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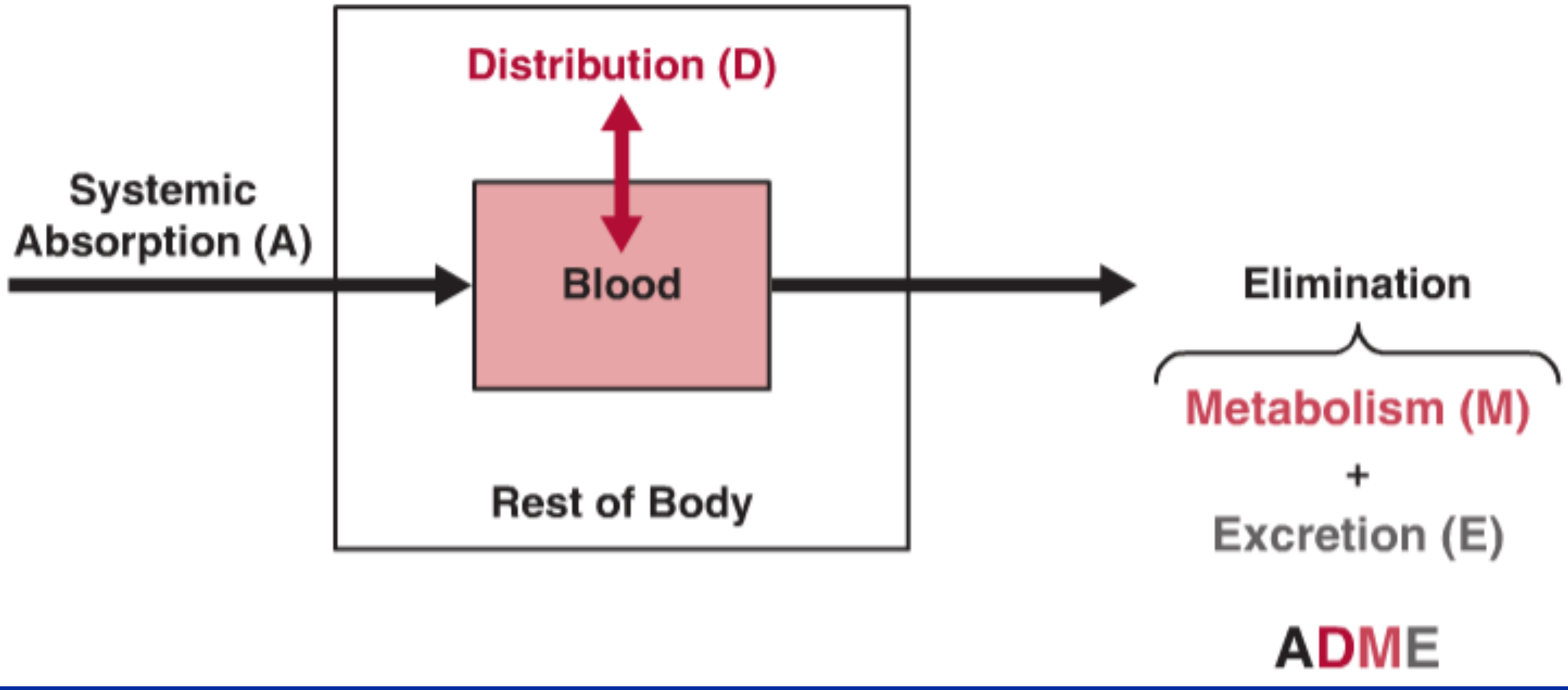
TOXICOCINÉTICA



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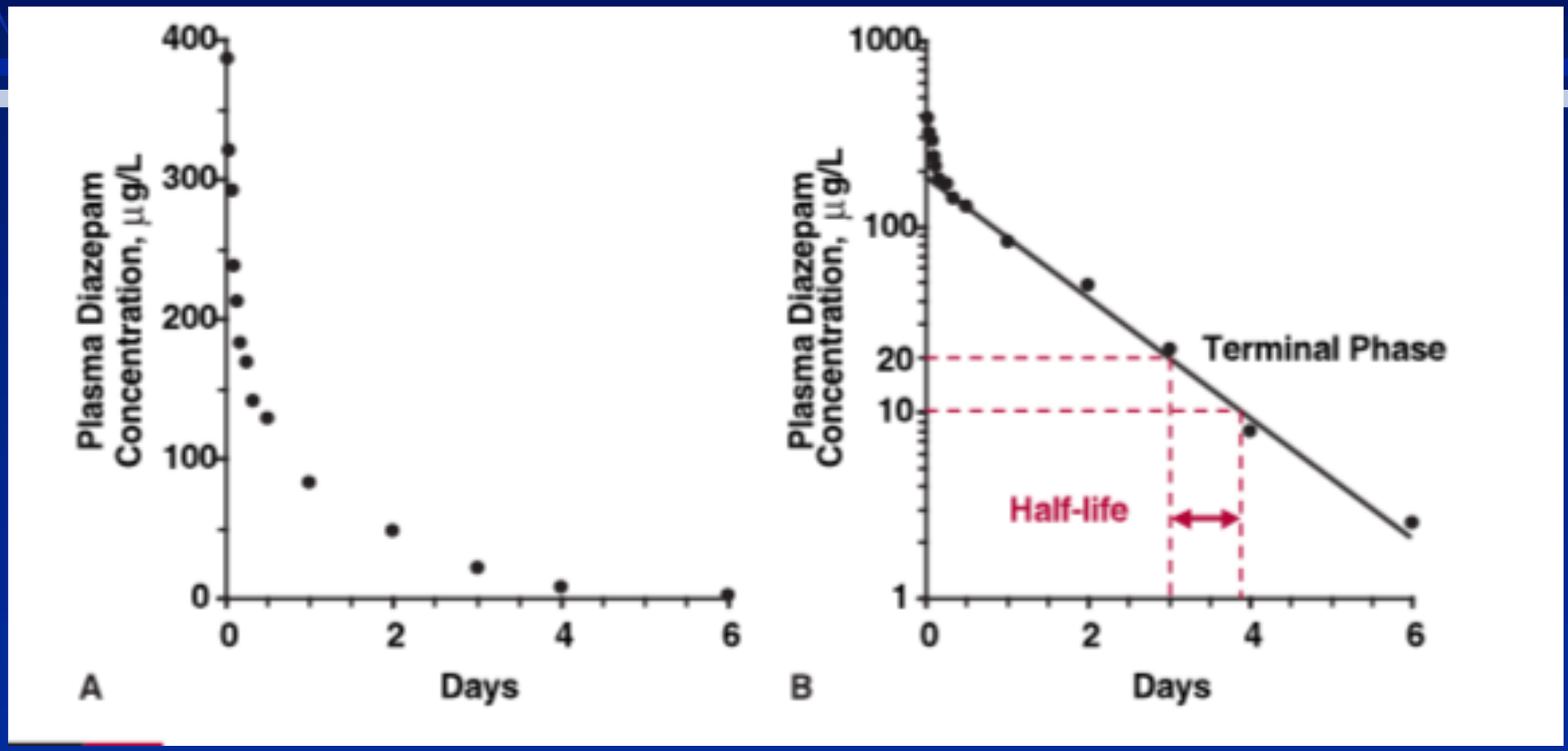
Distribution phase



