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Toxicante

1
Toxicocinética

2
Interação com a molécula alvo

3
Disfunção/dano celular

4
Reparo inapropriado

TOXICIDADE

TOXICIDADE

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Transporte do sítio de exposição ao sítio alvo

1º estágio

Exposição

Toxicante

absorção

distribuição sítio alvo

reabsorção

bioativação

TOXICOCINÉTICA

eliminação pré-sistêmica

distribuição sítios de armazenamento

excreção

desintoxicação

toxicante

molécula alvo

Sítio alvo

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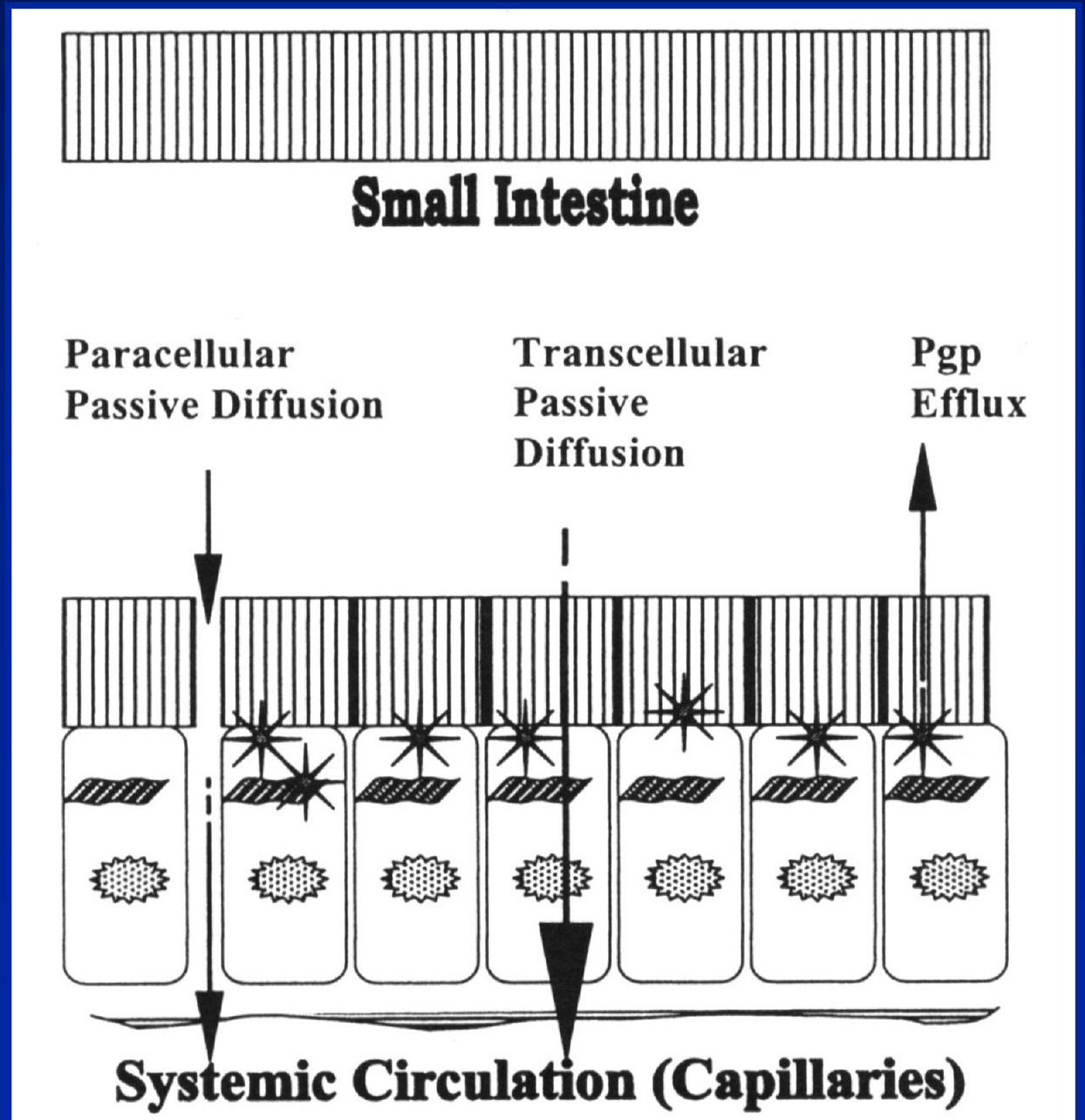
Passive diffusion

Transcellular and Paracellular



OCTANOL/WATER PARTITION COEFFICIENTS (P)

COMPOUND	LOG *P*
Paraquat	Charged molecule
Cephalosporin C	–4.72
Glycine	–3.21
Glutathione	–3.05
Cysteine	–2.35
Glucose	–2.21
Ethylene glycol	–1.37
Lead acetate	–0.63
p-Aminohippuric acid	–0.25
Dimercaprol	0.18
Scopolamine	0.30
Aspirin (acetyl salicylic acid)	1.02
Colchicine	1.19
Atropine	1.32
Benzoic acid	1.88
Benzene	2.14
Salicylic acid	2.19
Methyl salicylate	2.34
2,4-D	2.73
Warfarin	2.89
Digitoxin	3.05
Parathion	3.47
DDT	6.76
TCDD	7.05

2,4-D, 2,4-dichlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin.

Log P: physicochemical parameter relative to assessing potential membrane permeability

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Examples of Drugs Showing low Oral Bioavailability Becauseof Low Intestinal Permeability

Alendronate	Gentamicin
Amikacin	Ibandronate
Carbenicillin	Neomycin
Cefamandole	Pyridostigmine
Ceftazidime	Streptomycin
Flumazenil	Vancomycin

Absorção no trato gastrintestinal

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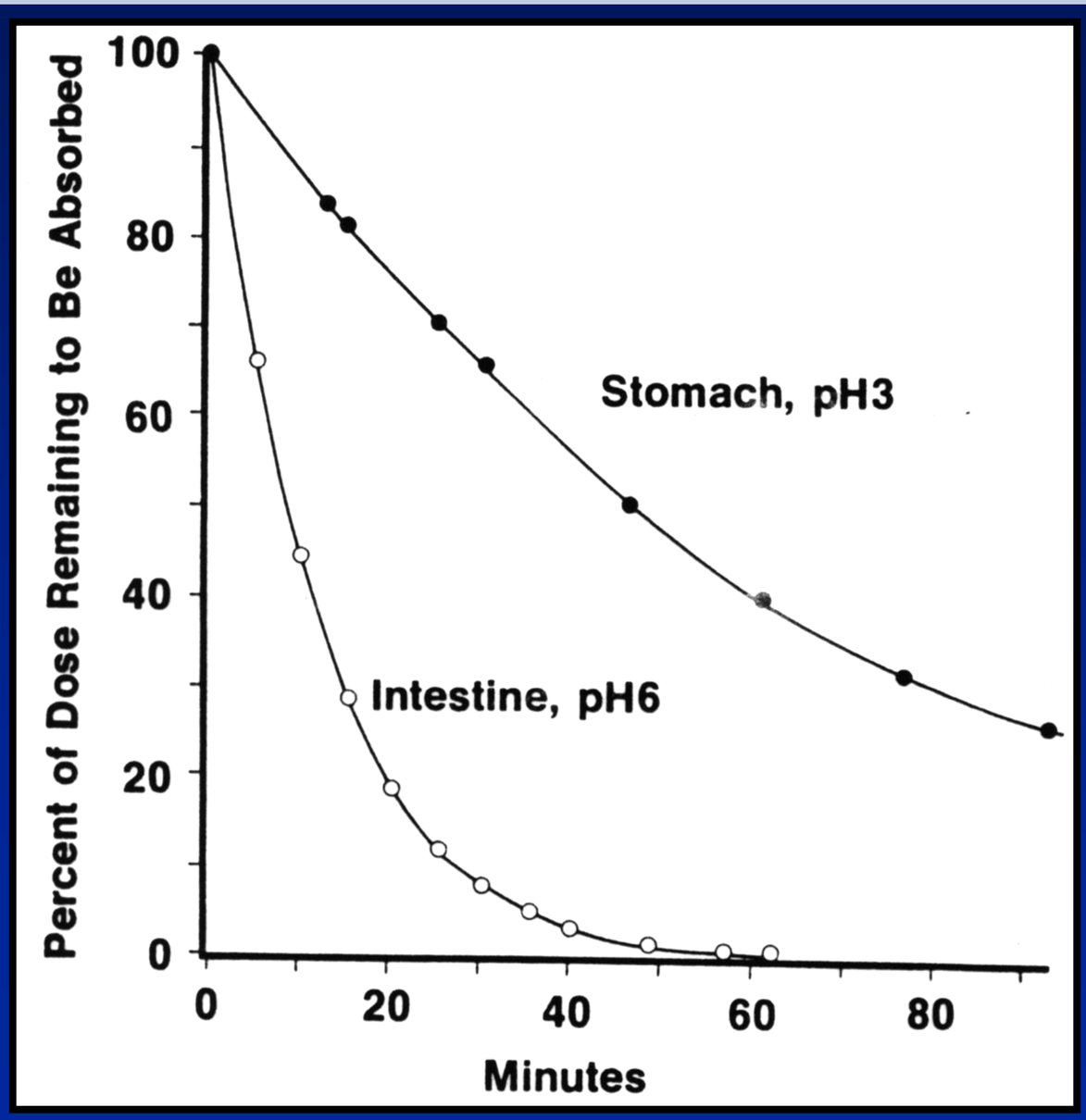
Difusão Passiva

Ácido salicílico (pKa=3)

	estômago	intestino delgado
pH	1 – 3,5	5 – 7
área absortiva	1 m^2	200 m^2
perfusão	150 mL/min	1 L/min
permeabilidade	-	+



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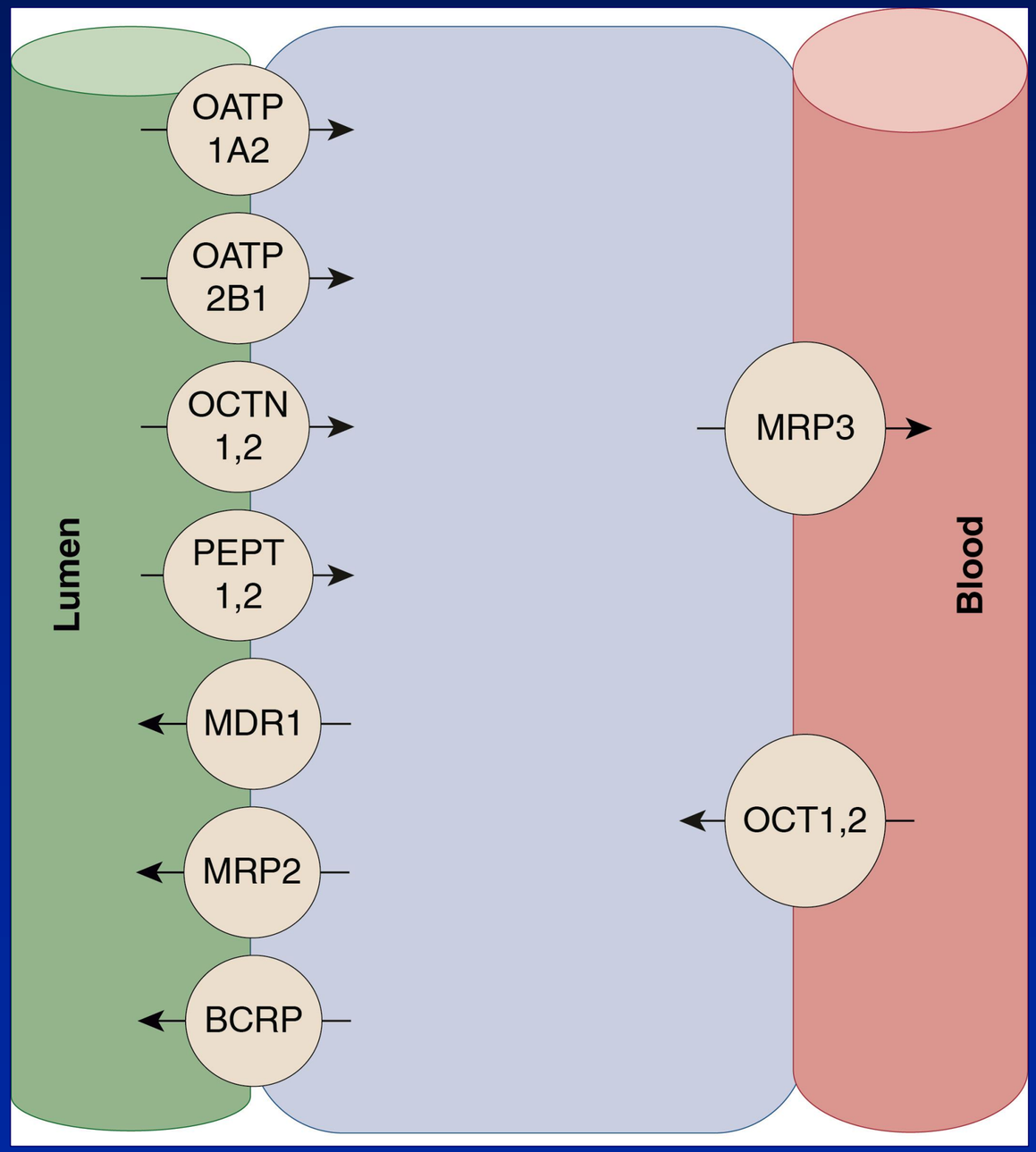
XENOBIOTIC TRANSPORT SYSTEMS PRESENT IN THE GASTROINTESTINAL TRACT



OATP
Organic-anion transporting peptides
OCTN
Organic-cation transporters
PEPT
Peptide transporters

MRP2
Multidrug resistance associated protein 2
BCRP
Breast cancer resistance protein
MDR1/P-gp
Multidrug resistant protein
P-glycoprotein

Synergic action of P-gp and CYP3A4 in the enterocytes

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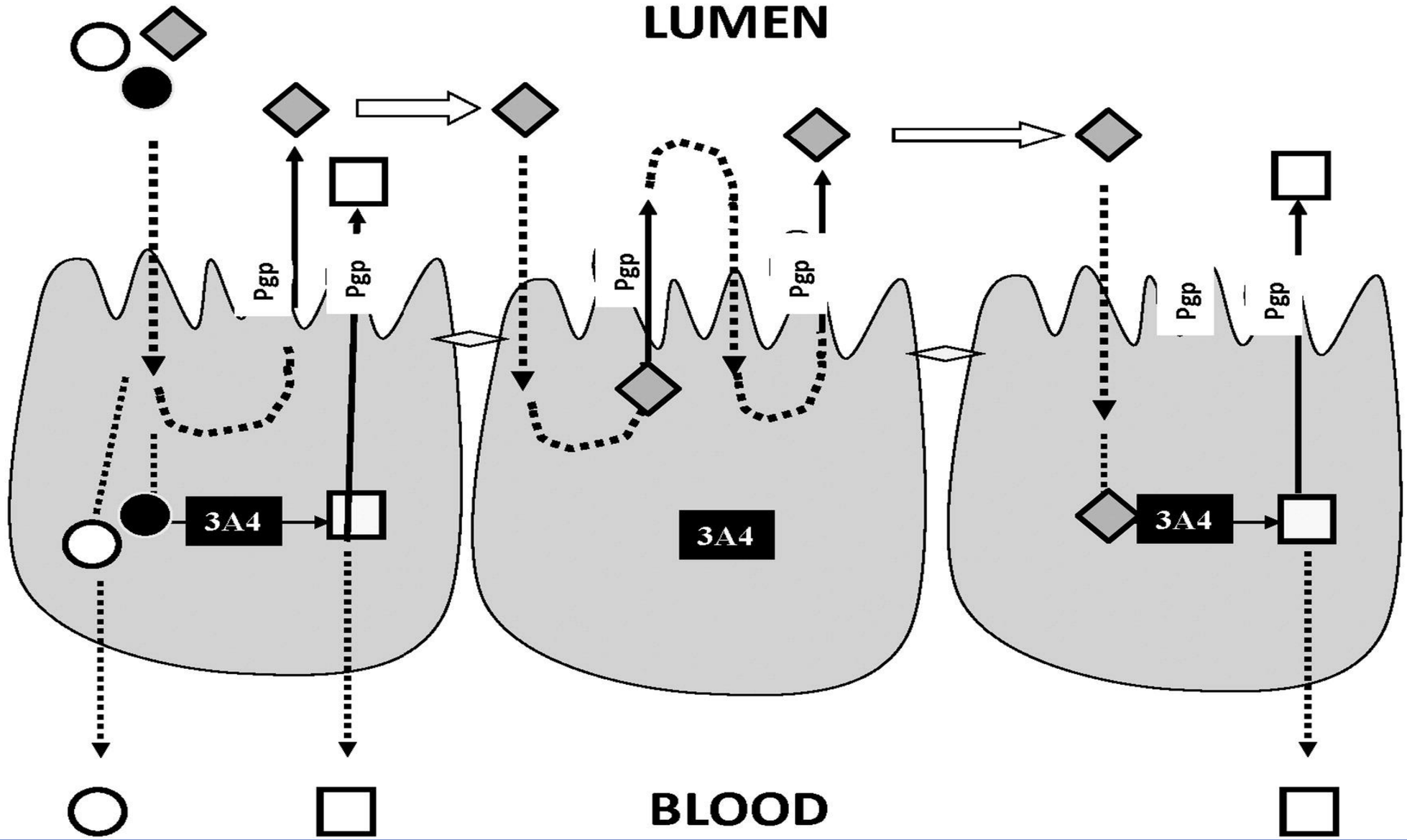
Drug not metabolized or transported in the gut

Drug metabolized on first entrance

Drug cycled 4 times before metabolized

Drug metabolites



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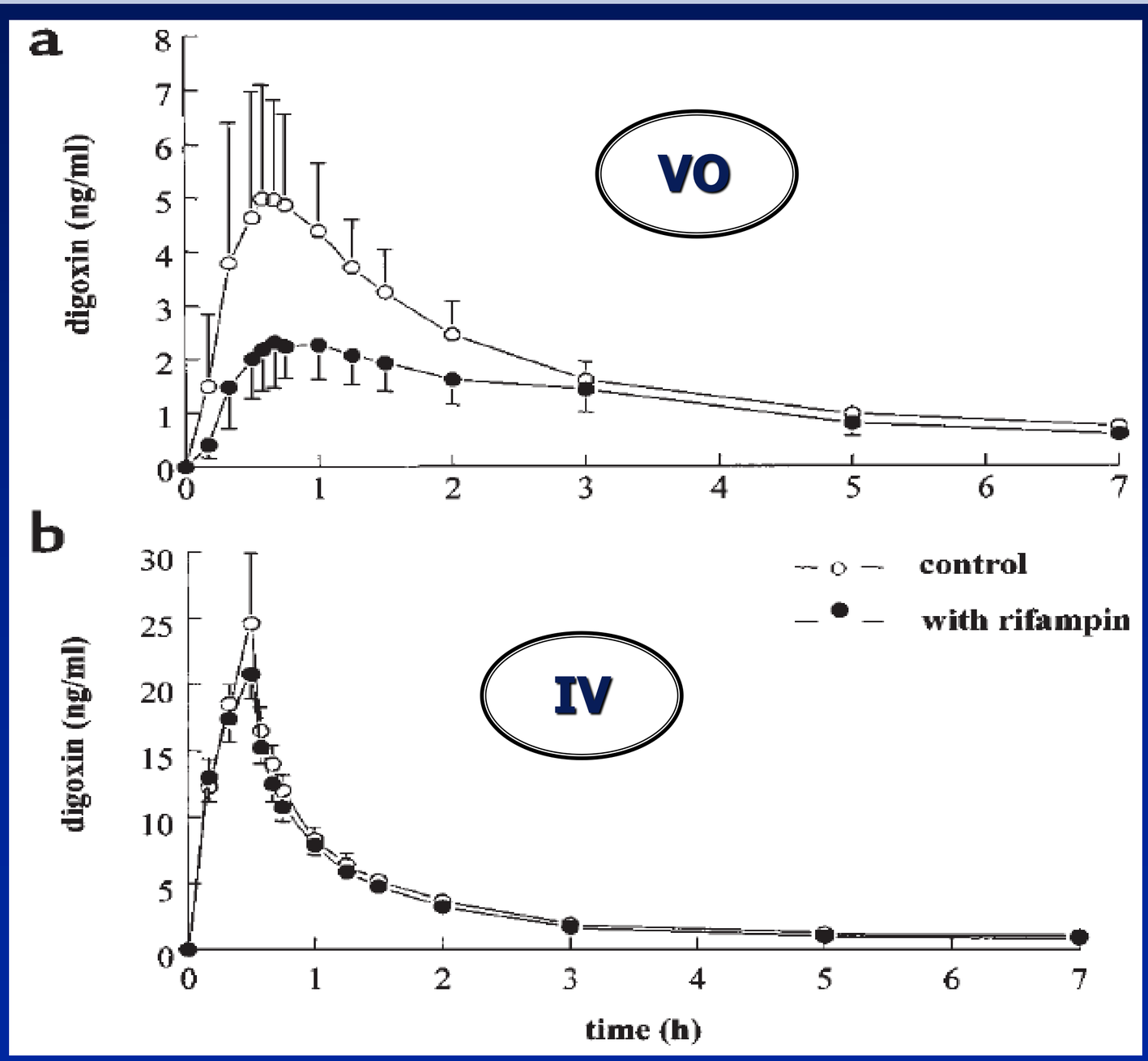
The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin



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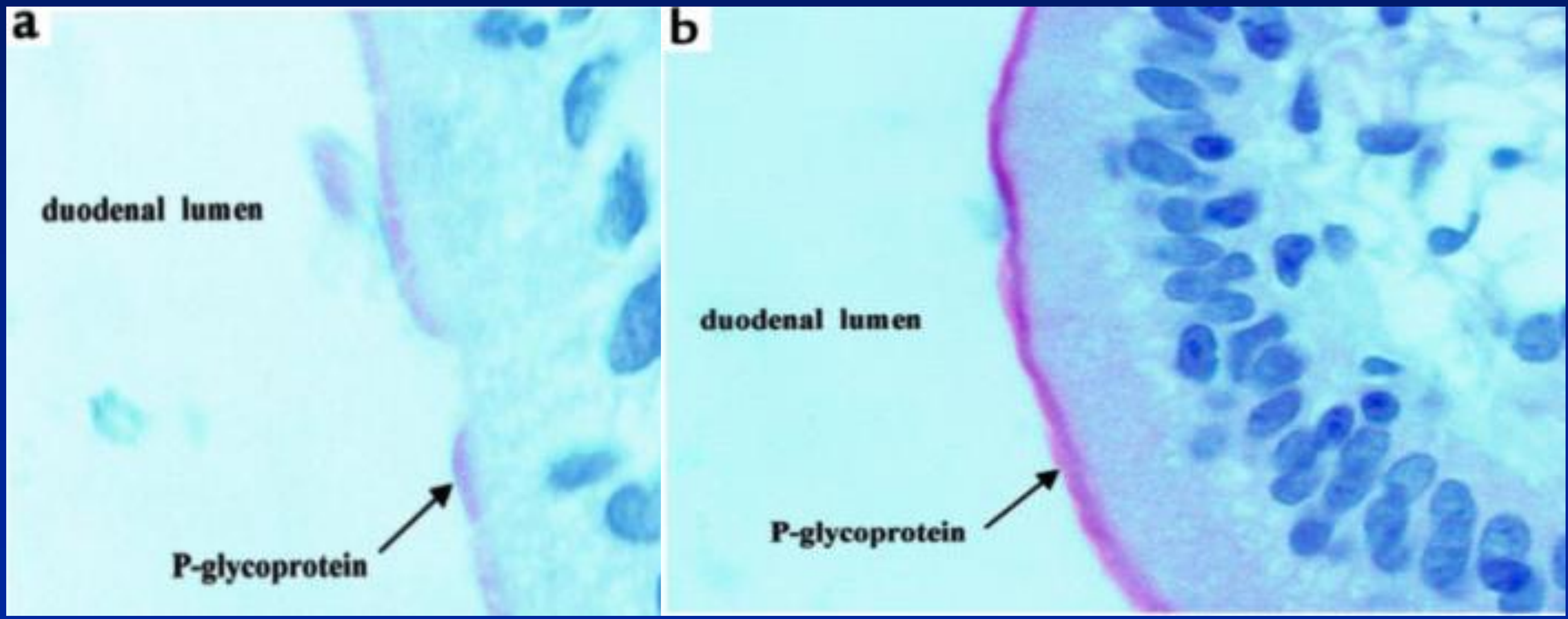
(a) Duodenal biopsy immunostained for P-gp before administration of rifampin (b) Duodenal biopsy after 9 days administration of rifampin (600 mg)



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Biopharmaceutical Drug Disposition Classification System

CLASS 1 **High Solubility** **High Permeability**	**CLASS 2** **Low Solubility** **High Permeability**
CLASS 3 **High Solubility** **Low Permeability**	**CLASS 4** **Low Solubility** **Low Permeability**

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Biopharmaceutical Drug Disposition Classification System

CLASS 1 **Transporter effects minimal**	CLASS 2 **Efflux transporter effects predominate in the gut, while absorptive and efflux transporter effects occur in the liver**
CLASS 3 **Absorptive transporter effects predominate (but may be modulated by efflux transporters)**	CLASS 4 **Absortive and efflux transporter effects could be important**

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Examples of Drugs in Class I of the Biopharmaceutics Classification System

Abacavir	Chlorpheniramine	Ergonovine	Lidocaine	Prednisolone
Acetaminophen	Cyclophosphamide	Ethambutol	Lomefloxacin	Primaquine
Acyclovir	Desipramine	Ethinyl estradiol	Meperidine	Promazine
Amiloride	Diazepam	Fluoxetine	Metoprolol	Propranolol
Amitriptyline	Diltiazem	Imipramine	Metronizadol	Quinidine
Atropine	Diphenhydramine	Ketorolac	Midazolam	Rosiglitazone
Buspirone	Disopyramide	Ketoprofen	Minocycline	Theophylline
Caffeine	Doxepin	Labetalol	Misoprostol	Valproic Acid
Captopril	Doxycycline	Levodopa	Nifedipine	Verapamil
Chloroquine	Enalapril	Levofloxacin	Phenobarbital	Zodovudine

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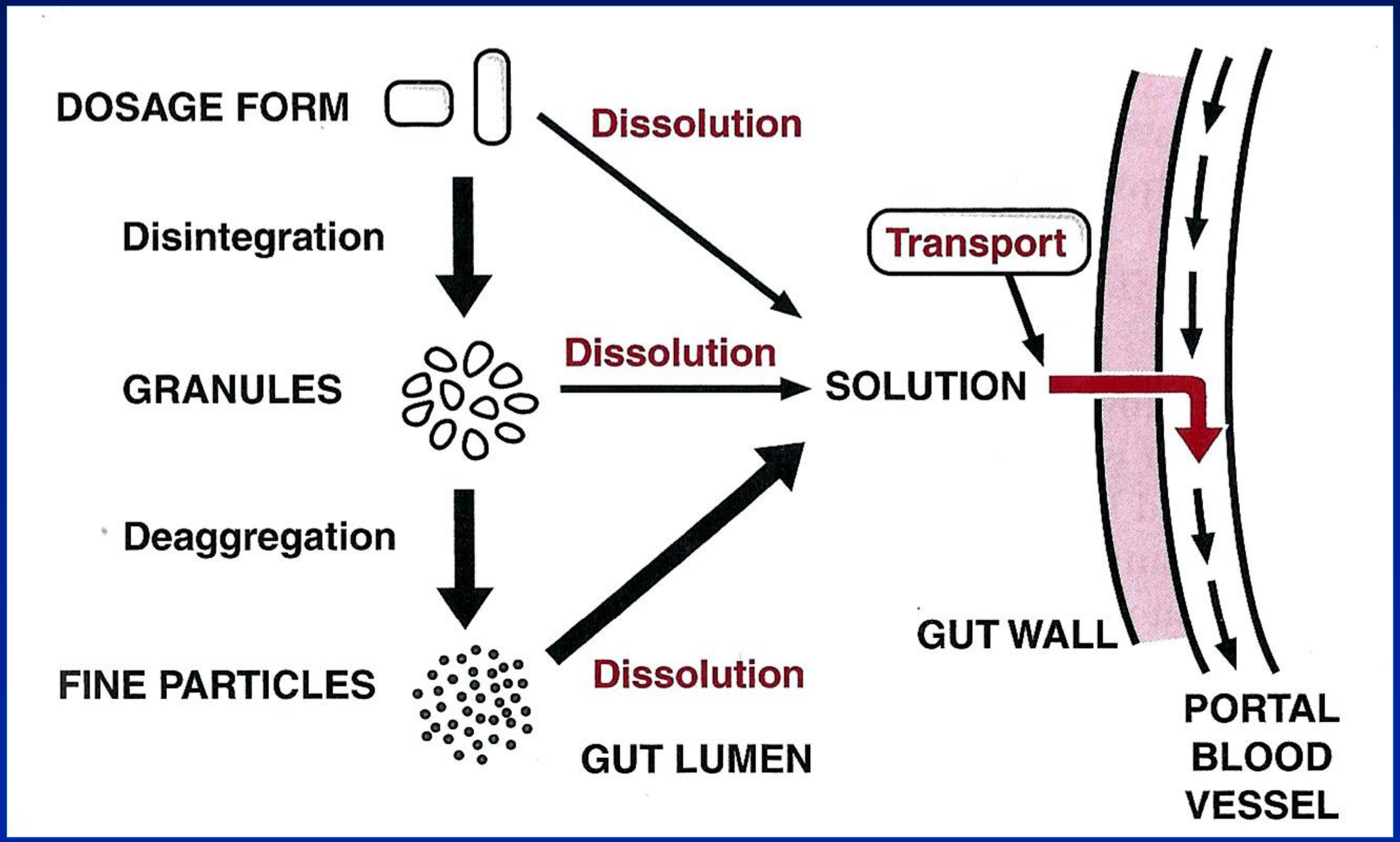
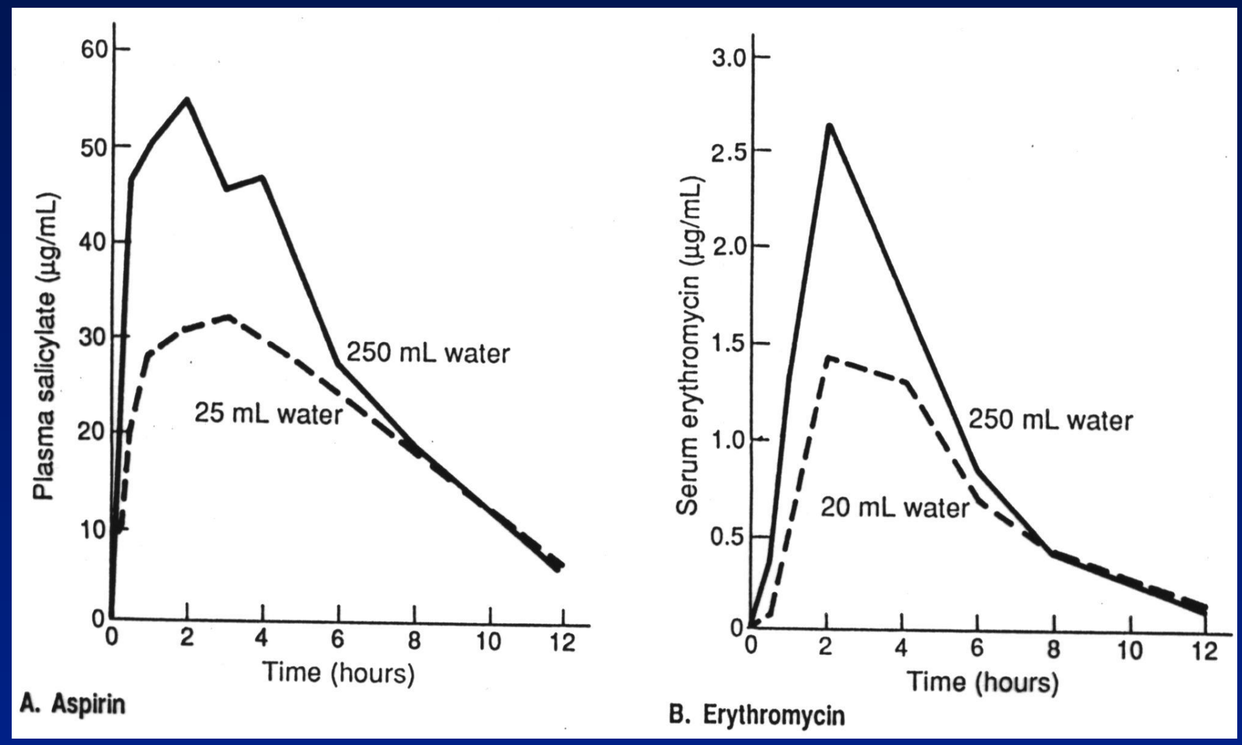
Absorção no trato gastrintestinal

