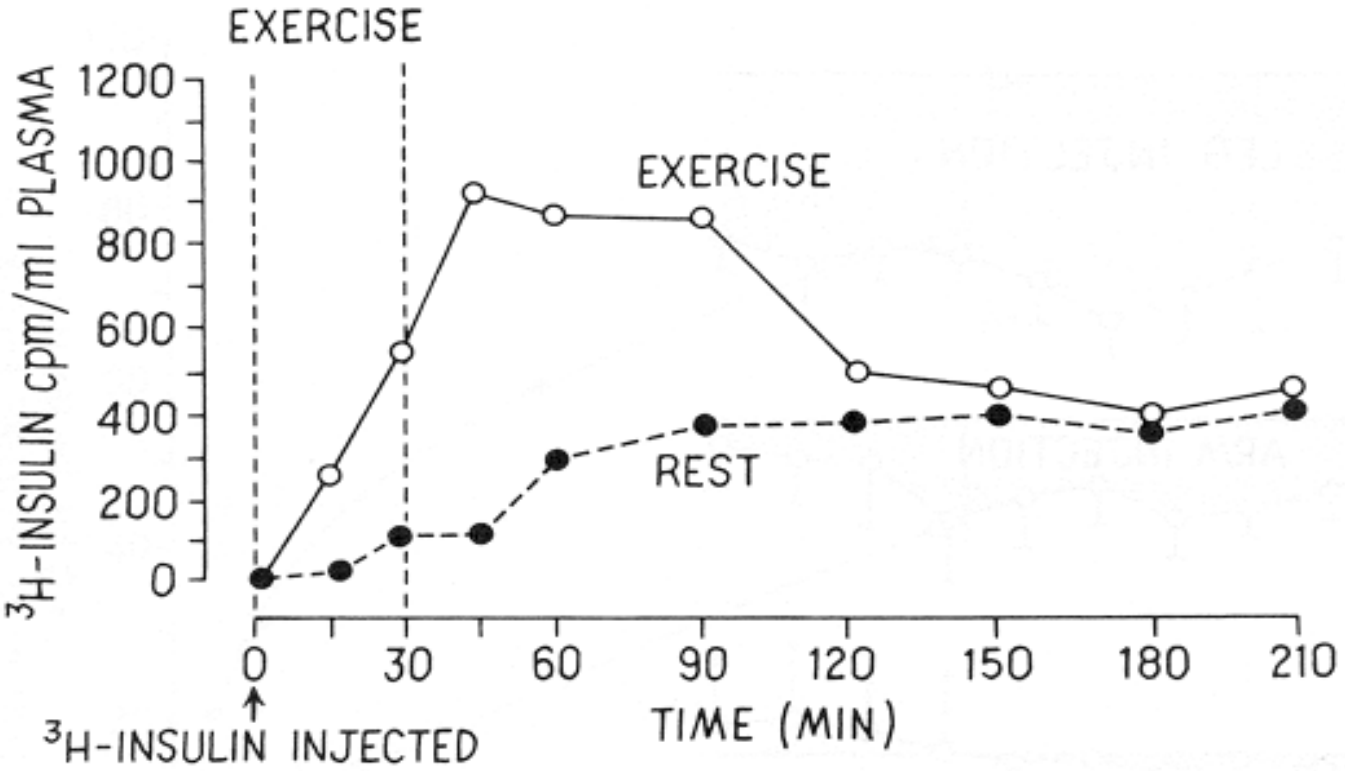

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ABSORPTION
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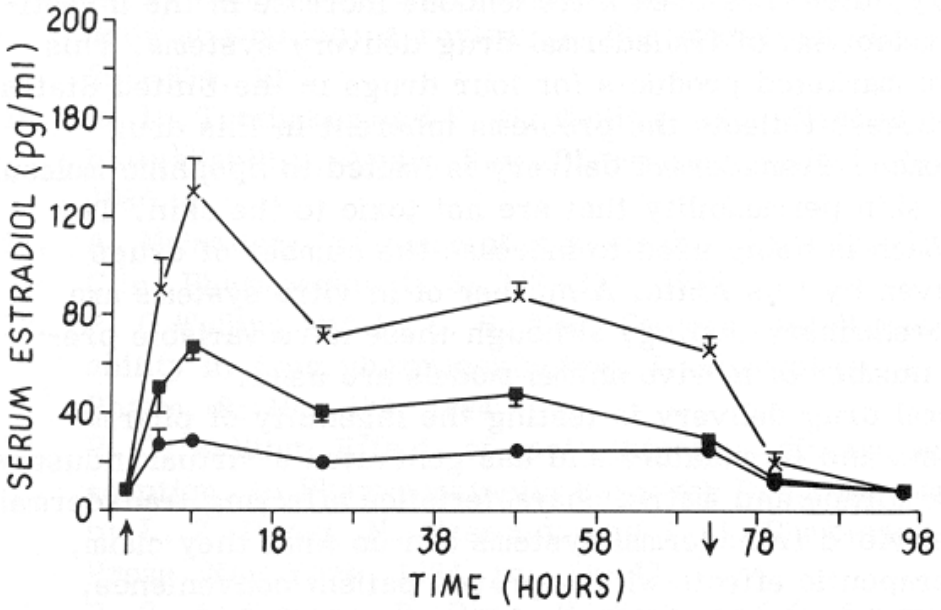
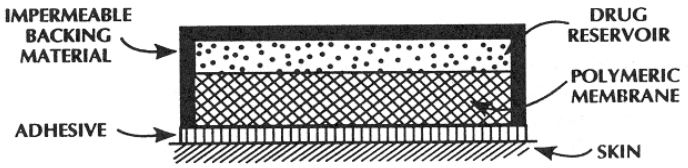


Plasma concentrations of estradiol following application to the skin of ESTRADERM 0.025 (5 cm^3), ESTRADERM 0.05 (10 cm^3) or ESTRADERM 0.1 (20 cm^3).

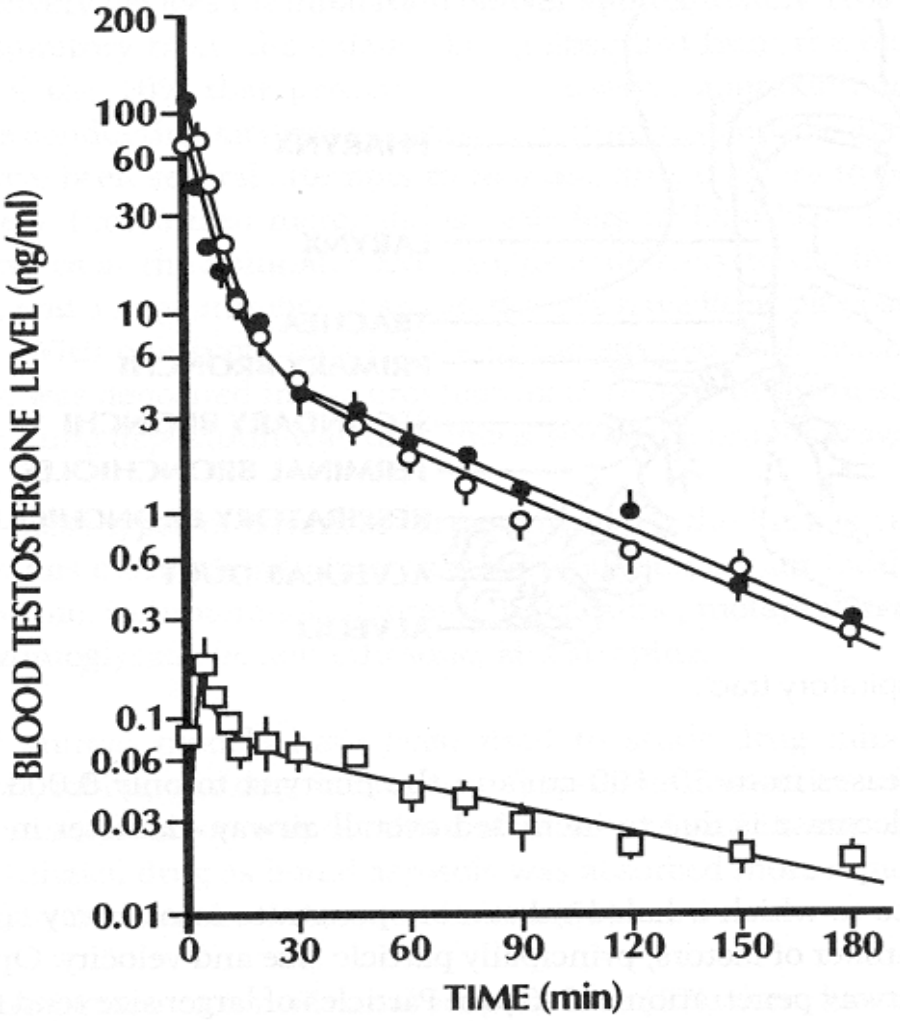


The absorption rate from a transdermal patch is controlled by a permeable polymeric membrane. Therefore, it is possible to obtain relatively stable and sustained concentrations of the active substance in the circulation.

ABSORPTION
intranasal

- may be used for local or systemic effects
- the use of intranasal delivery is currently the focus of considerable activity but the limited surface area of the nasal cavity and the local toxicity of many compounds limit its usefulness
- promising results are obtained for some small peptides, e.g. vasopressin, oxytocin, …
- avoids degradation by GIT and hepatic/intestinal FPE

ABSORPTION
intranasal



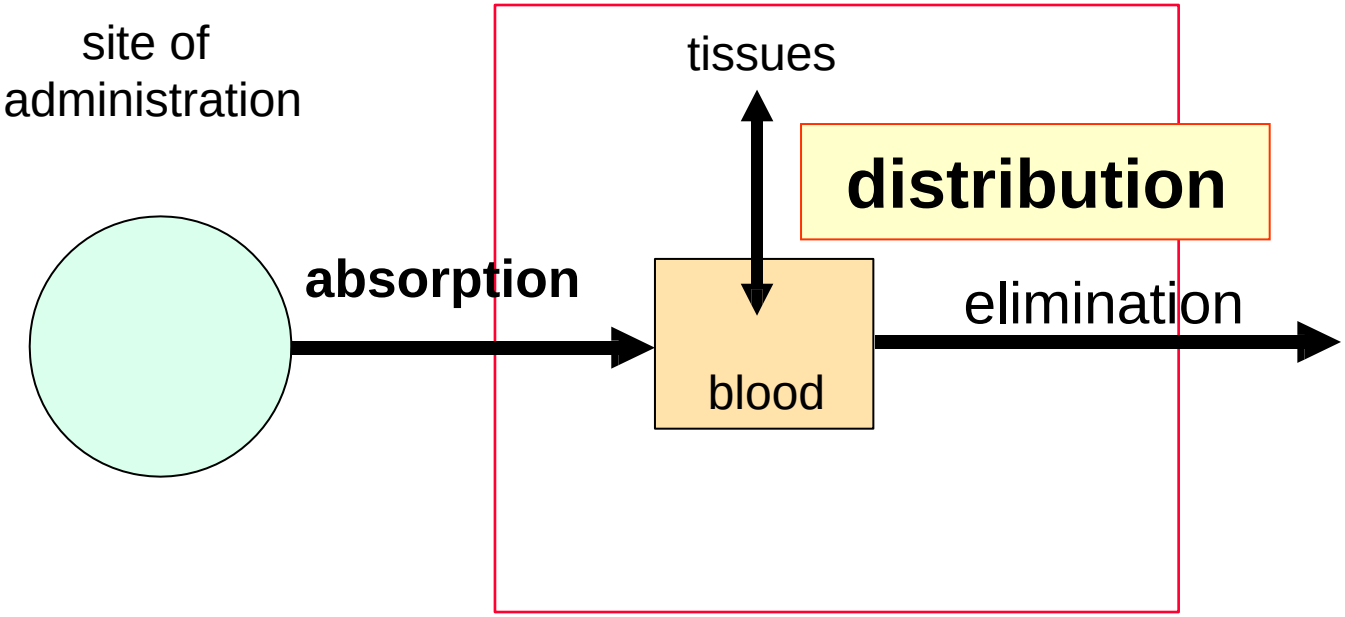
blood concentrations of testosterone in rats following iv (•), intranasal (o) and intraduodenal (·) administration of 25 µg testosterone per rat

Hussain et al., J. Pharm. Sci. 73: 1300-1301, 1984.

ABSORPTION
buccal, sublingual

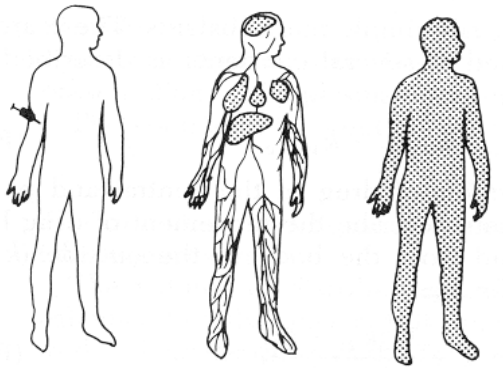
- avoids degradation in the GIT and intestinal/hepatic first pass effect
- the oral cavity is well perfused and the mucosa is very thin (0.15 mm) $\Rightarrow$ both factors favor rapid absorption
- in many cases buccal absorption from a special buccal dosage form can result in the same bioavailability as when the active substance is injected intravenously
- examples: nitroglycerin, isosorbide dinitrate, oxytocin, …

Distribution



DISTRIBUTION

- distribution refers to the **reversible transfer** of drug from one location to another within the body
- distribution of drug to and from blood and other tissues occurs at various rates and to various extents
- several factors determine the distribution pattern of a drug with time: delivery of drug to tissues by blood, ability to cross tissue membranes, binding within blood and tissues, partitioning into fat
- tissue uptake, commonly called extravasation, continues toward equilibrium of the diffusible form between tissue and blood perfusing it



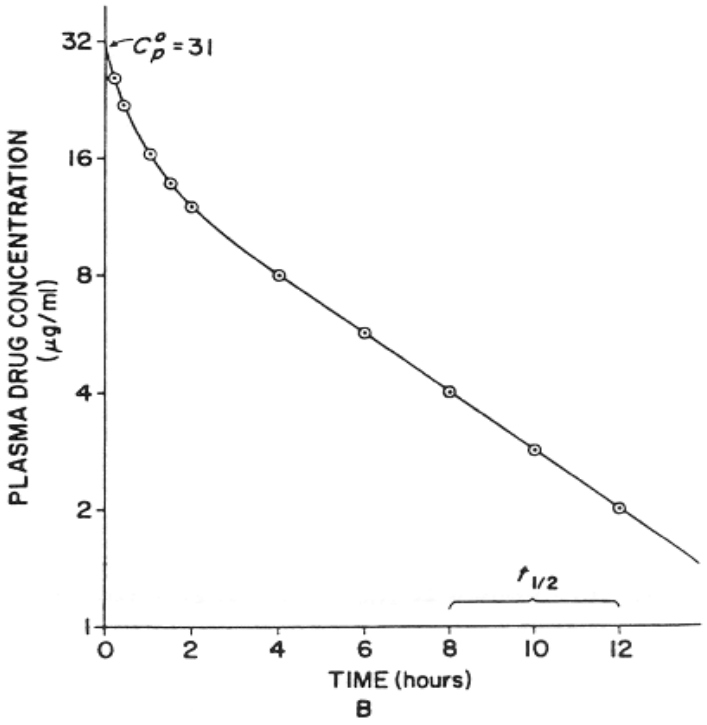
- lipophilicity
- tissue perfusion
- reversible binding

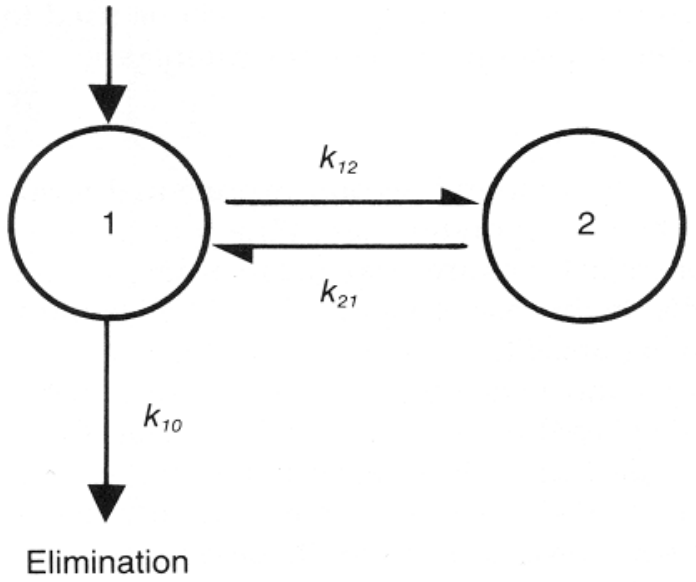
DISTRIBUTION
perfusion limitation

Organ	Percent of Body Volume	Blood Flow (ml/minute)	Percent of Cardiac Output	Perfusion Rate (ml/minute per ml of tissue)
1. Adrenal glands	0.03	25	0.2	1.2
2. Blood	7	(5000)[b]	(100)	—
3. Bone	16	250	5	0.02
4. Brain	2	700	14	0.5
5. Fat	10	200	4	0.03
6. Heart	0.5	200	4	0.6
7. Kidneys	0.4	1100	22	4
8. Liver	2.3	1350	27	0.8
Portal		(1050)	(21)	
Arterial		(300)	(6)	
9. Lungs	0.7	(5000)	(100)	10
10. Muscle (inactive)	42	750	15	0.025
11. Skin (cool weather)	18	300	6	0.024
12. Thyroid gland	0.03	50	1	2.4
Total Body	100	5000	100	0.071

blood flow, perfusion rate and relative size of different organs and tissues under basal conditions in a standard 70-kg human