Plasma concentration of diazepam with time

10 mg IV bolus dose of diazepam in a young male adult

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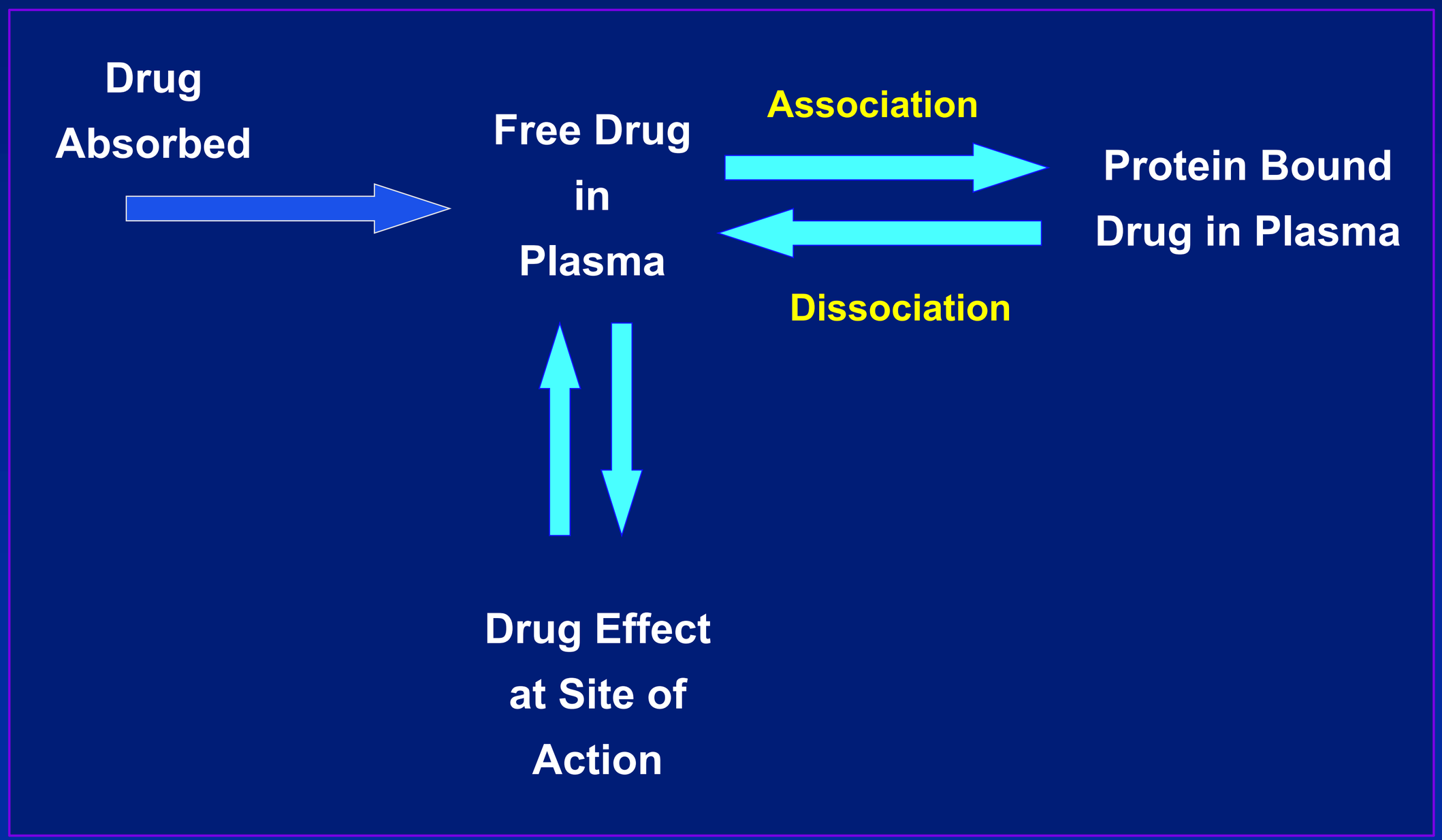
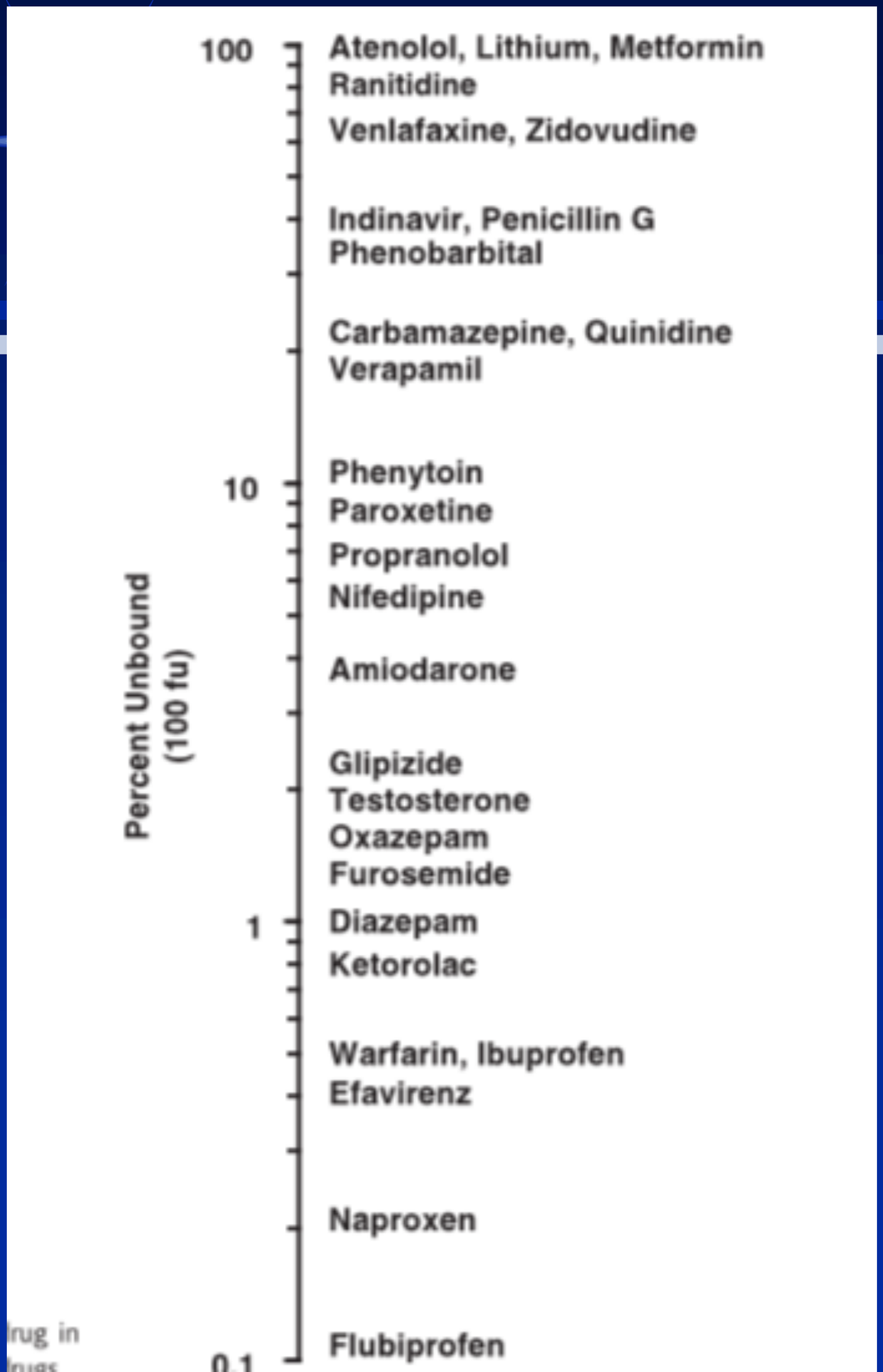
Protein Binding