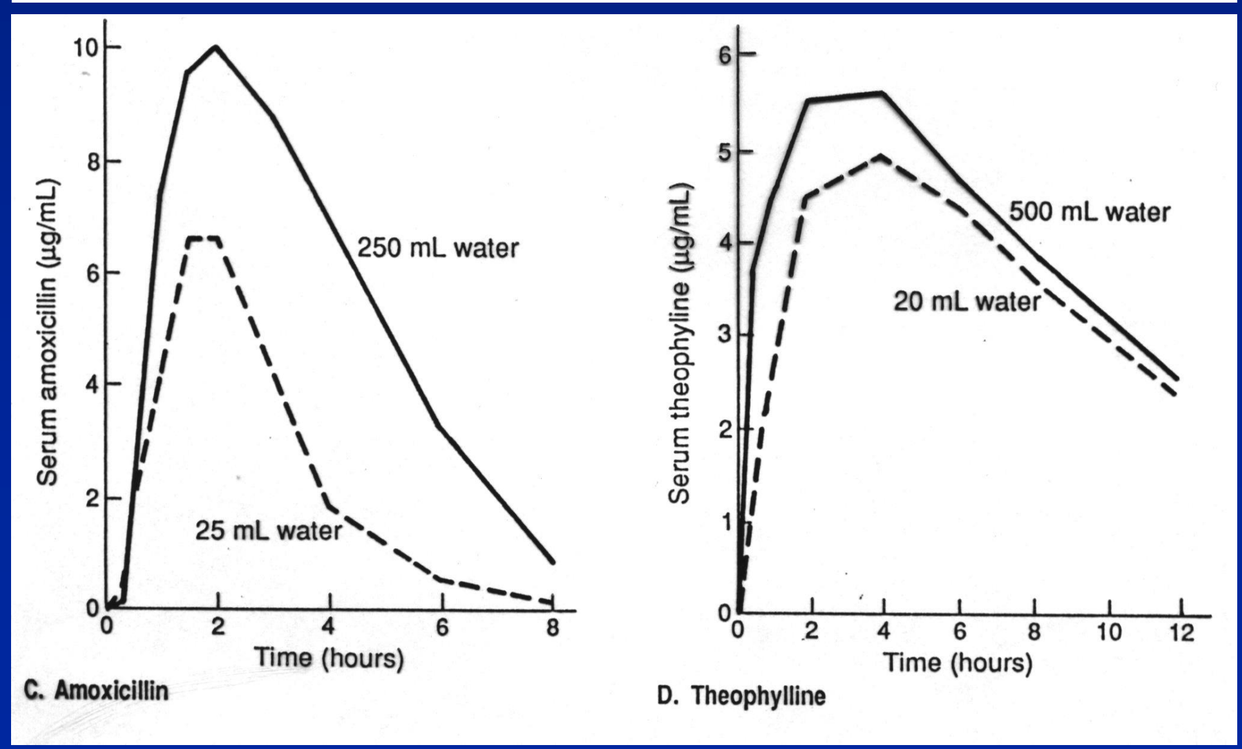
Solubilidade



Absorção no trato gastrintestinal

Influência do tempo de esvaziamento gástrico





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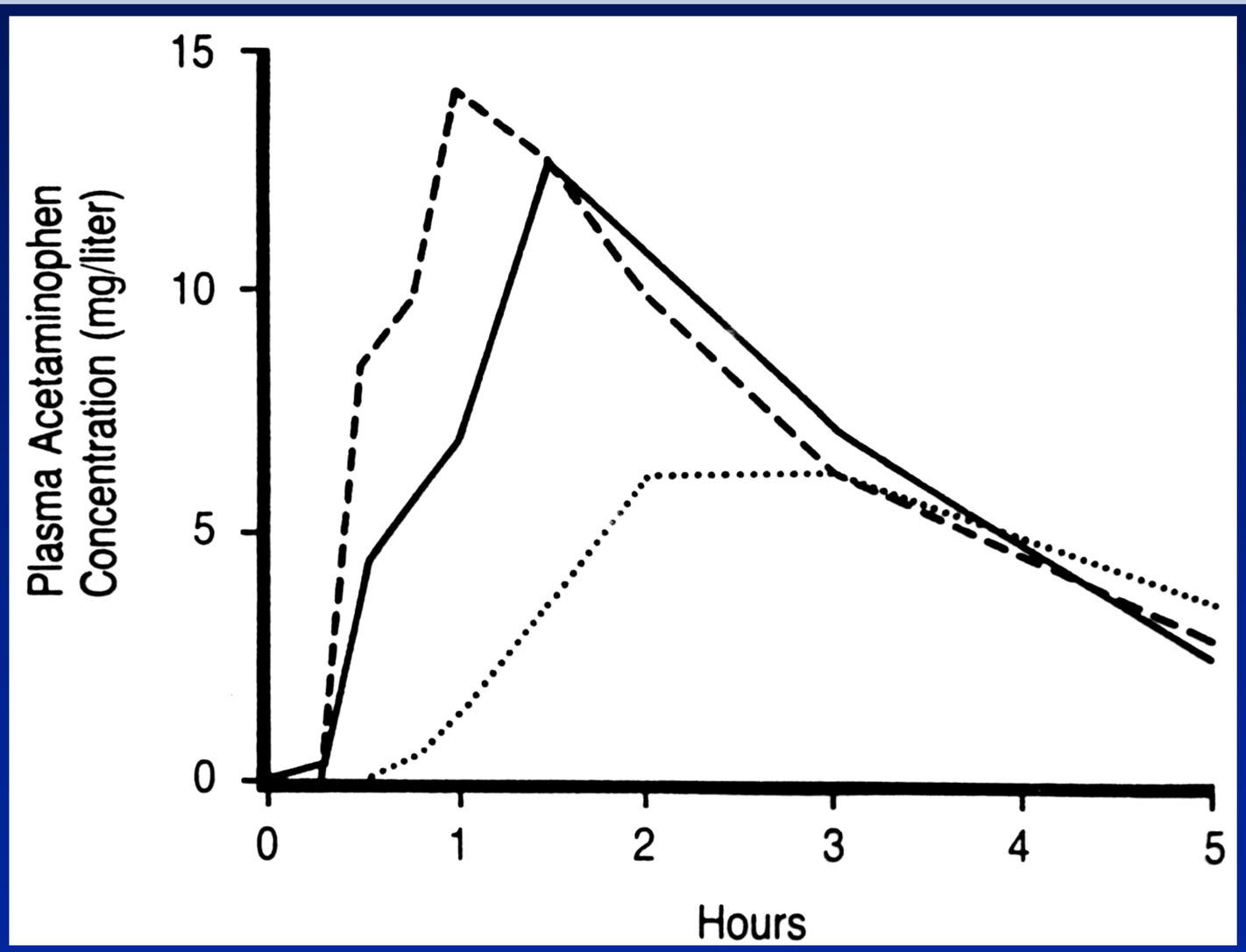
Absorção no trato gastrintestinal

Influência do tempo de esvaziamento gástrico



acetaminofeno

acetaminofeno + metoclopramida

acetaminofeno + propantelina

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Influência de alimentos na biodisponibilidade de fármacos

ANVISA. Resolução RE nº·1170 de 19 de abril de 2006

atualizada em 31 de julho de 2013

ALIMENTAÇÃO

Acarbose	Etionamida	Lercanidipine	Propafenona
Acitretina	Exemestano	Lovastatina	Ritonavir
Albendazol	Fenofibrato	Metformina	Rivastigmina
Axetil cefuroxima susp	Ganciclovir	Metformina + Pioglitazona	Rosiglitazona + Glimepirida
Biperideno	Glicosamina	Nelfinavir	Saquinavir
Bromocriptina	Glibenclamida + Metformina	Nitrendipino	Selegilina
Capecitabina	Hidroxicloroquina	Nitrofurantoína	Ticlopidina
Cetoconazol	Imatinib	Ornidazol	Trazodona
Cetoprofeno	Isotretinoína	Pentoxifilina	Valganciclovir
Diacereína	Itraconazol	Pinavério	Ziprasidona

ALIMENTAÇÃO e JEJUM

Alfuzosina	Ciclosporina	Pitavastatina	Tacrolimo
Amiodarona	Everolimo	Propiltiouracil	Tenofovir
Buspirona	Medroxiprogesterona	Sulpirida	

Influence of a mexican diet on the bioavailability of albendazole

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REFEIÇÃO:

- **2 OVOS FRITOS COM TOMATE, CEBOLA E CHILI;**
- **2 FATIAS DE BACON, 55g DE TORTILLAS COM TOMATE, CHILI E CREME**
- **1 COPO DE LEITE (240mL)**

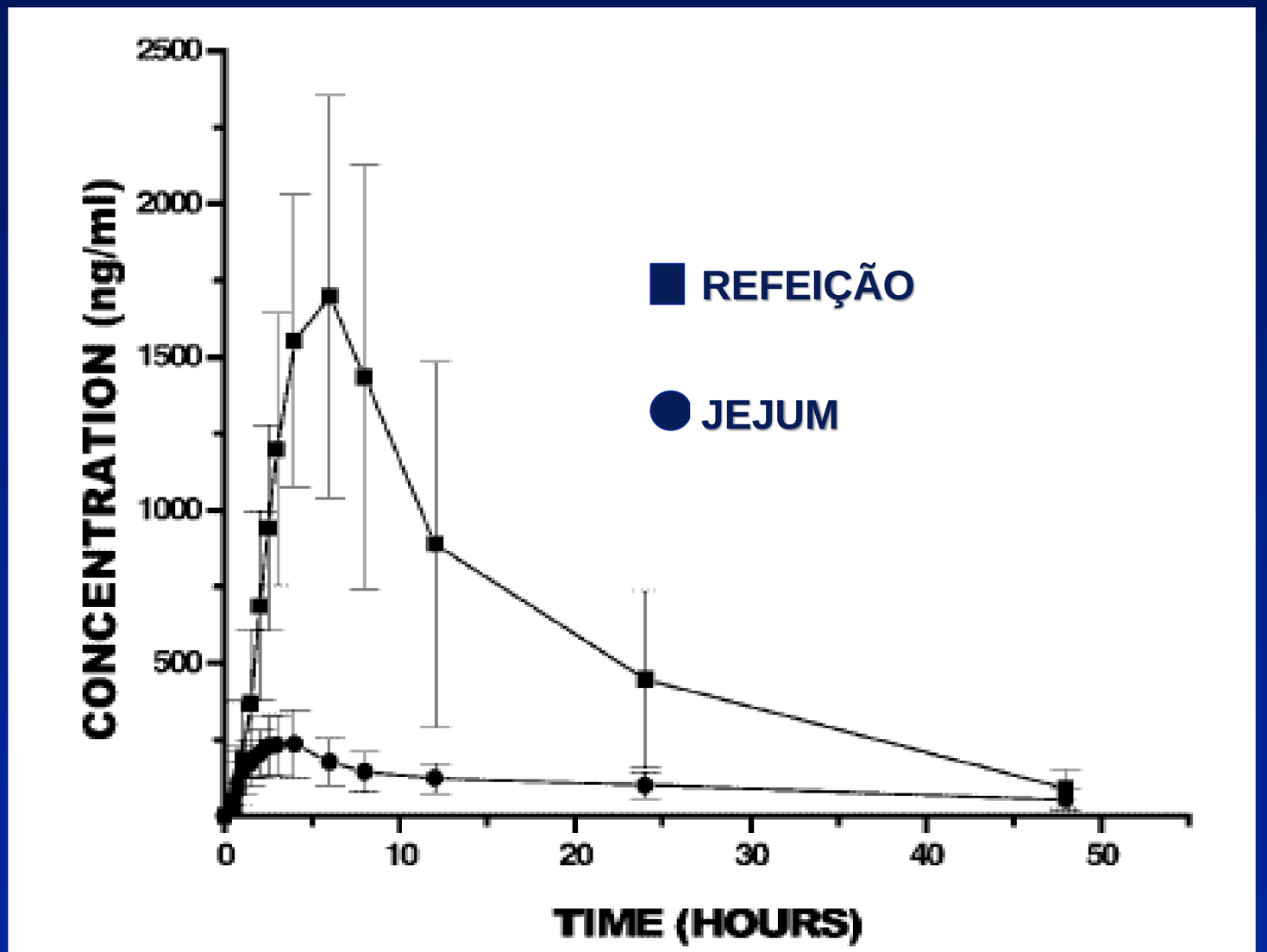

Fig. 1. Mean plasma concentration of albendazole sulfoxide after a single oral dose of 800 mg of albendazole in fasting state (●) and after a fatty meal (■).

Basic & Clinical Pharmacology & Toxicology, v. 97, p. 122-124, 2005.

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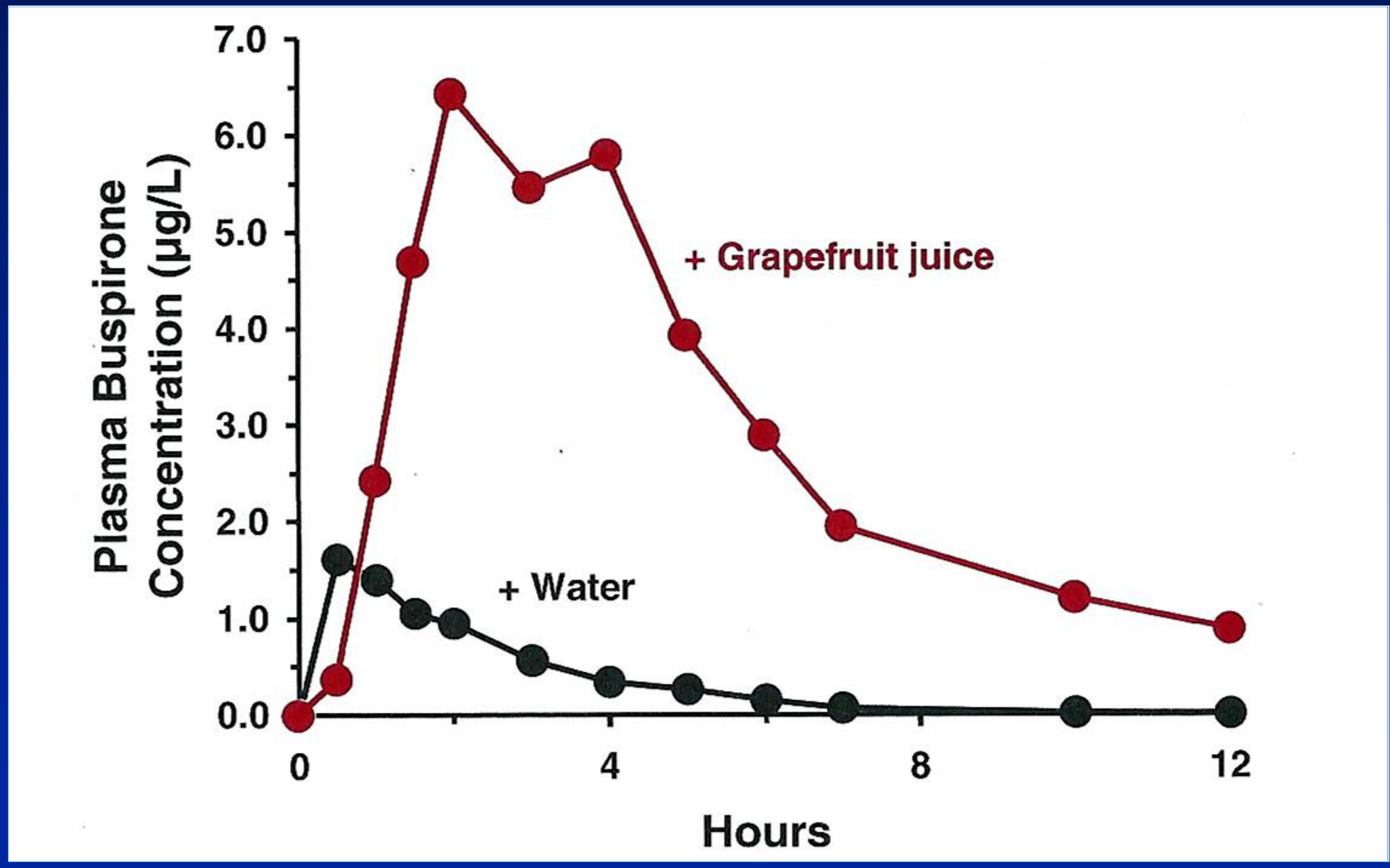
Dose Sinvastatin with and without grapefruit Juice



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Mean (±SD) Peak Concentration (C*max*) and Total *AUC* after a Single 40-mg Dose Sinvastatin with and without grapefruit Juice (GFJ)

Measure	Control (Water Only)	Concurrent Administration of GFJ	Time After Discontinuing GFJ		
			24 Hr	3 Days	7 Days
Cmax (µg/L)	9.3 ±4.5 (100)*	112 ±44.8 (1200)*	22.0 ±9.7 (237)*	14.2 ±4.6 (153)*	12.4 ±7.2 (133)*
AUC (µg-hr/L)	28.9 ±14.5 (100)*	390 ±126 (1350)*	59.4 ±27.6 (206)*	39.6 ±11.9 (137)*	30.6 ±15.8 (106)*

*Percent of the control value

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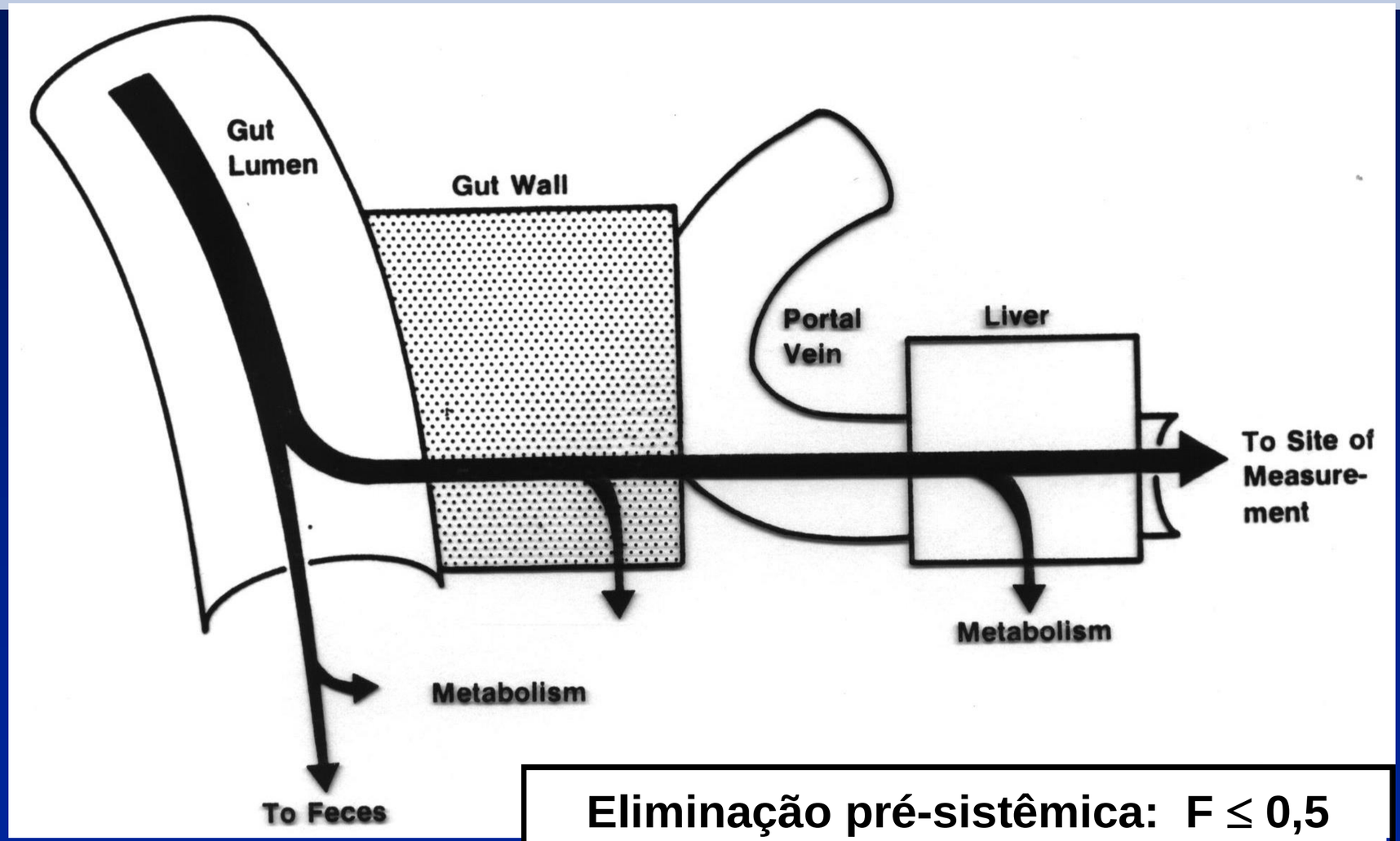
Eliminação pré-sistêmica



Eliminação pré-sistêmica: F ≤ 0,5	
Amitriptilina	Nifedipina
Lidocaina	Propranolol
Morfina	5-fluorouracila

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Amount of Drug Absorbed or Reaching Systemic Circulation

(F) . (Dose)

$$F = F_a . F_G . F_H$$

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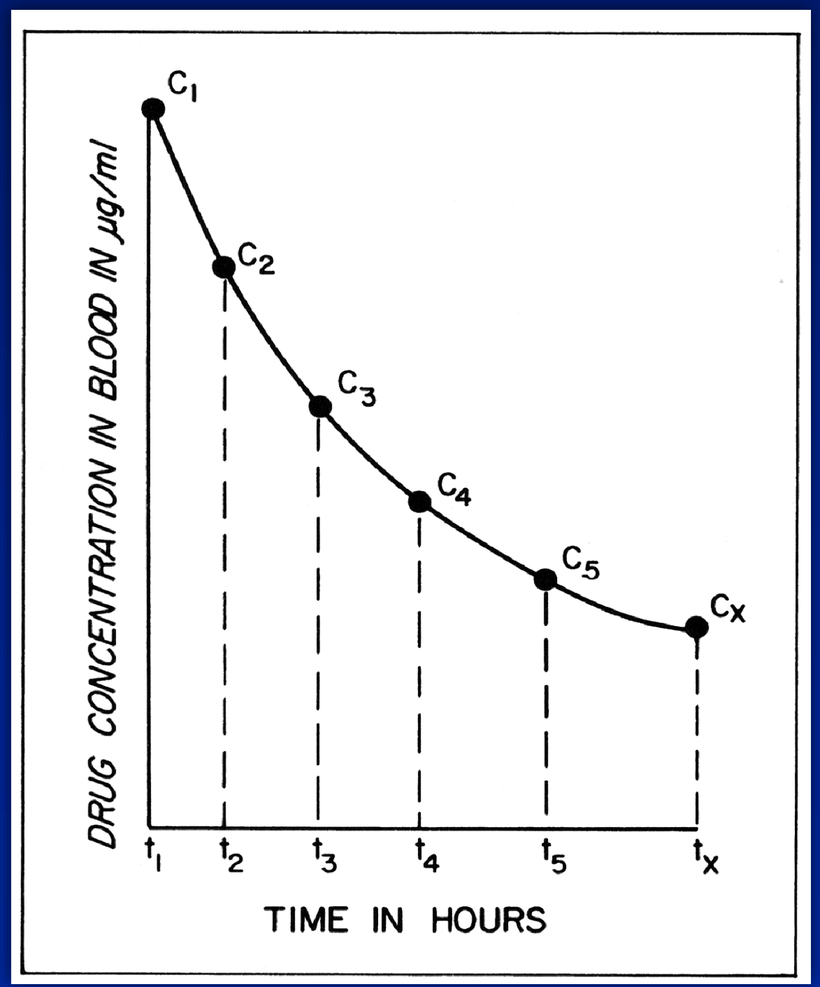
Uses of Bioavailability

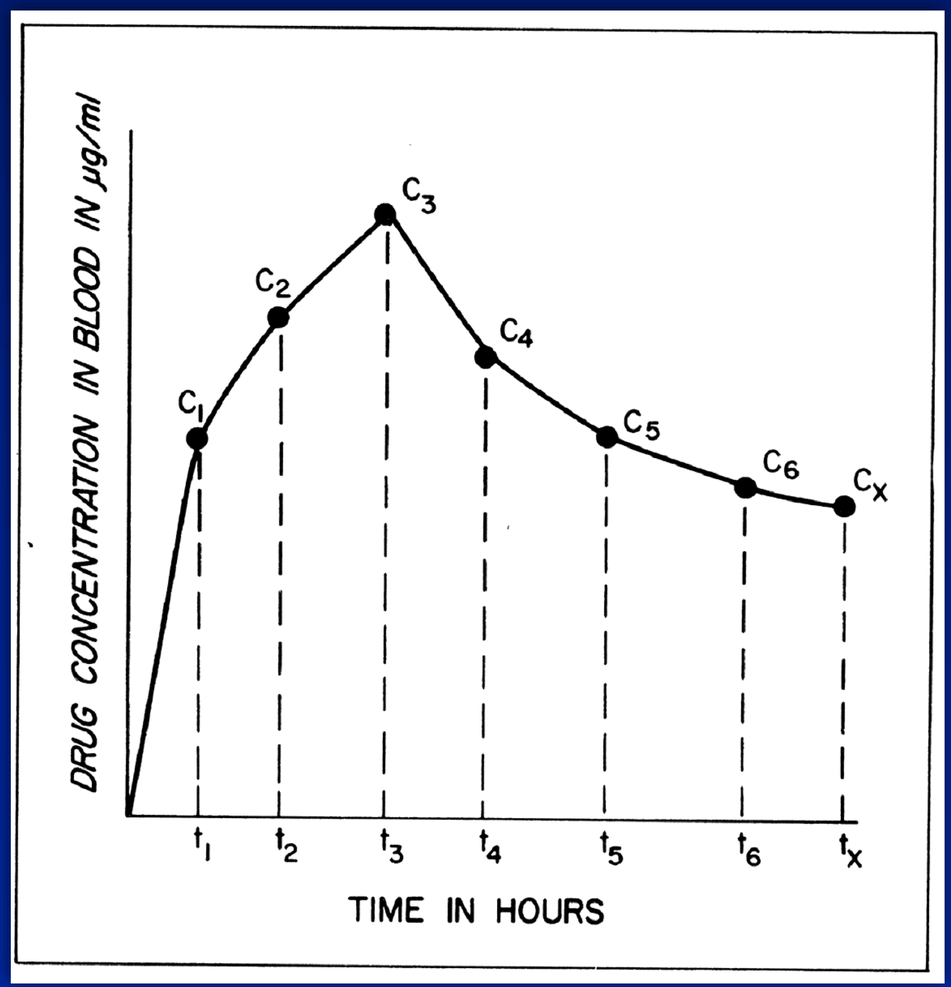
Bioavailability is a key determinant in the difference in dose sizes between intravenous and oral preparations

Area under the blood level-time curve

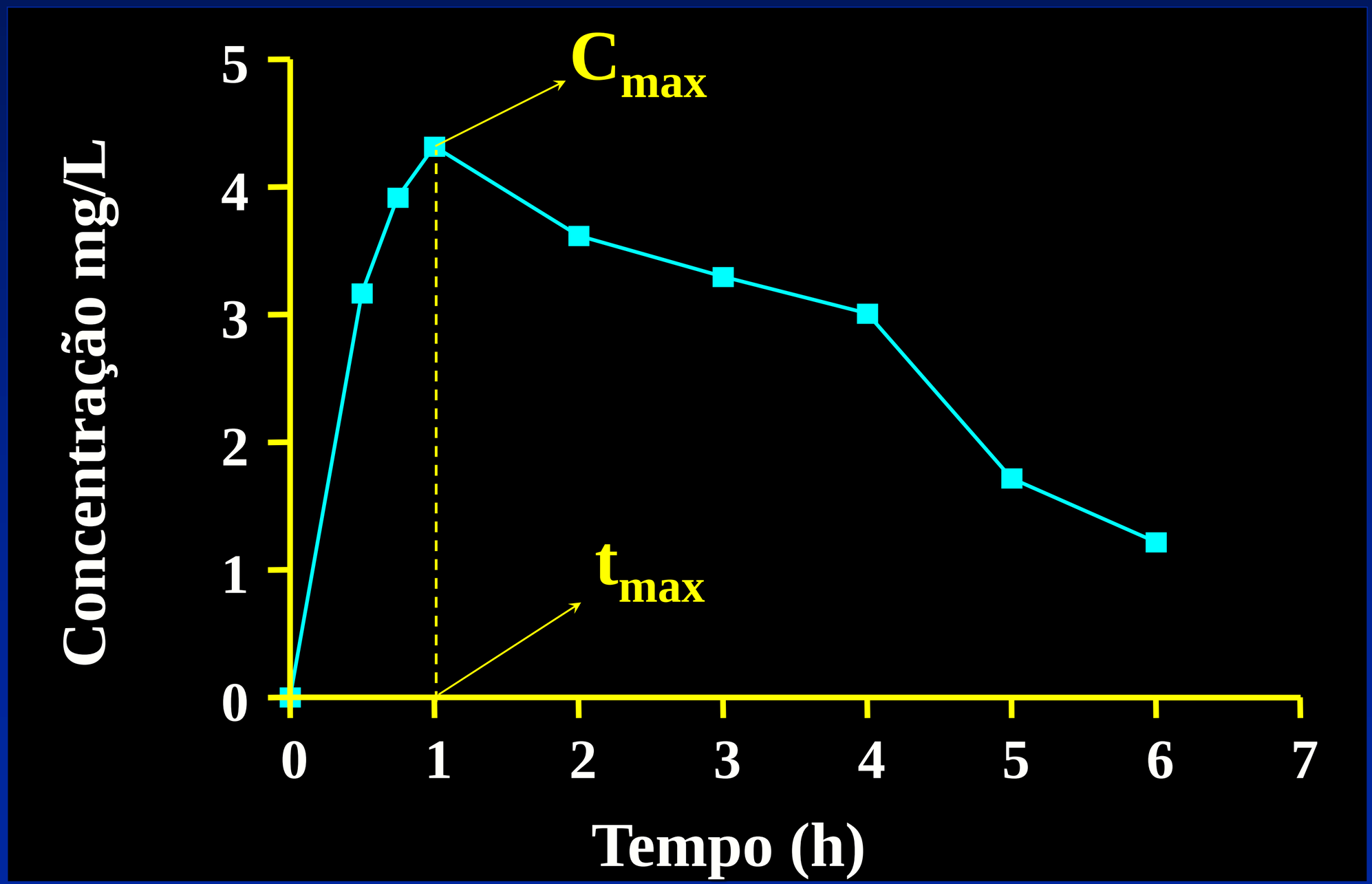
Intravascular route



Extravascular route



Administração Oral
Concentração vs Tempo



Como calcular a biodisponibilidade (F)?