DISTRIBUTION
disposition kinetics

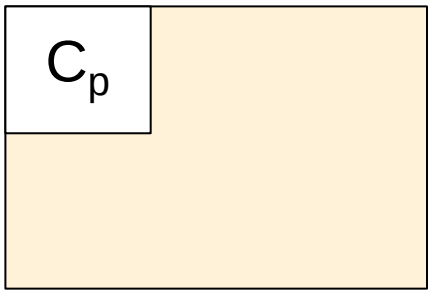




following iv bolus administration drug plasma concentrations decline bi-exponentially and the body can be represented by a two-compartment model in which drug distributes between compartments 1 and 2 and is eliminated via compartment 1

plasma protein binding and volume of distribution

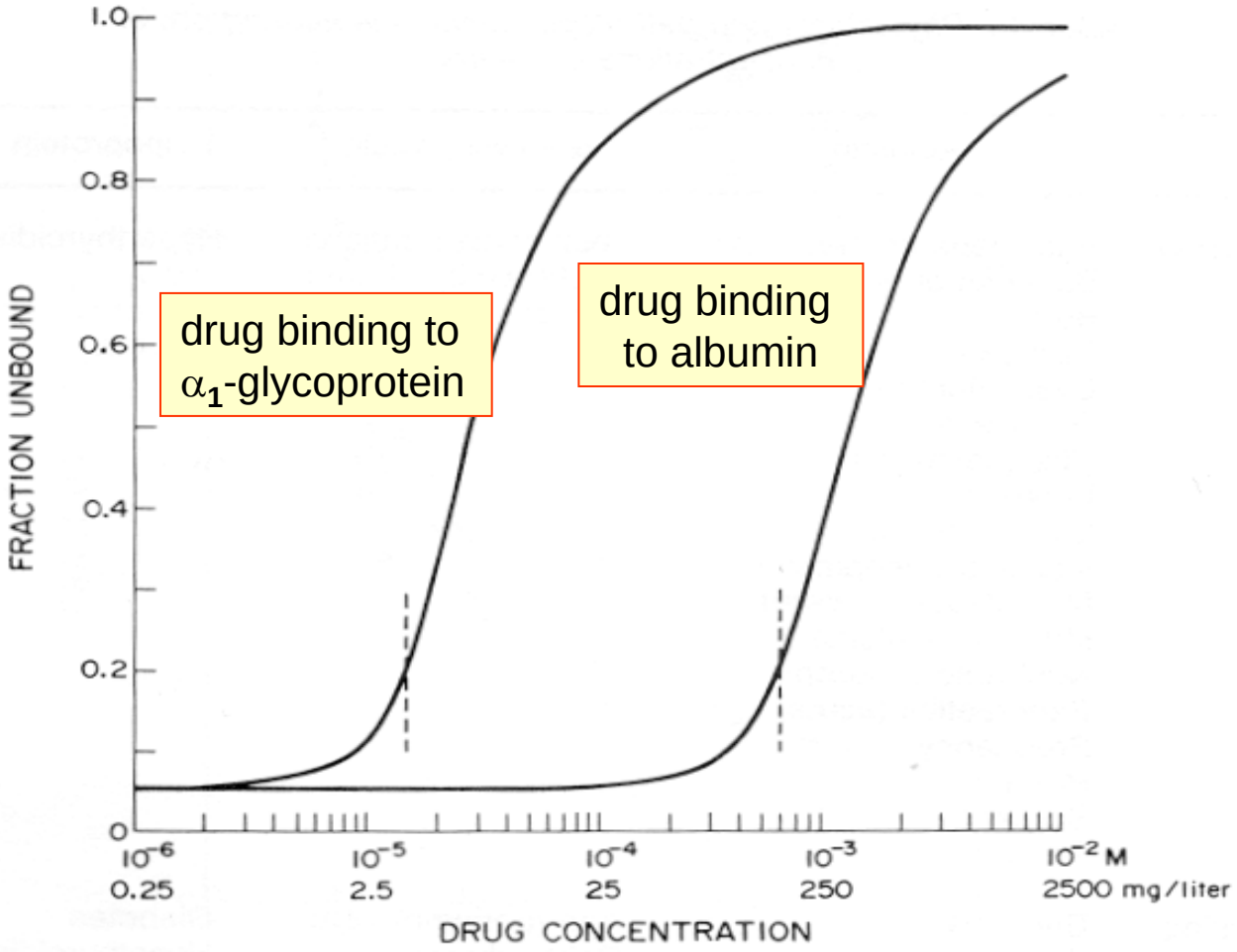
drug	V L/70 kg	f_u	% bound in plasma
naproxen	10	0.002	99.8
warfarin	10	0.01	99.0
cephalexin	18	0.86	14.0
amikacin	19	0.96	4.0
indomethacin	20	0.10	90.0
erythromycin	55	0.16	84.0
tetracycline	105	0.35	65.0
verapamil	350	0.10	90.0
labetalol	660	0.50	50.0
fluoxetine	2500	0.06	94.0
chloroquine	13 000	0.39	61.0



$$V = \frac{A_b}{C_p}$$

PLASMA PROTEIN BINDING

saturation of binding sites



Pharmacokinetic Basis for Drug Treatment (Benet et al., eds), p. 178, Raven Press, 1984.

DISTRIBUTION
blood-brain barrier (BBB)

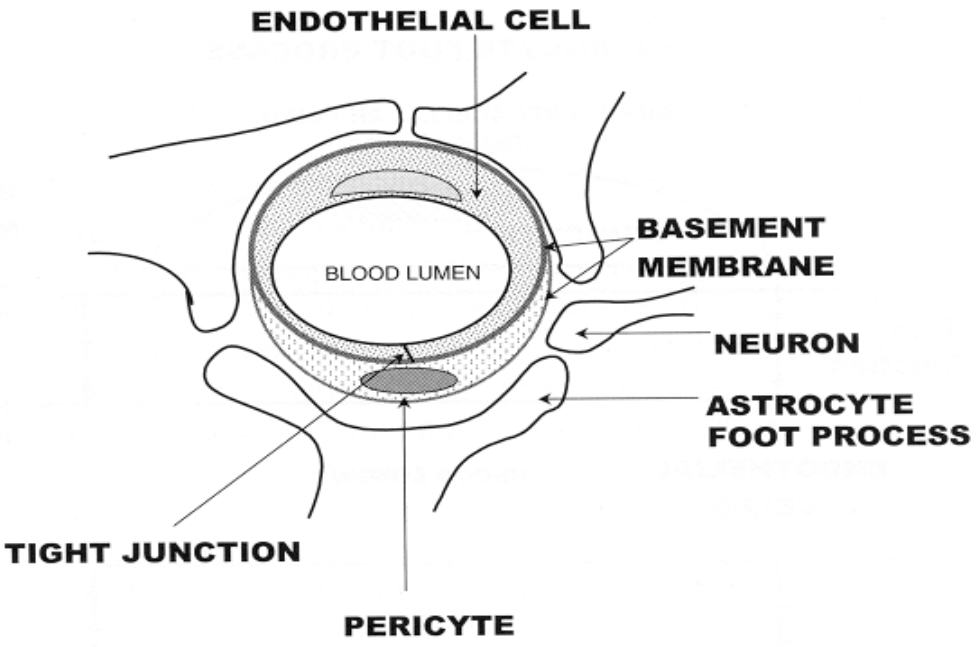
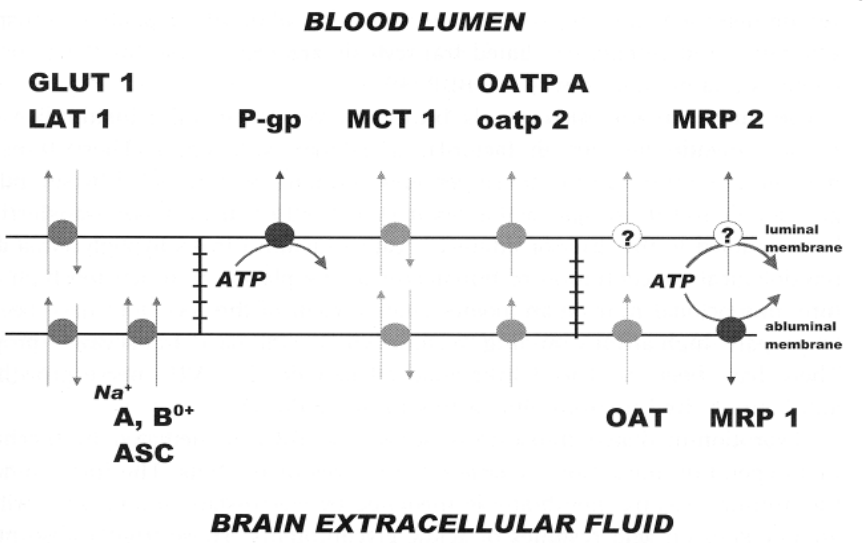


Diagram showing a transverse cross-section of a cerebral capillary. The endothelial cells, responsible for the main barrier properties of the blood-brain barrier, are separated from the astrocytes foot processes, pericytes and occasional neurons by the basement membrane. All these components make up the BBB.

DISTRIBUTION
blood-brain barrier (BBB)



GLUT: glucose transporter

LAT: large neutral amino acid transporter

MCT: monocarboxylic acid transporter

OATP: organic anion transport protein

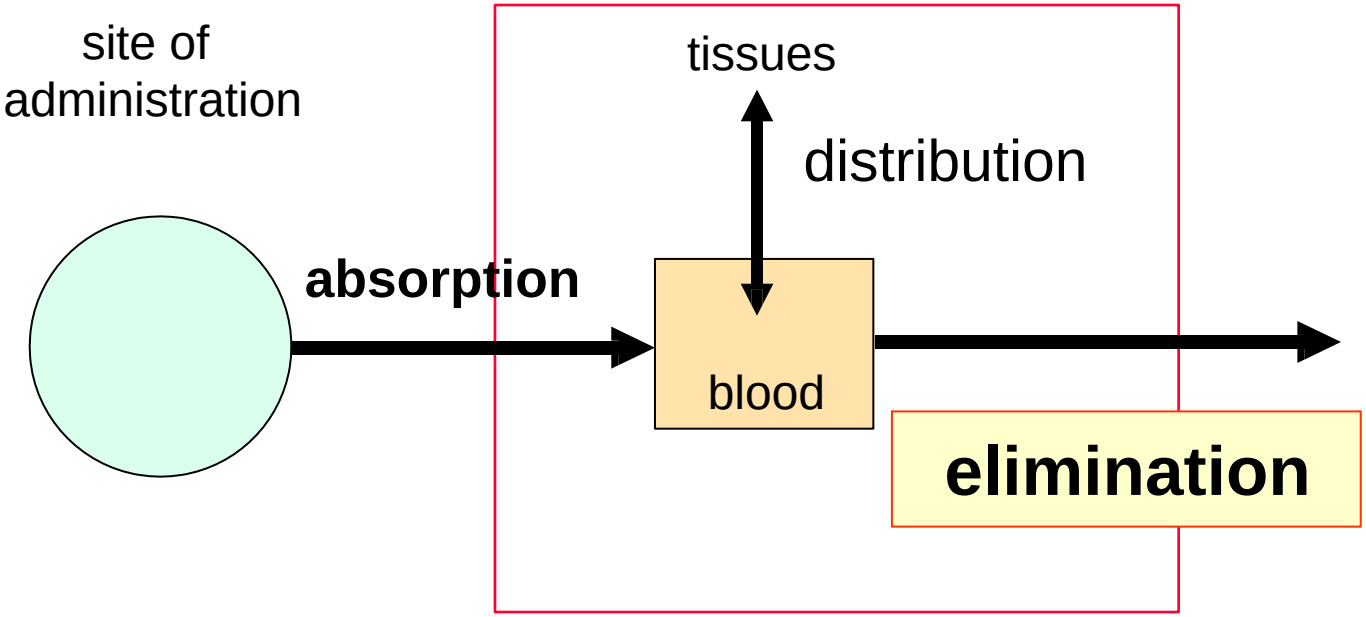
OAT: organic anion transporter

MRP: multidrug resistance associated protein

P-gp: permeability glycoprotein

Diagram showing some of the nutrient and drug transport processes associated with the brain capillary endothelial cells from the BBB. Note that transport may be unidirectional or bidirectional.

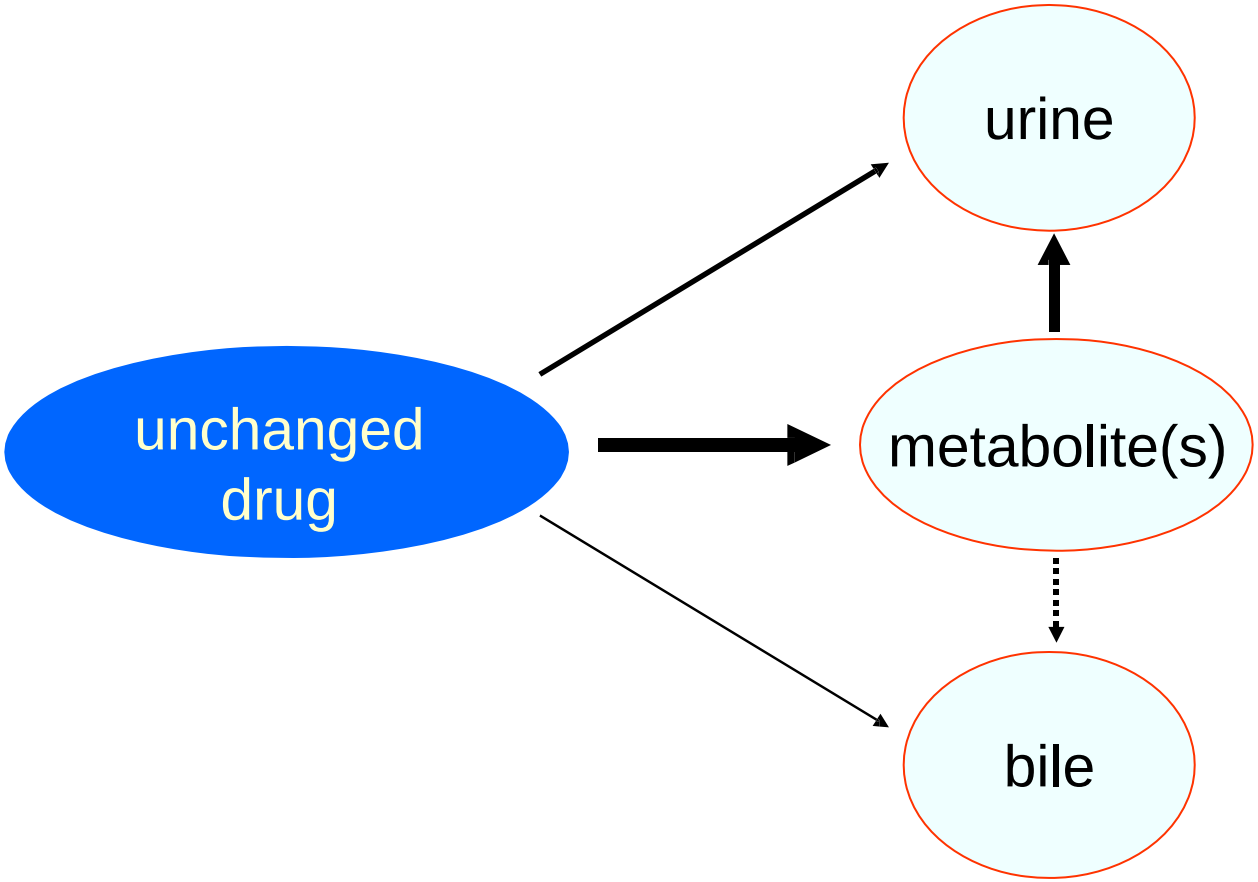
Distribution



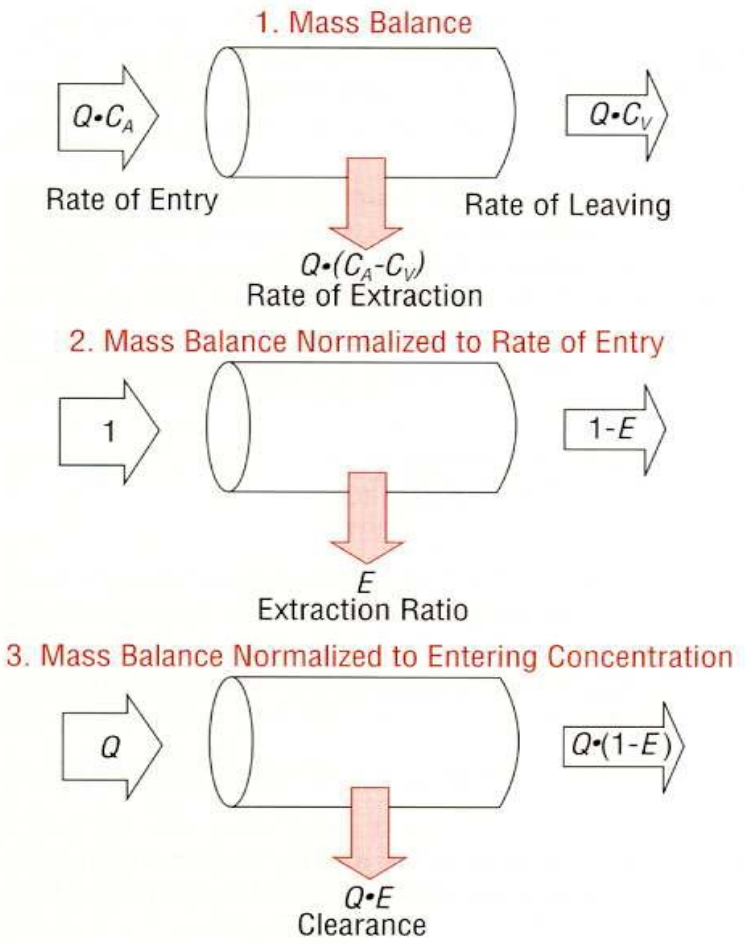
ELIMINATION

- elimination is the *irreversible loss of drug from the site of measurement (circulation)*
- elimination occurs by two processes, ***metabolism*** and ***excretion***
- metabolism is the conversion of one chemical species to another
- excretion is the irreversible loss of chemically unchanged drug and can occur via urine, bile, sweat, saliva, …