Proteins to which drugs bind in plasma

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



The fraction of drug in plasma unbound varies widely among drugs

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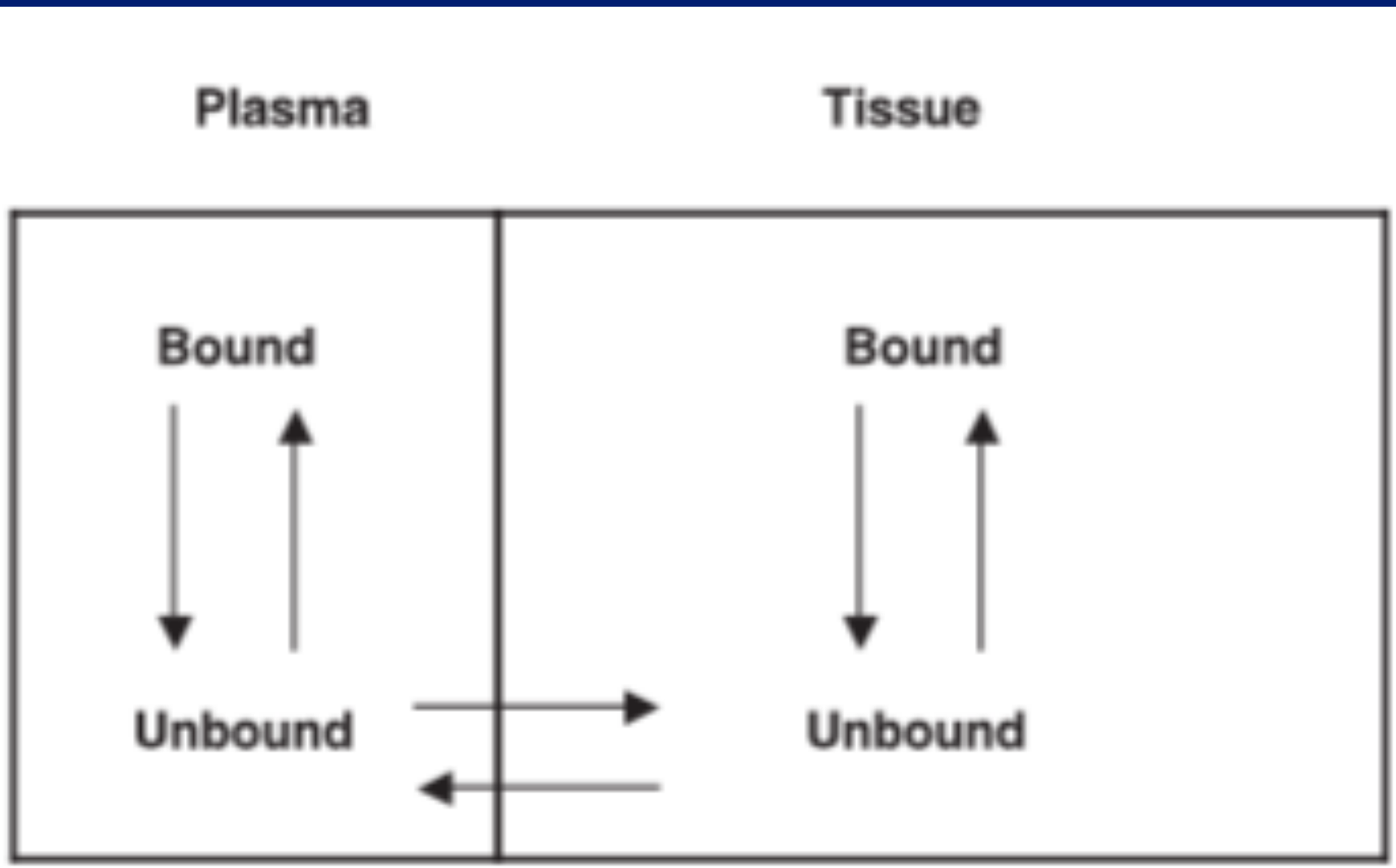
Protein binding