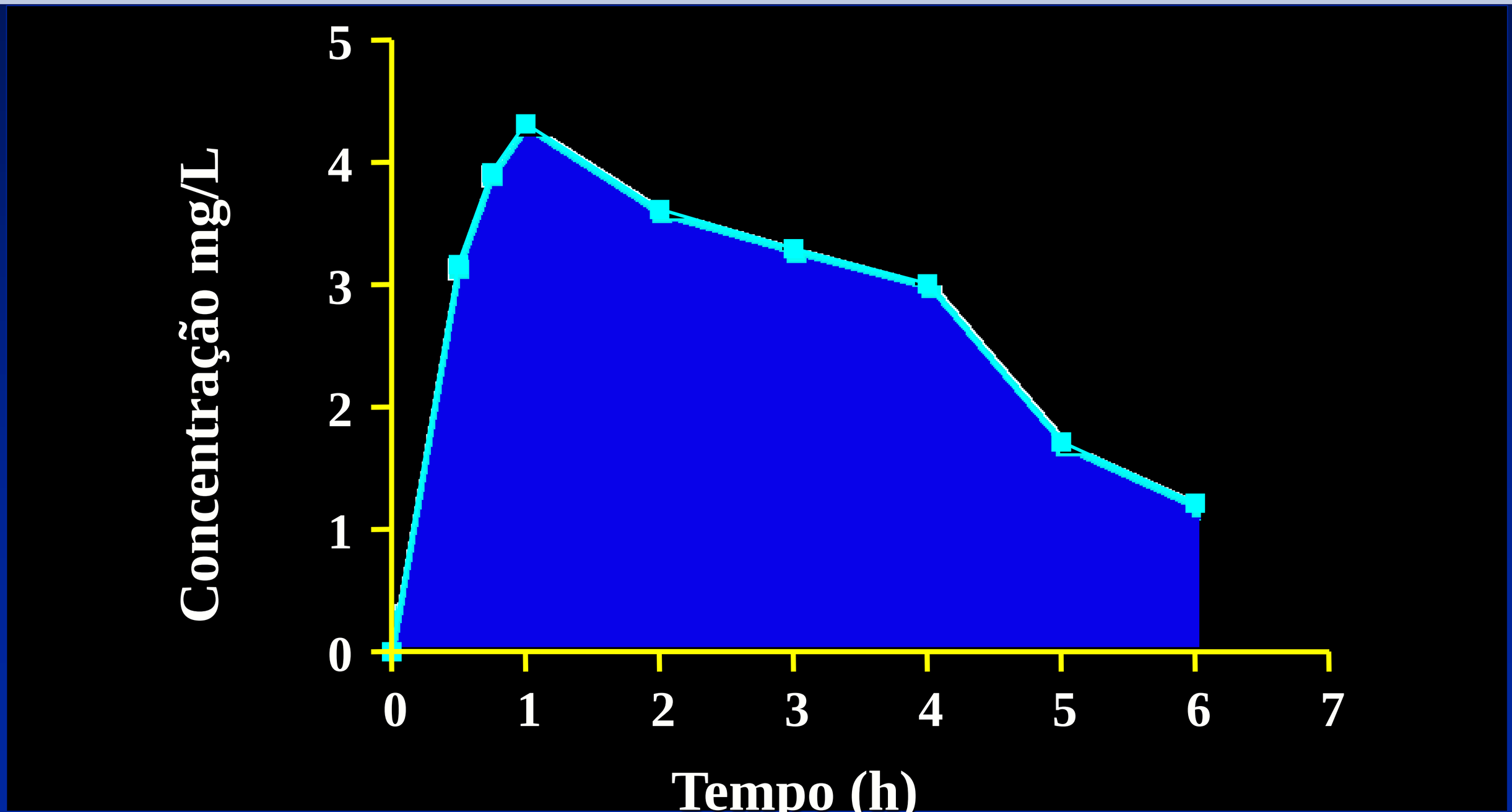
$$F = \frac{AUC\ ev\ .\ dose\ iv}{AUC\ iv\ .\ dose\ ev}$$

Cálculo de AUC

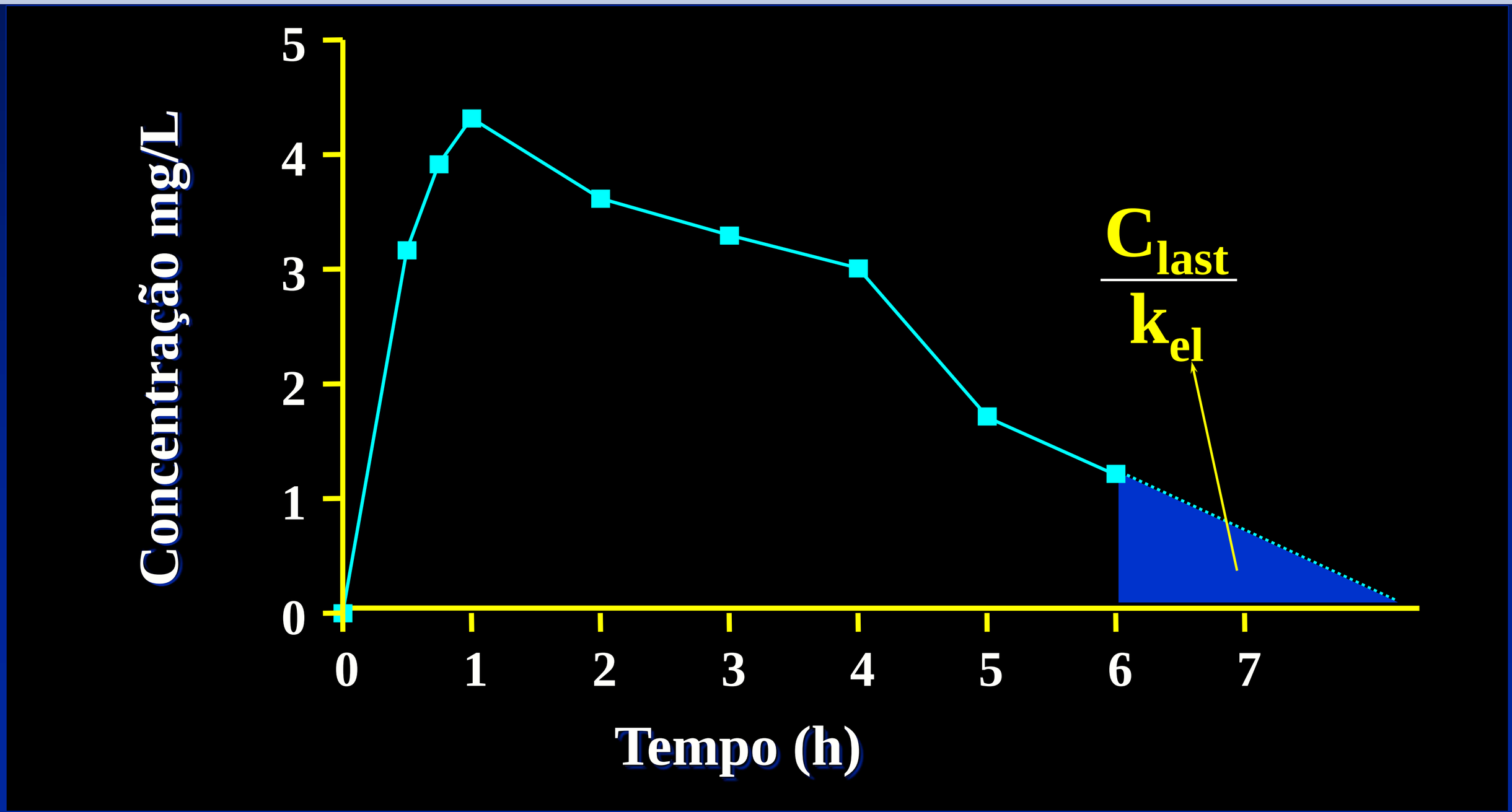
Área do triângulo = $\frac{\text{base x altura}}{2}$

Área do trapézio = $\frac{\text{altura menor + altura maior}}{2}$ x base

Area sob a curva $AUC_{0\text{-}6h}$



Area extrapolada até o infinito (∞)



Cálculo de AUC

$$\text{Área do triângulo} = \frac{\text{base x altura}}{2}$$

$$\text{Área do trapézio} = \frac{\text{altura menor + altura maior}}{2} \text{ x base}$$

$$\text{Área extrapolada para o infinito} = \frac{\text{Clast}}{\text{kel}}$$

Plasma protein binding

Plasma protein binding indicates how much of the total amount of drug in plasma is bound to plasma proteins

Important determinant of drug action

Plasma Protein Concentration

Protein	Normal Concentration	Type of Drugs Bound	Example
Albumin	3.5 – 4.5 g/L	Anionic Cationic	Phenytoin
Alpha-1-acid glycoprotein	0.4 – 1.0 g/L	Cationic	Lidocaine
Lipoproteins	Variable	Lipophilic	Cyclosporine

Protein Binding

Drug	Binding (%)
Ampicilin	18
Chloranphenicol	53
Digoxin	25
Gentamicin	< 10
Lidocaine	70
Phenitoin	89
Vancomicin	30

Plasma Concentration Changes

Condition	Albumin	Alpha-1-Acid glycoprotein
Renal failure	↓	↑
Hepatic cirrhosis	↓	—
Arthritis	—	↑
Surgery	—	↑
Burns	↓	—
Myocardial infarction	—	↑
Stress / trauma	↓	↑
Pregnancy	↓	—

— = no data available; ↓ = decreased; ↑ = increased

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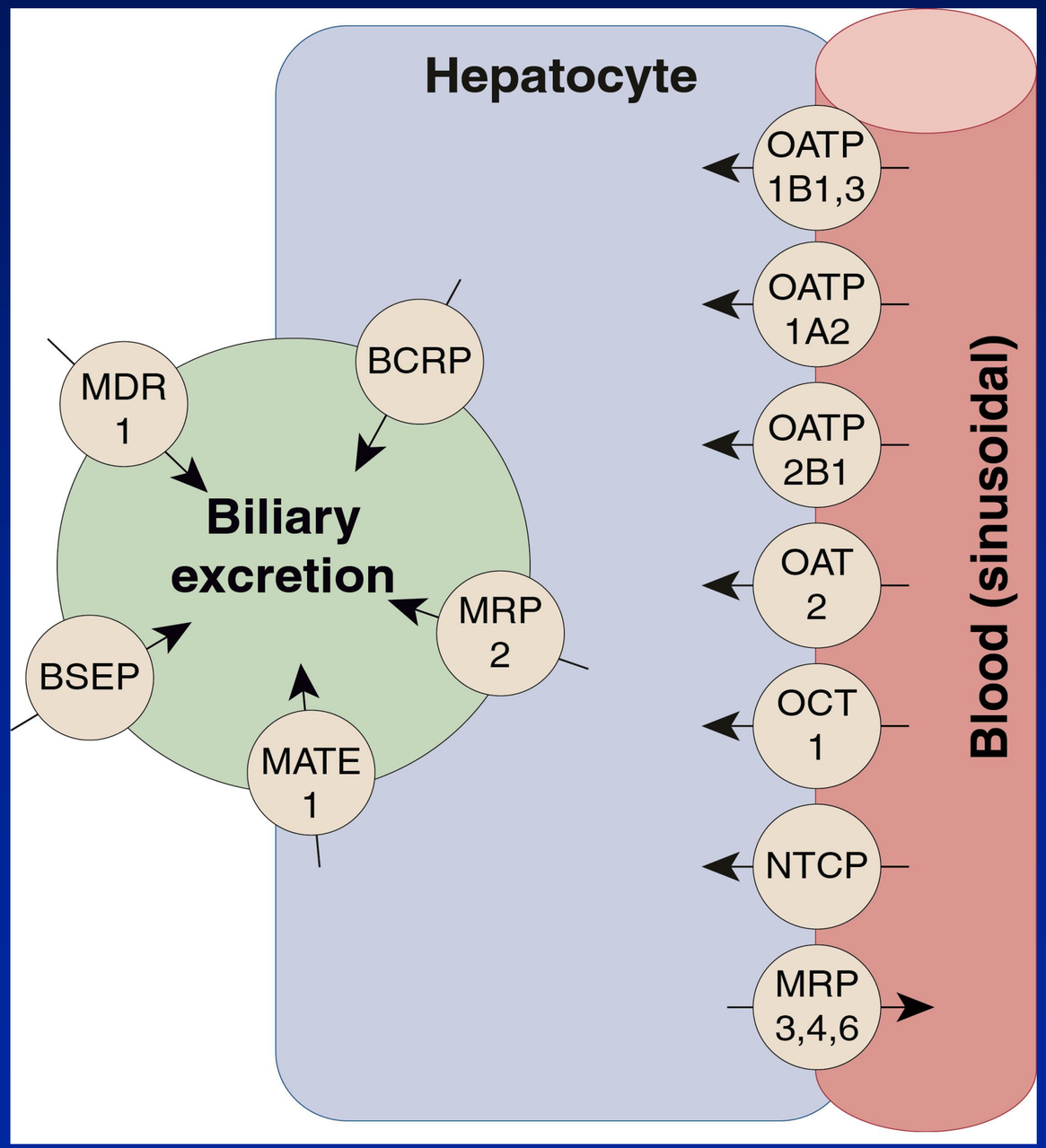
XENOBIOTIC TRANSPORTING SYSTEMS PRESENT IN THE LIVER



OATP Organic anion transporting peptides

OAT Organic-anion transporter

OCT Organic-cation transporter

P-gp P-glycoprotein

BCRP Breast cancer resistance protein

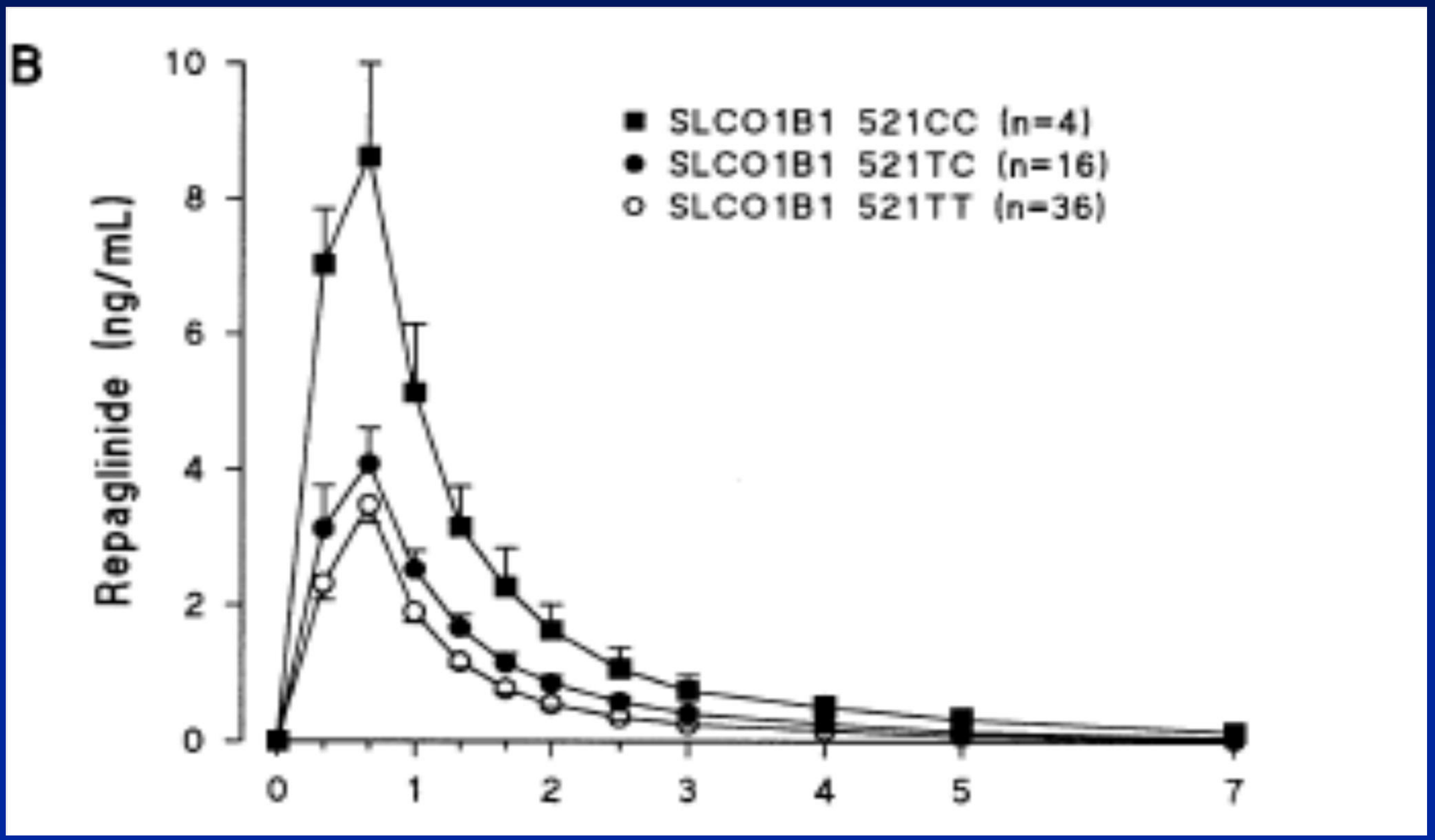
MRP2 Multiresistant drug protein

BSEP Bile salt excretory protein

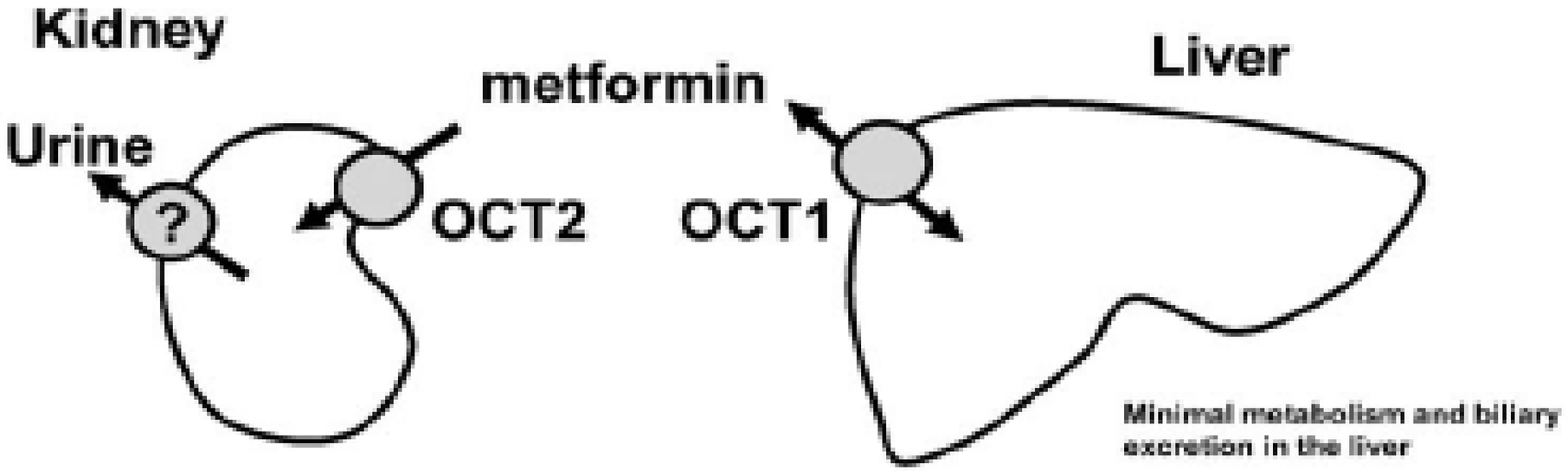
HEPATIC TRANSPORTERS AND DRUG DISPOSITION

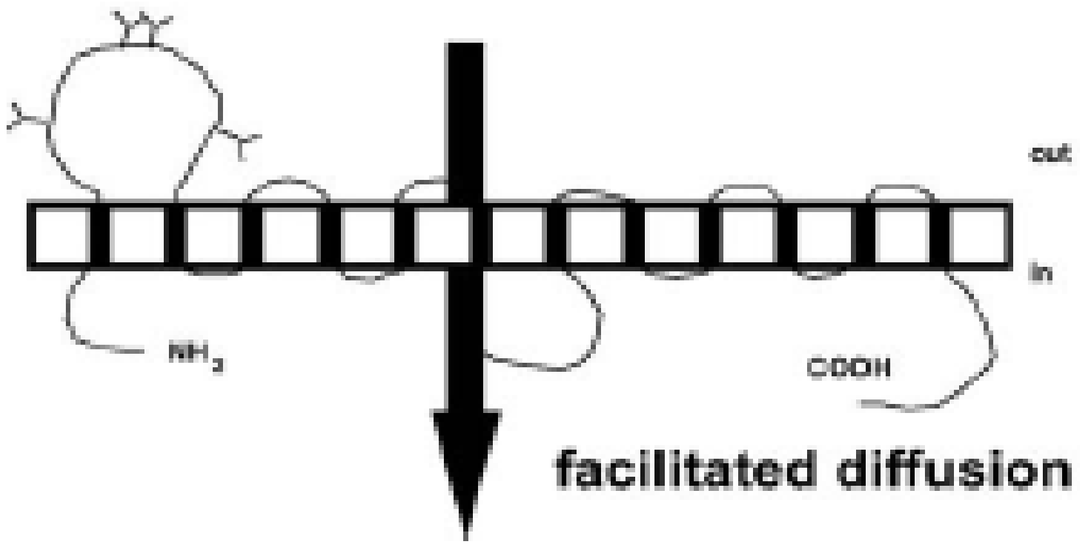
	Uptake Transporters	Metabolizing Enzymes	Bile Canalicular Transporters
Atorvastatin	OATP1B1	CYP3A4	———
Cerivastatin	OATP1B1	CYP3A4 CYP2C8	———
Pravastatin	OATP1B1 OATP2B1	———	MRP2 MDR1
Rosuvastatin	OATP1B1 OATP1B3 OATP2B1	———	MRP2 MDR1

Polymorphic OATP 1B1 is a major determinant of repaglinide pharmacokinetics: CYP2C8 and CYP3A



MECHANISMS OF TISSUE DISTRIBUTION OF METFORMIN



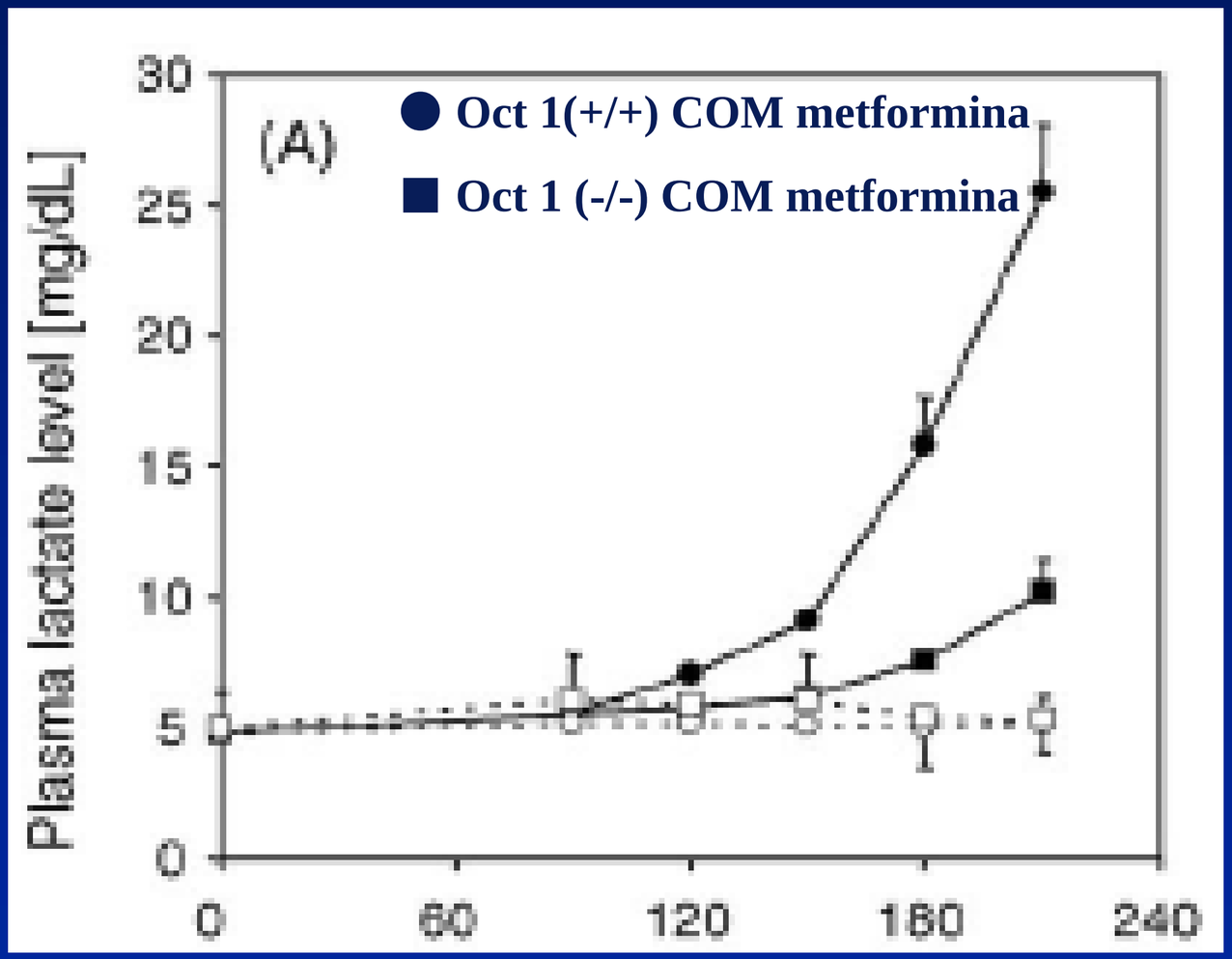


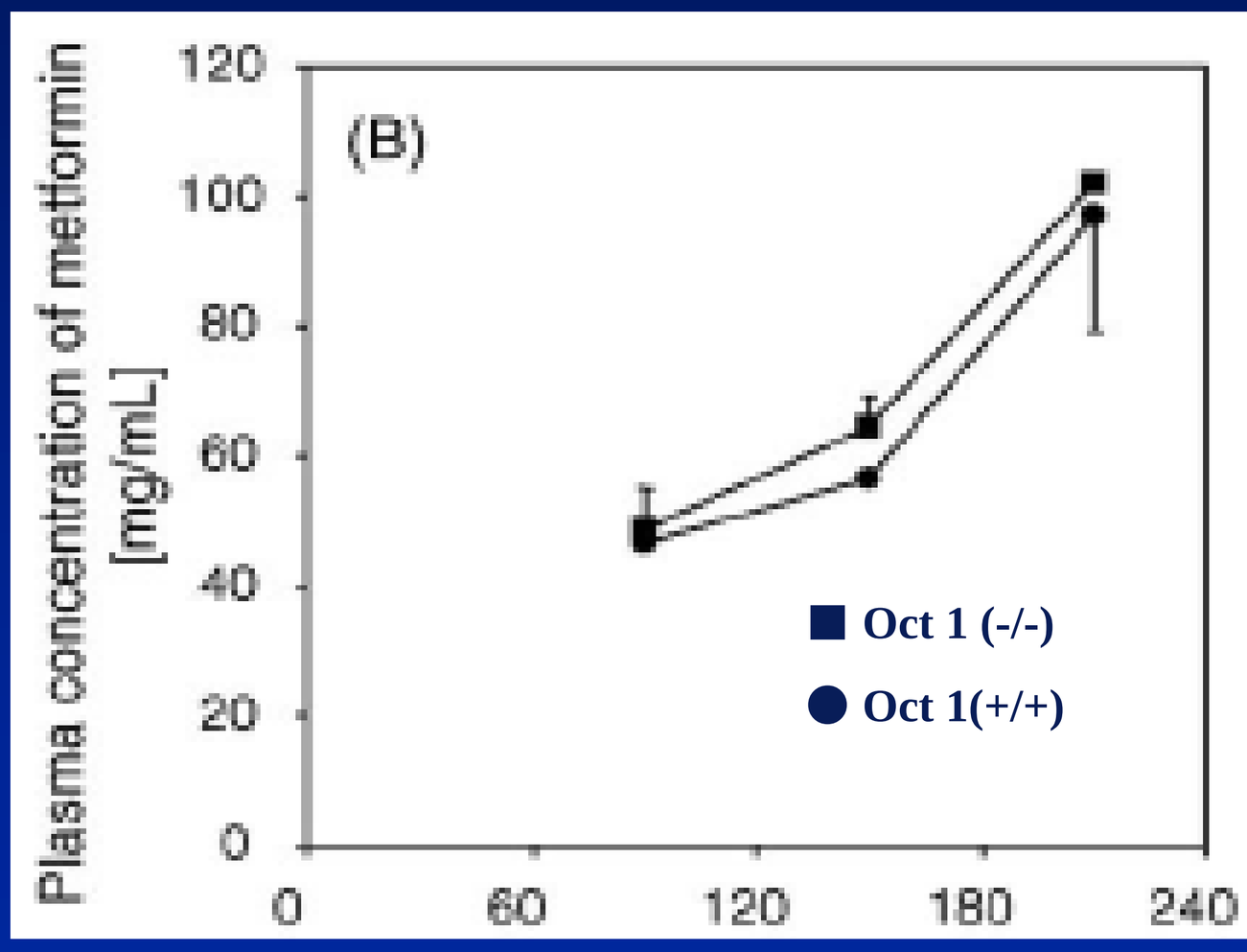
Organic cation transporter
(OCT/*SLC22A1~3*)

Tissue distiribution :
OCT1 liver （sinusoidal membrane）
OCT2 kidney (basolateral membrane)

Mol. Pharmacol., v. 63, p. 844-848, 2003.