ELIMINATION



ELIMINATION
organ clearance



$$CL = \frac{Q \times (C_A - C_V)}{C_A}$$

$$CL = Q \times E = \frac{Q \times fu \times CL_{int}}{Q + fu \times CL_{int}}$$

CL = organ clearance

Q = organ blood flow

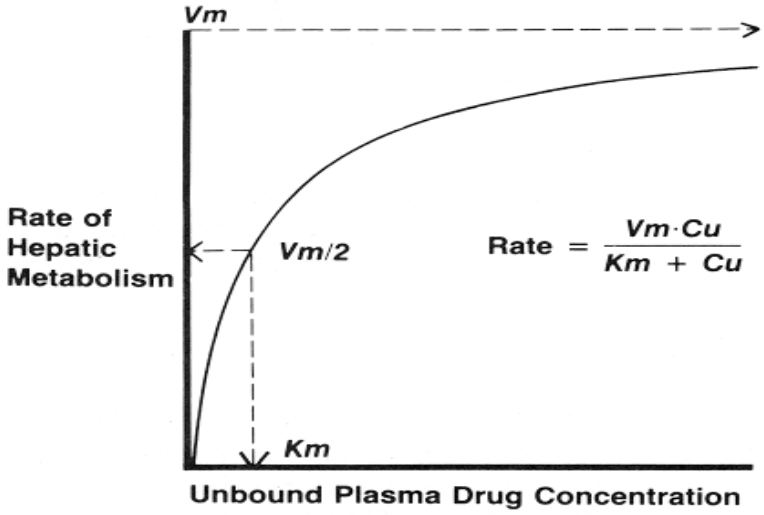
E = extraction ratio

fu = unbound drug

CL_{int} = intrinsic clearance

ELIMINATION

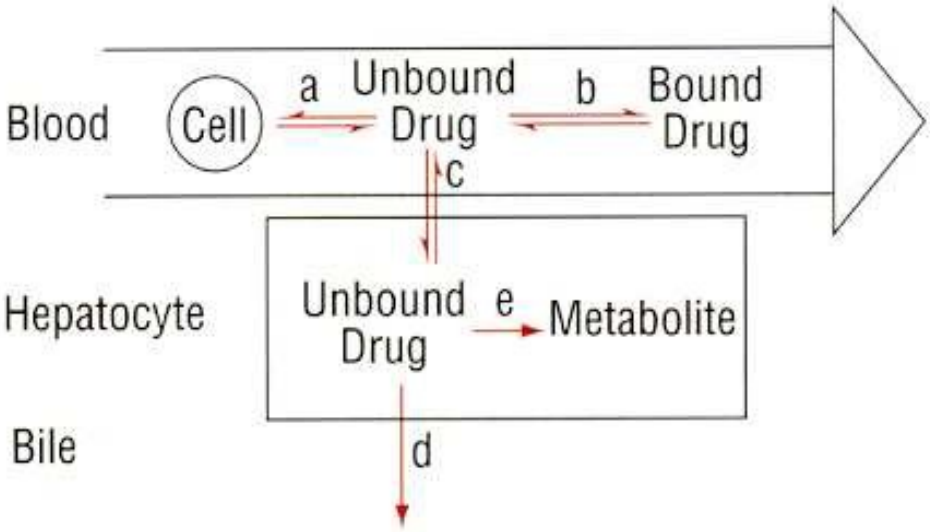
saturation and intrinsic clearance



$$CL_u = \frac{V_{max}}{K_m + C_u}$$

The highest value for (unbound) clearance is found when $C_u << K_m$. This maximum value is V_{max}/K_m and is called *intrinsic clearance*.

ELIMINATION
hepatic clearance and excretion



Drug in blood is bound to blood cells (process a) and to plasma proteins (process b).

However, it is the unbound drug that diffuses (process into the hepatocytes.

Within the hepatocyte, the unbound drug is subject to secretion into bile (process d) or to biotransformation (process e)

Clinical Pharmacokinetics: concepts and applications (Rowland and Tozer), p. 162, Williams & Wilkins, 1995.

ELIMINATION : *extraction ratio*

	Extraction Ratio		
	Low (<0.3)	Intermediate (0.3–0.7)	High (>0.7)
Hepatic[a] extraction	Carbamazepine Diazepam Digitoxin Indomethacin Phenobarbital Phenytoin Procainamide Salicylic Acid Theophylline Tolbutamide Valproic Acid Warfarin	Aspirin Quinidine Codeine Nortriptyline	Alprenolol Arabinosyl-cytosine Desipramine Doxepin Isoproterenol Lidocaine Meperidine Morphine Nitroglycerin Pentazocine Propoxyphene Propranolol
Renal[a] extraction	Atenolol Cefazolin Chlorpropamide Digoxin Furosemide Gentamicin Lithium Phenobarbital Sulfisoxazole Tetracycline	Cimetidine Cephalothin Procainamide (Some) Penicillins	(Many) Glucuronides Hippurates (Some) Penicillins (Many) Sulfates

[a]At least 30 percent of the drug is eliminated by this route.

ELIMINATION
clearance

- drug clearance can be described in terms of the eliminating organ (hepatic, renal, pulmonary, …), the elimination process (metabolic, excretory) or the site of measurement (blood, plasma, serum)
- the total body clearance is the sum of the clearances by each of the eliminating organs
- for practical purposes, the total body clearance of a drug can be considered as the sum of its renal and nonrenal clearances; the nonrenal clearance is most often hepatic

ELIMINATION
systemic clearance

$$CL_{iv} = CL_R + CL_{NR}$$

$$CL_{iv} = \frac{DOSE_{iv}}{AUC_{0\text{-}\infty}}$$

$$CL_R = \frac{A_u^{0\text{-}\infty}}{AUC_{0\text{-}\infty}}$$

CL_{NR} is for most drugs hepatic metabolic clearance

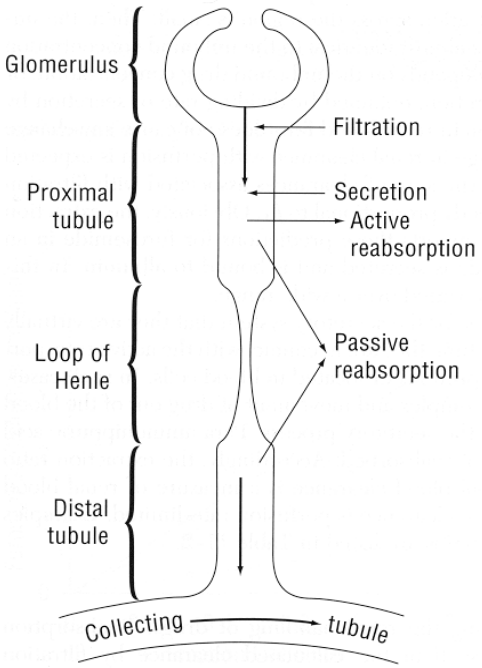
$$CL_R = fe \times CL_{iv}$$

ELIMINATION

biliary excretion

1. Bile flow is relatively steady at 0.5 – 0.8 ml/min.
2. Bile is not a product of filtration but rather of secretion: transporters.
3. Molecules with relatively high MW are more likely to be excreted into bile.
4. Biliary excretion of a molecule may be followed by reabsorption from the small intestine: enterohepatic cycling

ELIMINATION
renal excretion



- glomerular filtration
- tubular secretion
- tubular reabsorption

renal excretion = filtration + secretion - reabsorption

RENAL EXCRETION
glomerular filtration

- glomerular filtration rate (GFR) = 120 ml/min
- only unbound drug in plasma can be filtered

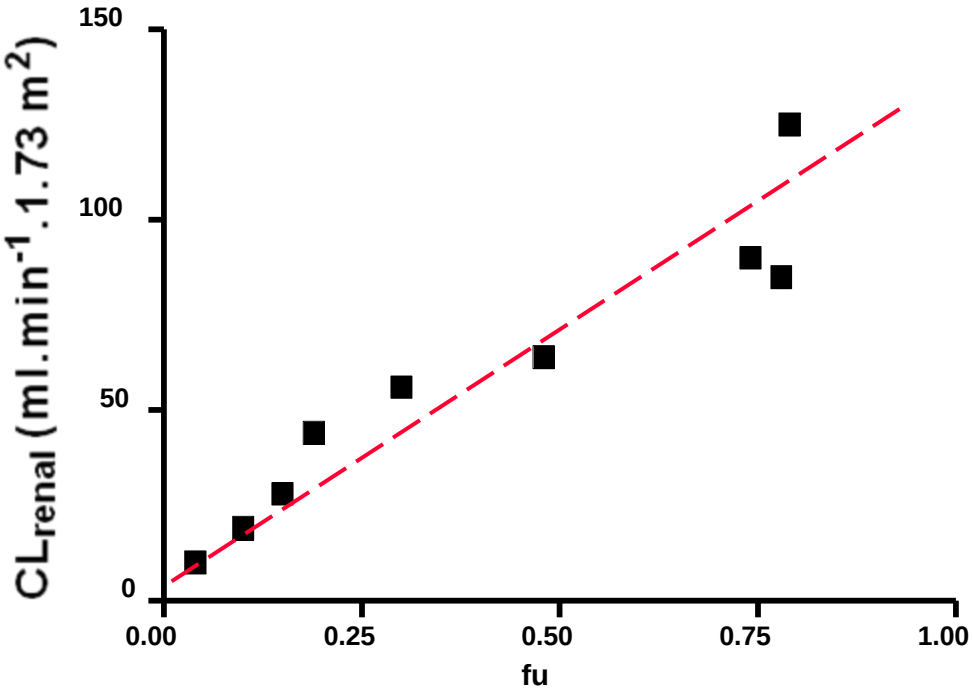
$\Rightarrow$ $CL_{filtration}$ = GFR x fu (where fu is the % unbound)

creatinine clearance serves as a reference value

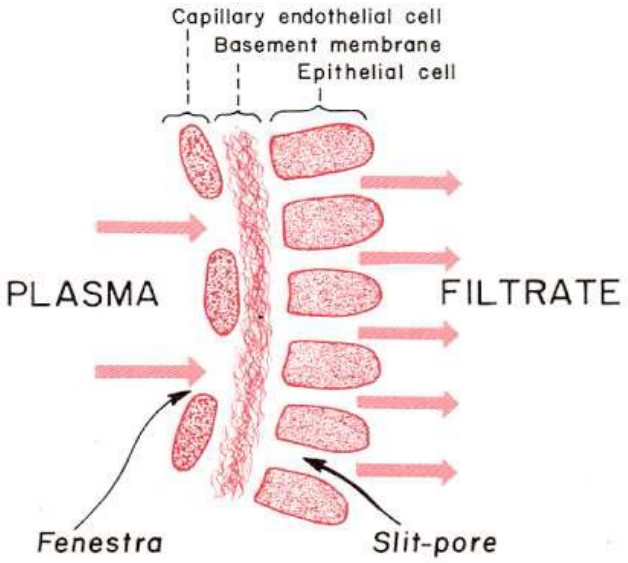
RENAL EXCRETION

glomerular filtration: importance of protein binding

drug	fu	CL_{renal} ml/min/1.73 m^2
Ceftriaxone	0.04	10
Cefoperazone	0.10	19
Cefotetan	0.15	28
Ceforanide	0.19	44
Cefazolin	0.30	56
Moxalactam	0.48	64
Cefsulodin	0.74	90
Ceftazidime	0.78	85
cefaloridine	0.79	125



RENAL EXCRETION



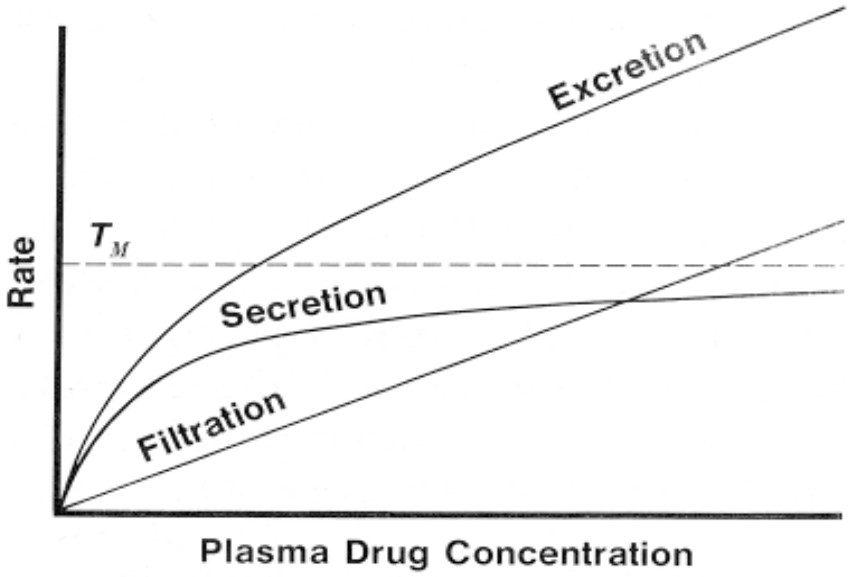
glomerular filtration: importance of the molecule size

- the basement membrane prevents the filtration of most substances with a MW equal to or greater than the plasma proteins
- low molecular weight proteins are substantially filtered in the glomerulus and are metabolized in the proximal tubule

protein	MW	filtrate/plasma
insulin	6 000	0.89
myoglobin	16 900	0.75
superoxide dismutase	32 000	0.33
albumin	69 000	0.001

ELIMINATION
tubular secretion

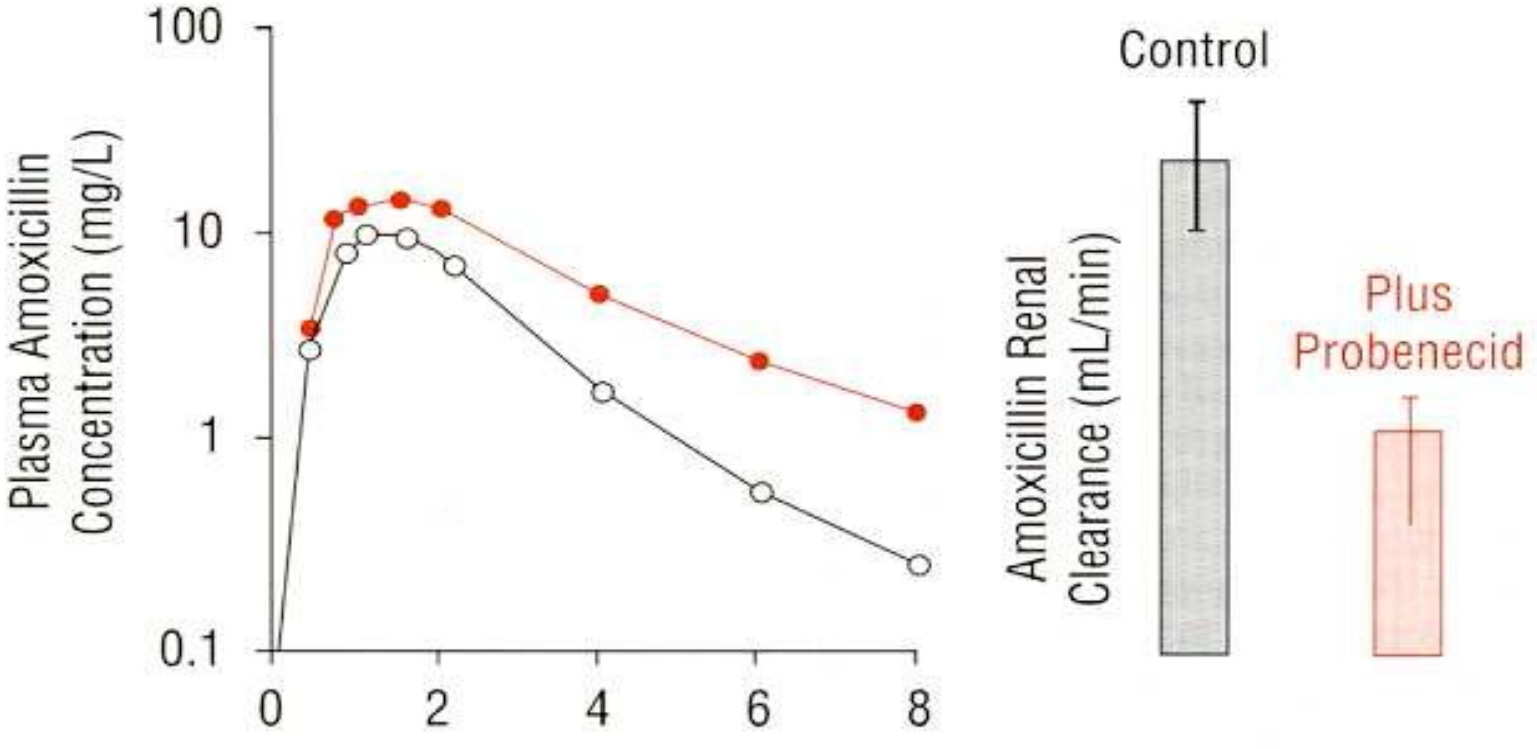
- tubular secretion is an active process involving specific transport proteins
- active transport is specific (competition between 2 or more substrates is possible) and saturable (Michaelis-Menten kinetics)