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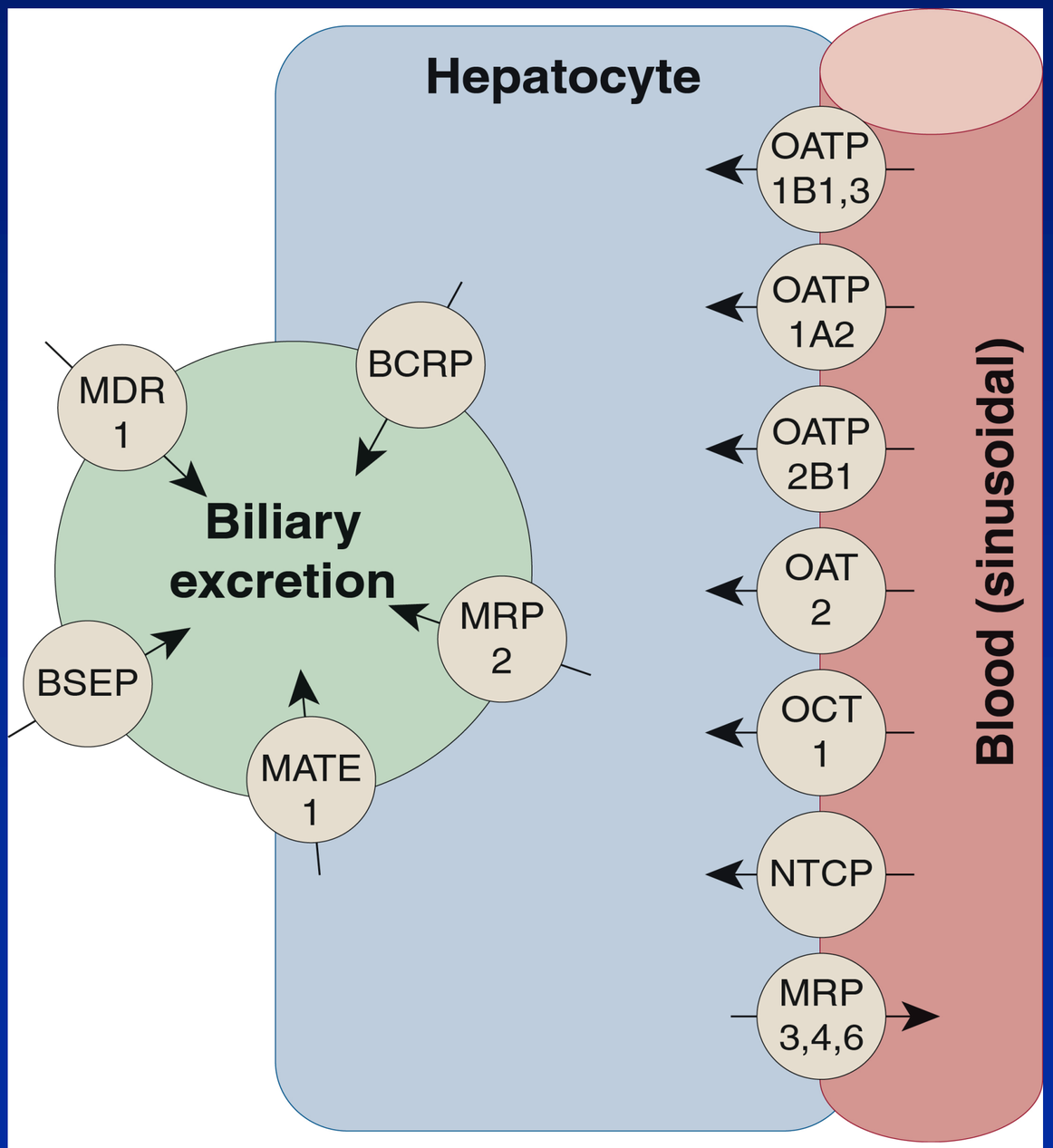
XENOBIOTIC TRANSPORTING SYSTEMS PRESENT IN THE LIVER



OATP Organic anion transporting polypeptide

OAT Organic anion transporter

OCT Organic cation transporter

MDR1/P-gp P-glycoprotein
BCRP Breast cancer resistance protein
MRP2 Multidrug resistance protein 2
BSEP Bile salt excretory protein
MATE Multidrug and toxin extrusion transporter

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Uptake transporter-based interactions at the liver

HEPATIC INTERACTION

Drug	Interaction	Mechanism	Vd/F
Atorvastatin	Rifampin	Inhibition of OATP1B1 uptake	↓ 94.3%
Cerivastatin	Cyclosporine	Inhibition of OATP1B1 uptake	↓ 66.7%
Glyburide	Rifampin	Reduced OATP2B1 uptake	↓ 67.4%
Metformin	OCT1 reduced function allele	Reduced OCT1 uptake	↓ 53.9%
Repaglinide	Cyclosporine	Inhibition of OATP1B1 uptake	↓ 59.0%
Rosuvastatin	Cyclosporine	Inhibition of OATP1B1 uptake	↓ 90.6%
Rosuvastatin	Gemfibrozil	Inhibition of OATP1B1 uptake	↓ 27.5%