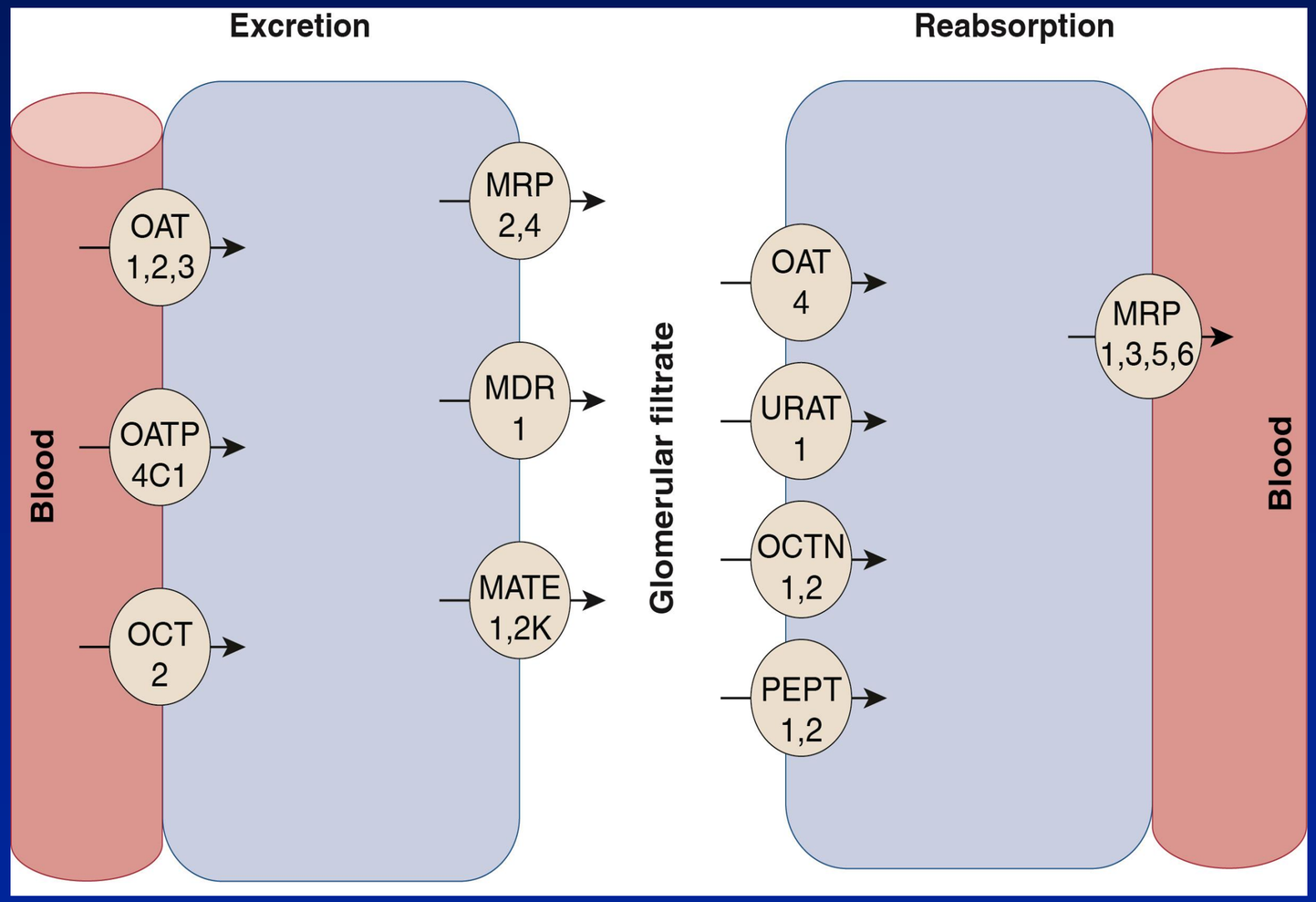
MECHANISMS OF TISSUE DISTRIBUTION OF METFORMIN





Mol. Pharmacol., v. 63, p. 844-848, 2003.

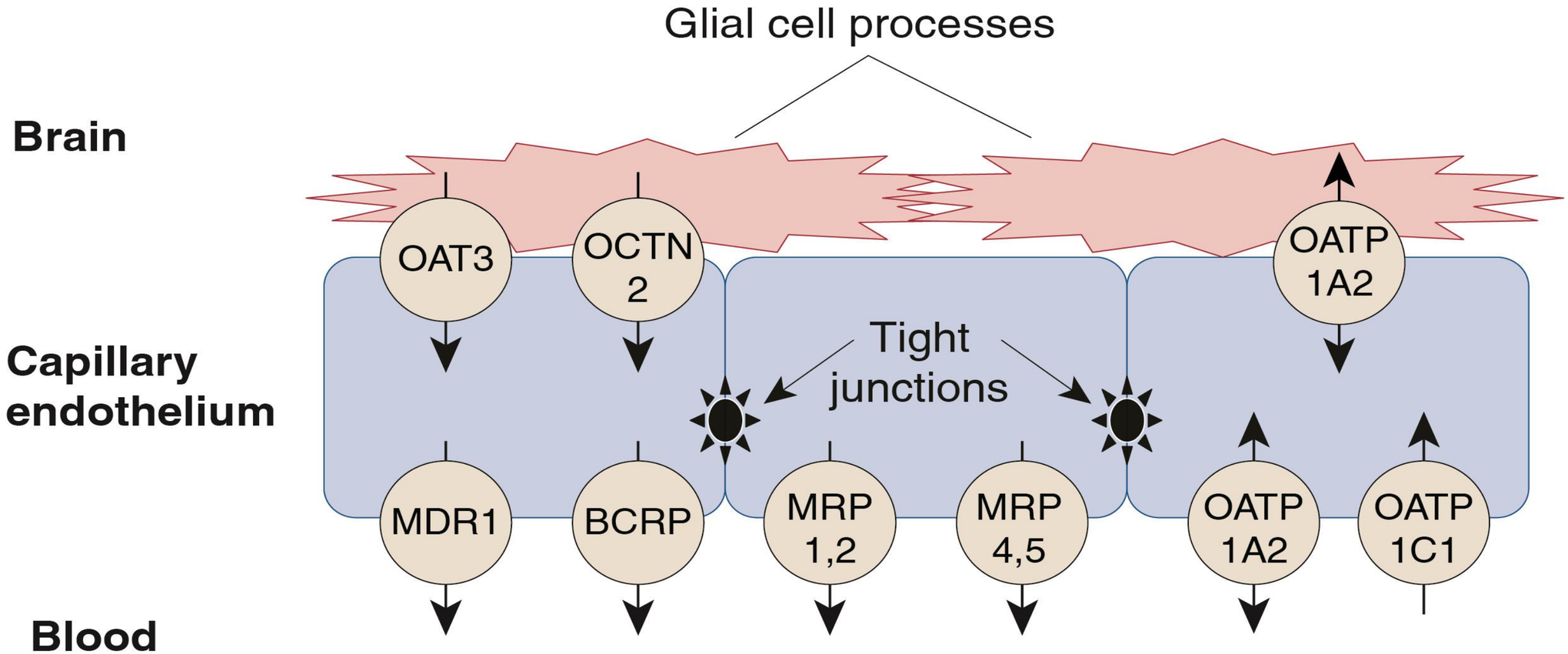
XENOBIOTIC TRANSPORT SYSTEMS IN THE PROXIMAL TUBULE OF THE KIDNEY



OAT
Organic-anion transporter
OCT
Organic-cation transporter
OATP
Organic-anion transporting peptides

MRP
Multiresistant drug protein
MDR1
Multidrug resistant protein
MATE
Multidrug and toxin extrusion transporter

XENOBIOTIC TRANSPORTING SYSTEMS THAT CONTRIBUTE TO THE BLOOD-BRAIN BARRIER



P-gp P-glycoprotein (MDR1)

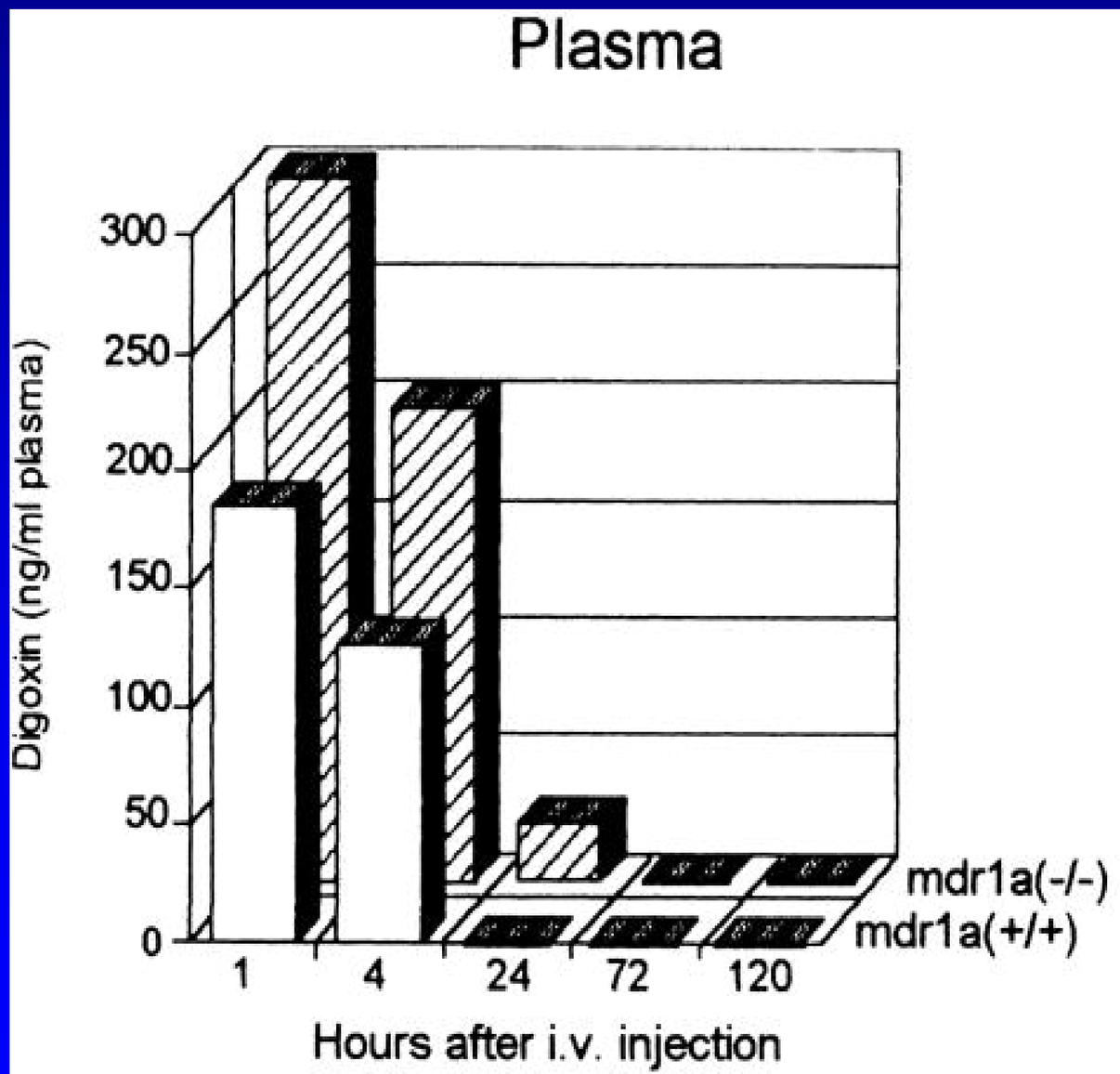
BCRP Breast cancer resistance protein

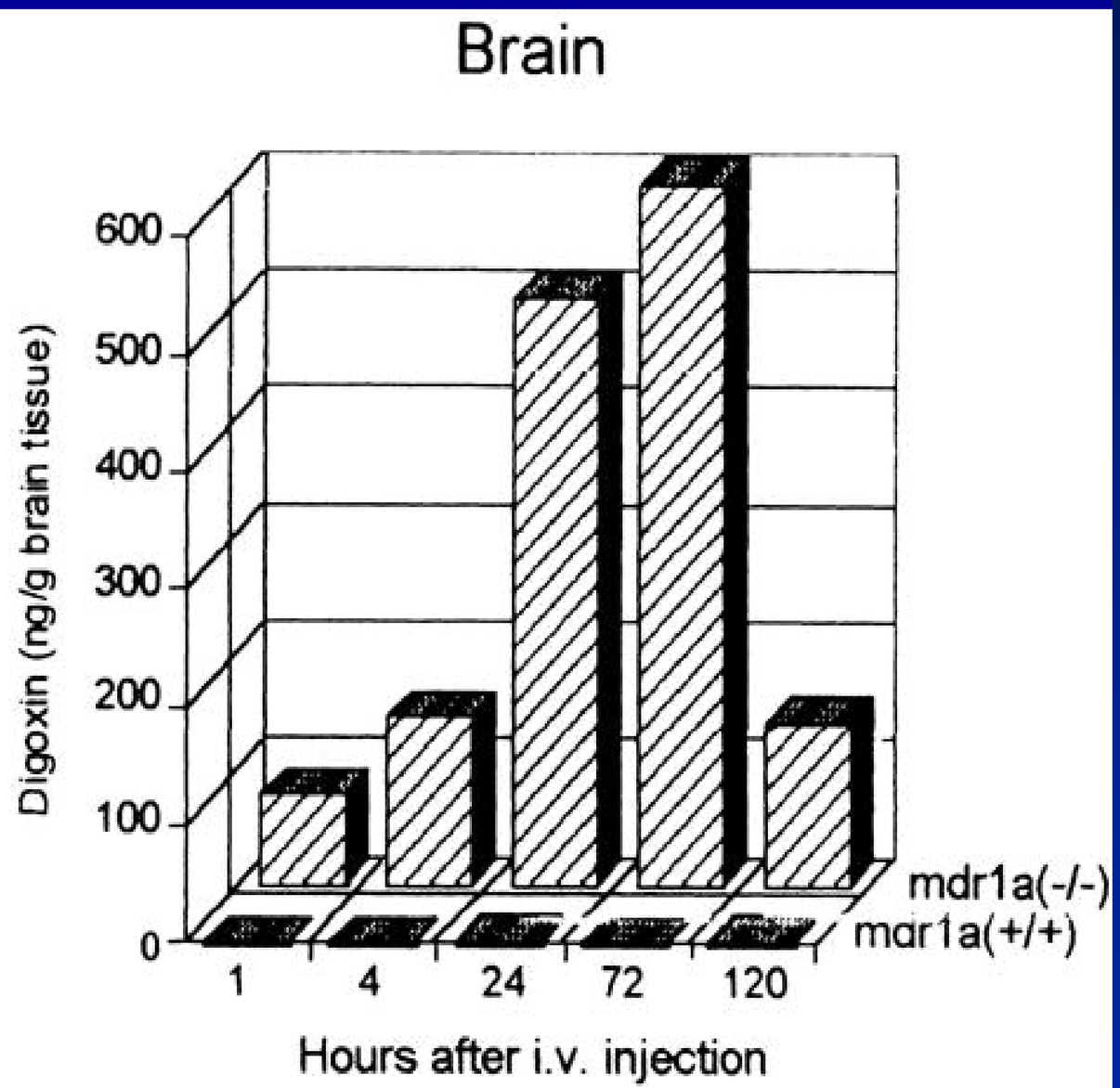
MRP1 Multidrug resistance associated protein 1

MRP2 Multidrug resistance associated protein 2

OATP Organic anion transporting polypeptide

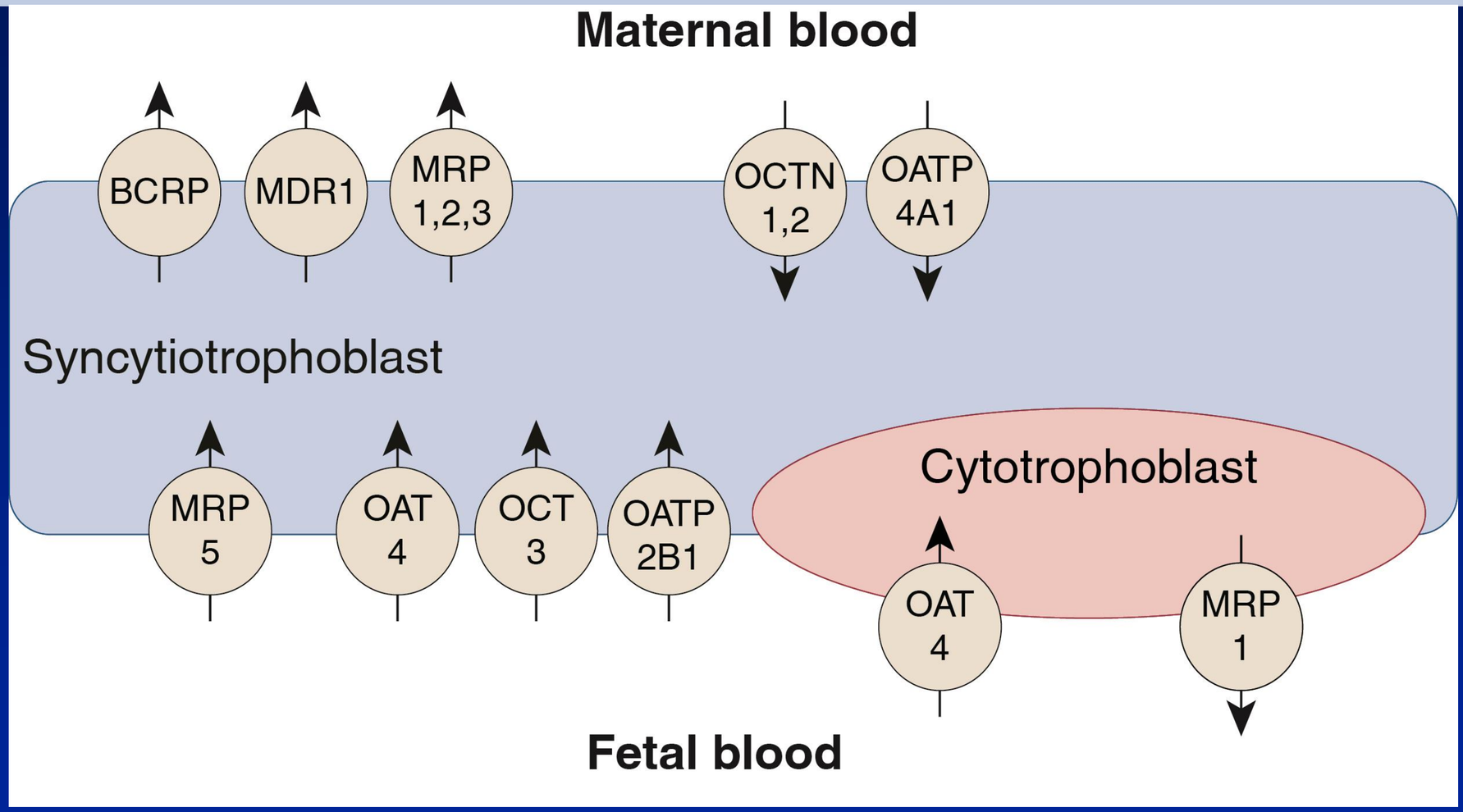
Levels of digoxin in plasma and brain of wild-type mdr1 a(+/+) and mdr1 a(-/-) mice at various time points after a single digoxin





Ther. Drug Monit., v.22, p.137-140, 2000

TRANSPORT SYSTEMS THAT CONTRIBUTE TO THE BARRIER FUNCTION OF THE PLACENTA



P-gp P-glycoprotein

MRP2 Multidrug resistance associated protein 2

BCRP Breast cancer resistance protein

MRP1 Multidrug resistance associated protein 1

P-gp in the placenta: substrates and inhibitors

Clinically significant P-gp substrates

Cytotoxic drugs
Vinca alcaloids, taxanes, antracyclines, actinomycin D, epipodophyllotoxins

HIV protease inhibitors
amprenavir, saquinavir, ritonavir, nelfinavir, indinavir

Antibiotics
erythromycin, levofloxacin, gramicidin D

Cardiac drugs
digoxin, quinidine, carvedilol, celiprolol, talinolol

Antiemetics
domperidone, ondansetrone

Others
ivermectine, colchicine, losartan, phenytoin
morphine

P-gp inhibitors

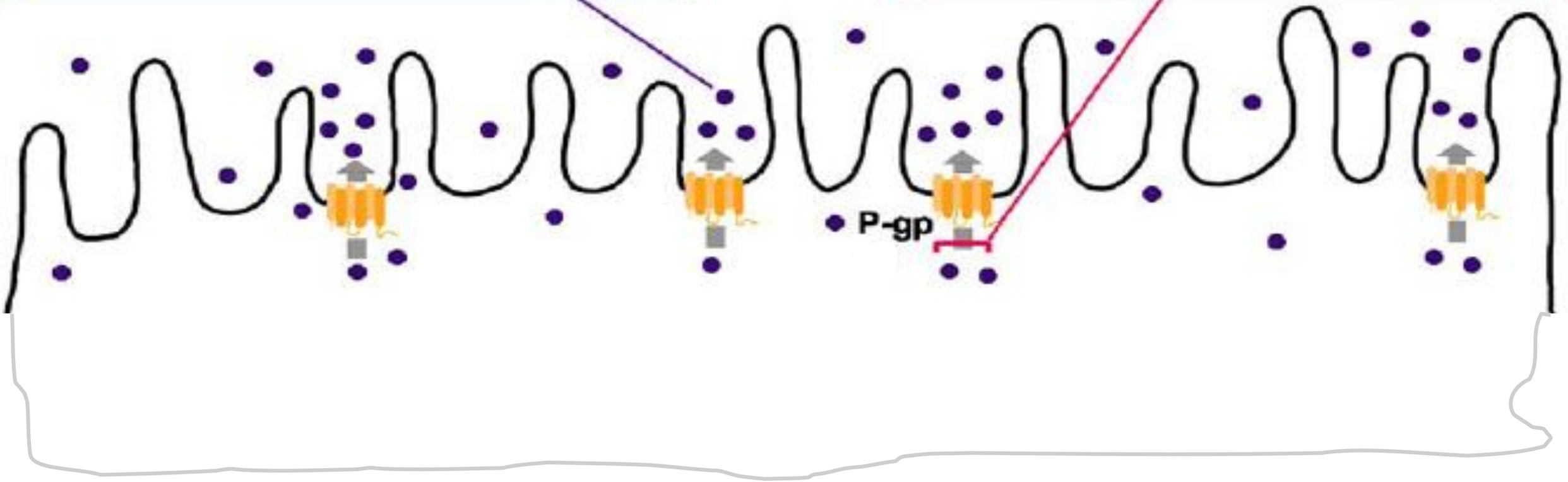
First generation chemosensitizers
verapamil,quinidine
cyclosporine A
progesterone, tamoxifen
trifluoperazine, trifluopromazine,flupentixol

Second generation chemosensitizers
dexverapamil, PSC833
biricodar (VX-710), GF120918, MS-209

Third generation chemosensitizers
LY335979, OC144093, XR9576

Herbal extracts
St John's wort, Rosemary, Rhei Rhizoma, Ephedrae herba

Antibodies
MRK16



Volume de distribuição (Vd)

Vd é uma constante de proporcionalidade que relaciona a quantidade do fármaco no sistema biológico com a concentração no plasma

$$Vd = \frac{\text{Dose}}{\text{Cp no tempo zero}}$$

Unidade	volume **(mL, L)**

Volume de distribuição (Vd)

$$Vd = \frac{\text{Dose (iv)}}{C_0}$$

$$Vd = \frac{\text{Dose} \cdot F}{\text{AUC} \cdot \text{Kel}}$$

Volume de distribuição

Droga	L/70kg
Quinacrina	40000
Cloroquina	20000
Amiodarona	5000
Clopromazina	2000
Minoxidil	1000
Digoxina	500
Morfina	200
Ampicilina	20
Ibuprofeno	10
Eritropoetina	5

Volume of distribution

1

It can be used to compute a loading dose

$$D_L = Vd \times C_{ss,\ target}$$

Volume of distribution

It can be used to calculate the amount of drug in the body at any given time

$$\text{Amount in the body} = Vd \times C_{observed}$$

Volume of distribution

It can be used to estimate the feasibility of using hemoperfusion or dialysis for drug removal in cases of drug overdoses

> Vd < efficient any drug removal

Uptake transporter-based interactions at the liver

HEPATIC INTERACTION			
Drug	**Interaction**	**Mechanism**	**V**
Atorvastatin	Rifampin	Inhibition of OATP1B1 uptake	↓ 94.3% (V_{ss}/F)
Cerivastatin	Cyclosporine	Inhibition of OATP1B1 uptake	↓ 66.7% (V_1/F)
Glyburide	Rifampin	Reduced OATP2B1 uptake	↓ 67.4% (V_{ss}/F)
Metformin	OCT1 reduced function allele	Reduced OCT1 uptake	↓ 53.9% (V_{area}/F)
Repaglinide	Cyclosporine	Inhibition of OATP1B1 uptake	↓ 59.0% (V_{area}/F)
Rosuvastatin	Cyclosporine	Inhibition of OATP1B1 uptake	↓ 90.6% (V_{area}/F)
Rosuvastatin	Gemfibrozil	Inhibition of OATP1B1 uptake	↓ 27.5% (V_{area}/F)
Rosuvastatin	OATP1B1 reduced function allele	Reduced OATP1B1 uptake	↓ 50.9% (V_{area}/F)

EFFECT OF CHANGE IN TRANSPORTER FUNCTION ON THE DISTRIBUTION VOLUME

	(ml/kg)	CONTROL	+RIFAMPIN	% DECREASE
DIGOXIN (Oatp1a4)	V_i	933	454	51.2
	V_{ss}	7140	1640	77.1
	V_{area}	7360	1790	75.7
	(L/kg)	**CONTROL**	**+PANTOPRAZOLE**	**% DECREASE**
METHOTREXATE (Bcrp)	V_i	417	315	24.4
	V_{ss}	933	651	30.3
	V_{area}	1010	689	31.9
	(ml/kg)	**CONTROL**	**+CYCLOSPORINE**	**% DECREASE**
ULIFLOXACIN (Oat/Oatp)	V_i	831	702	15.6
	V_{ss}	4450	3070	31.0
	V_{area}	4880	3320	31.9
	(ml/kg)	**CONTROL**	**in EHBR rats**	**% DECREASE**
VALSARTAN (Mrp2)	V_i	51.0	44.7	12.4
	V_{ss}	258	111	57.2
	V_{area}	420	118	71.9

EFFECTS OF TRANSPORTER INHIBITION/DYSFUNCTION ON VOLUME OF DISTRIBUTION

	Kidney	Liver
Uptake	↔	↓
Efflux	↑	↓

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Central and Peripheral Compartments