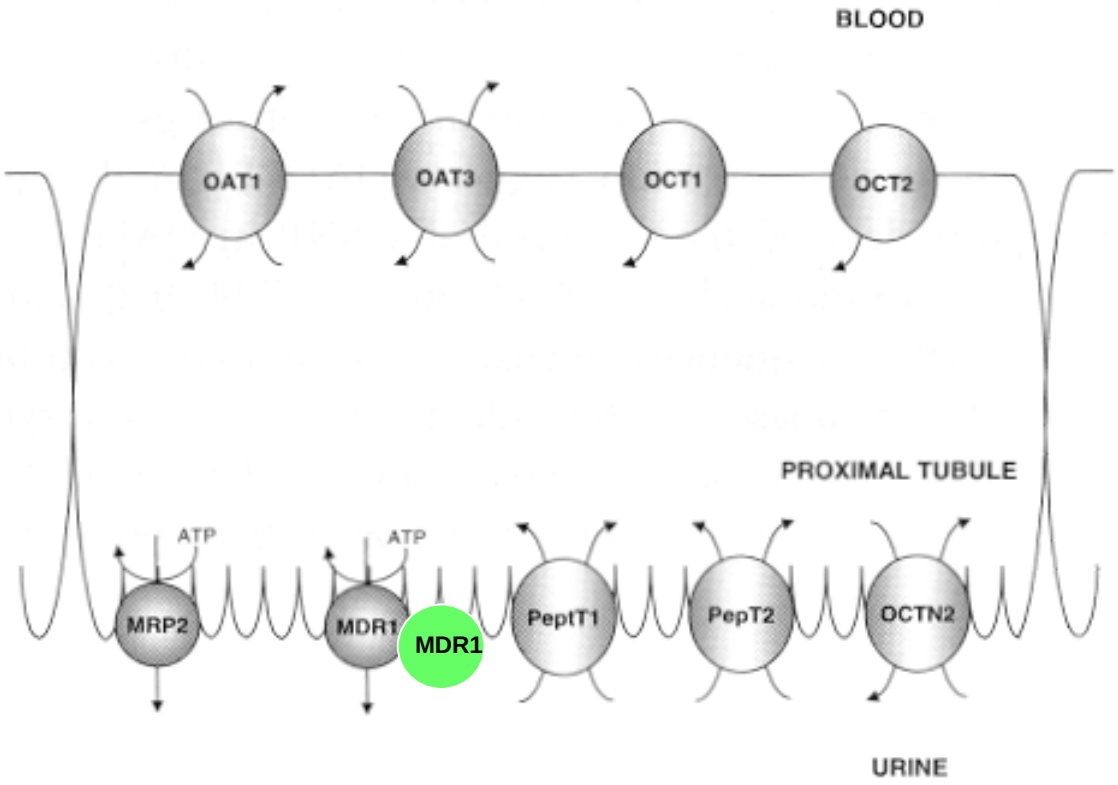
$$\text{secretion rate} = \frac{T_{max} \times C_u}{K_d + C_u}$$

ELIMINATION *and tubular secretion*

amoxicillin-probenecid interaction



ELIMINATION
tubular secretion



OAT organic anion Ts

OCT organic cation Ts

MDR multidrug resistance proteins

MRP multidrug resistance related proteins

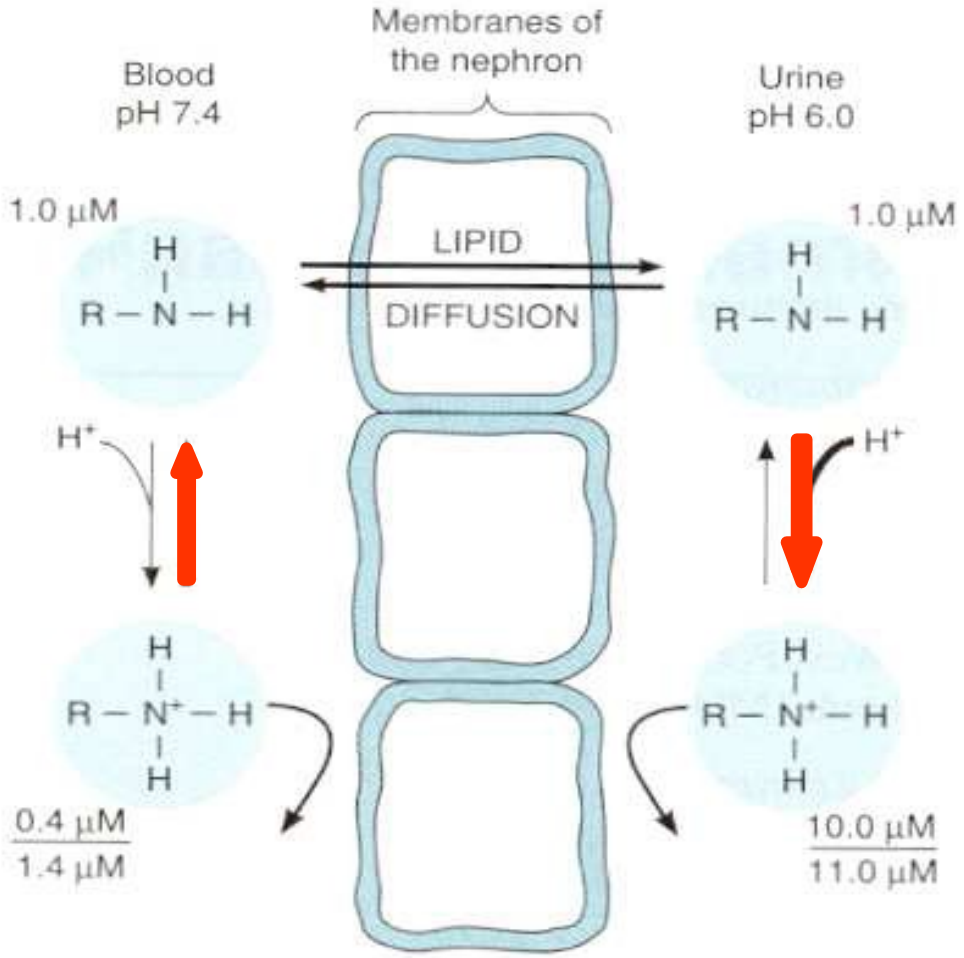
PepT peptide transporters

OCTN novel organic cation transporters

ELIMINATION
tubular reabsorption

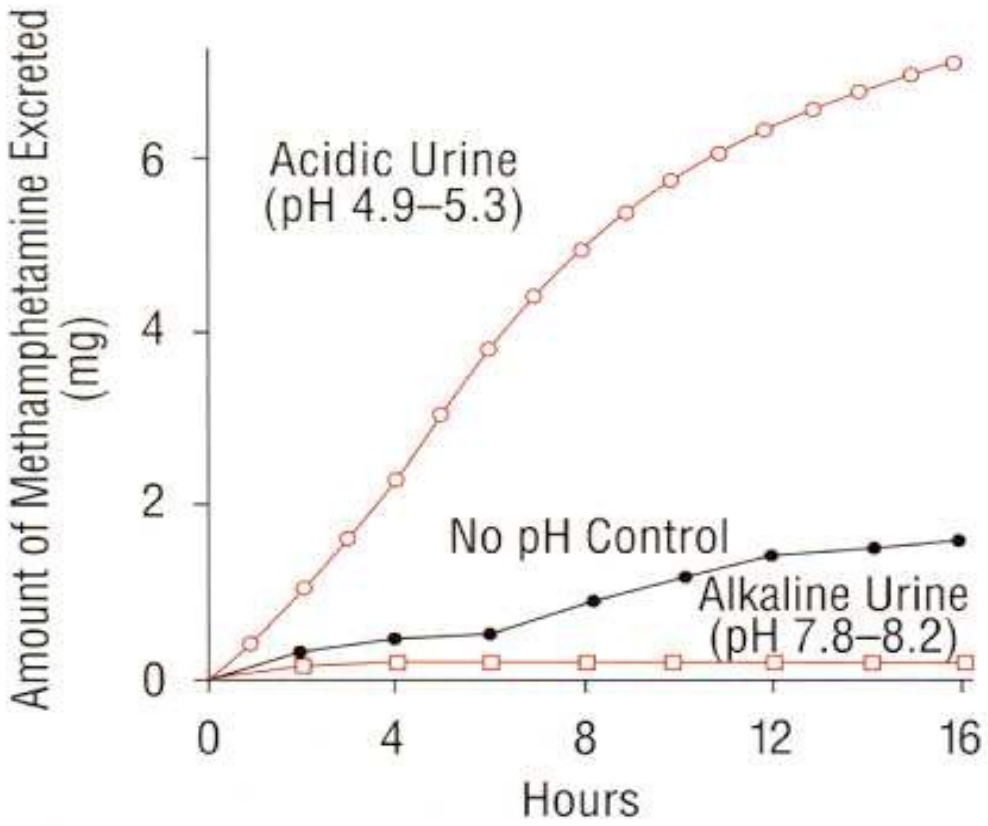
- tubular reabsorption of drugs is a passive process occurring mainly in the distal renal tubule
- it depends on the gradient between the concentration of drug in the filtrate present in the tubular lumen and in the the surrounding blood
- since only unionized drug molecules can pass across biological membranes, the degree of ionization of the drug at the pH of the fluid (‘urine’) in the distal tubular lumen together with the pKa of the drug will determine its reabsorption

ELIMINATION
tubular reabsorption



A weak base (pKa = 7.0) will be more ionized at the lower pH and therefore at pH 6.0 tubular reabsorption will be smaller and renal excretion rate will be higher.

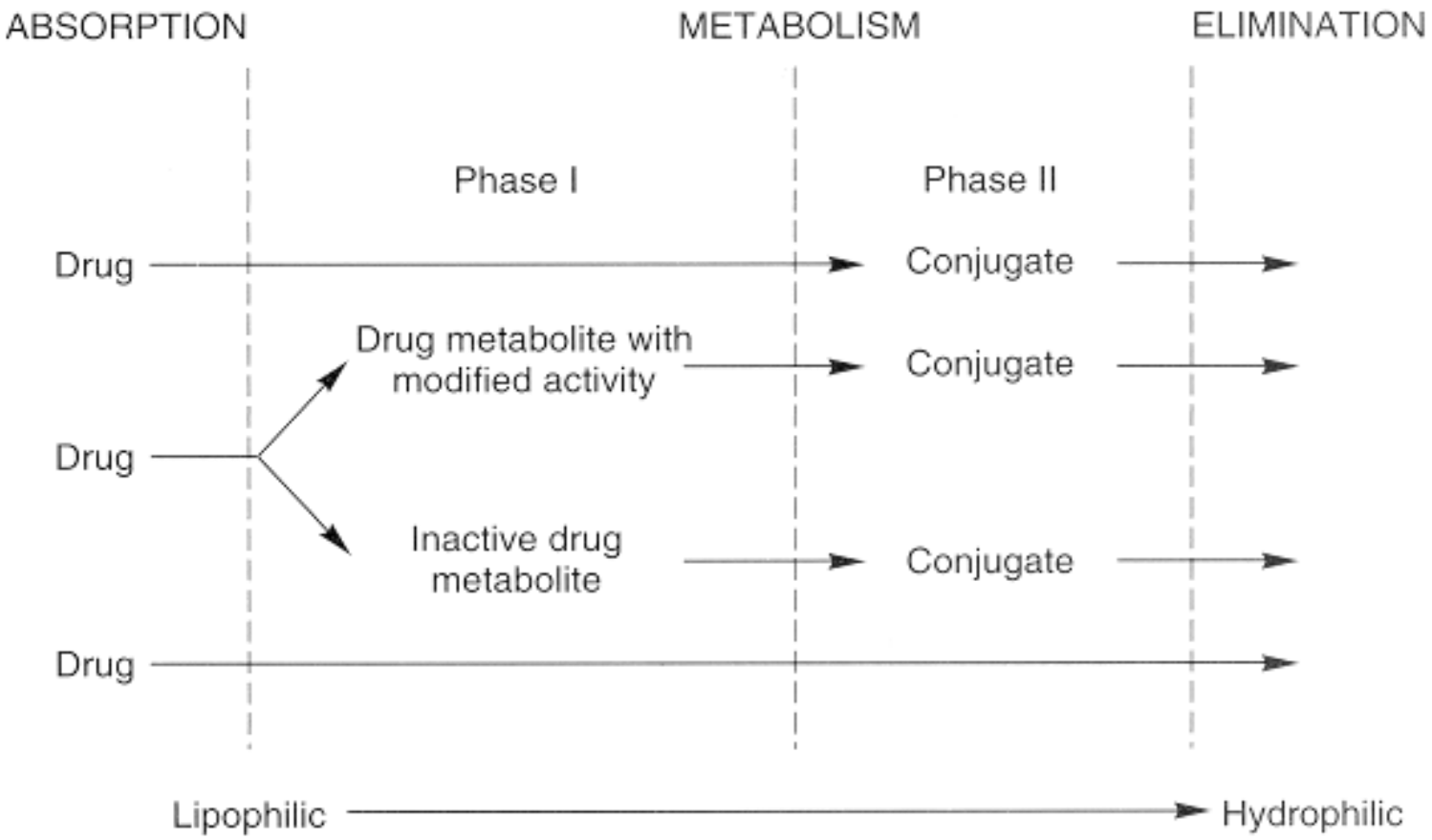
ELIMINATION
tubular reabsorption



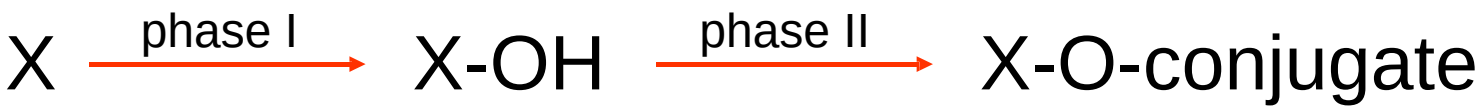
Methamphetamine is a weak base (pKa = 10.0). Its cumulative urinary excretion (oral dose: 11 mg) in man varies with urine pH.

Beckett and Rowland: Urinary excretion kinetics of methylamphetamine in man. Nature 206: 1260-1261, 1965.