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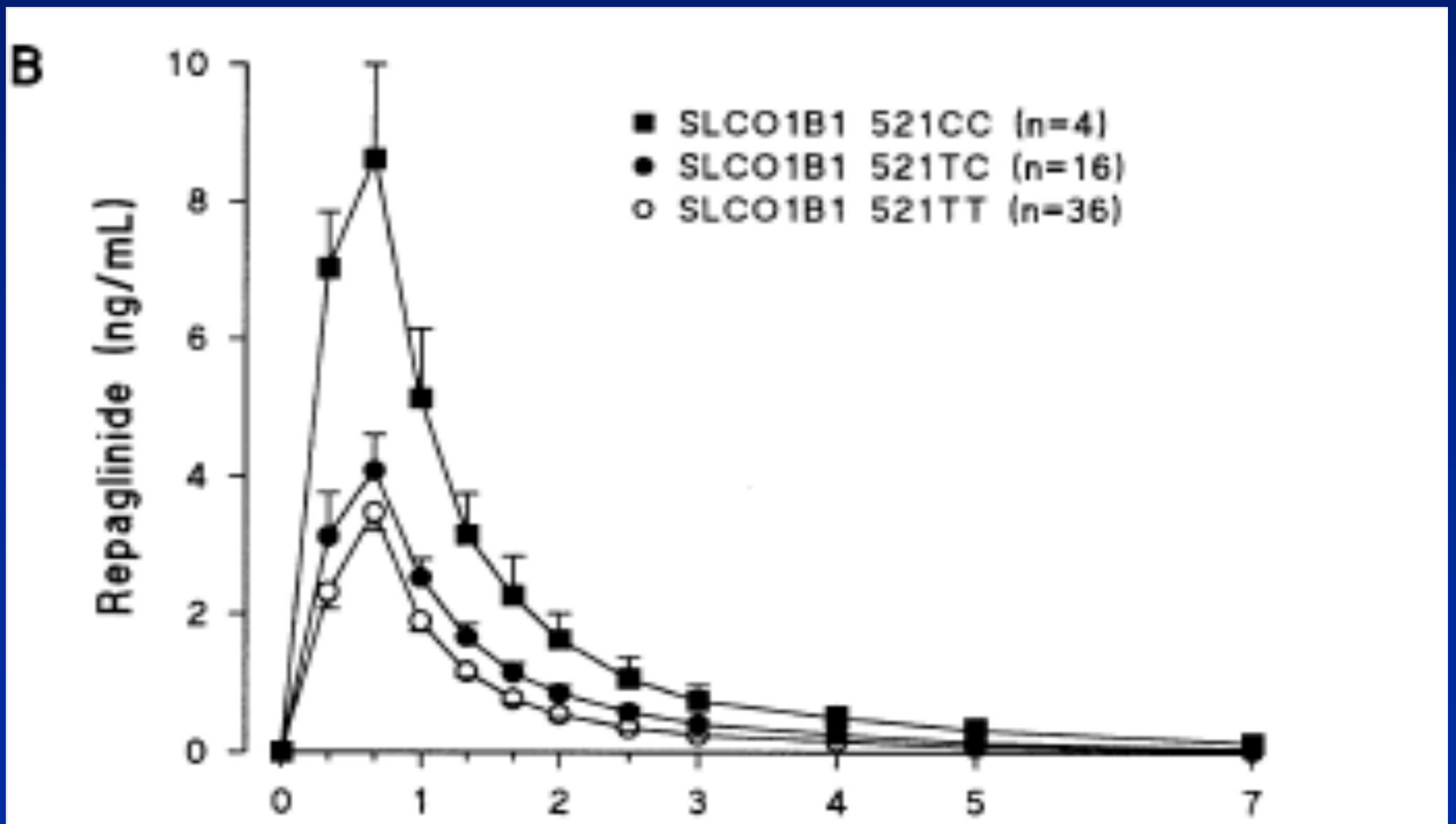
Polymorphic OATP 1B1 is a major determinant of repaglinide pharmacokinetics: CYP2C8 and CYP3A



2005

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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

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TREZOR
rosuvastatina cálcica

- Polimorfismo genético (variedade de genes): dependendo da sua constituição genética, o nível de rosuvastatina pode aumentar no seu organismo. Neste caso, seu médico poderá ajustar a dose de Trezor. Genótipos de SLCO1B1 (OATP1B1) c.521CC e ABCG2 (BCRP) c.421AA têm mostrado ser associados com um aumento da exposição à rosuvastatina (ASC) em comparação com SLCO1B1 c.521TT e ABCG2 c.421CC. Para os pacientes com genótipo c.521CC ou c.421AA, recomenda-se uma dose máxima de 20 mg de rosuvastatina, uma vez por dia.

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TREZOR
rosuvastatina cálcica

- **Terapia concomitante:** a rosuvastatina é um substrato de várias proteínas transportadoras (por exemplo, OATP1B1 e BCRP). O risco de miopatia (incluindo rabdomiólise) é maior quando Trezor é administrado concomitantemente com certos medicamentos que podem aumentar a concentração plasmática da rosuvastatina devido às interações com essas proteínas transportadoras (por exemplo, ciclosporina e alguns inibidores de protease, incluindo combinações de ritonavir com atazanavir, lopinavir, e/ou tipranavir. É recomendado que seu médico consulte as informações relevantes dos medicamentos quando considerar administrar esses medicamentos concomitantemente com Trezor. Seu médico poderá considerar um tratamento alternativo ou a interrupção temporária de Trezor. Em situações em que a coadministração destes medicamentos com Trezor é inevitável, o benefício e o risco do tratamento concomitante e ajustes da posologia de Trezor devem ser cuidadosamente considerados.