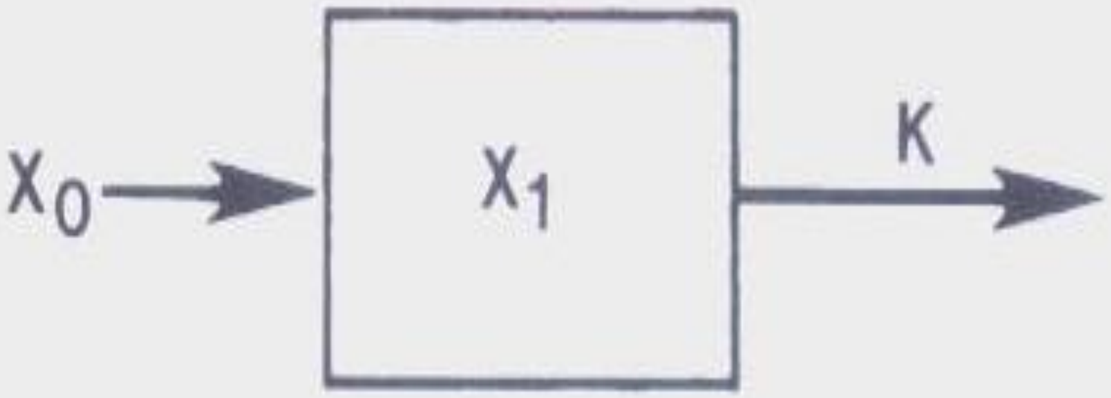
Central COMPARTIMENTS

- Heart
- Liver
- Lungs
- Kidney
- Blood

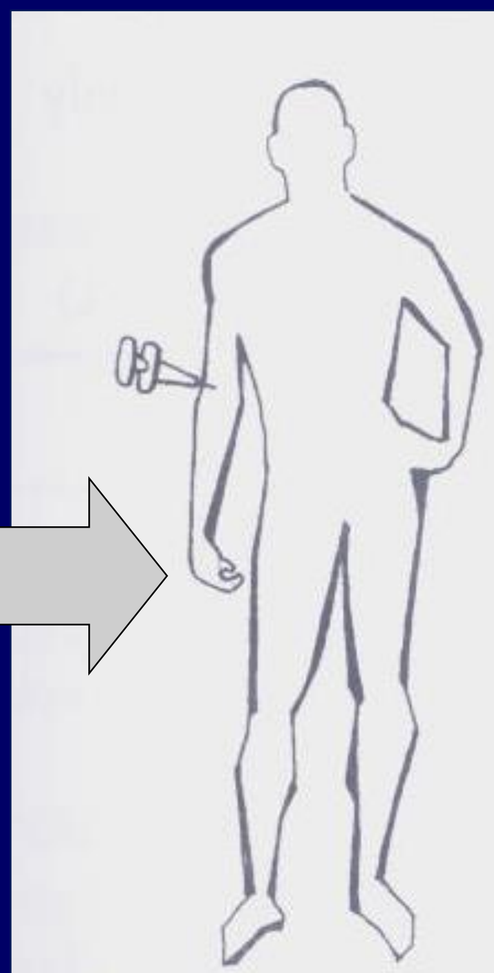
Examples of Peripheral Compartments

- Fat Tissue
- Cerebral Fluid
- Muscle Tissue

One-compartment model



Where: X_0 = Dose of drug
X_1 = Amount of drug in body
K = Elimination rate constant



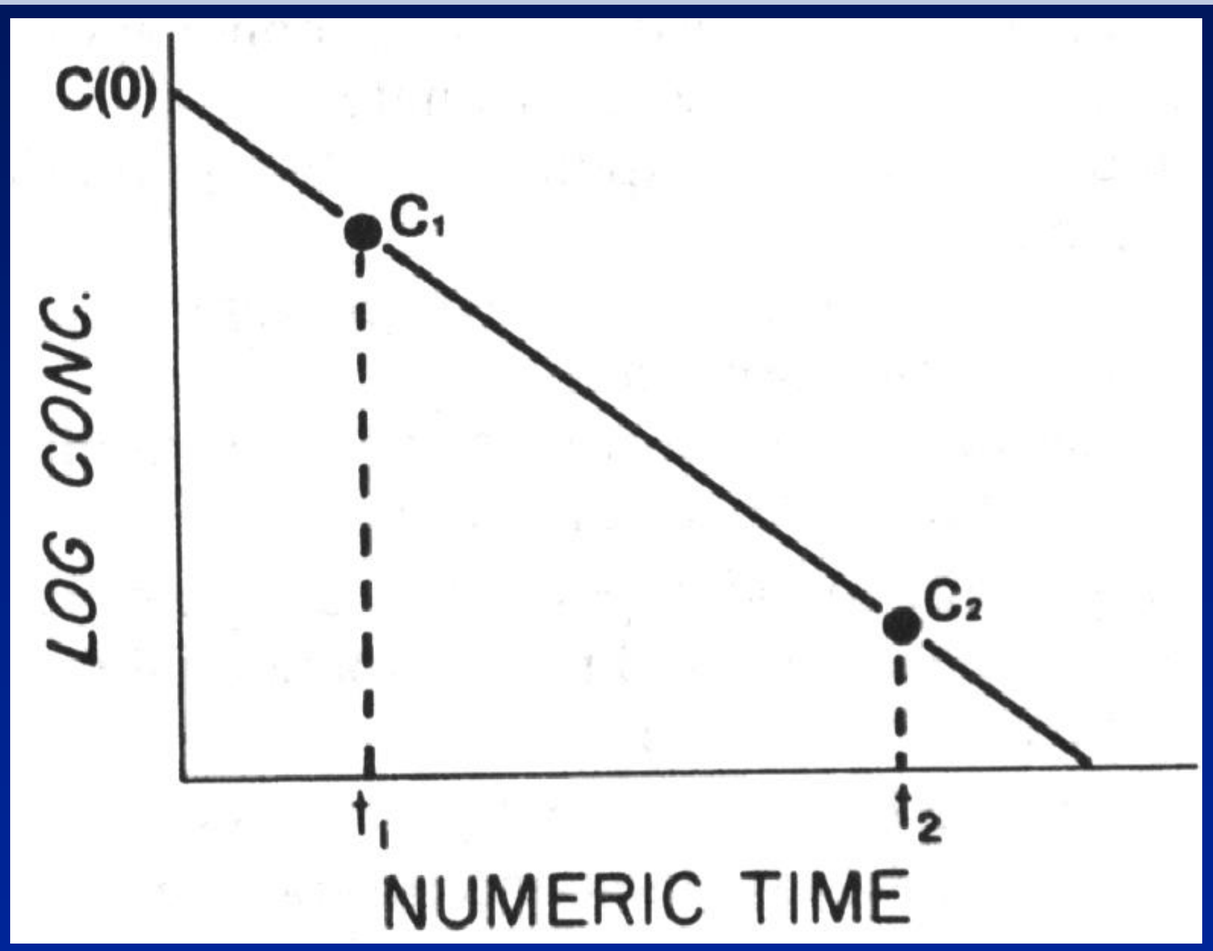
One-compartment model before administration

One-compartment model immediately after administration

Determination of rate constants

One - compartment model Intravascular route

Step 1



$C^{o}p = B$ $\quad AUC^{0-\infty} = \frac{B}{Kel}$ $\quad Cp = B.e^{-kel.t}$

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Elimination rate constant (Kel)

$$C = C_0 \cdot e^{-Kel.t}$$

$$\ln C = \ln C_0 - Kel.t$$

$t = T1/2$, $C = 0.5C_0$

$$\ln 0.5C_0 = \ln C_0 - Kel.(T1/2)$$

$C_0 = 1$

$$\ln 0.5 = \ln 1 - Kel.(T1/2)$$

$$Kel.(T1/2) = \ln 1 - \ln 0.5$$

$$T1/2 = \frac{0-(-0.693)}{Kel}$$

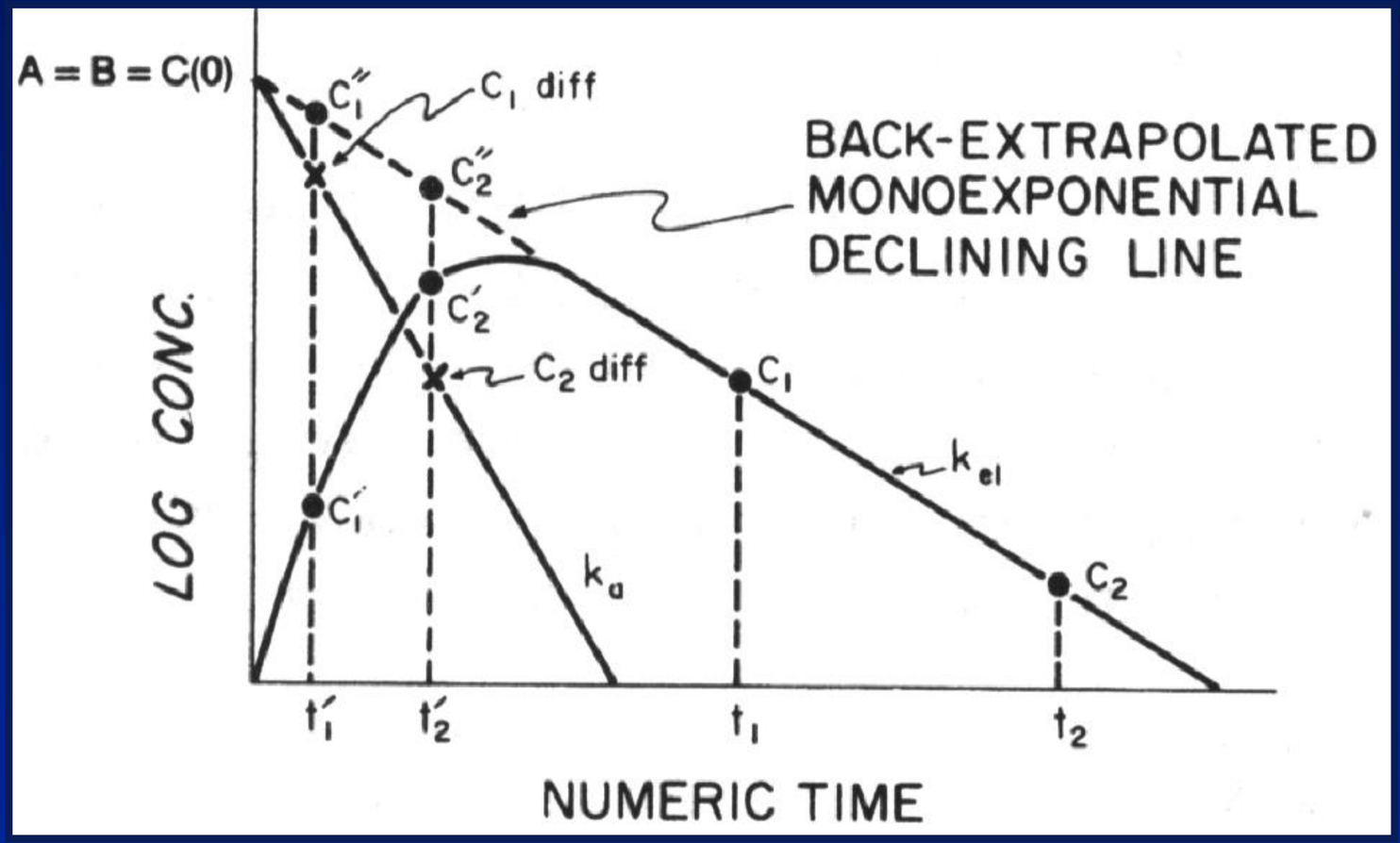
$$T1/2 = \frac{0.693}{Kel}$$

$$Kel = \frac{0.693}{T1/2}$$

Determination of rate constants

One - compartment model Extravascular route

Step 1

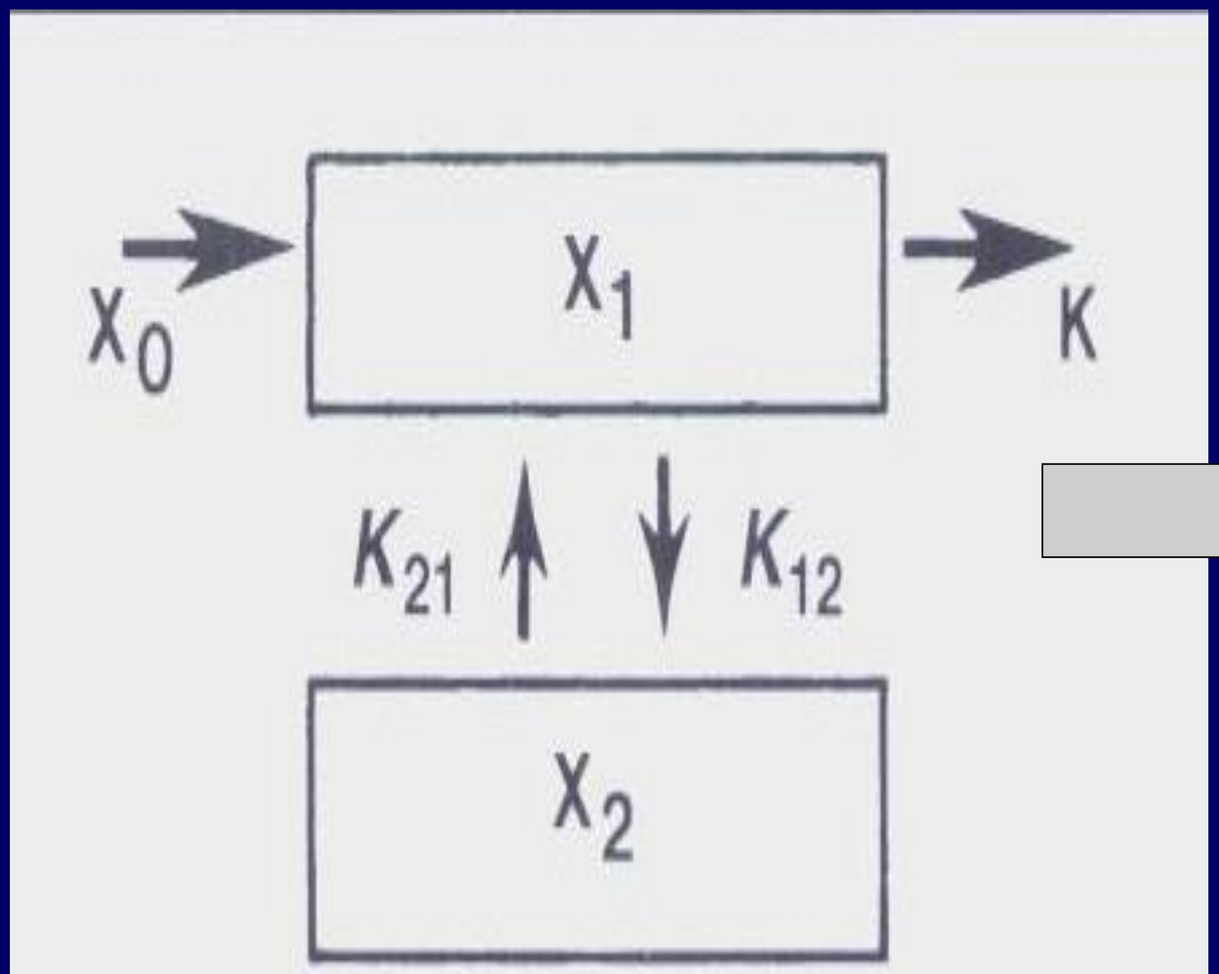


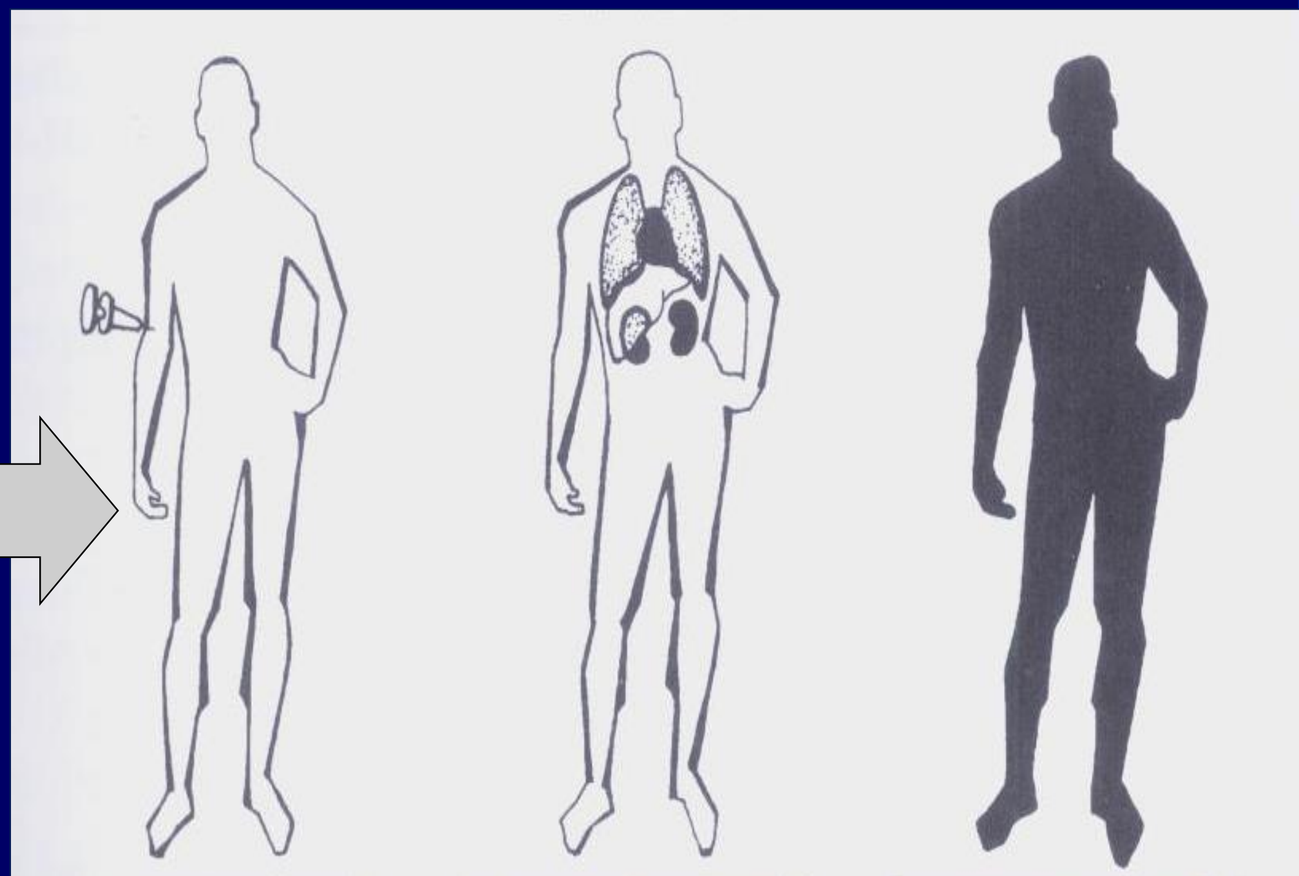
$C^{o}p = B = A$

$$AUC^{0-\infty} = \frac{B}{Kel} - \frac{A}{Ka}$$

$$Cp = B.e^{-kel.t} - A.e^{-ka.t}$$

Two-compartment model



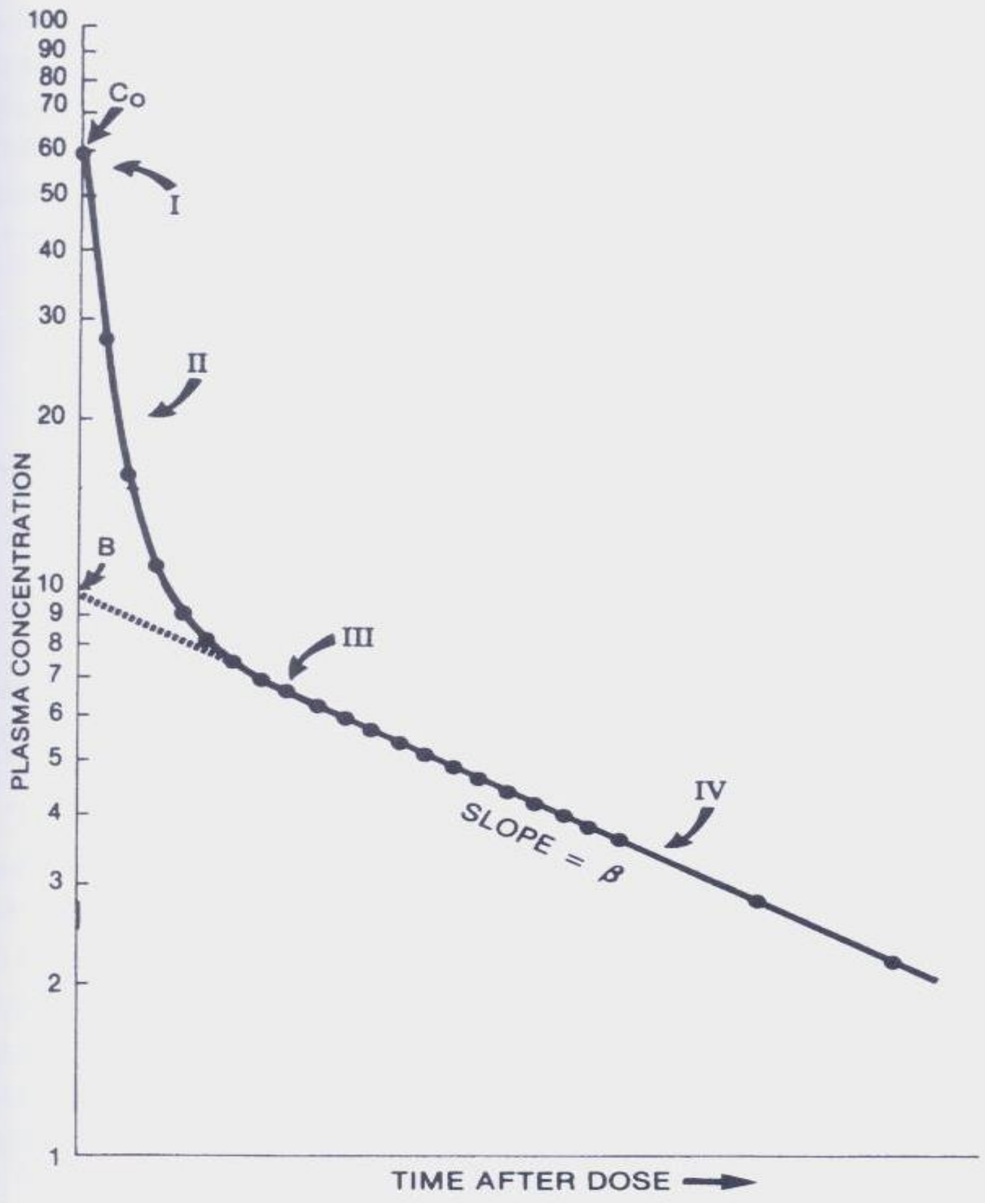


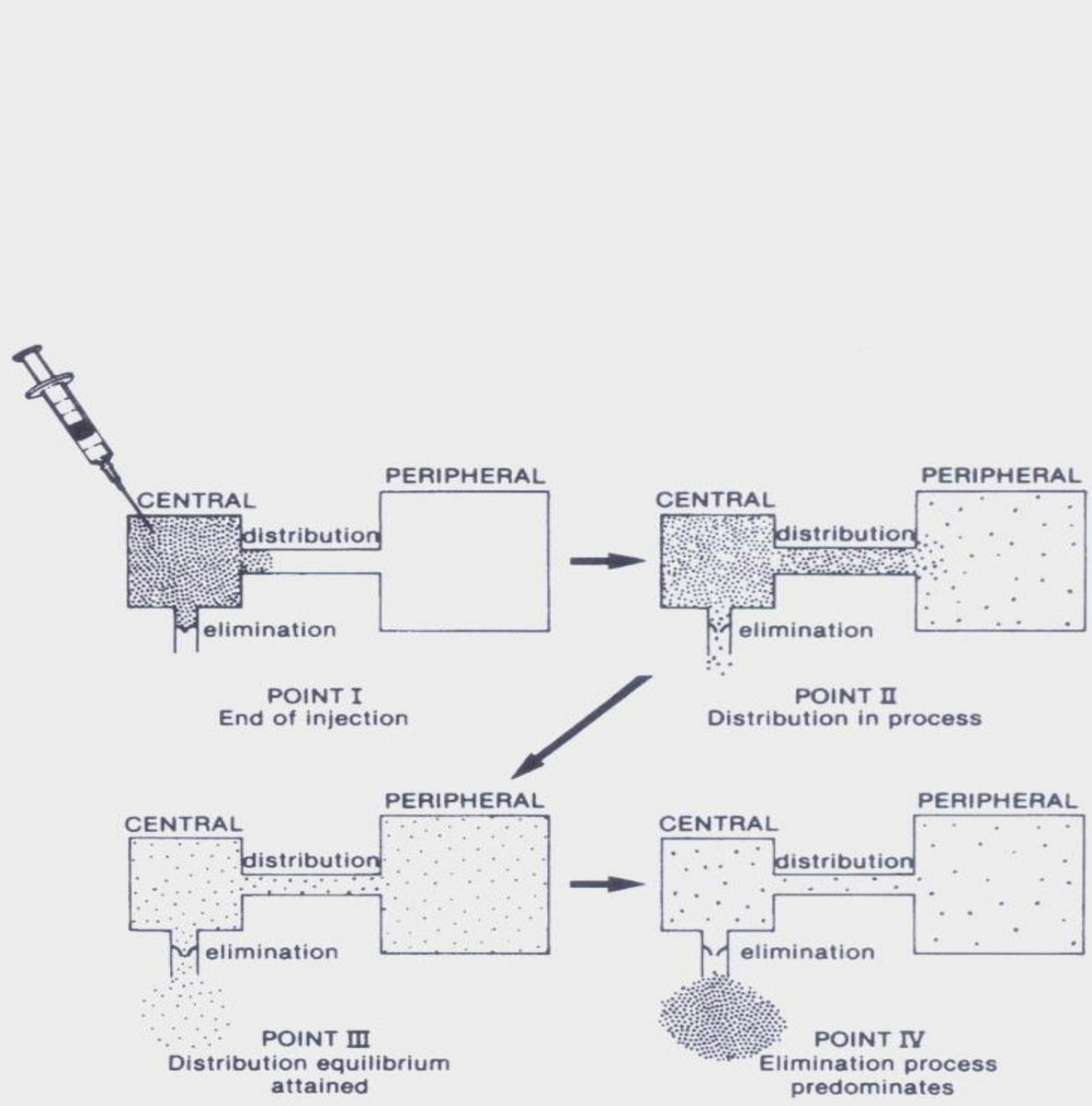
Two-compartment model before administration