ELIMINATION
metabolism

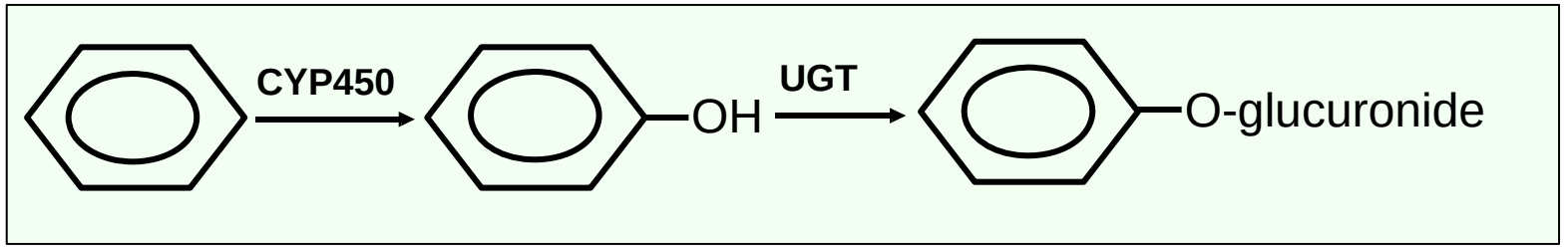


ELIMINATION
metabolism



- major elimination mechanism
- leads to inactive and/or active (toxic) metabolites
- generally increases polarity
- major site for drug metabolism: liver

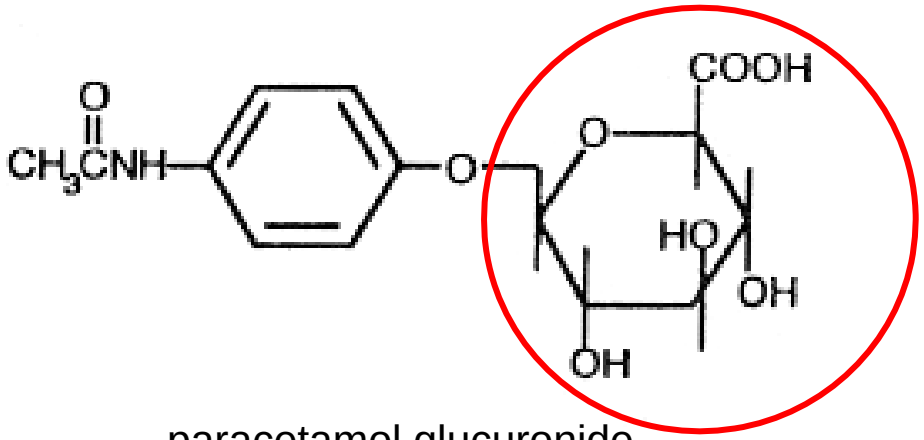
DRUG METABOLISM



benzene phenol phenyl-β-glucuronide

phase I/phase II metabolism of benzene

DRUG METABOLISM



paracetamol glucuronide

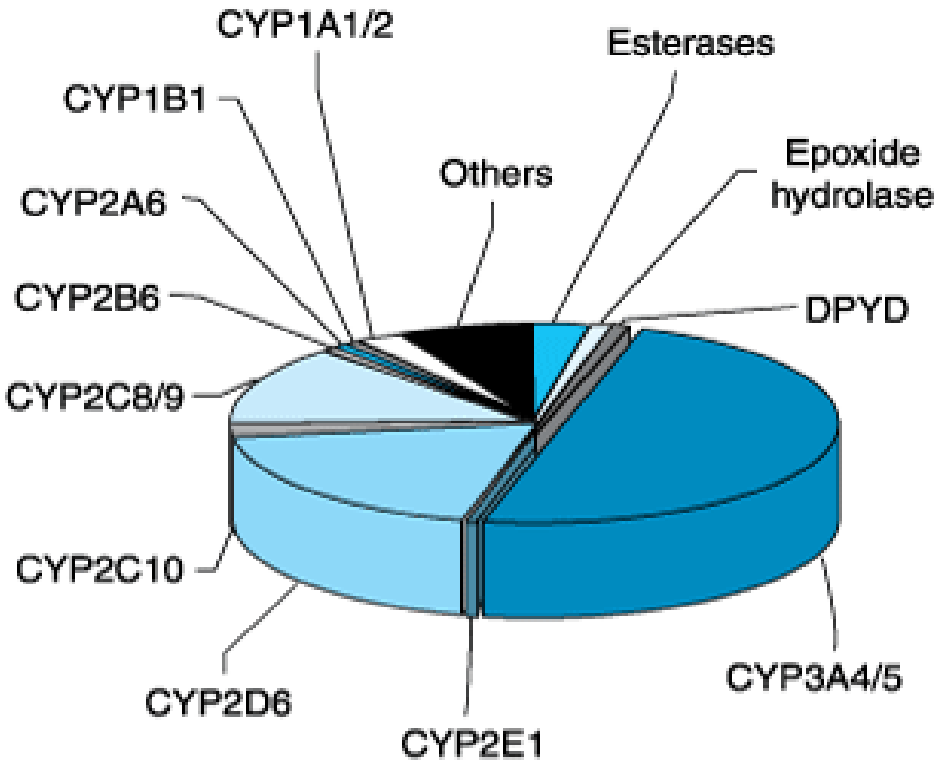
- increased hydrosolubility: pKa 3-4 $\Rightarrow$ renal excretion
- increased MW: + 176 daltons $\Rightarrow$ biliary excretion
- in most cases inactive/nontoxic

ELIMINATION
phase I metabolism

oxidation

reduction

hydrolysis



ELIMINATION
phase II metabolism

glucuronidation (UGTs)

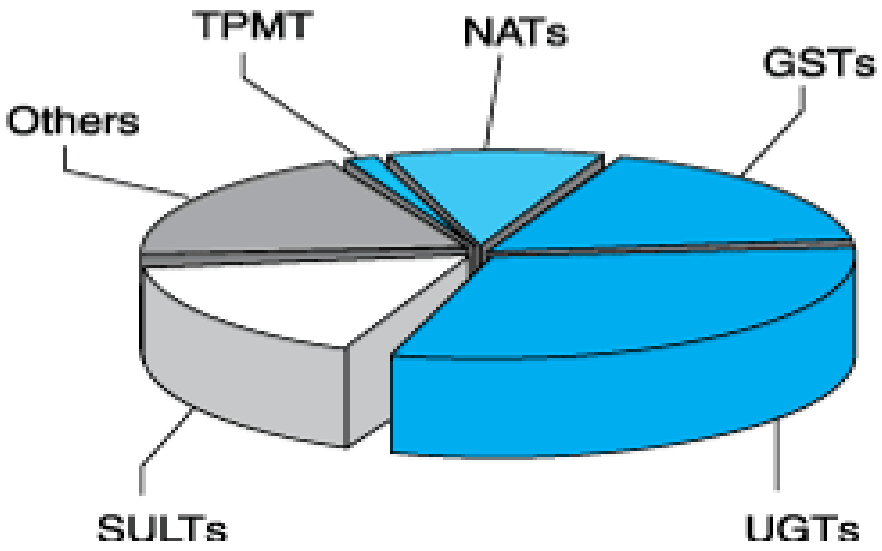
sulfation (SULTs)

acetylation (NATs)

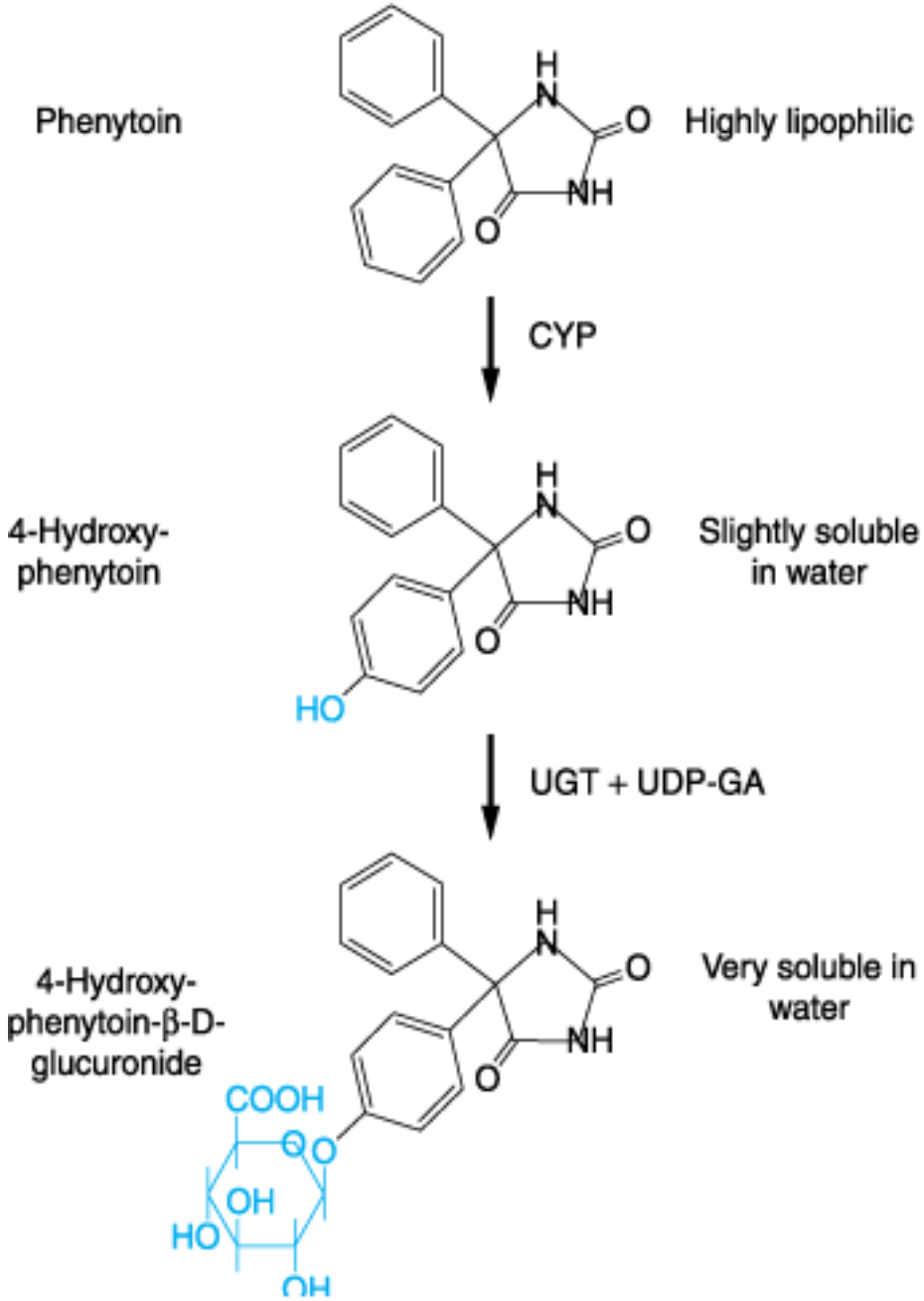
glutathione conjugation (GSTs

methylation (TPMT)

others

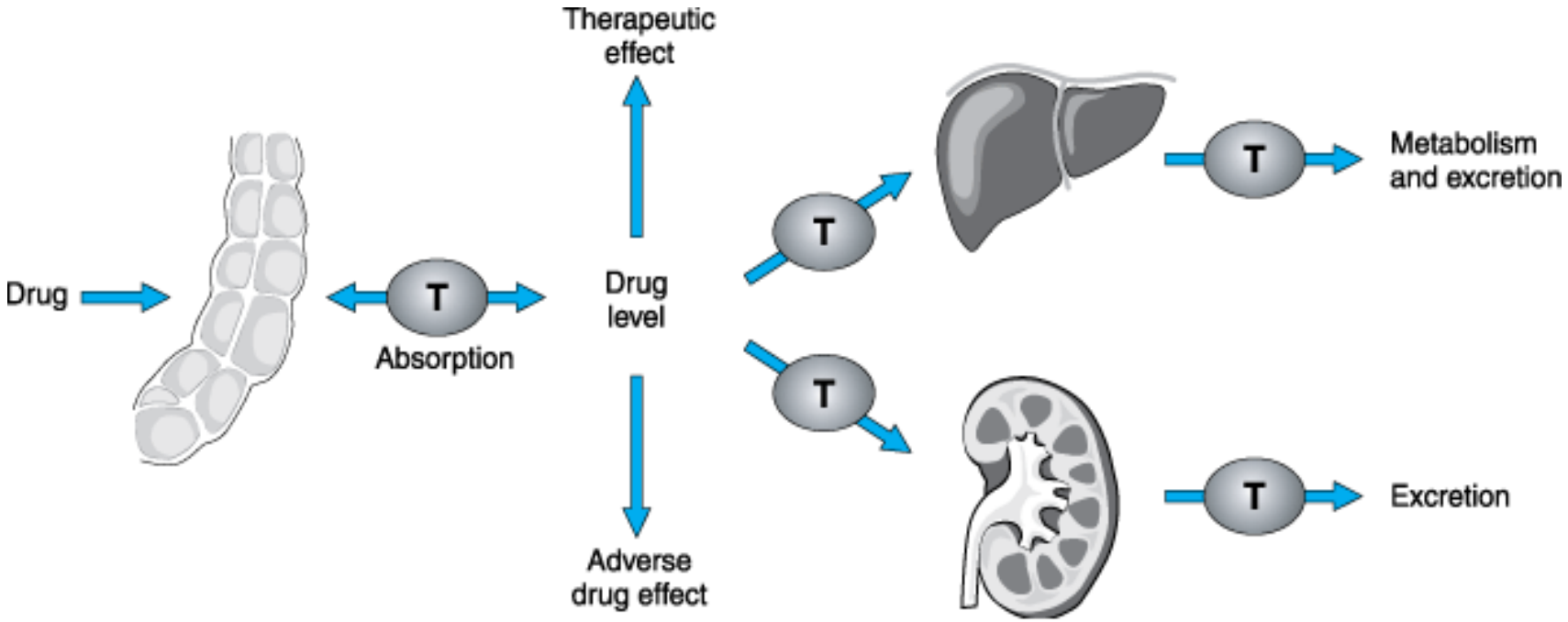


ELIMINATION
metabolism



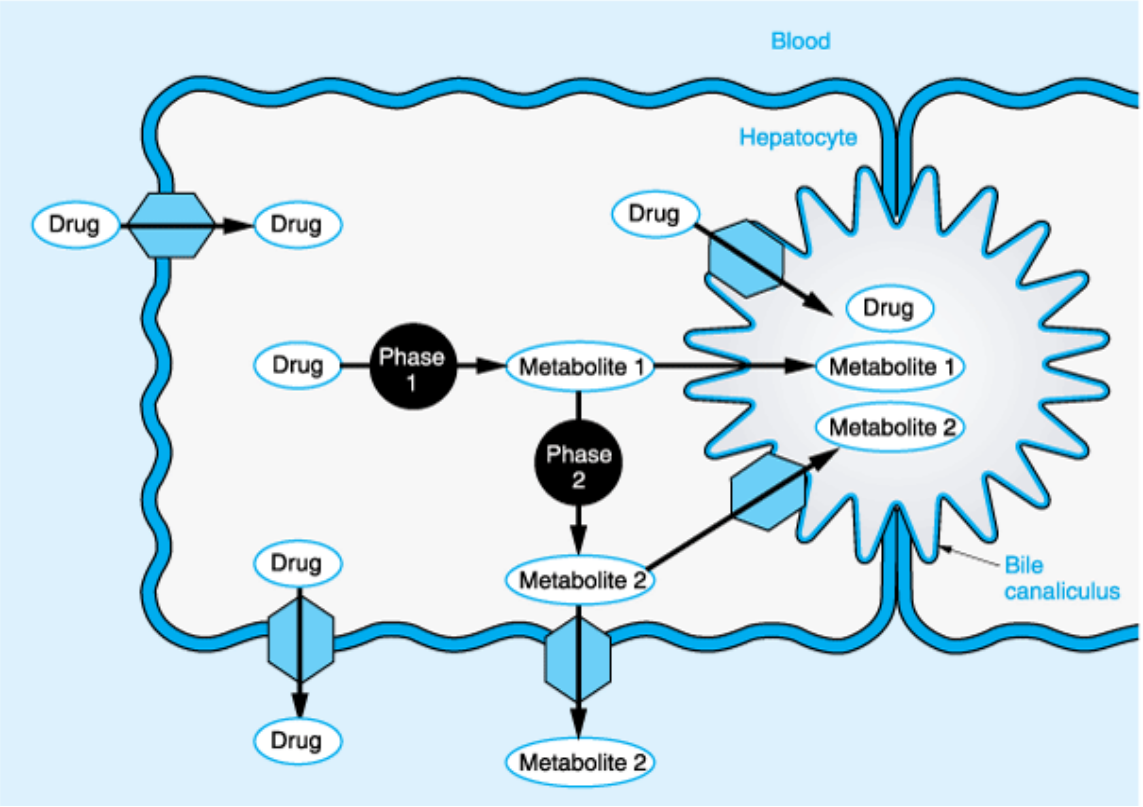
from lipophilic
to hydrophilic

ELIMINATION
metabolism and transporters



Membrane transporters (T) play roles in pharmacokinetic pathways (drug absorption, distribution, metabolism, and excretion), thereby setting systemic drug levels. Drug levels often drive therapeutic and adverse drug effects.

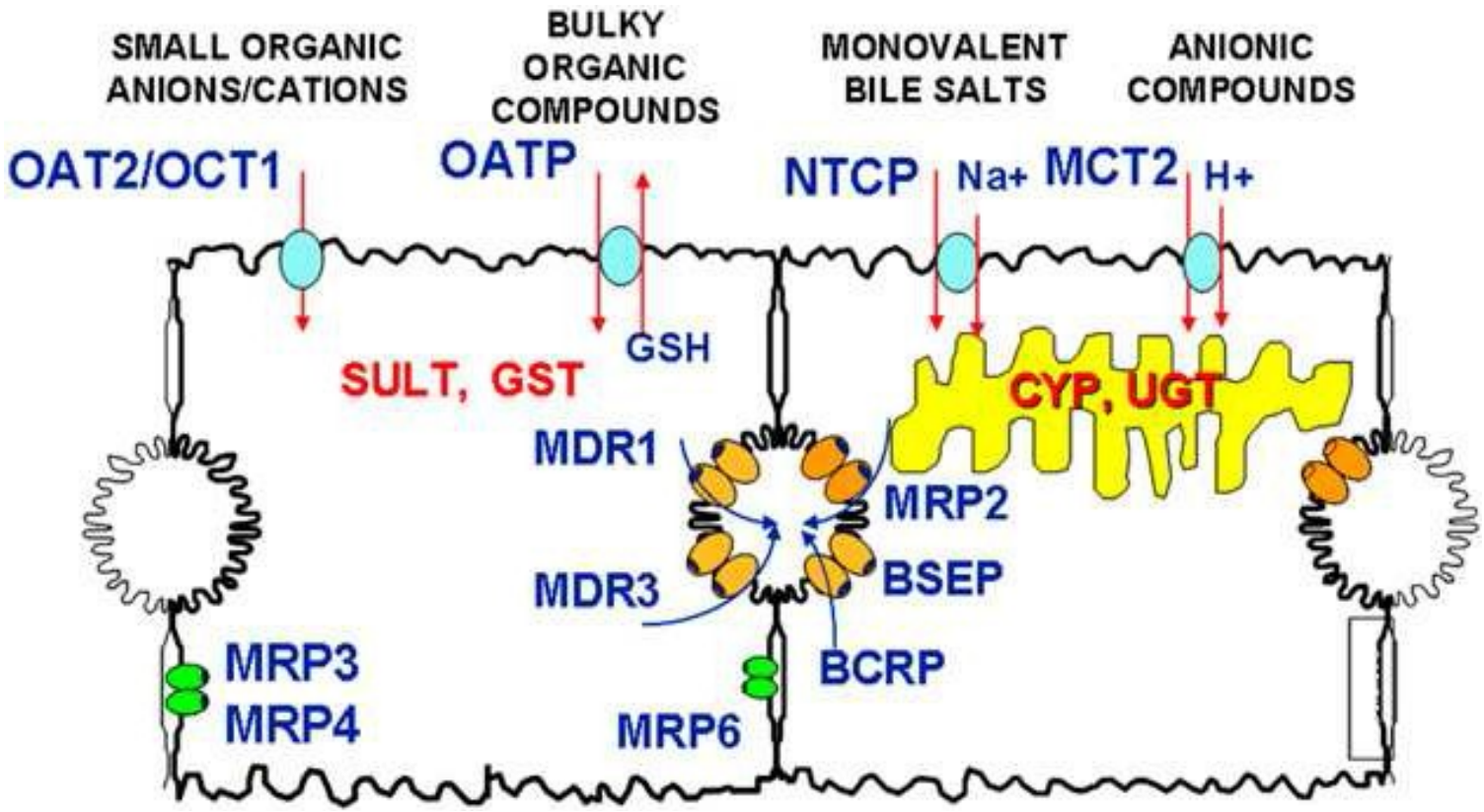
MEMBRANE TRANSPORTERS



Membrane transporters, shown as hexagons with arrows, work in concert with phase 1 and phase 2 drug-metabolizing enzymes in the hepatocyte to mediate the uptake and efflux of drugs and their metabolites.