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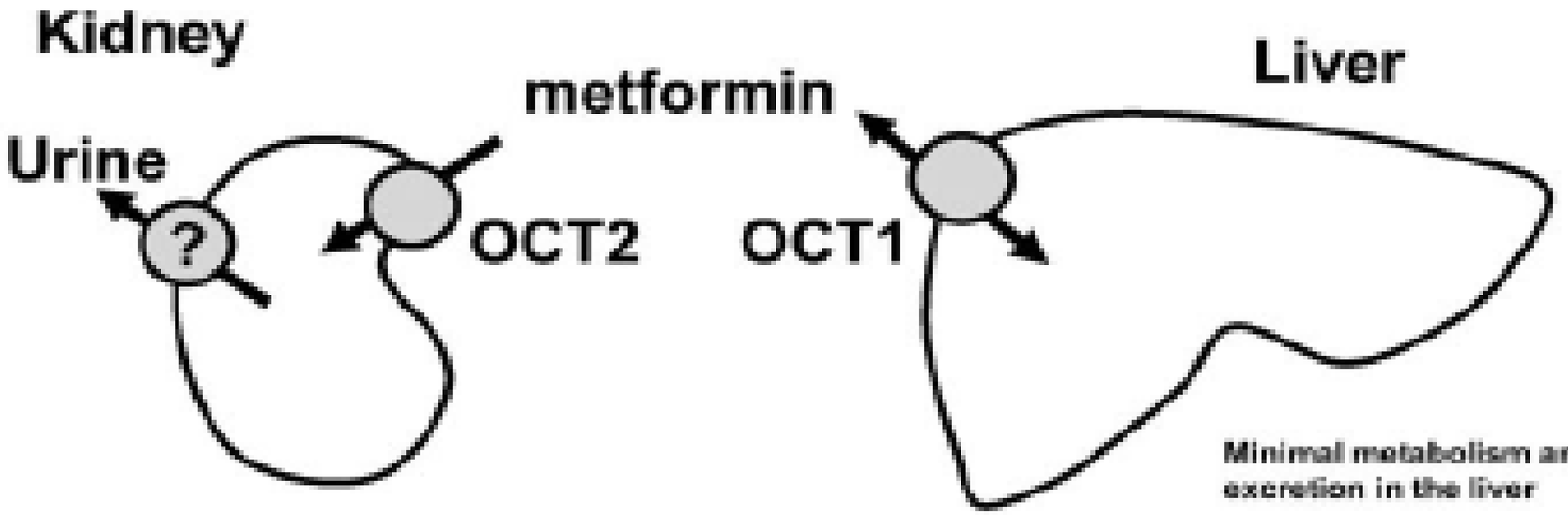
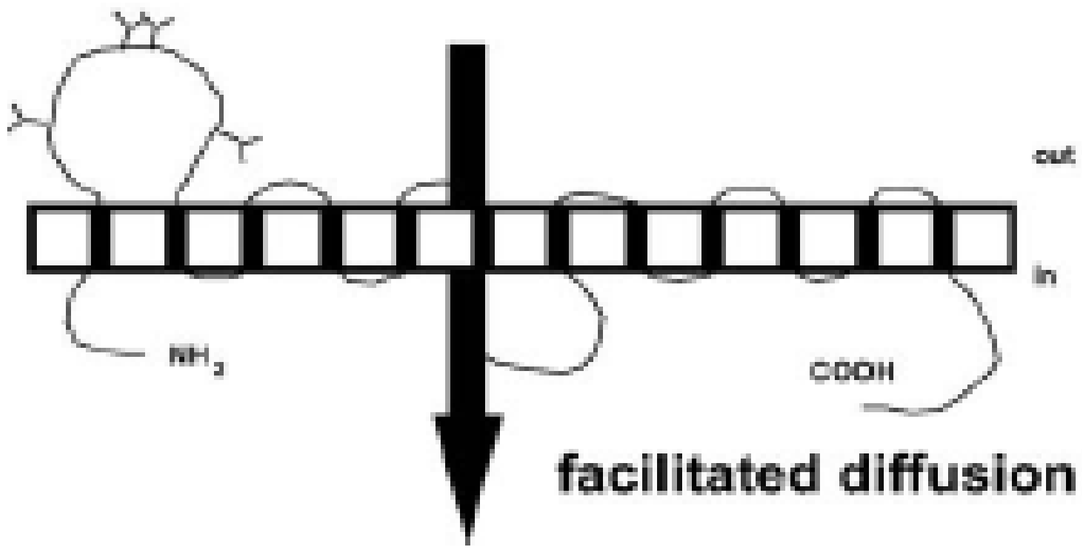
MECHANISMS OF TISSUE DISTRIBUTION OF METFORMIN





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

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

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

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Formyn®

cloridrato de metformina

MULTILAB®

Transportadores de catións orgânicos (OCT): a metformina é um substrato tanto de transportadores OCT1 quanto de OCT2. A coadministração de metformina com:

- Substratos/inibidores de OCT1 (como verapamil) podem reduzir a eficácia de metformina.

- Indutores do OCT1 (como a rifampicina) podem aumentar a absorção gastrointestinal e a eficácia.

- Substratos/inibidores de OCT2 (como cimetidina, dolutegravir, crizotinibe, olaparibe, daclatasvir, vandetanibe) podem diminuir a eliminação renal da metformina e assim levar a uma concentração aumentada de metformina no plasma.

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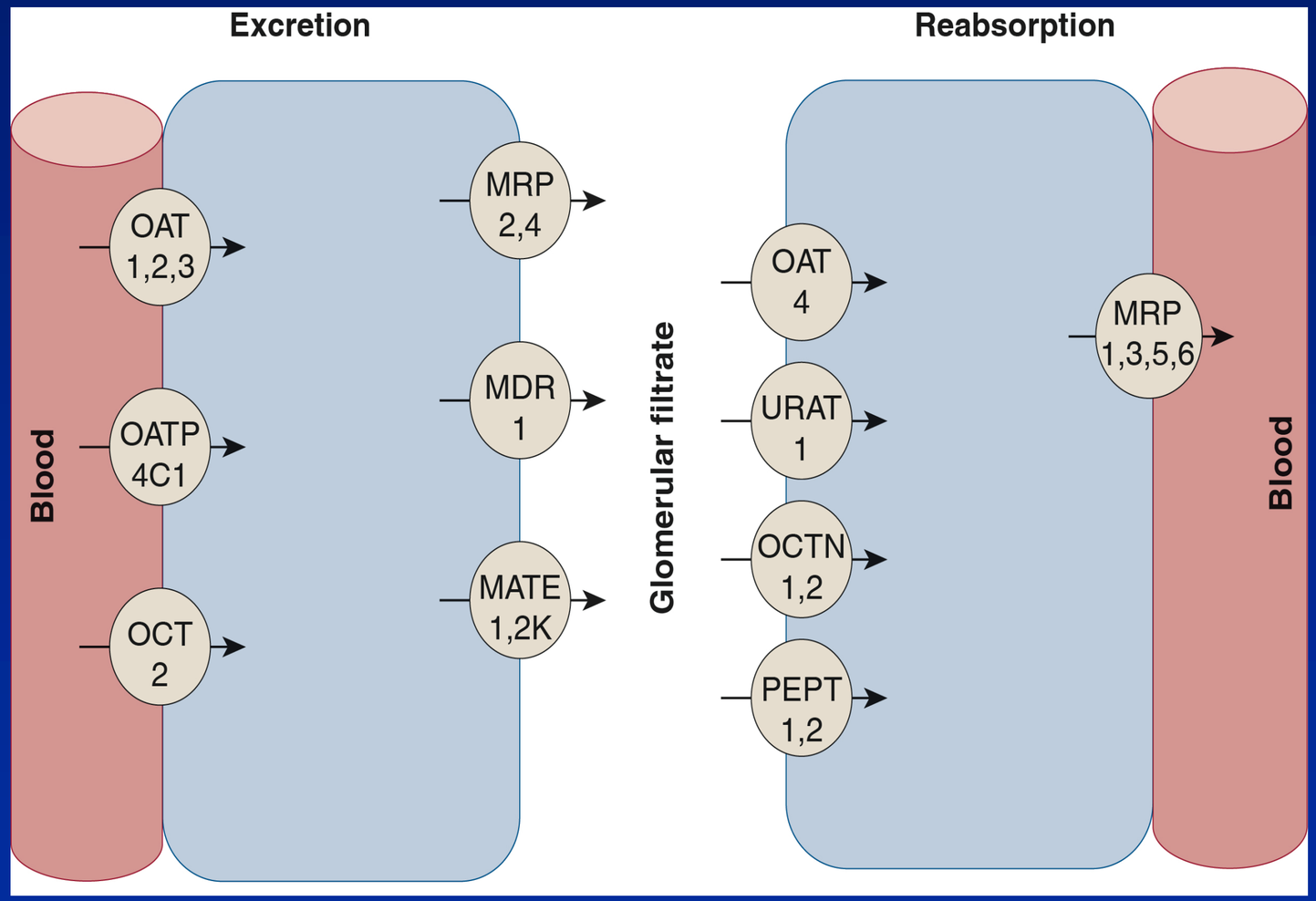
XENOBIOTIC TRANSPORT SYSTEMS IN THE PROXIMAL TUBULE OF THE KIDNEY