Two-compartment model immediately after administration

Two-compartment model after distributive equilibrium

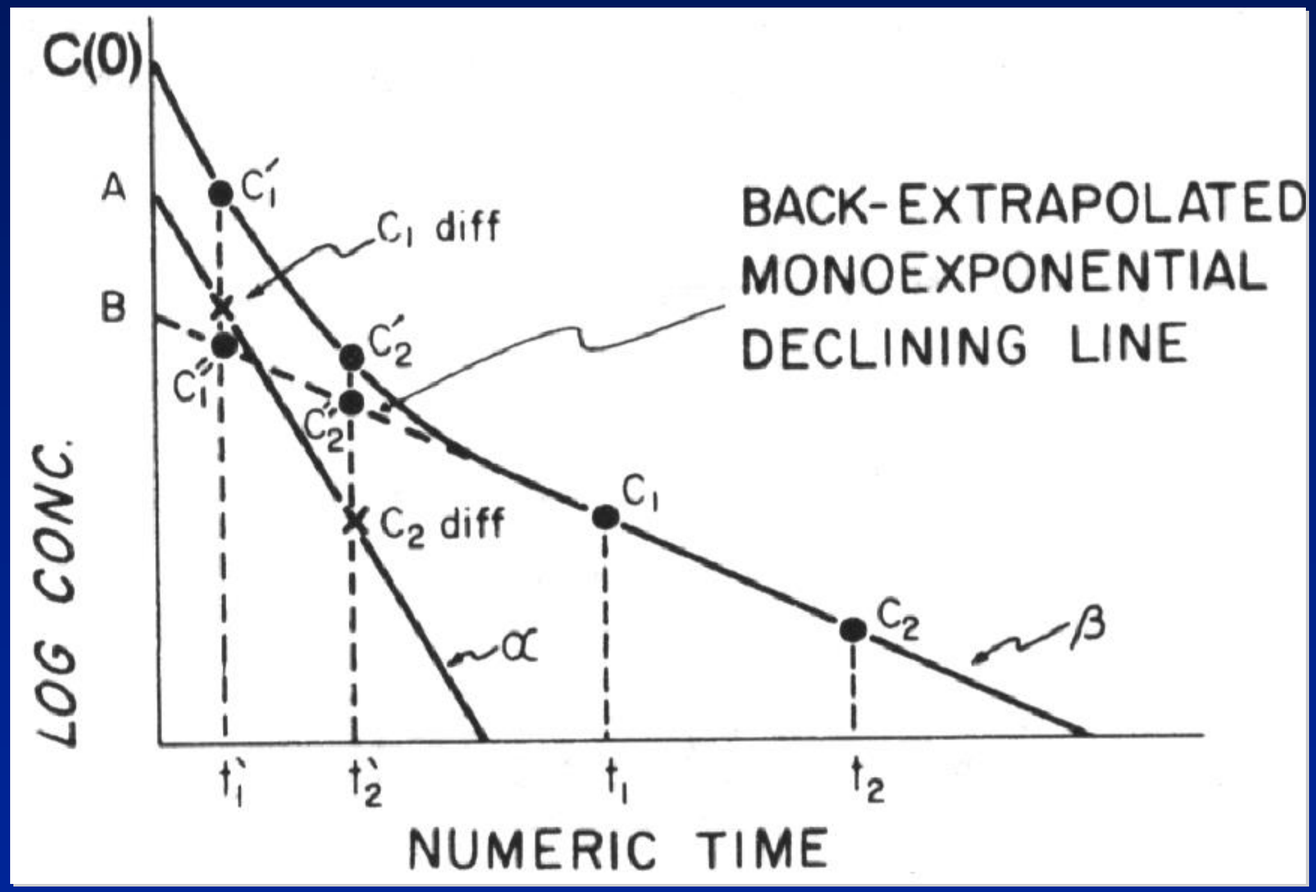
Two-compartment model





Determination of rate constants

Two - compartment model Intravascular route

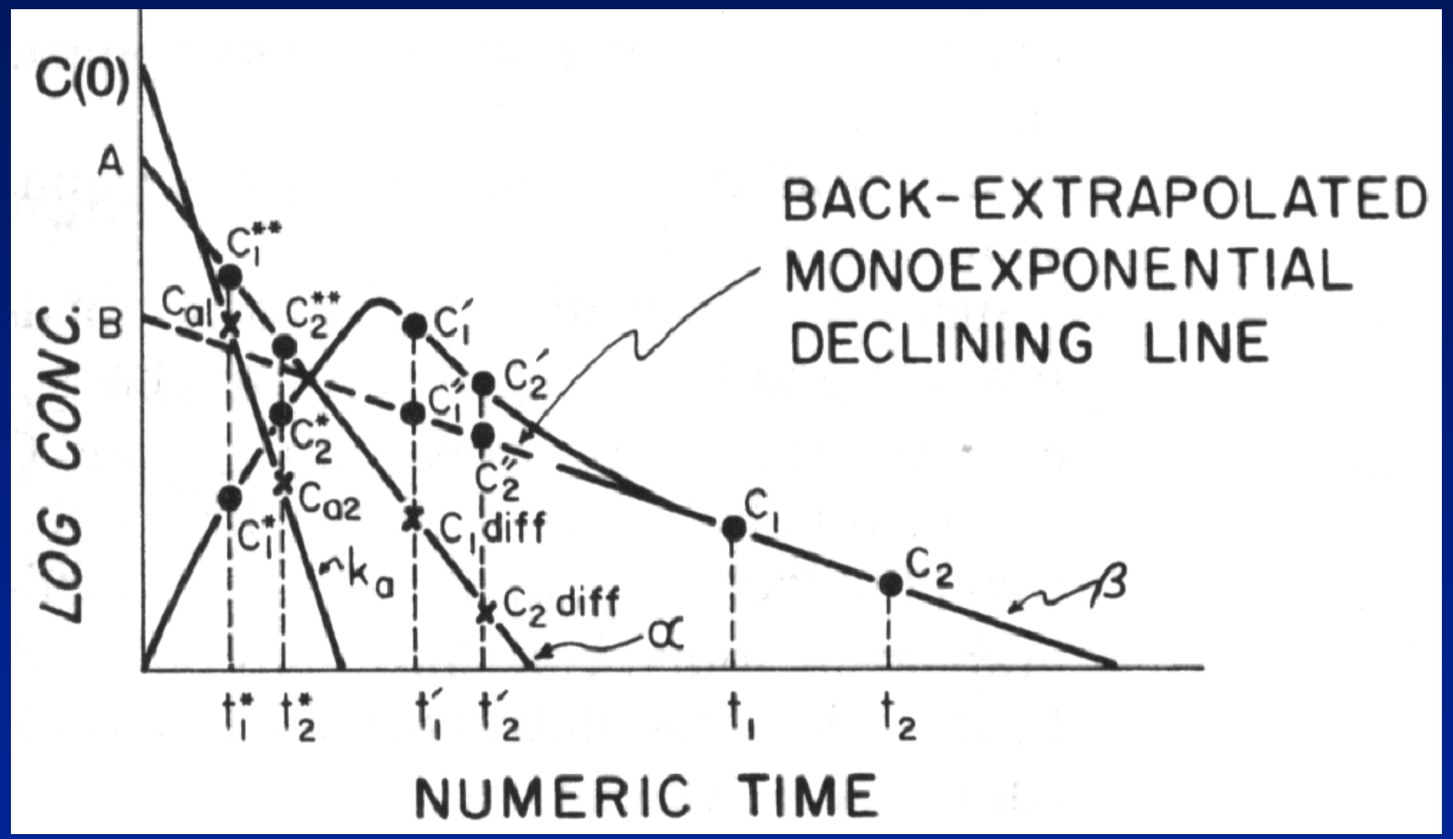


$$C^{o}p = A + B \qquad AUC^{0-\infty} = \frac{B}{\beta} + \frac{A}{\alpha} \qquad Cp = B.e^{-\beta.t} + A.e^{-\alpha.t}$$

Determination of rate constants

Two - compartment model Extravascular route

Step 1

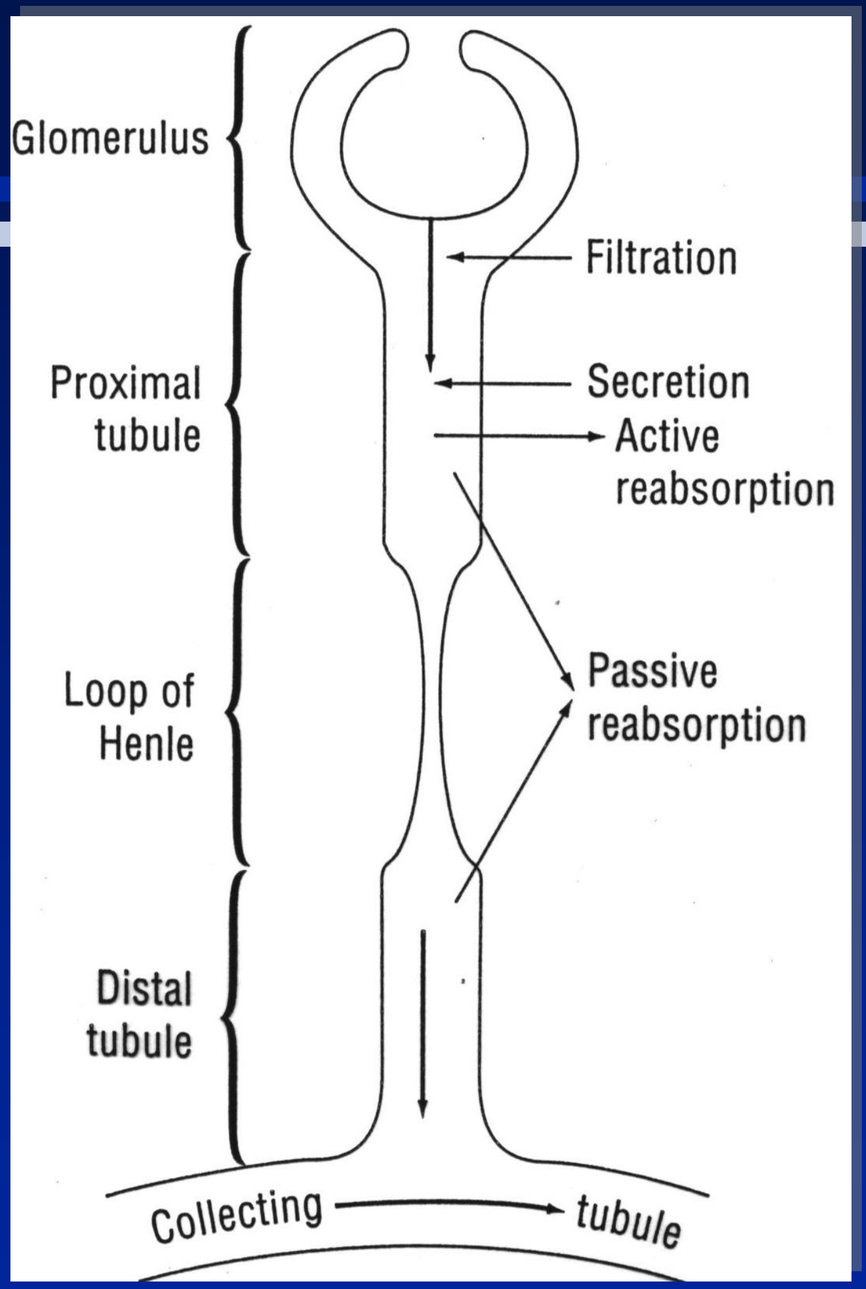


$$C^o p = A + B$$

$$AUC^{0-\infty} = \frac{B}{\beta} + \frac{A}{\alpha} - \frac{C^o p}{Ka}$$

$$Cp = B.e^{-\beta.t} + A.e^{-\alpha.t} - C^o p\ .e^{-kat}$$

Excreção renal de toxicantes



velocidade excreção = (**velocidade filtração** + **velocidade secreção**) **1 – fração reabsorvida**

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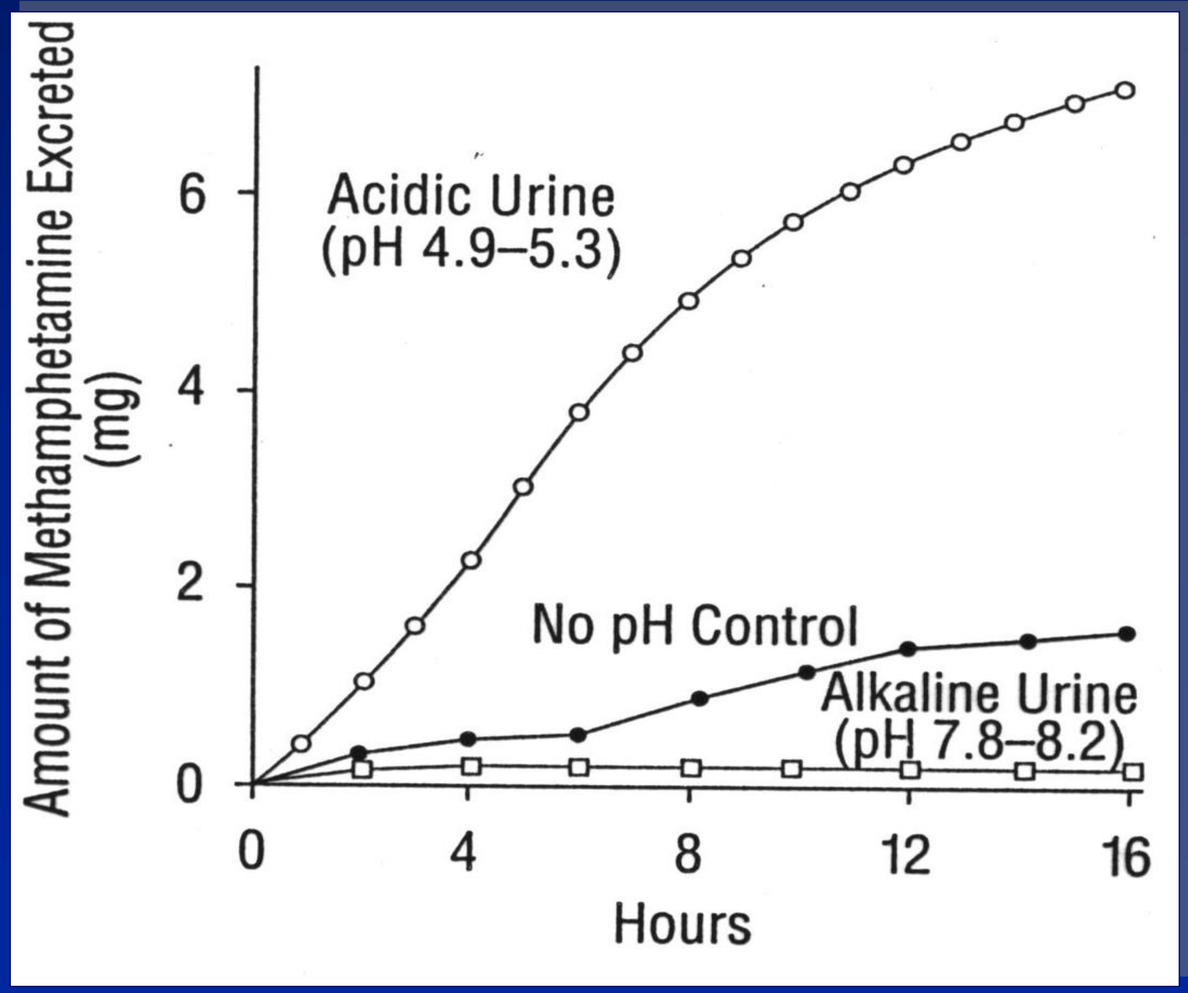
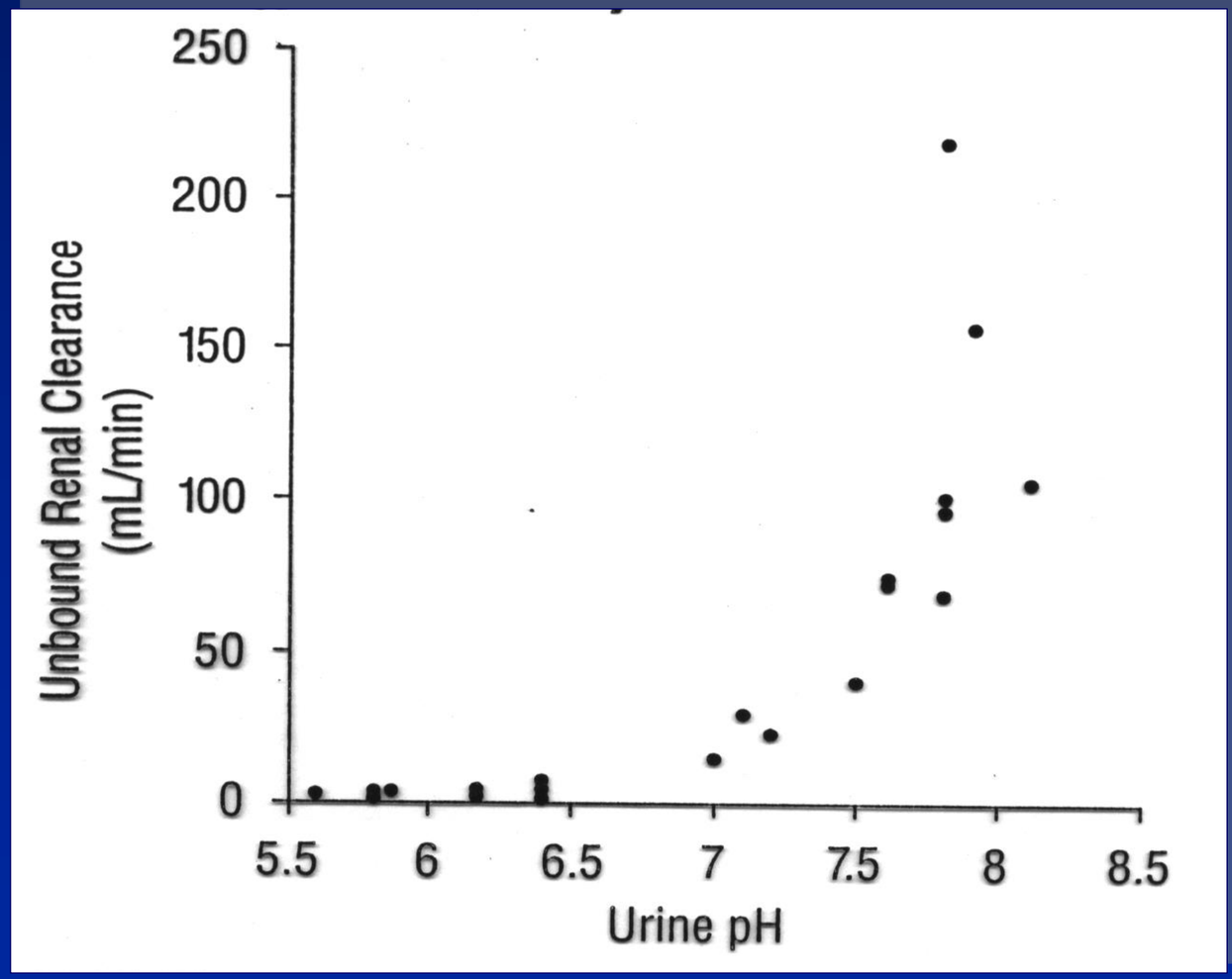
Excreção renal de toxicantes

Influência do pH da urina

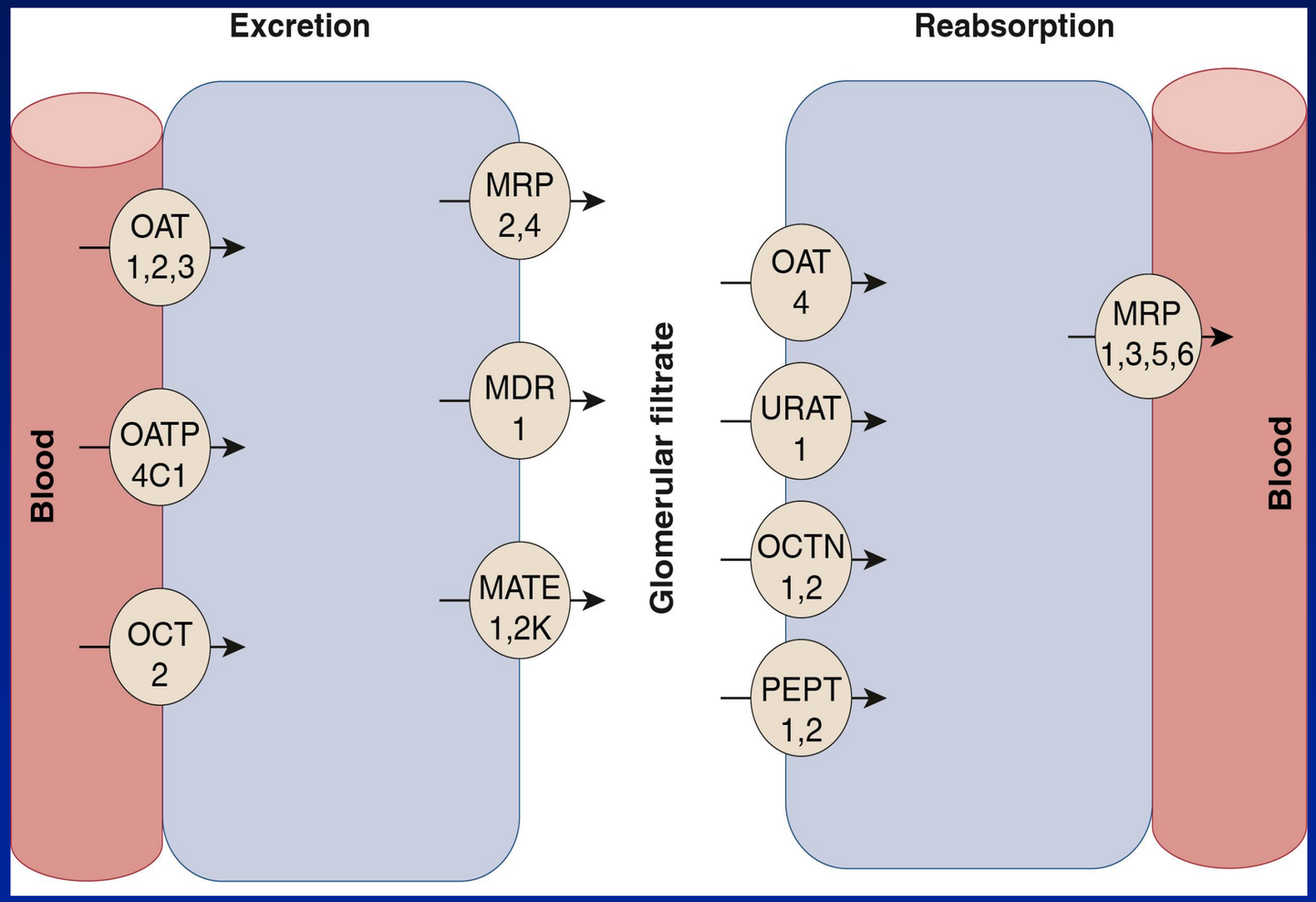
Metanfetamina (pKa=10)



Ácido salicílico (pKa=3)



TRANSPORT SYSTEMS IN THE PROXIMAL TUBULE OF THE KIDNEY



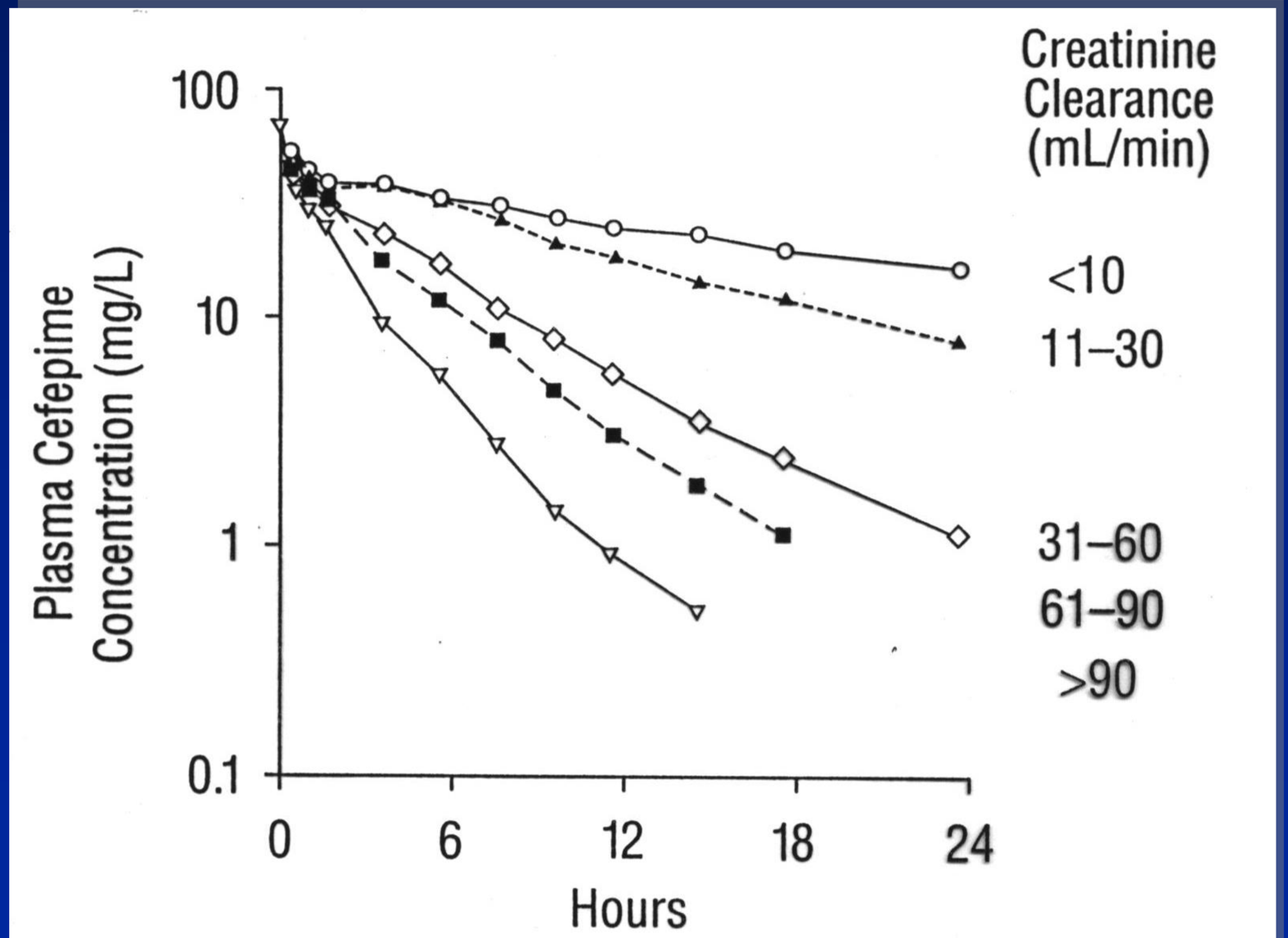
OAT
Organic-anion transporter
OCT
Organic-cation transporter
OATP
Organic-anion transporting peptides

MRP
Multiresistant drug protein
MATE
Multidrug and toxin extrusion transporter
MDR1
Multidrug resistant protein

Insuficiência renal

Acúmulo de fármacos de excreção renal

Cefepima

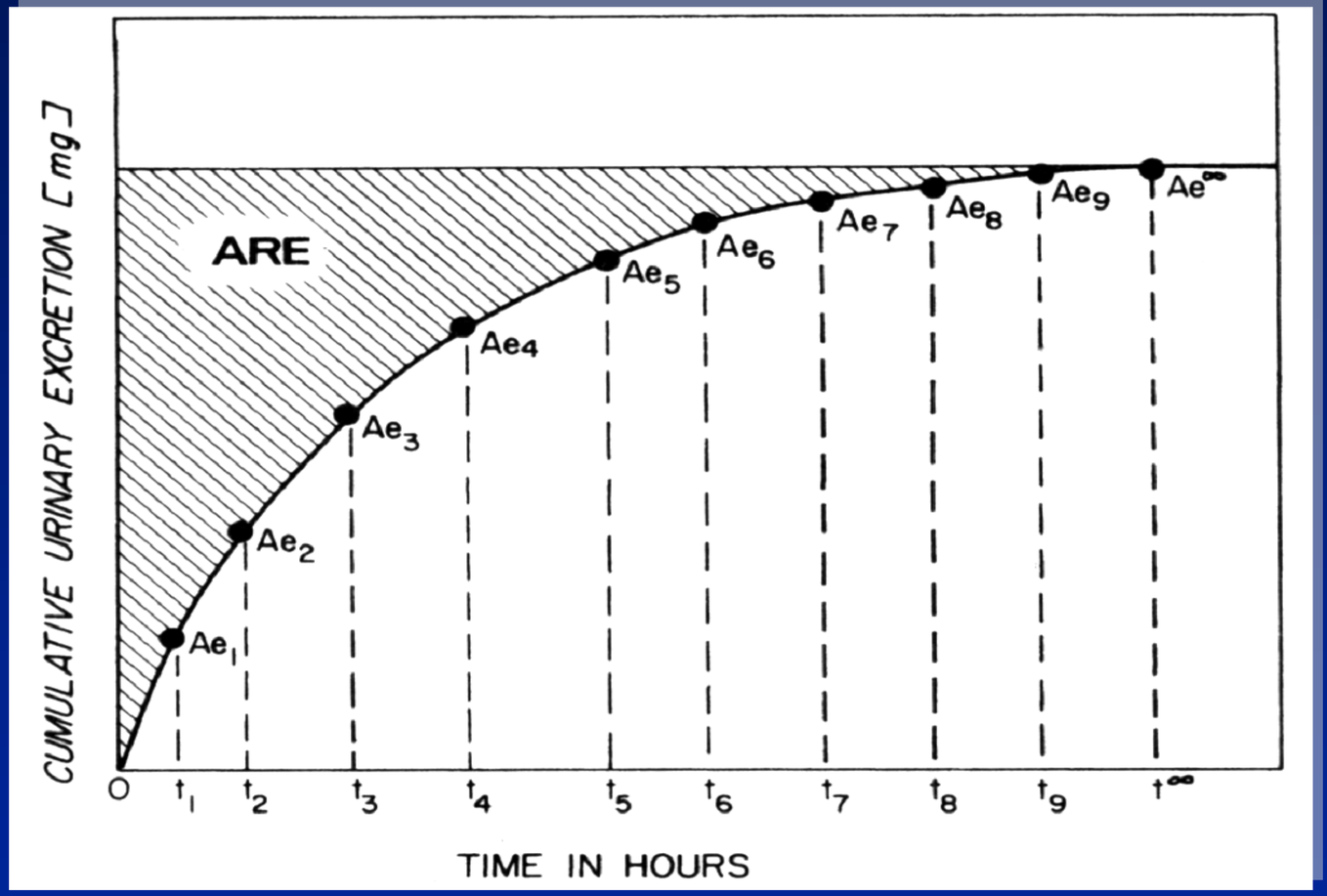


Fraction of dose eliminated by the Kidneys (fe)

This fraction refers to the fraction of the drug dose that is eliminated unchanged by the kidneys in subjects with normal renal function

$$Fe = \frac{Ae}{Dose}$$

Cumulative urinary excretion



Amount excreted (Ae)

$$Ae = Cu \cdot V \quad [mg]$$

Fraction of dose eliminated by the Kidneys

It can be used to compute adjusted drug dosage regimens in patients with reduced renal function

Fe > 0.6 ➔ a consideration should be given to dosage regimen adjustment

Excreção biliar de toxicantes

$$\text{clearance biliar} = \frac{\text{(fluxo biliar) . (concentração na bile)}}{\text{(concentração no plasma)}}$$

fluxo biliar = 0,5 - 0,8 mL/min

- **toxicantes polares**
- **alto peso molecular**
  PM > 325

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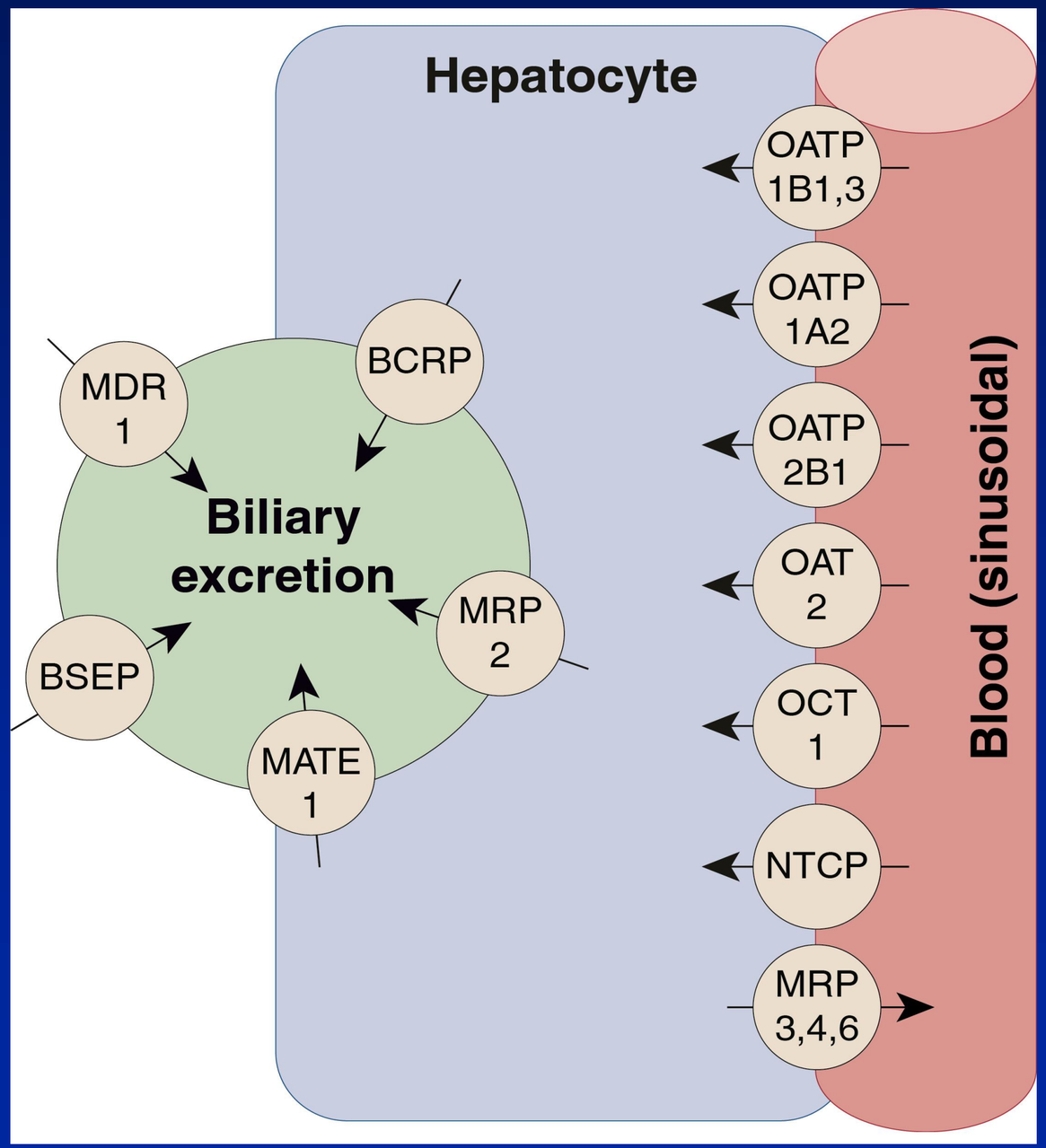
XENOBIOTIC TRANSPORTING SYSTEMS PRESENT IN THE LIVER