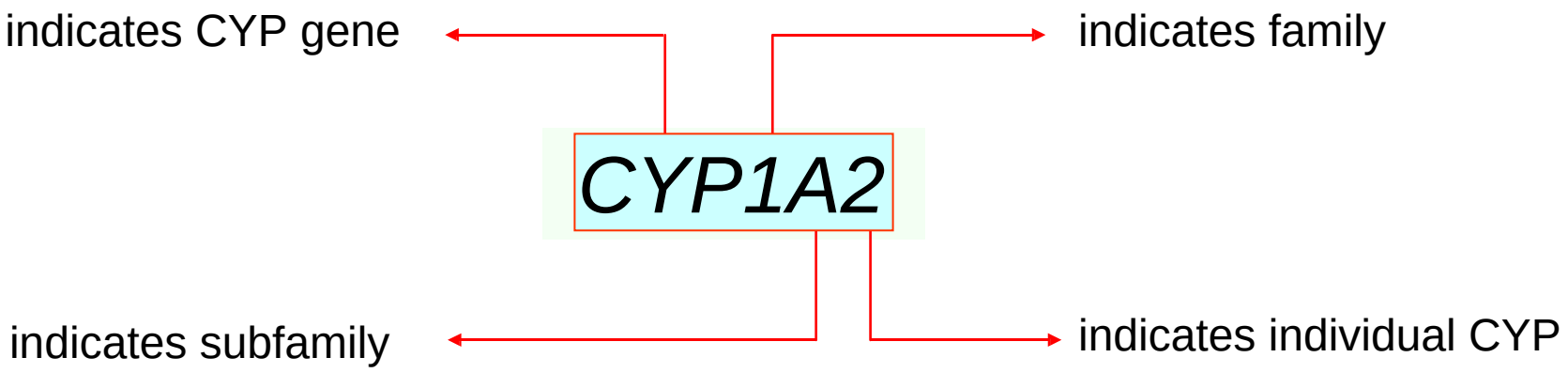
ELIMINATION

metabolism and transporters



Schematic diagram of transport and metabolism of drugs in the hepatocyte that shows influx transporters, such as OATP, NTCP, OAT2, OCT1, and MCT2 at the sinusoidal membrane, and efflux transporters such as MRP3, MRP4, and MRP6 at the basolateral membrane, and efflux transporters, such as Pgp or MDR1, MDR3, MRP2, BSEP, BCRP at the canalicular membrane. The enzymes, such as CYP, UGT, SULT, and GST are present to mediate intracellular metabolism.

cytochrome P450
nomenclature



- CYP450 enzymes within a family are ≥ 40% identical
- CYPs within a subfamily are ≥ 60% identical

CYTOCHROME P450 SUPERFAMILY

Family	Subfamilies	No. of enzymes	Best-described substrates
1	A, B	3	Drugs/xenobiotics
2	A, B, C, D, E, F, J	12	Drugs/xenobiotics
3	A	3	Drugs/xenobiotics
4	A, B, F	4	Fatty acids/leukotrienes
5	A	1	Thromboxane
7	A	1	Cholesterol
8	—	1	Prostacyclin
11	A, B	3	Steroids
17	A	1	Steroids
19	—	1	Estrogen
21	A, B	2	Steroids
24	—	1	Vitamin D/steroids
27	—	1	Vitamin D/steroids
51	—	1	Steroids

only the P450's in families 1, 2 and 3 appear to be responsible for the metabolism of drugs

DRUG METABOLISM

hepatic/extrahepatic

tissue	1A2	2A6	2C	2D6	2E	3A
hepatic	x	x	x	x	x	x
lung		x	x		x	x
kidney						x
GIT			x	x		x
placenta					x	x
nasal		x				

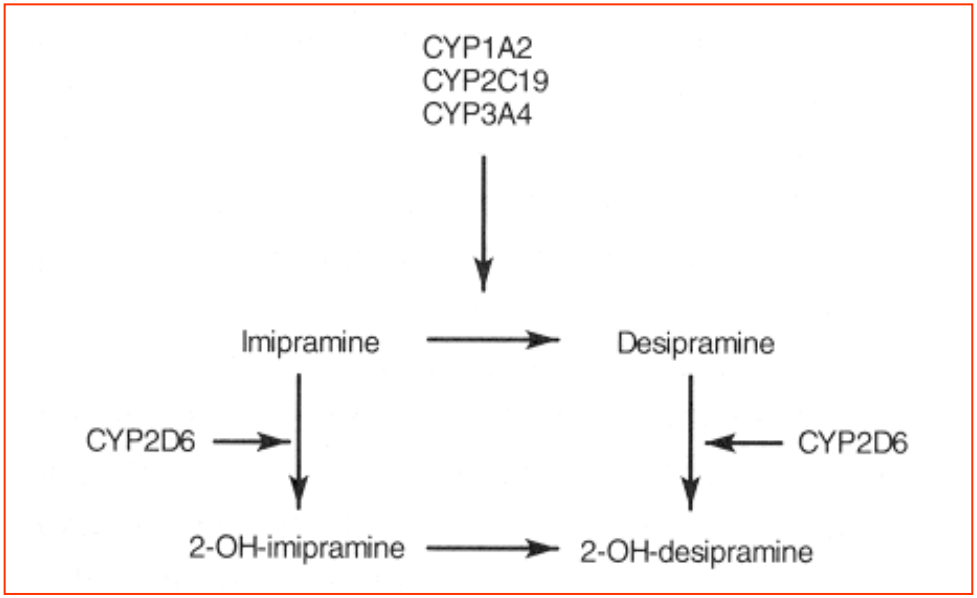
Clin. Pharmacokinet. 42: 969-984, 2003

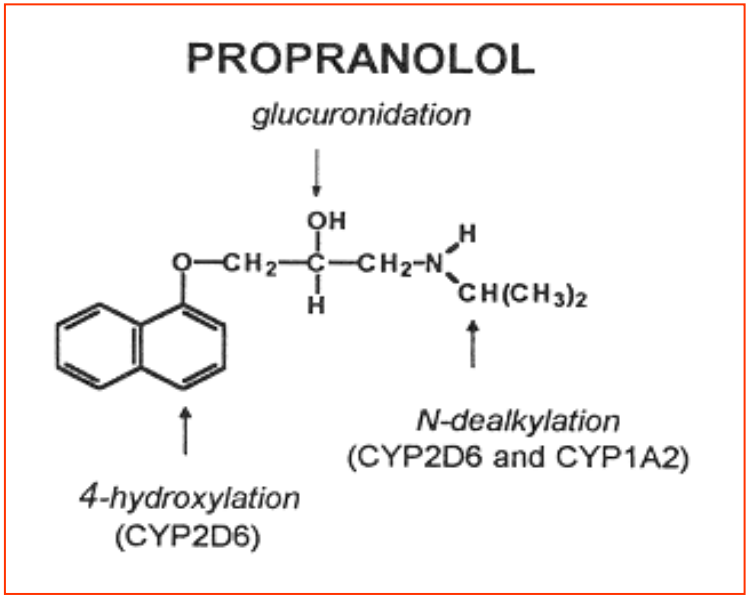
DRUG METABOLISM

CYP450 superfamily

- classified in families, subfamilies and specific isoenzymes
- broad and overlapping substrate specificity
- tissue distribution: liver, small intestine, kidney, lung, skin, …
- **high interindividual variability in enzyme activity: genetic and epigenetic factors**
- **many clinically significant CYP450 metabolism-based drug-drug interactions**

DRUG METABOLISM
CYP450 superfamily





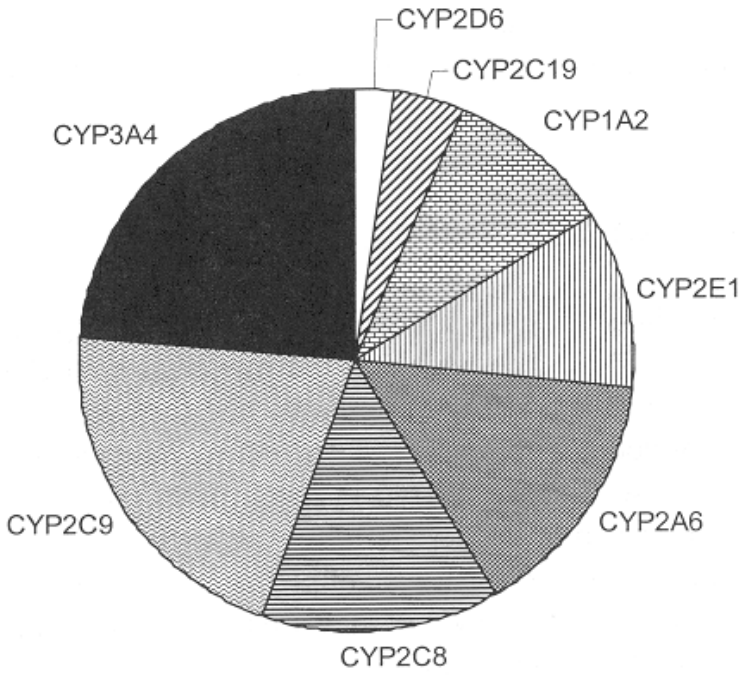
- two or more CYP450 enzymes can contribute to the metabolism of a single compound (broad substrate specificity)
- it is also possible for a single pathway to be catalyzed by several CYP450 enzymes

DRUG METABOLISM
CYP450 superfamily

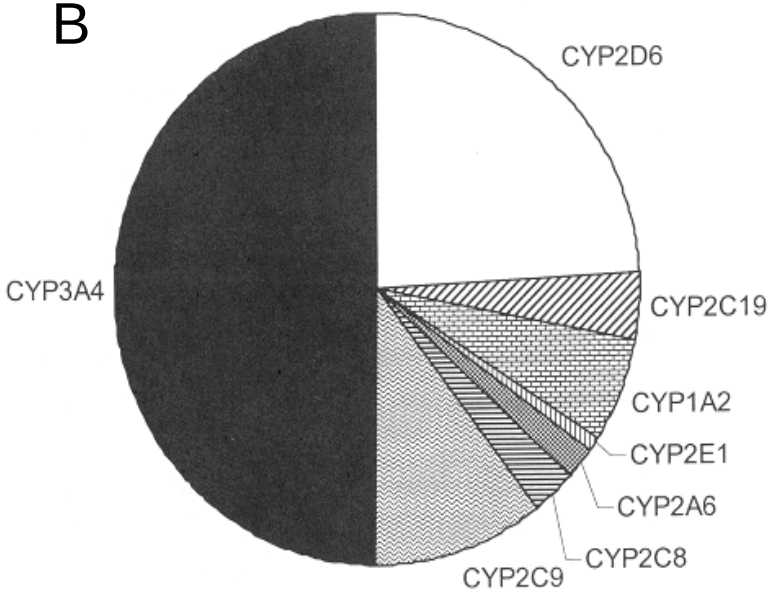
- CYP1A2 acetaminophen, caffeine, estradiol, theophylline
- CYP2C9 diclofenac, phenytoin, piroxicam, tolbutamide, S-warfarin
- CYP2C19 diazepam, phenytoin, S-mephenytoin, omeprazole, propranolol
- CYP2D6 captopril, codeine, debrisoquine, desipramine, dextromethorphan, metoprolol
- CYP3A4 acetaminophen, cyclosporin, diazepam, erythromycin, lidocaine, midazolam, nifedipine, quinidine, tacrolimus, verapamil, warfarin

DRUG METABOLISM

A



B

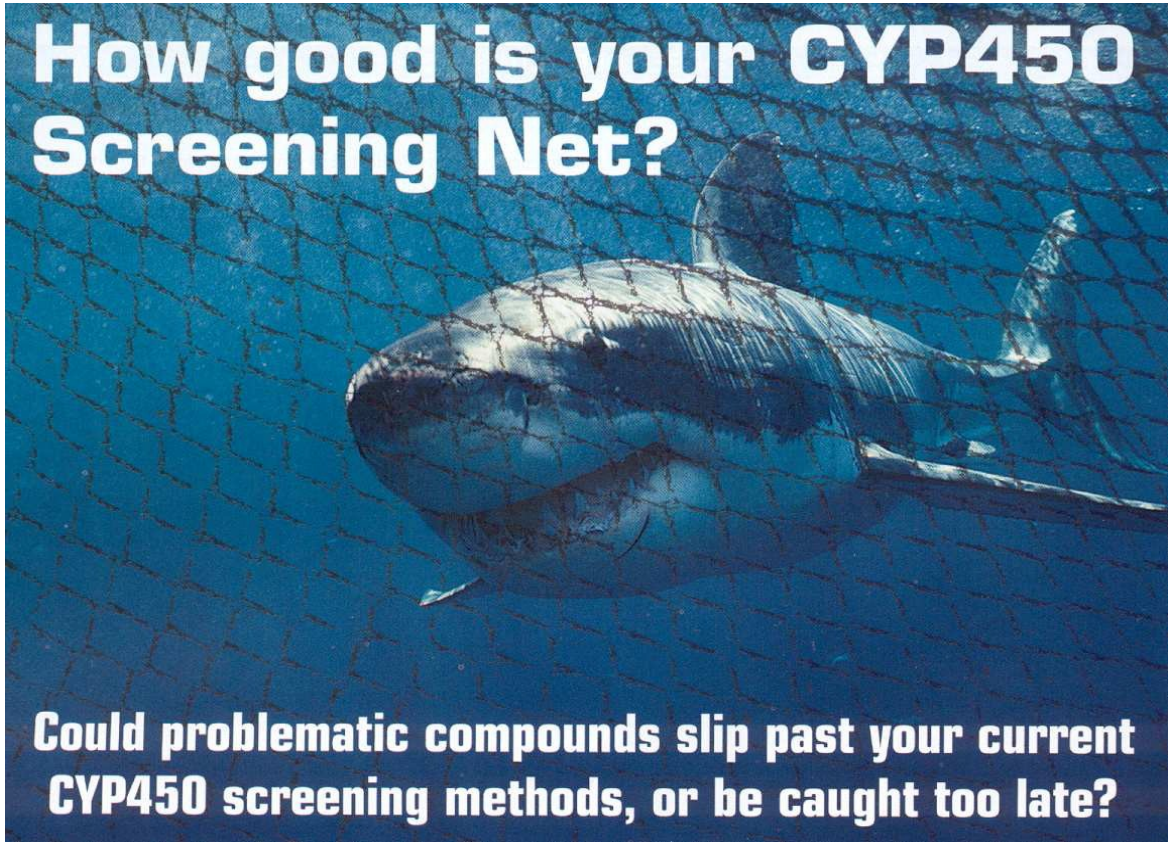


A: relative hepatic abundance of the major cytochrome P450's in man

B: relative significance of the major hepatic CYP450's in the P450 mediated clearance of drugs marketed in the USA and/or Europe

DRUG-DRUG INTERACTIONS (A.D. Rodrigues ed.), p. 58, Marcel Dekker Inc., New York, 2002

IN VITRO METABOLISM



IN VITRO METABOLISM

- aim: which metabolites are formed? which isoenzyme(s) is (are) involved? what is the activity/toxicity profile of the metabolites?
- in vitro methods
  - animal liver, intestine, kidney, … human liver, intestine, kidney (biopsies,
  - autopsies, organ donors)
  - subcellular fractions (tissue homogenate, 9000 x g supernatant, microsomes, cytosol)
  - hepatocytes, organ slices
  - cDNA expressed/purified enzymes

IN VITRO METABOLISM

découvertes souvent intéressantes !