OAT
Organic anion transporter
OCT
Organic cation transporter
OATP
Organic anion transporting polypeptide

MRP
Multidrug resistance protein
MDR1/P-gp
P-glycoprotein
MATE
Multidrug and toxin extrusion transporter

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Effects of transporter inhibition/dysfunction on volume of distribution

	Kidney	Liver
Uptake	↔, (↓)	↓
Efflux	↑	↓, ↔

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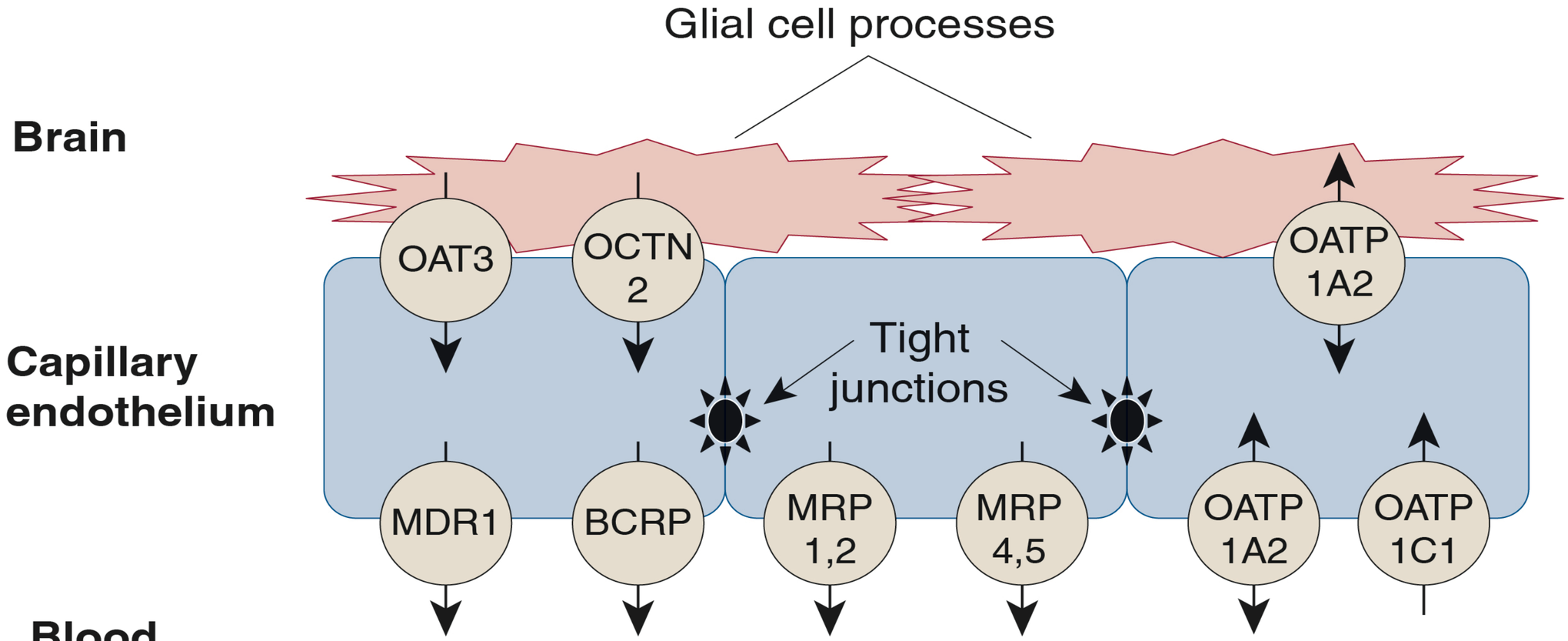
XENOBIOTIC TRANSPORTING SYSTEMS THAT CONTRIBUTE TO THE BLOOD-BRAIN BARRIER



MDR1/P-gp P-glycoprotein (MDR1)