OATP Organic anion transporting peptides

OAT Organic-anion transporter

OCT Organic-cation transporter

P-gp P-glycoprotein

BCRP Breast cancer resistance protein

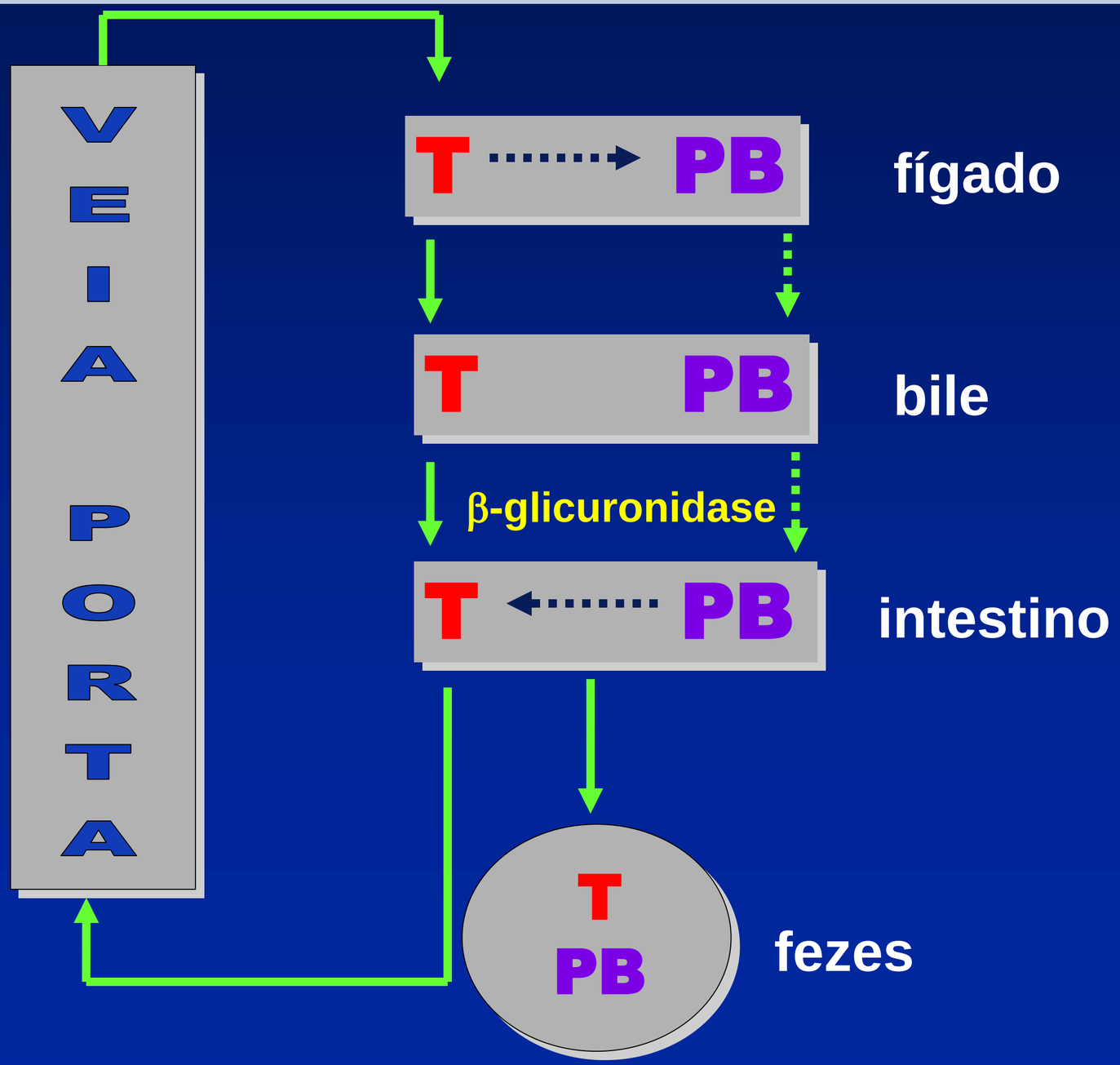
MRP2 Multiresistant drug protein

BSEP Bile salt excretory protein

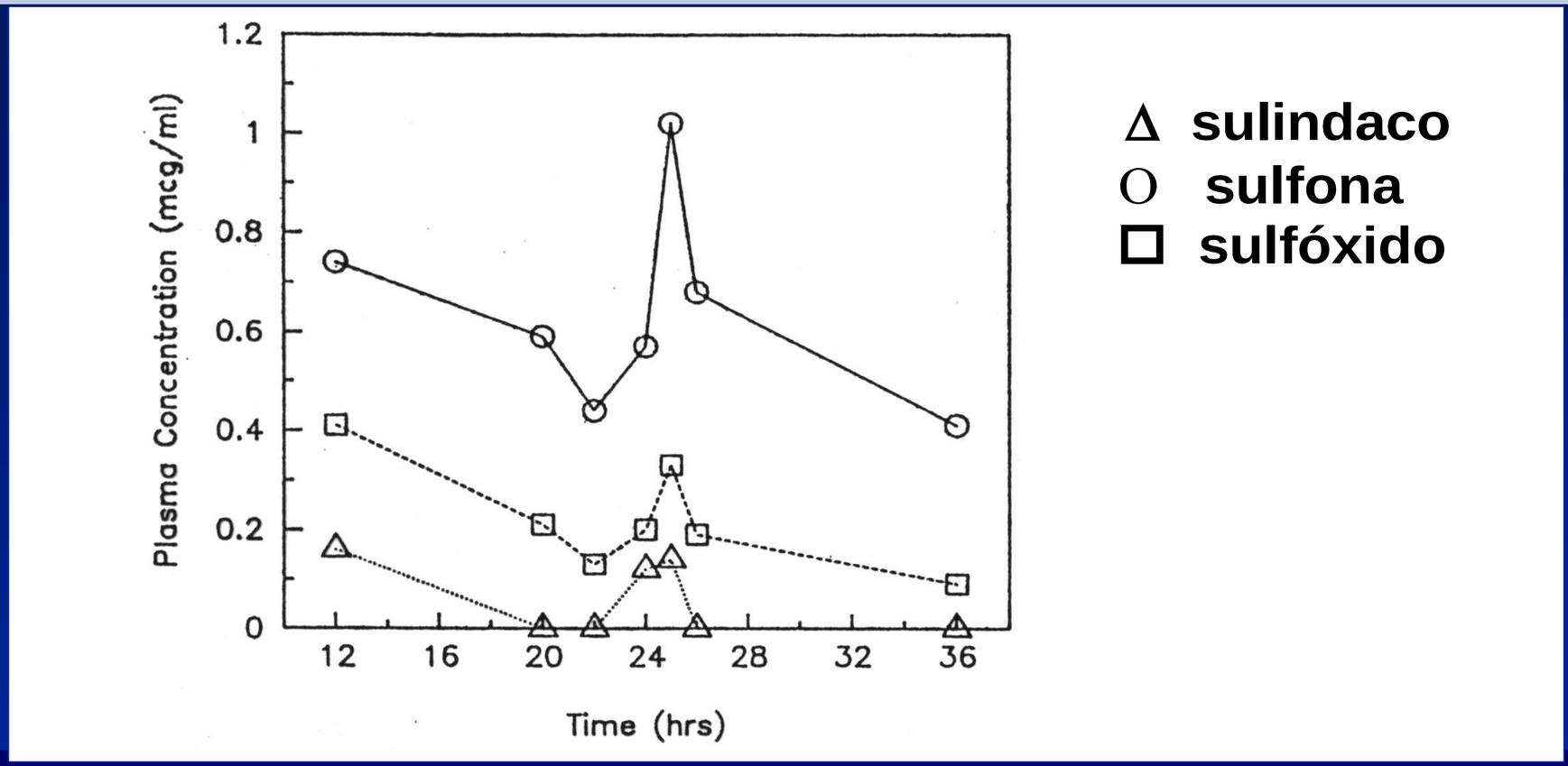
FCFRP-USP

Excreção biliar de toxicantes

Ciclo entero-hepático



Excreção biliar e ciclo entero-hepático



Δ sulindaco
O sulfona
□ sulfóxido

Outros exemplos

- Conjugados de testosterona e vitamina A
- Conjugados com o ácido glicurônico de cloranfenicol, indometacina e ácido valpróic
- Imipramina e desipramina
- Metabólitos da espironolactona

Total Clearance (Cl)

Total clearance represents that part of the distribution volume that is totally cleared of drug per unit time

Unit | **volume/time** (mL/min, L/h)

$$Cl = Vd \times K = \frac{dose}{AUC}$$

$$Cl = Cl_H + Cl_R$$

$$Cl_H = Q \times E$$

$$Cl_H = Cl - Cl_R$$

$$Cl_R = Cl \times \frac{Ae}{dose}$$

→ **blood flow through the liver is about 1.5 L/min**

→ **blood flow through the kidneys is about 1.2 L/min**

Total Clearance (Cl)

Average Clearances of Common Drugs

Aspirin	650 mL/minute
Cephalexin	300 mL/minute
Digoxin	130 mL/minute
Gentamicin	90 mL/minute
Lovastatin	4–18 mL/minute
Ranitidine	730 mL/minute
Vancomycin	98 mL/minute
Zidovudine	26 mL/minute

Source: Shargel L, Yu ABC. *Applied Biopharmaceutics an*
Pharmacokinetics. 4th ed. New York: McGraw-Hill; 1999.
732–6.

Total Clearance

1

Total clearance determines the average steady-state concentration of a drug during continuous drug administration

$$\overline{C}_{ss} = \frac{R}{Cl} = \frac{(F)\quad(dose/\tau)}{Cl}$$

R = dosing rate

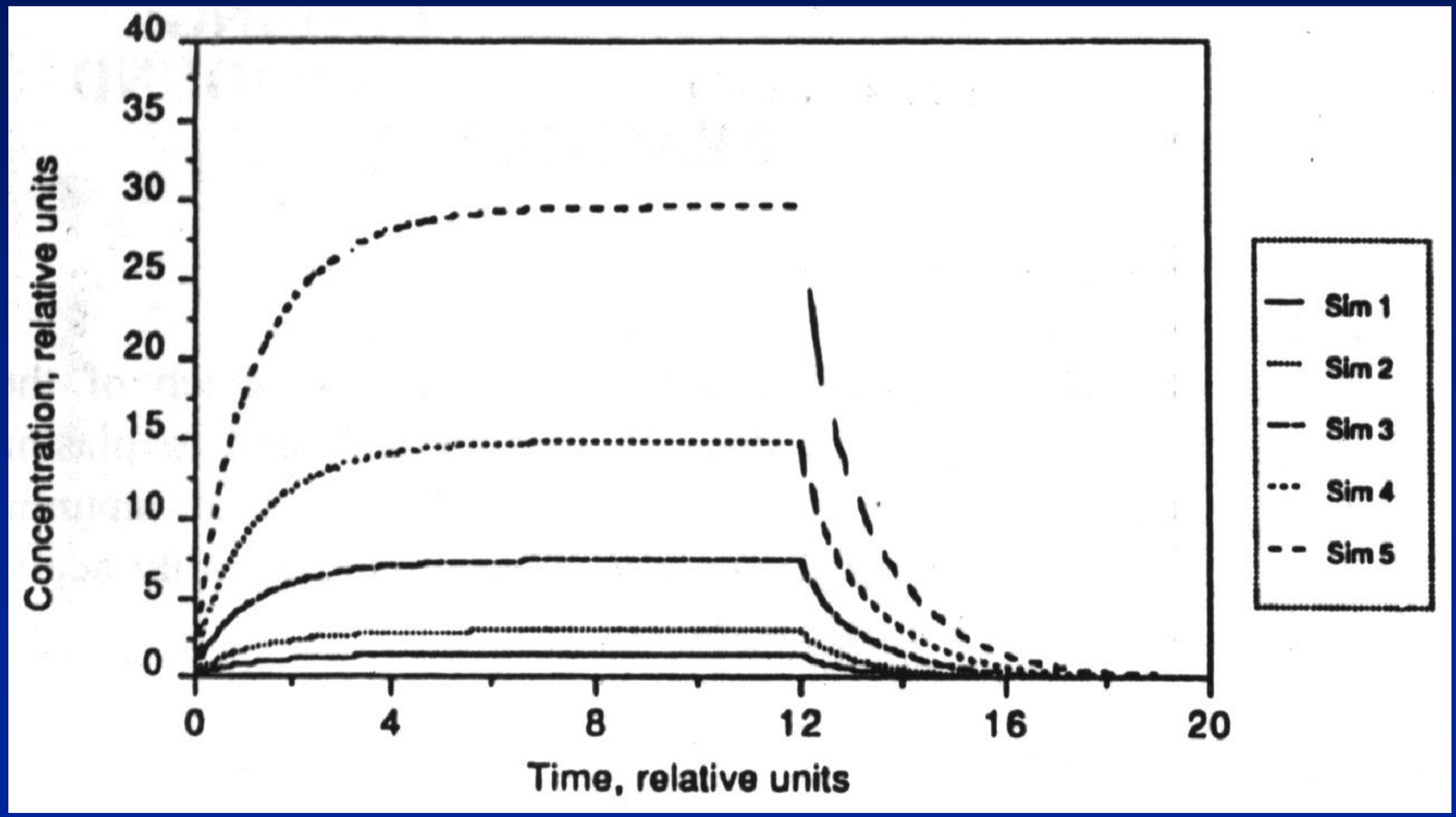
F = bioavailability

Total Clearance

Total clearance can be used to compute the dosing rate required to yeld the desired steady-state concentration

$$R = C_{ss,\ target} \times Cl$$

Total clearance determines steady-state levels for any given dosing rate

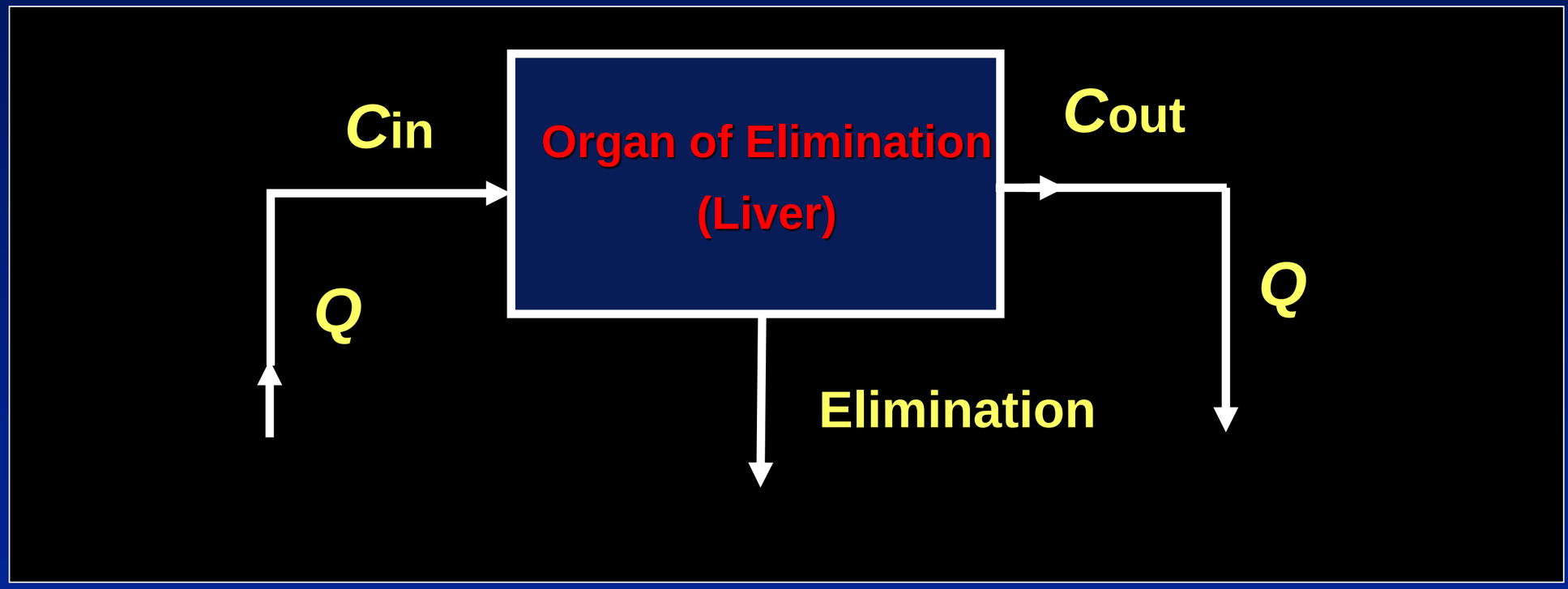


Bjornsson, 1997

Total Clearance

The numerical value of total clearance, Cl_H and Cl_R can provide important insights into the elimination processes and the potential needs for dosage regimen adjustments in patients with liver or kidney disorders

Model for organ clearance of a drug



$$Cl_{organ} = Q \times \frac{C_{in} - C_{out}}{C_{in}} = Q\,E$$

CLEARANCE FOR THE ELIMINATING ORGAN

$$CL_{organ} = \frac{Q \cdot (fu_b \cdot CL_{int})}{Q + (fu_b \cdot CL_{int})}$$

$(fu_b \cdot CL_{int}) >> Q$

$CL_{organ} \cong Q$

↑E

> 0.7

$Q >> (fu_b \cdot CL_{int})$

$CL_{organ} \cong (fu_b \cdot CL_{int})$

↓E

≤ 0.3

E is independent of the fraction of the dose eliminated by an organ

Diazepam

CL = 27 mL/min

< 1% is excreted unchanged in the urine

$$E_H = \frac{CL_H}{Q_H} = \frac{27 mL/min}{1500\ mL/min} = 0.018$$

On each pass through the liver only 1,8% of the diazepam will be eliminated, although almost all of the dizepam will be eliminated by the liver

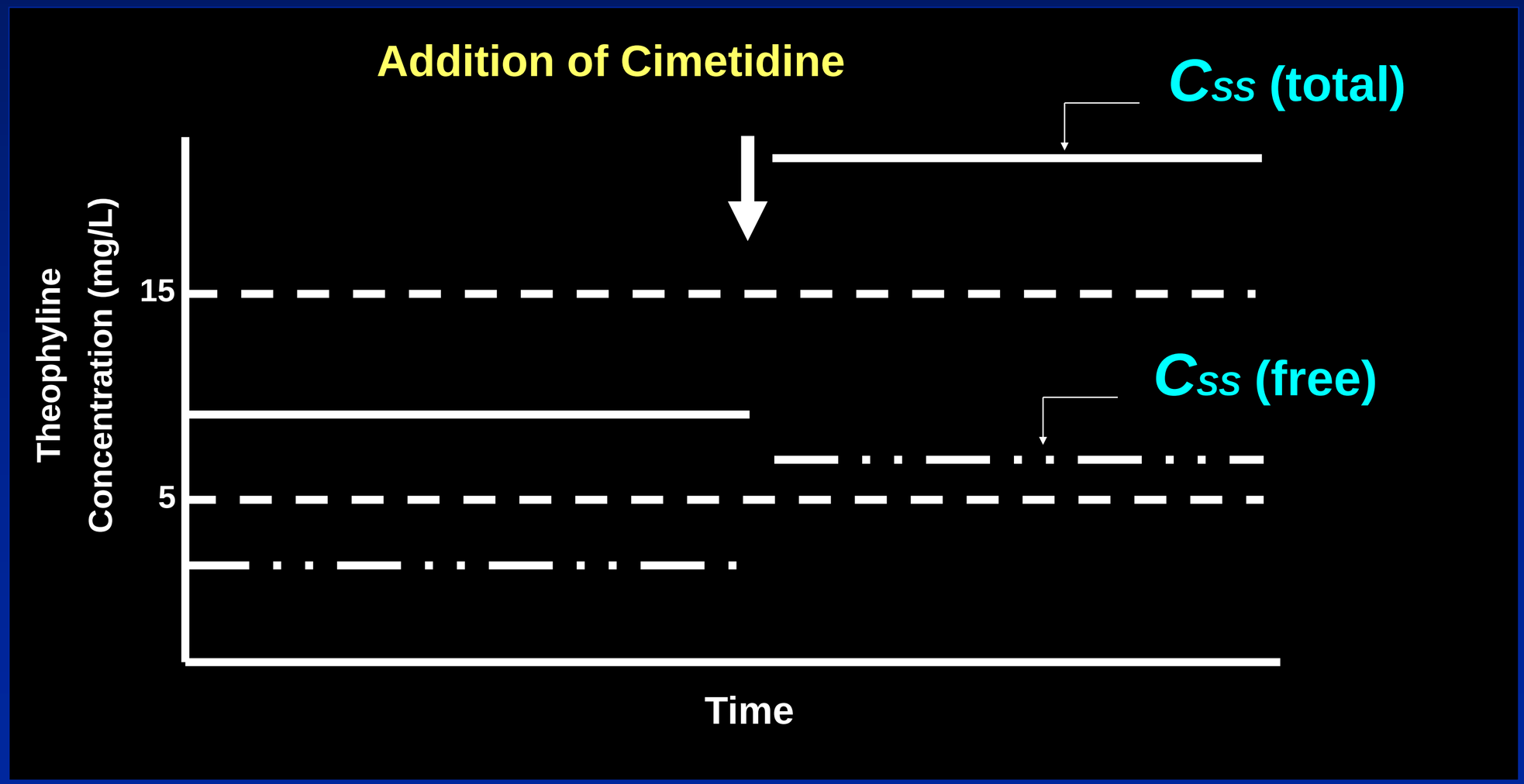
Effect on Clearance

Extraction Ratio (*E*)	Blood Flow (*Q*) (L/hour)	Clearance (Cl) (L/hour)
High (0.7-1.0)	Low	Low
Low (<0.3)	High	Low
High (0.7-1.0)	High	High
Low (<0.3)	Low	Low

Theophylline has a low E

Theophylline possesses low protein binding

Cimetidine is an inhibitor of the CYP1A2



INFLUENCE OF EXTRACTION RATIO ON DRUG AVAILABILITY

$$F_H = 1 - E_H = 1 - \frac{CL_H}{Q_H}$$

Labetalol

- CL_H = 1290 mL/min
- E_H = 0.86
- F = 14%

Uptake transporter-based interactions at the liver

HEPATIC INTERACTION			
Drug	**Interaction**	**Mechanism**	**Cl/F**
Atorvastatin	Rifampin	Inhibition of OATP1B1 uptake	↓ 87.0%
Cerivastatin	Cyclosporine	Inhibition of OATP1B1 uptake	↓ 73.3%
Glyburide	Rifampin	Reduced OATP2B1 uptake	↓ 54.6%
Metformin	OCT1 reduced function allele	Reduced OCT1 uptake	↓ 37.5%
Repaglinide	Cyclosporine	Inhibition of OATP1B1 uptake	↓ 59.0%
Rosuvastatin	Cyclosporine	Inhibition of OATP1B1 uptake	↓80.1%
Rosuvastatin	Gemfibrozil	Inhibition of OATP1B1 uptake	↓ 46.8%
Rosuvastatin	OATP1B1 reduced function allele	Reduced OATP1B1 uptake	↓38.5

INHIBITION OF EFFLUX TRANSPORTERS AT THE LIVER: CLEARANCE

BDDCS	CLEARANCE
I and II	↑
III and IV	↓

Drugs for which changes in protein binding are not clinically relevant

Drug	Low hepatic extraction ratio
Carbamazepine	0.08
Caftriaxone	0.01
Chlorpropamide	0.001
Diazepam	0.02
Ketoprofen	0.06
Methotrexate	0.06
Phenytoin	~0.03
Tolbutamide	0.01
Valproic acid	0.005
Warfarin	0.002

The 25 drugs in a list of 456 drugs
Protein binding may influence clinical drug exposure

	Protein binding (%)	CL (mL/min.kg)
Alfentanil	92	10.6
Amitriptyline	95	11.5
Buprenorphine	96	13.3
Butorphanol	80	22
Chlorpromazine	95	8.6
Cocaine	91	32
Diltiazem	78	11.4
Diphenhydramine	78	6.2
Doxorubicin	76	16.2
Erythromycin	84	8.0
Fentanyl	84	12.3
Gold sodium thiomalate	95	4.8
Haloperidol	92	11.8
Idarubicin	97	29
Itraconazole	99.8	12.7
Lidocaine	70	9.2
Methylprednisolone	78	6.2
Midazolam	98	6.6
Milrinone	70	5.2
Nicardipine	99	10.4
Pentamidine	70	16
Propofol	98	27
Propranolol	87	18
Remifentanil	92	40 - 60
Sulfentanil	93	12
Verapamil	90	15

Nonoral administration; protein binding > 70%

Elimination half-life ($t_{1/2}$)

Is the time it takes a drug concentration in the blood to decline to one half of its original value

$$t_{1/2} = \frac{0.693}{K} = \frac{0.693 \times Vd}{Cl}$$

Unit	time (min, h, day)

Half-Life (t1/2)

Half-Lives of Common Drugs

Drug	Half-Life (h)
Aspirin	0.3
Cephalexin	0.9
Digoxin	39
Gentamicin	2 - 3
Lovastatin	1.1 – 1.7
Vancomycin	5.6
Zidovudine	1.1

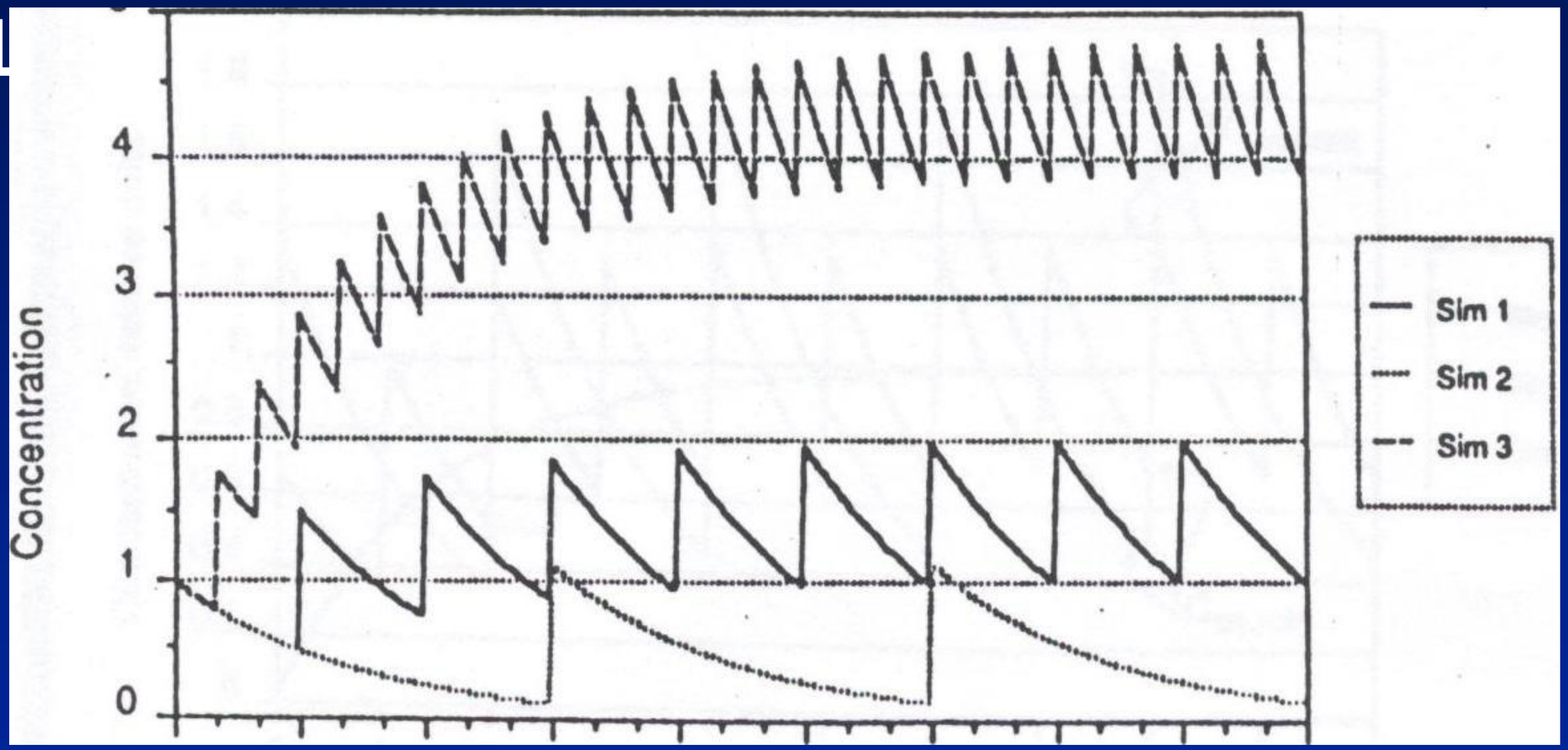
Elimination half-life

It is used to select lenghts of dosing intervals of drugs

When $\tau = t_{1/2}$	**drug levels at steady-state are approximaly 2 times those after the first dose**
When $\tau < t_{1/2}$	**drug levels at steady-state are more than 2 times those after the first dose**
When $\tau > t_{1/2}$	**drug levels at steady-state are less than 2 times those after the first dose**