- aim: which metabolites are formed? which isoenzyme(s) is (are) involved? what is the activity/toxicity profile of the metabolites?
- in vitro methods
  - animal liver, intestine, kidney, … human liver, intestine, kidney (biopsies,
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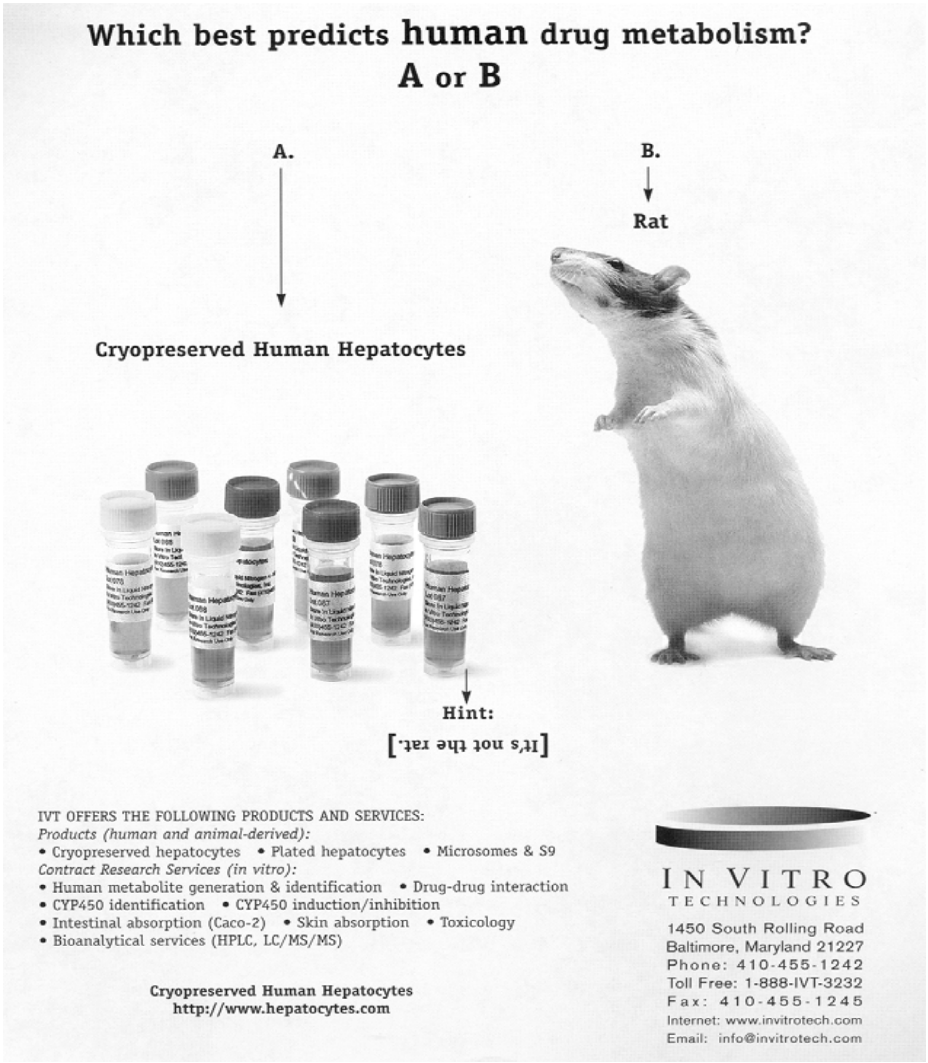
IN VITRO METABOLISM



Companies like IN VITRO TECHNOLOGIES (Baltimore, MD, USA) and GENTEST (Woburn, MA, USA) are specialized in offering reagents and services in the area of in vitro drug metabolism testing.

METABOLIC DRUG INTERACTIONS

ENZYME INHIBITION
competitive inhibition

- most CYP450 catalyzed reactions show hyperbolic saturation kinetics (Michaelis-Menten kinetics)
- competitive inhibition is the most common inhibition mechanism
- drug interactions can be predicted from in vitro inhibition studies

COMPETITIVE INHIBITION

- the binding of the inhibitor prevents binding of substrate to the active site of free enzyme

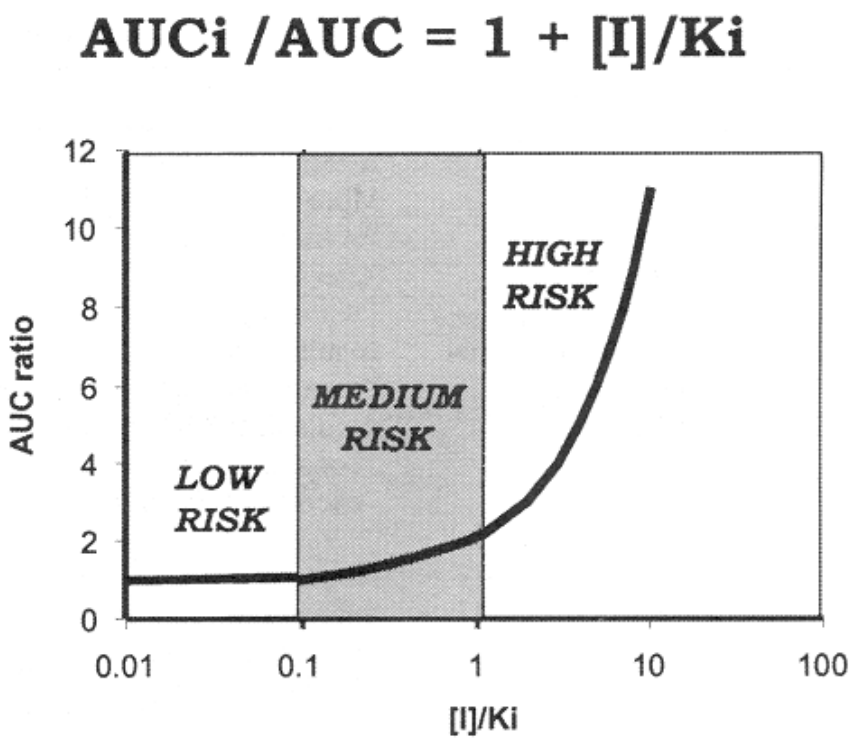
$$v_0 = \frac{V_{max}.S}{K_m + S}$$

velocity of the enzymatic reaction in the absence of inhibitor

$$v_i = \frac{V_{max}.S}{K_m\left(1+\frac{I}{K_i}\right)+S}$$

velocity of the enzymatic reaction in the presence of inhibitor I

IN VITRO/IN VIVO EXTRAPOLATION

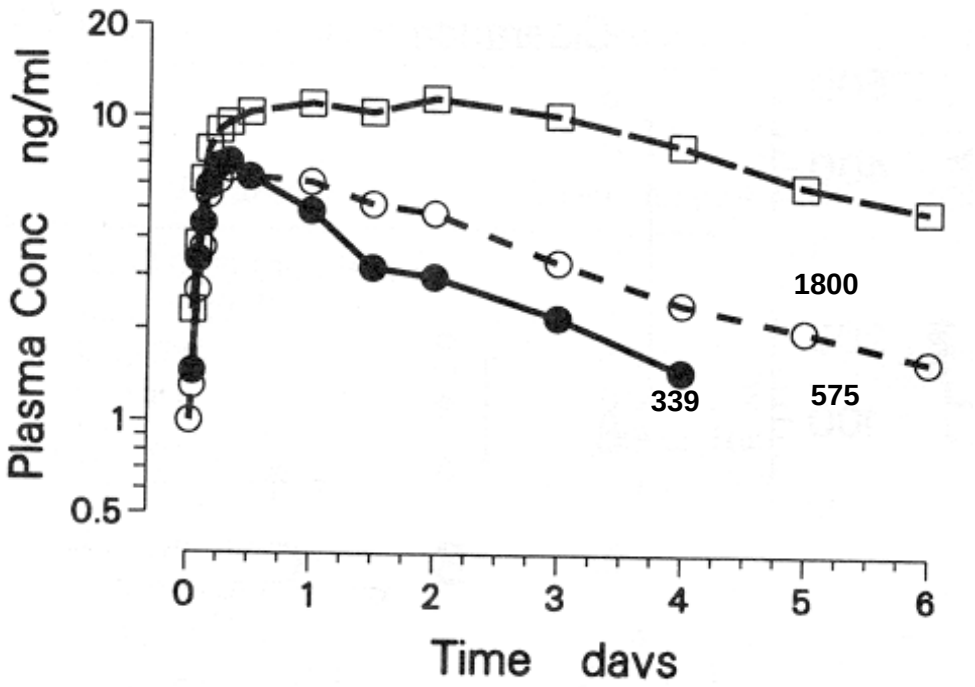


Prediction of in vivo CYP inhibition potential: a tentative guideline for evaluating risk on the basis of the impact of $[I]/K_i$ on the change in the AUC of substrate when inhibitor is present (competitive inhibition) is illustrated.

Tucker et al., Clin. Pharmacol. Ther. 70: 103-114, 2001.

correction

IN VITRO / IN VIVO EXTRAPOLATION



Mean plasma concentration-time profiles in 6 healthy volunteers after a 50 mg desipramine oral dose given alone (●), 3 hours following 60 mg fluoxetine (O), 3 hours following the 8th dose of 60 mg fluoxetine given once daily (□). The $AUC_{0-\infty}$ values (ng.h/ml) are shown on the graph.

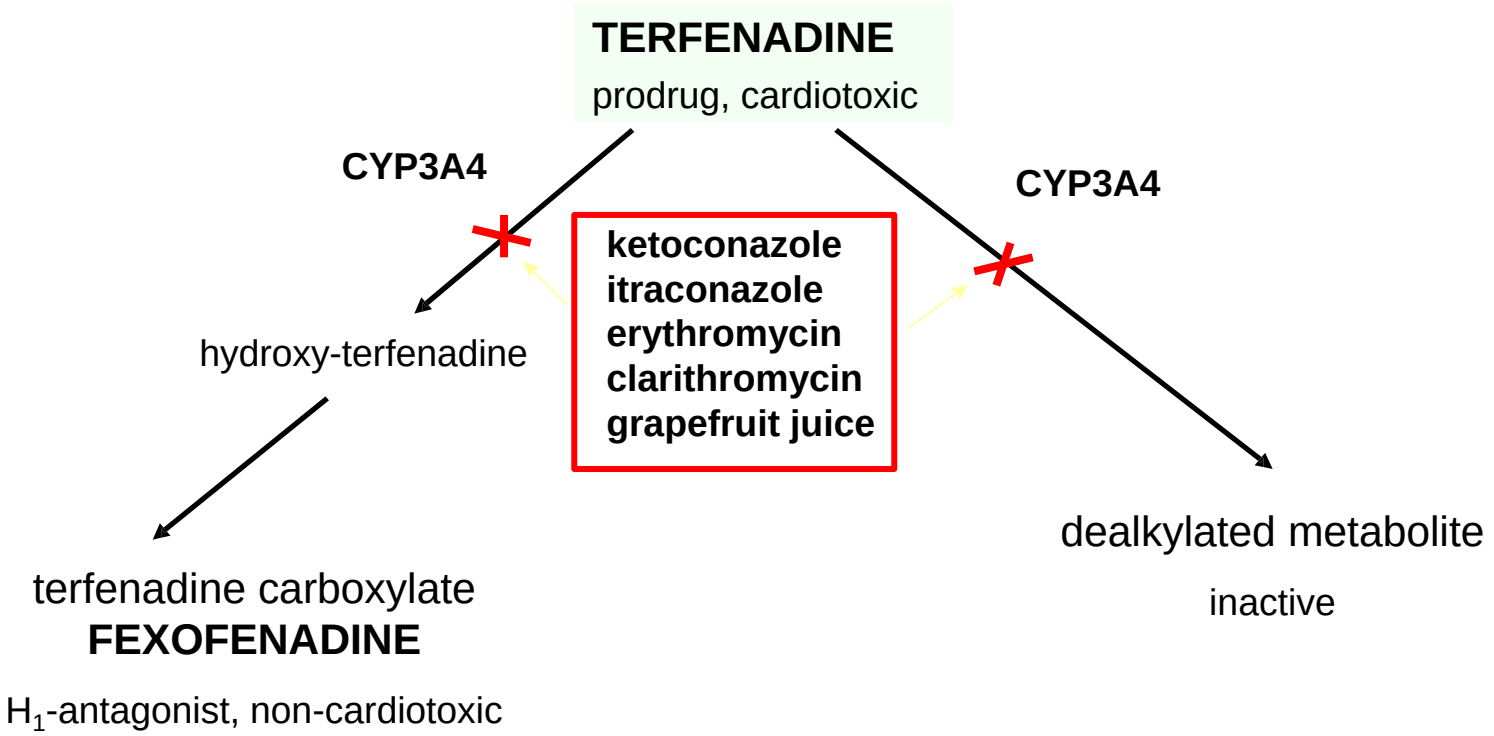
Bergstrom et al., Clin. Pharmacol. Ther. 51: 239-248, 1992.

DRUG-DRUG INTERACTIONS

- the issue of drug-drug interactions has generated significant concern within the pharmaceutical industry and among regulatory authorities in recent years
- this has arisen with respect to early termination of clinical development (e.g. furafylline, a xanthine derivative and potent inhibitor of CYP1A2), refusal of approval, severe prescribing restrictions and withdrawal from the market (e.g. terfenadine) and threatened litigation
- It is a **major problem with HIV protease inhibitors and antifungals**

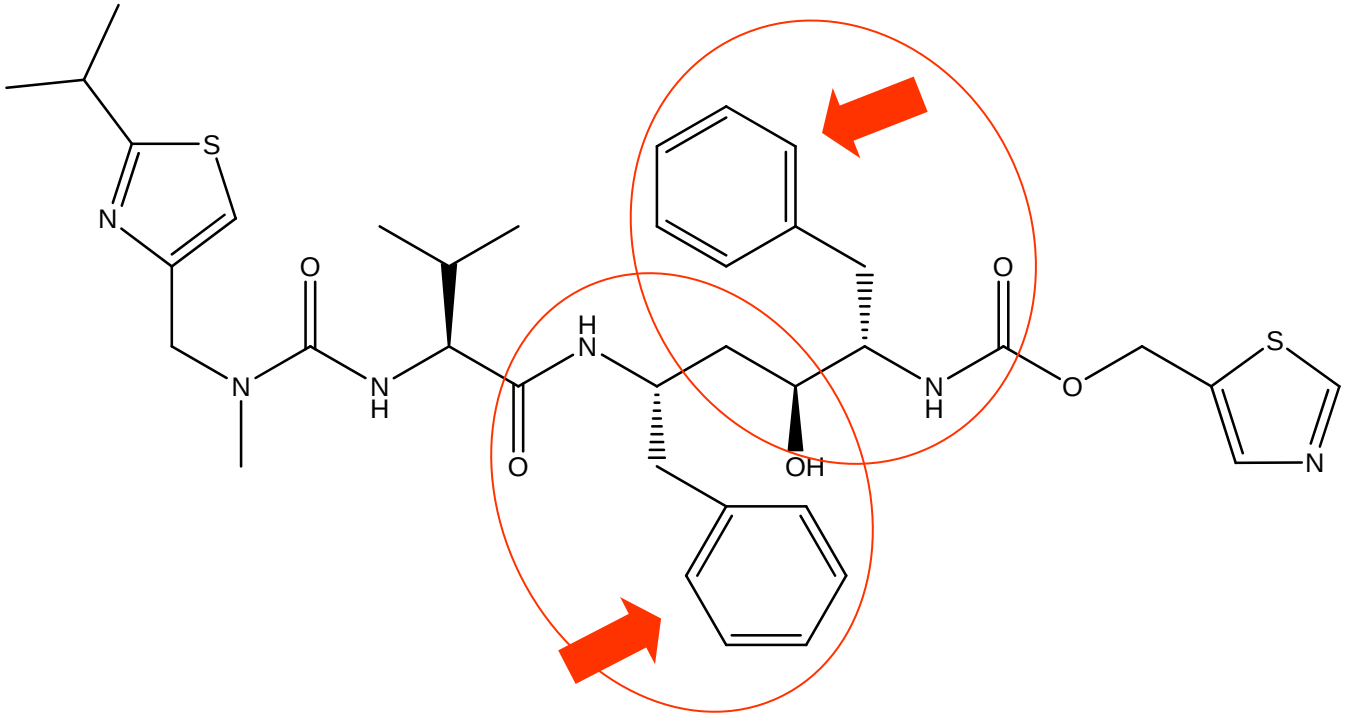
DRUG INTERACTIONS

enzyme inhibition



DRUG INTERACTIONS

enzyme inhibition for protease inhibitors



ritonavir

DRUG INTERACTIONS

enzyme inhibition for protease inhibitors

	ATV	DRV	FPV	IDV	LPV	NFV	RTV	SQV	TPV
Antiarrhythmics									
Amiodarone	■	●	●	●	●	●	●	●	●
Bepridil	●	●	●	●	■	■	●	●	●
Disopyramide	■	■	■	■	■	■	■	●	■
Flecainide	○	■	●	●	○	◆	●	●	●
Lidocaine (Lignocaine)	■	●	■	■	■	■	■	●	■
Mexiletine	■	■	■	■	■	◆	■	■	■
Propafenone	○	■	●	●	■	■	●	●	●
Quinidine	●	●	●	●	■	●	●	●	●

Key to symbols

Filled symbols indicate further information on the interaction is available at www.hiv-druginteractions.org.
Empty symbols indicate the combination has not been studied; an interaction has been predicted based on the metabolic profiles of the drugs.