Relationship between elimination half-life and dosing interval

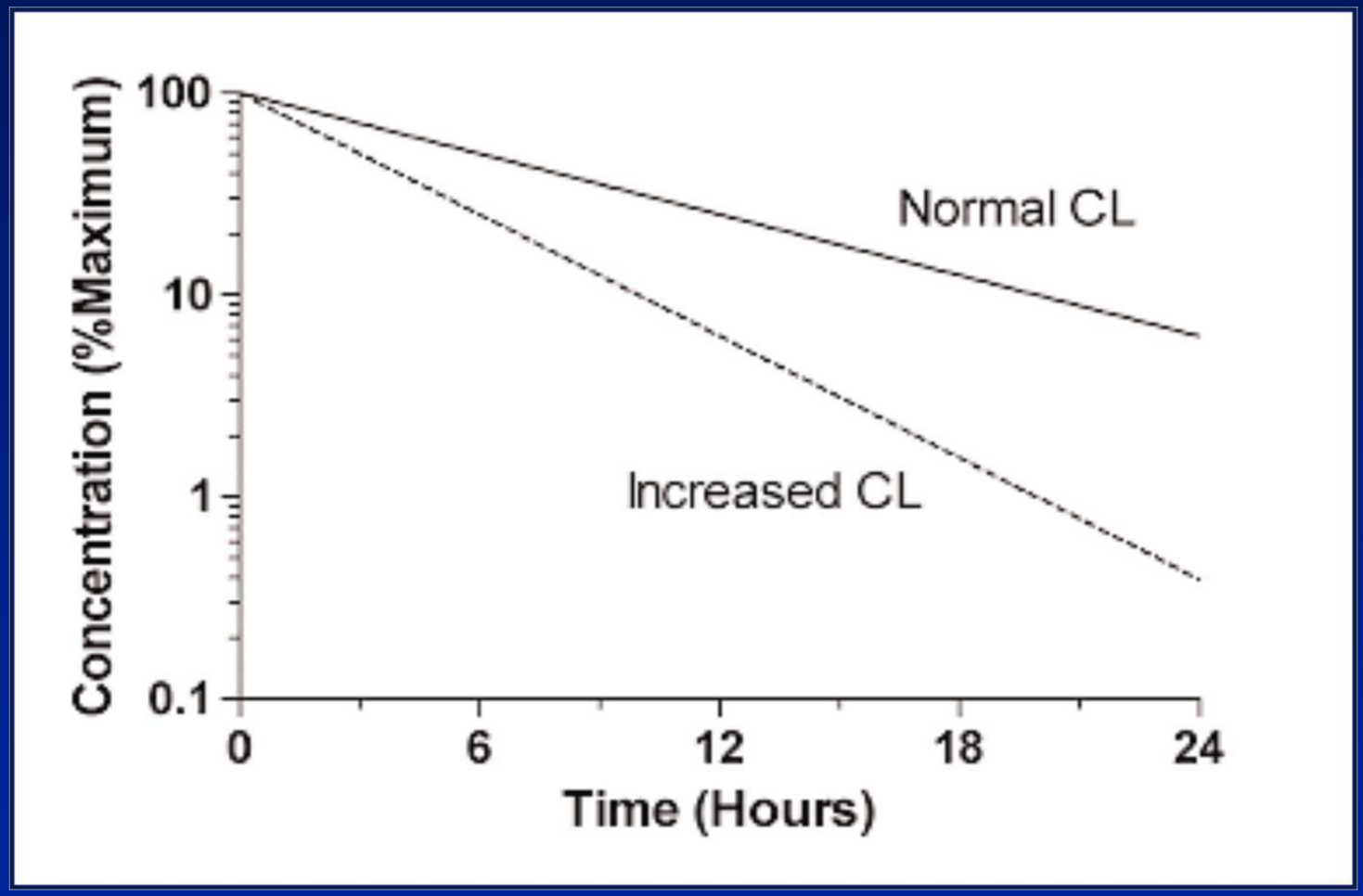
Step 1



The elimination half-life is the same for all three simulations

The effects of a two-fold increase in the clearance of a drug on its plasma concentration-time profile

IV bolus

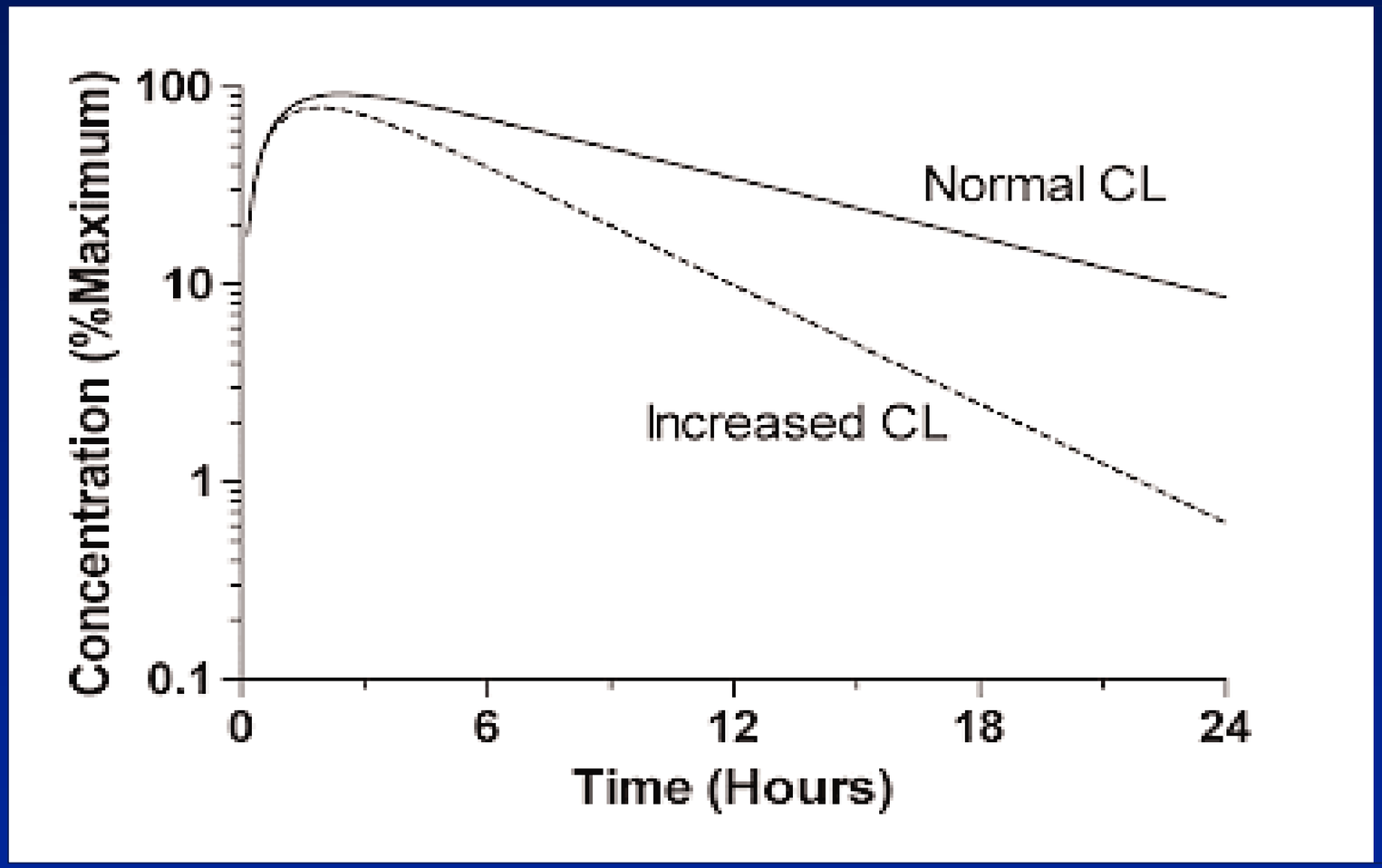


CL of 1.16 L/h and V of 10 L for the “Normal CL” scenario.

CL was increased to 2.32 L/h for the “Increased CL” scenario.

The effects of a two-fold increase in the clearance of a drug on its plasma concentration-time profile

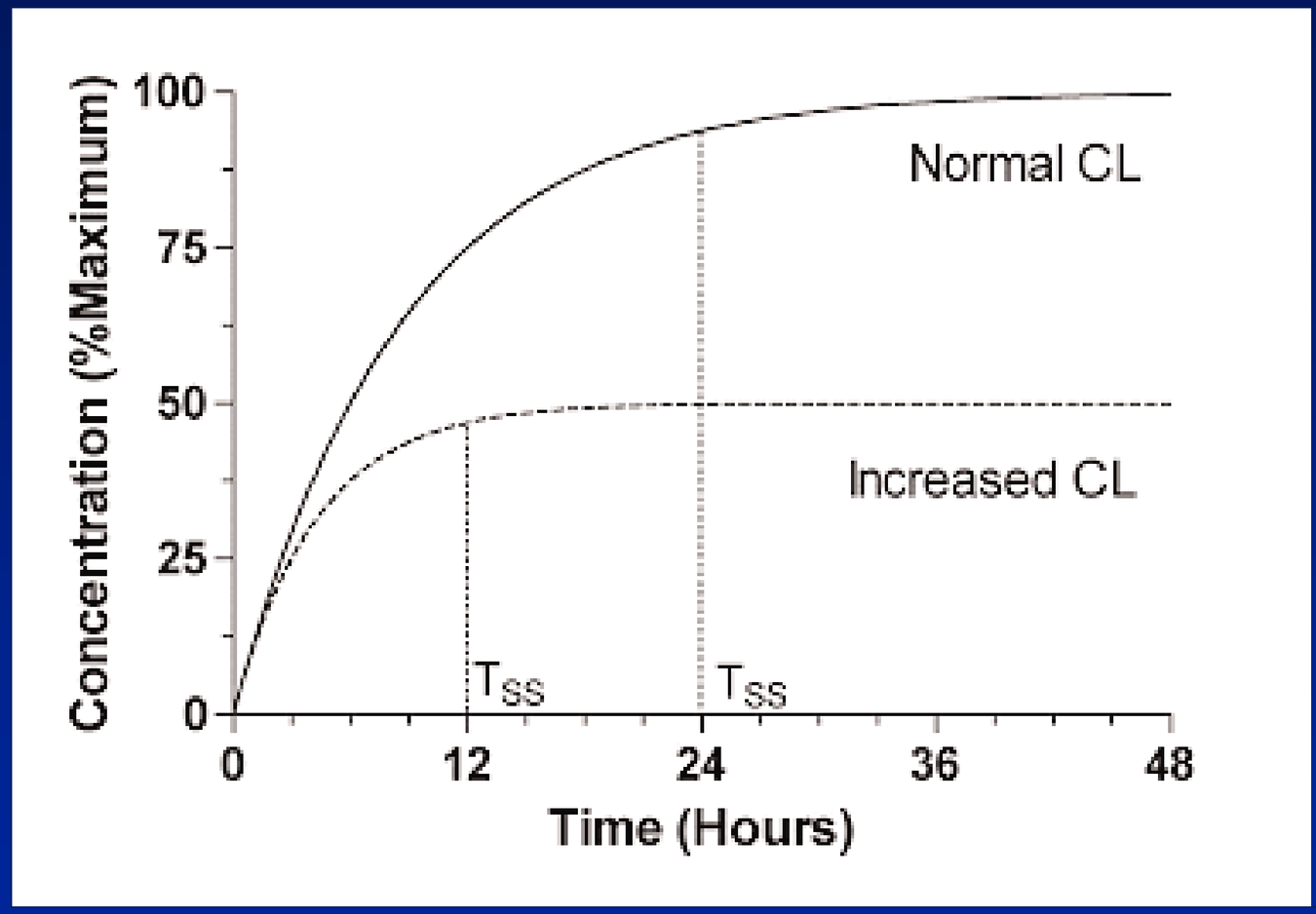
Oral



CL of 1.16 L/h, V of 10 L, absorption rate constant of 1 hr -1 , and F of 1 for the “Normal CL” scenario. CL was increased to 2.32 L/h for the “Increased CL” scenario.

The effects of a two-fold increase in the clearance of a drug on its plasma concentration-time profile

constant IV infusion



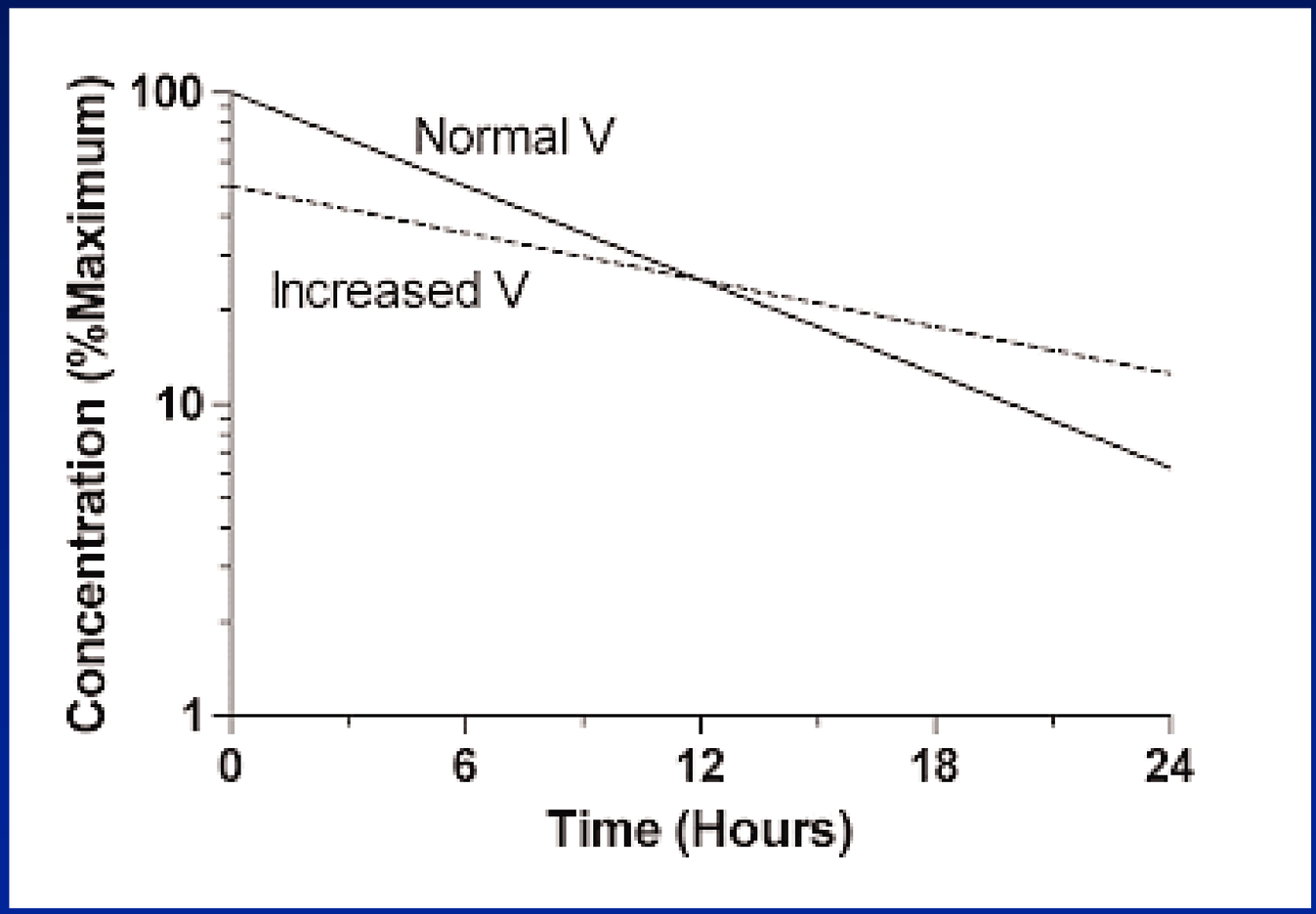
CL of 1.16 L/h and V of 10 L for the “Normal CL” scenario.

CL was increased to 2.32 L/h for the “Increased CL” scenario.

TSS indicates the time to reach 94% of steady state (ie, 4 t ½’s).

The effects of a two-fold increase in the volume of distribution of a drug on its plasma concentration-time profile

IV bolus

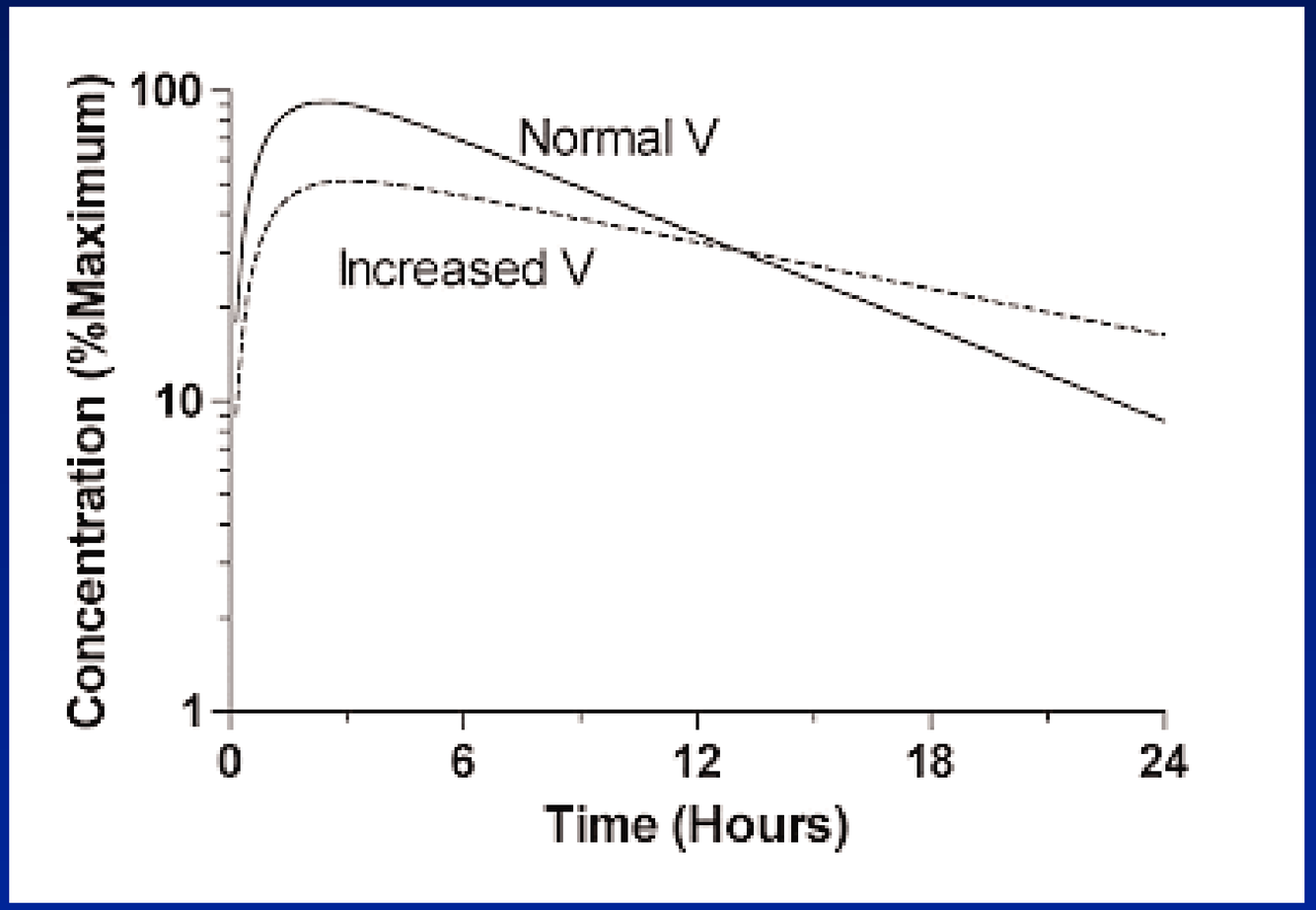


CL of 1.16 L/h and V of 10 L for the “Normal V” scenario.

V was increased to 20 L for the “Increased V” scenario.

The effects of a two-fold increase in the volume of distribution of a drug on its plasma concentration-time profile

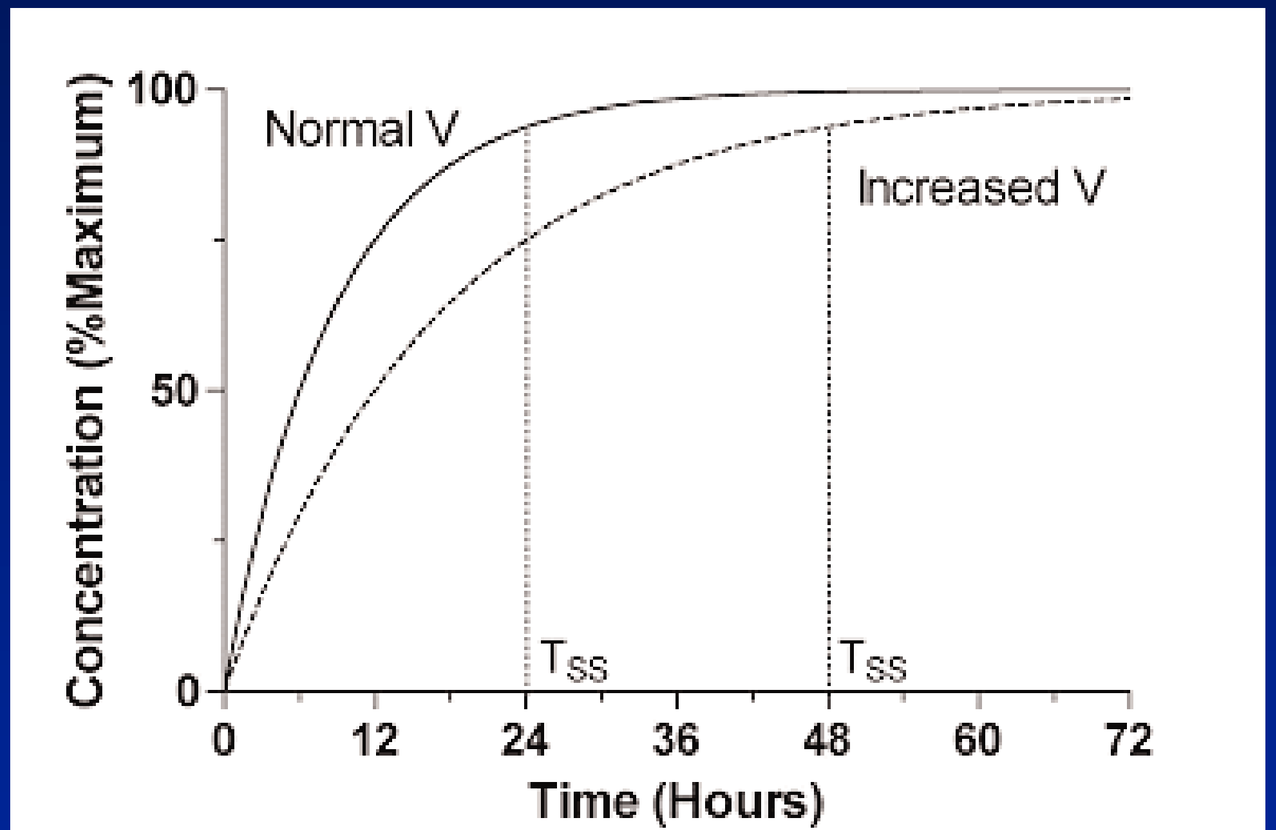
Oral



CL of 1.16 L/h, V of 10 L, absorption rate constant of 1 hr -1 , and F of 1 for the “Normal V” scenario. V was increased to 20 L for the “Increased V” scenario.

The effects of a two-fold increase in the volume of distribution of a drug on its plasma concentration-time profile

Constant IV infusion

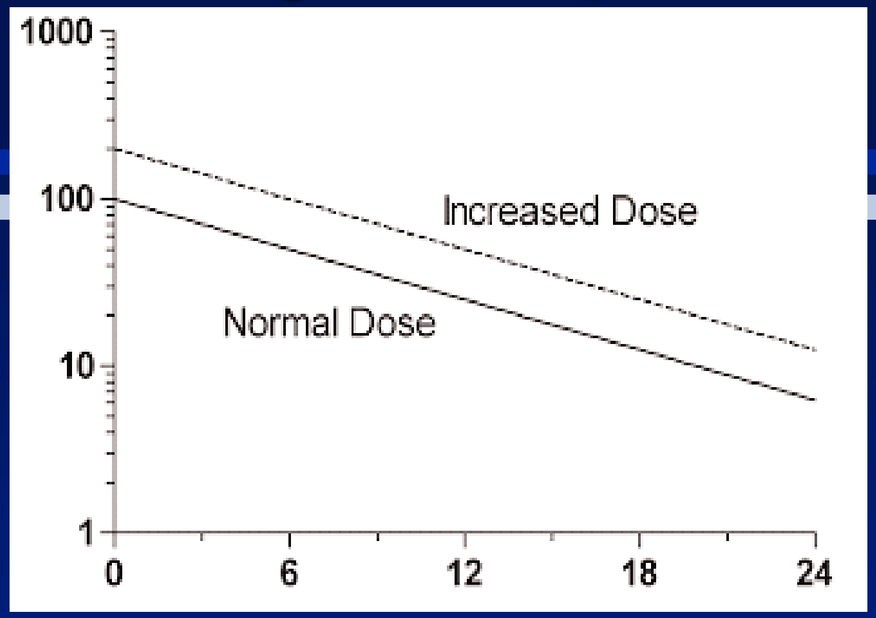


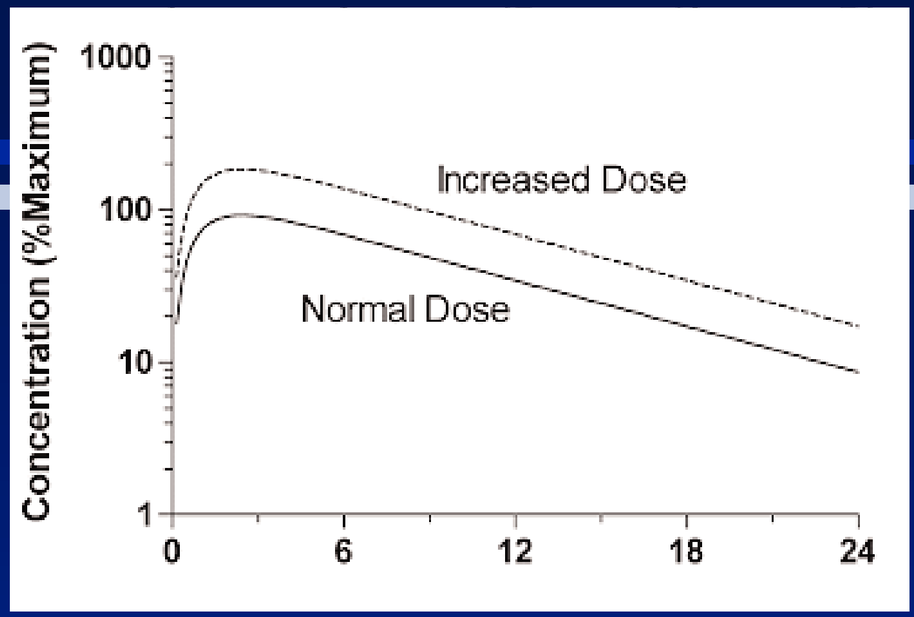
CL of 1.16 L/h and V of 10 L for the “Normal V” scenario.

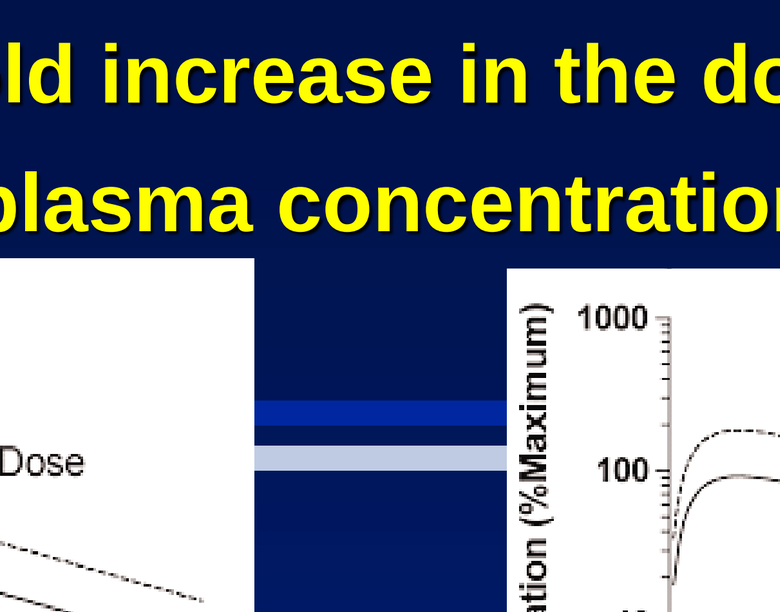
V was increased to 20 L for the “Increased V” scenario.

TSS indicates the time to reach 94% of steady state (ie, 4 t½’s).

The effects of a two-fold increase in the dose or infusion rate of a drug on its plasma concentration-time profile







CL of 1.16 L/h, V of 10 L, absorption rate constant of 1 hr -1 , and F of 1.

The dose or infusion rate constant was doubled for the “Increased Dose” or “Increased Infusion Rate”

TSS indicates the time to reach 94% of steady state (ie, 4 t½’s).