●/○	These drugs should not be coadministered
■/□	Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration
◆/◇	No clinically significant interaction expected
✦/✧	There are no clear data, actual or theoretical, to indicate whether an interaction will occur

Key to abbreviations

ATV	Atazanavir (Reyataz®)	LPV	Lopinavir (Kaletra®)
DRV	Darunavir (Prezista®)	NFV	Nelfinavir (Viracept®)
FPV	Fosamprenavir (Telzir®, Lexiva®)	RTV	Ritonavir (Norvir®)
		SQV	Saquinavir (Invirase®)
IDV	Indinavir (Crixivan®)	TPV	Tipranavir (Aptivus®)

source:http://www.hiv-druginteractions.org.

DRUG INTERACTIONS

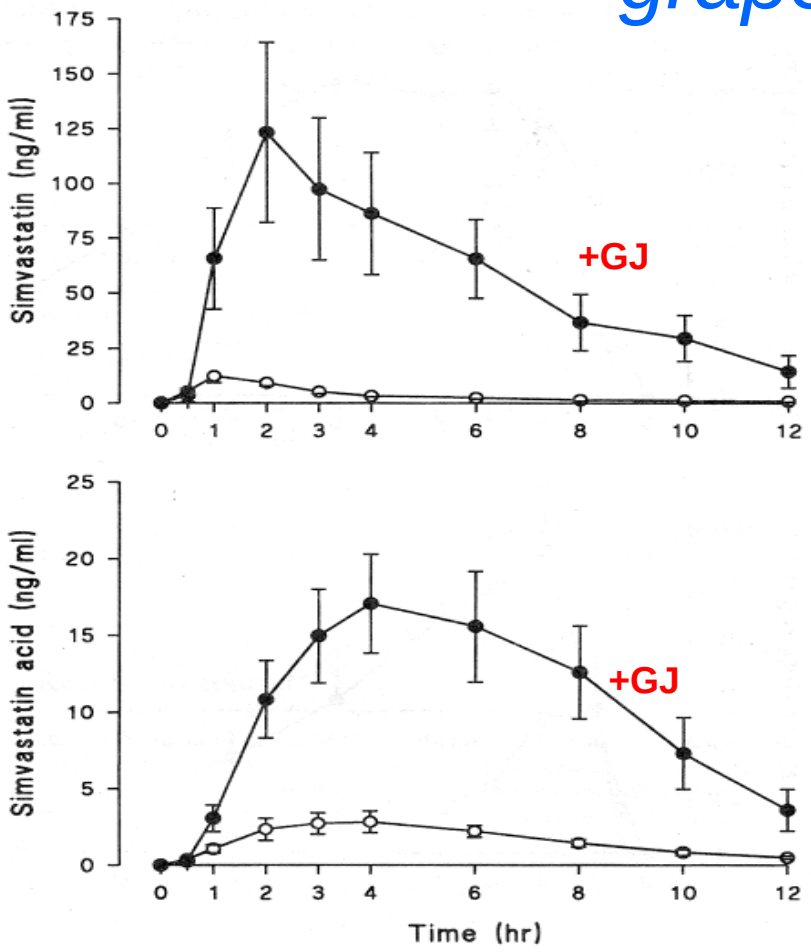
dietary effects

- A relatively large number of metabolic (transporter) food-drug interactions have been reported recently.
- Foods that contain complex mixtures of phytochemicals: e.g. fruits, vegetables, herbs, spices and teas, …
- CYP3A appears to be especially sensitive to dietary effects as demonstrated by reports of potentially clinically important interactions involving orally administered drugs that are substrates of this enzyme.
- Food-drug interactions involving CYP1A2, CYP2E1, UGTs, GSTs have also been documented.

Harris et al., Clin. Pharmacokinet. 42: 1071-1088, 2003.

DRUG INTERACTIONS

grapefruit juice

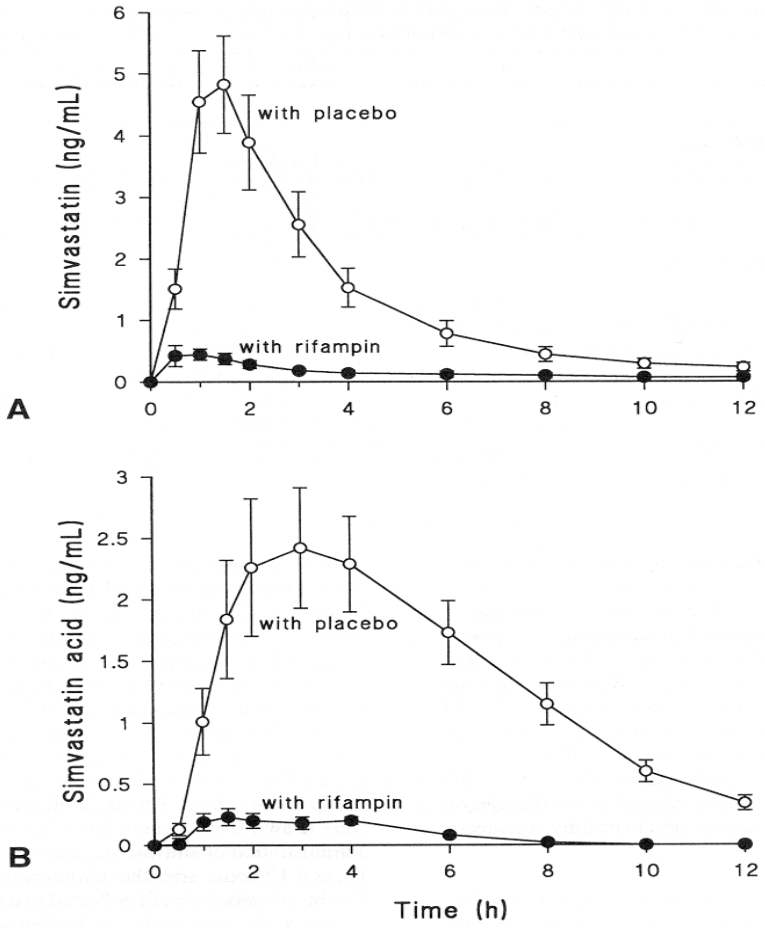


Mean ±SEM serum concentrations of simvastatin (upper panel) and simvastatin acid (lower panel) in 10 healthy volunteers after a single oral dose of 60 mg simvastatin, after ingestion of 200 ml double-strength grapefruit juice (solid circles) or water (open circles) 3 times a day for 2 days and on day 3 with simvastatin and 0.5 h and 1.5 hours later.

Lilja et al., Clin. Pharmacol. Ther. 64: 477-483, 1998).

DRUG INTERACTIONS

enzyme induction



Plasma concentrations (mean ± SEM) of simvastatin (A) and simvastatin acid (B) in 10 healthy subjects after administration of 40 mg of simvastatin following pretreatment with 600 mg of rifampin (solid circles) or placebo (open circles) once daily for 5 days.

Kyrklund et al., Clin. Pharmacol. Ther. 68: 592-597, 2000.

DRUG-DRUG INTERACTIONS
inhibitions vs. induction

Mechanistic comparison of CYP450 inhibition and induction.

	Inhibition	Induction
Mechanism	Direct chemical effect on enzyme	Indirect effect through enhanced quantities of CYP protein
Onset and reversibility	Rapid	Slow
Immediate exposure	Needed	Not needed
Prior exposure	Not needed	Needed
In vitro study	Straightforward	Difficult

PHARMACOGENETICS

interindividual variability

- interindividual variability may be due to:

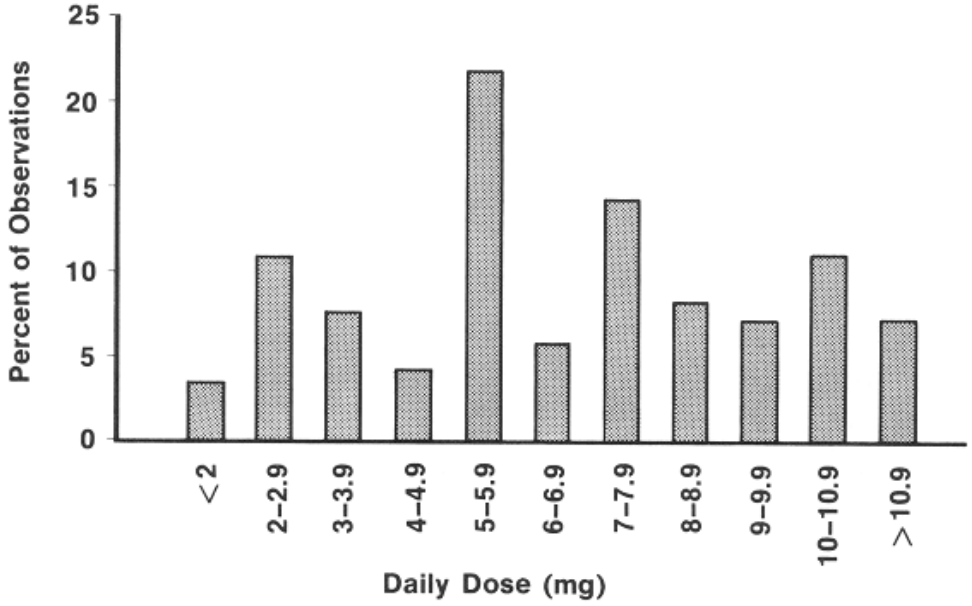
  - pharmacodynamics

  - pharmacokinetics → metabolism
  - pharmacokinetics → transporters

interindividual variability

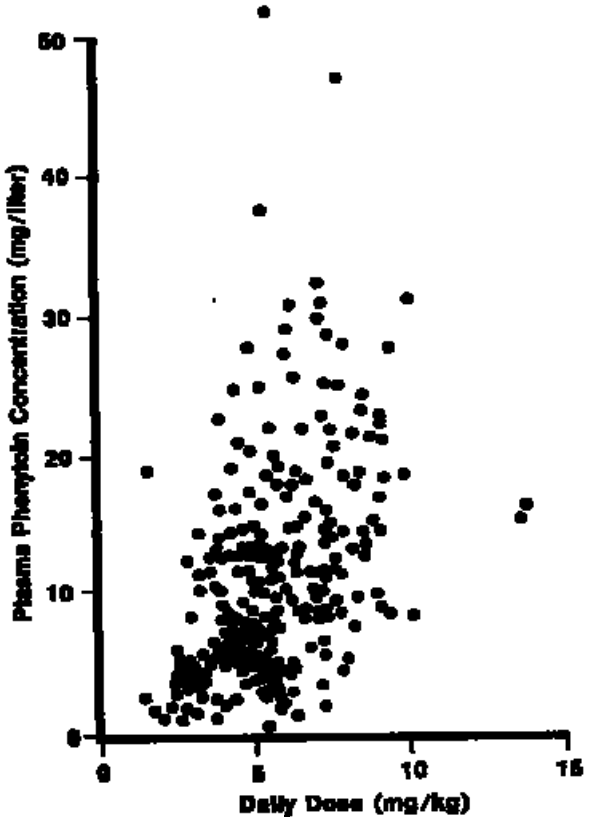
- the daily dose of warfarin, required to produce similar prothrombin times in 200 adult patients, varies widely

(Eur J Clin Pharmacol 9:1-8, 1975)

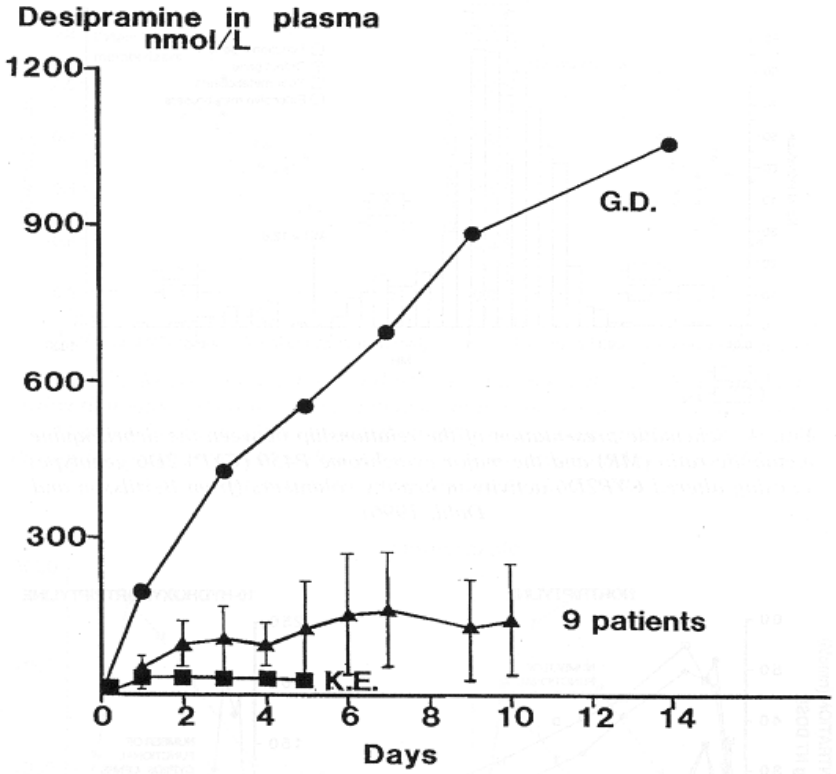


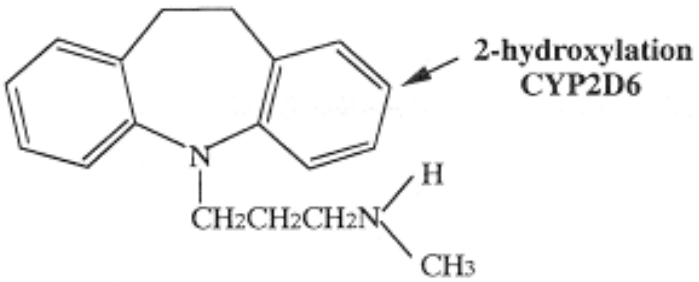
interindividual variability

- plasma concentrations of phenytoin vary considerably between patients even when they are administered the same daily dose due to ***pharmacokinetic variability***



interindividual variability





plasma concentrations of desmethylimipramine after dosing 25 mg t.i.d. to 11 patients (*Sjöqvist et al., 1967*)

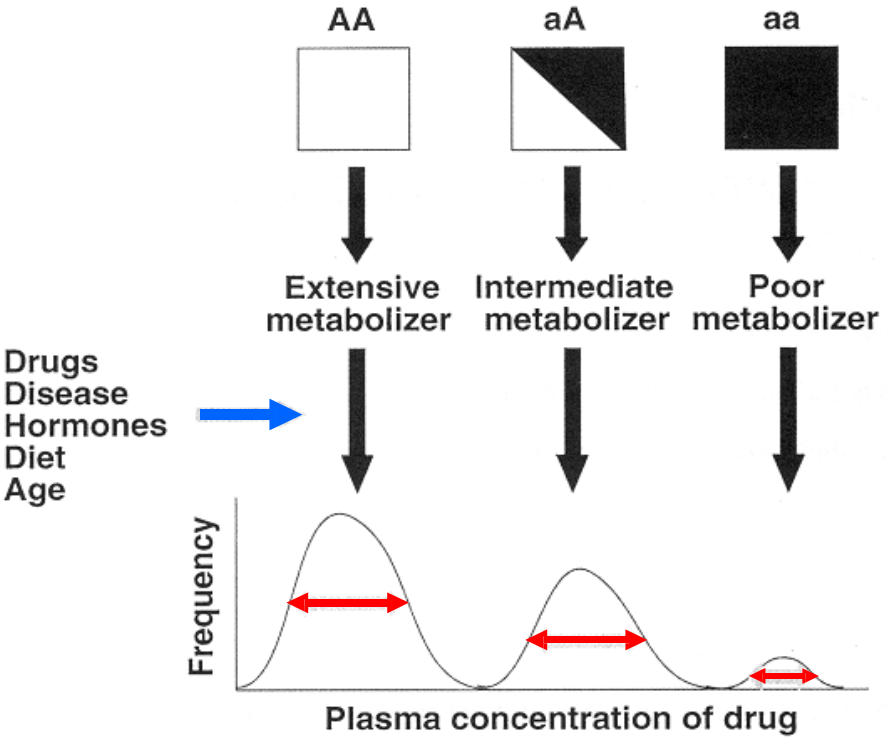
interindividual variability

- individual variation in drug response is a major problem in clinical practice and in drug development
- variation can lead to therapeutic failure or adverse, or even fatal, effects of drugs in some patients
- adverse drug reactions (ADR) are the 4th to 6th leading cause of death in the US (~100,000 deaths per year)
- ***pharmacogenetics*** and ***pharmacogenomics*** help to understand and prevent the inherited risk of an individual patient to develop an ADR or to have no beneficial drug effect

interindividual variability

- **pharmacogenetics**: the study of variability in drug response due to heredity
- **pharmacogenomics**: reflects the change of the human technical ability to investigate and pinpoint variations in DNA, a change that encouraged geneticists to study the genome rather than merely single genes

interindividual variability



A: wild-type allele

a: mutant

(deficient) allele

interaction between genetic and epigenetic factors in the determination of drug metabolizing activity

Julio Licinio and Ma-Li Wong (Eds.)

Pharmacogenomics

The Search
fo r Individualized Therap ies