BCRP Breast cancer resistance protein

MRP Multidrug resistance protein

OATP Organic anion transporting polypeptide

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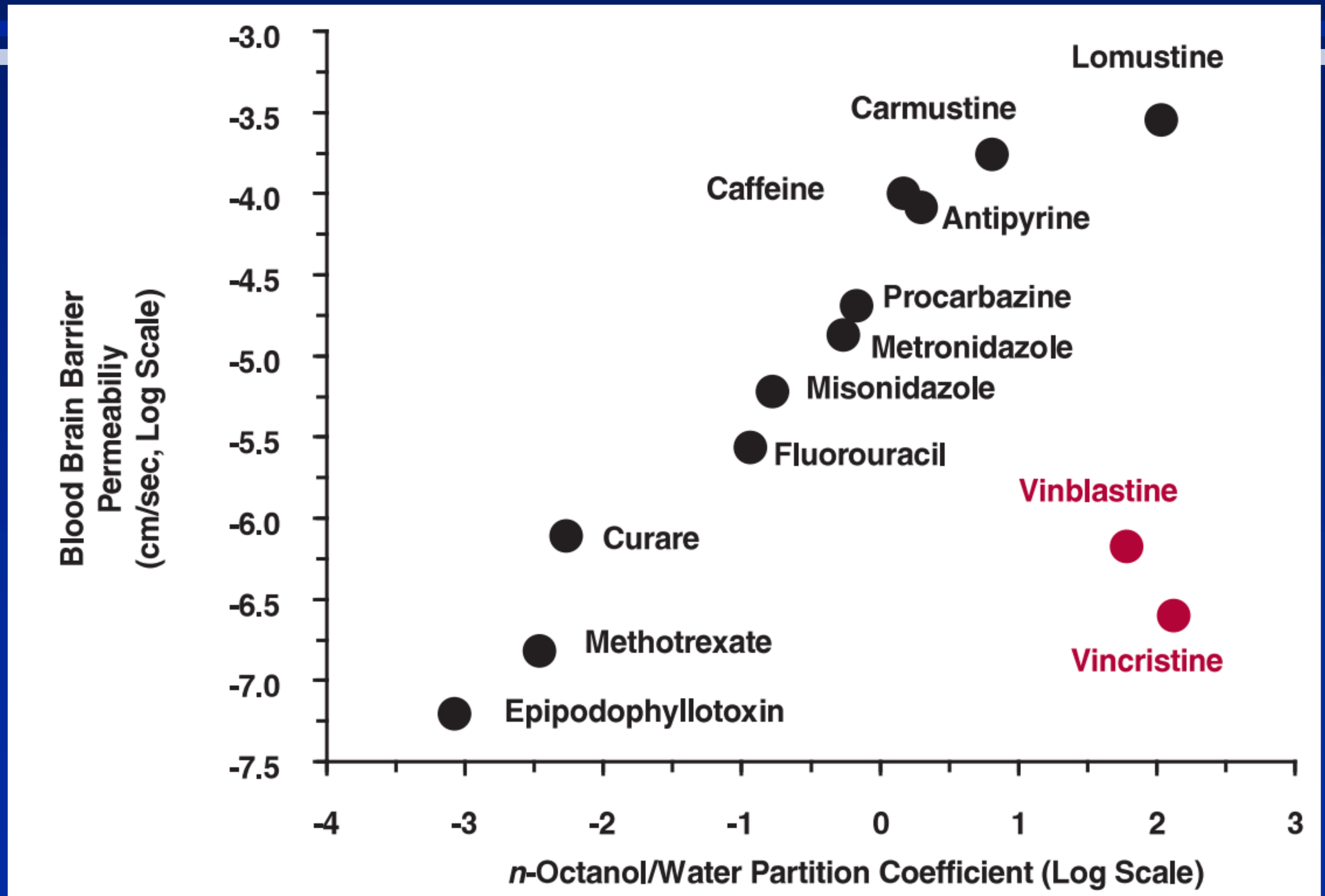
XENOBIOTIC TRANSPORTING SYSTEMS THAT CONTRIBUTE TO THE BLOOD-BRAIN BARRIER



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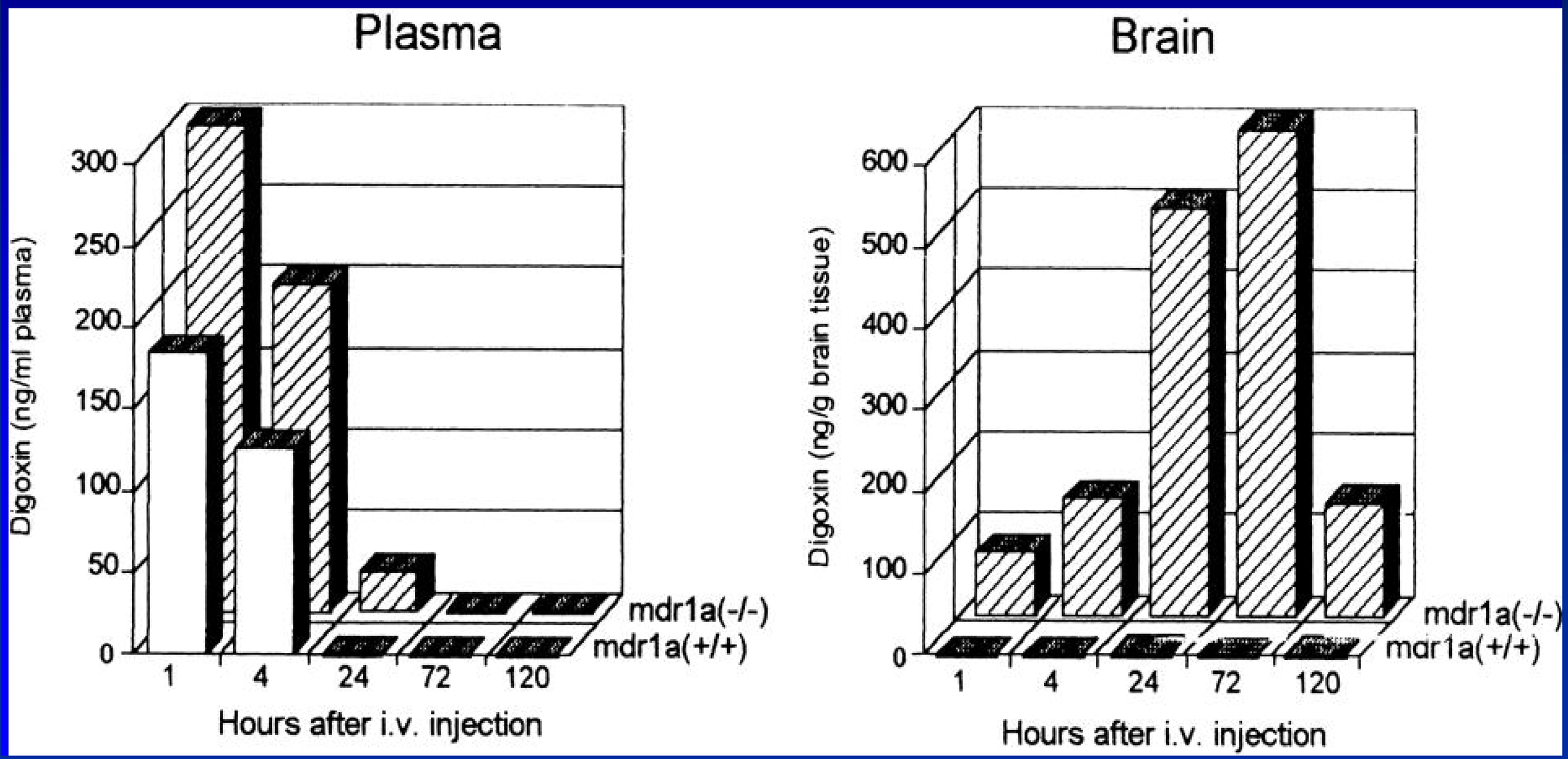
Levels of digoxin in plasma and brain of mice

MDR1/P-gp (+/+) and (-/-)



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

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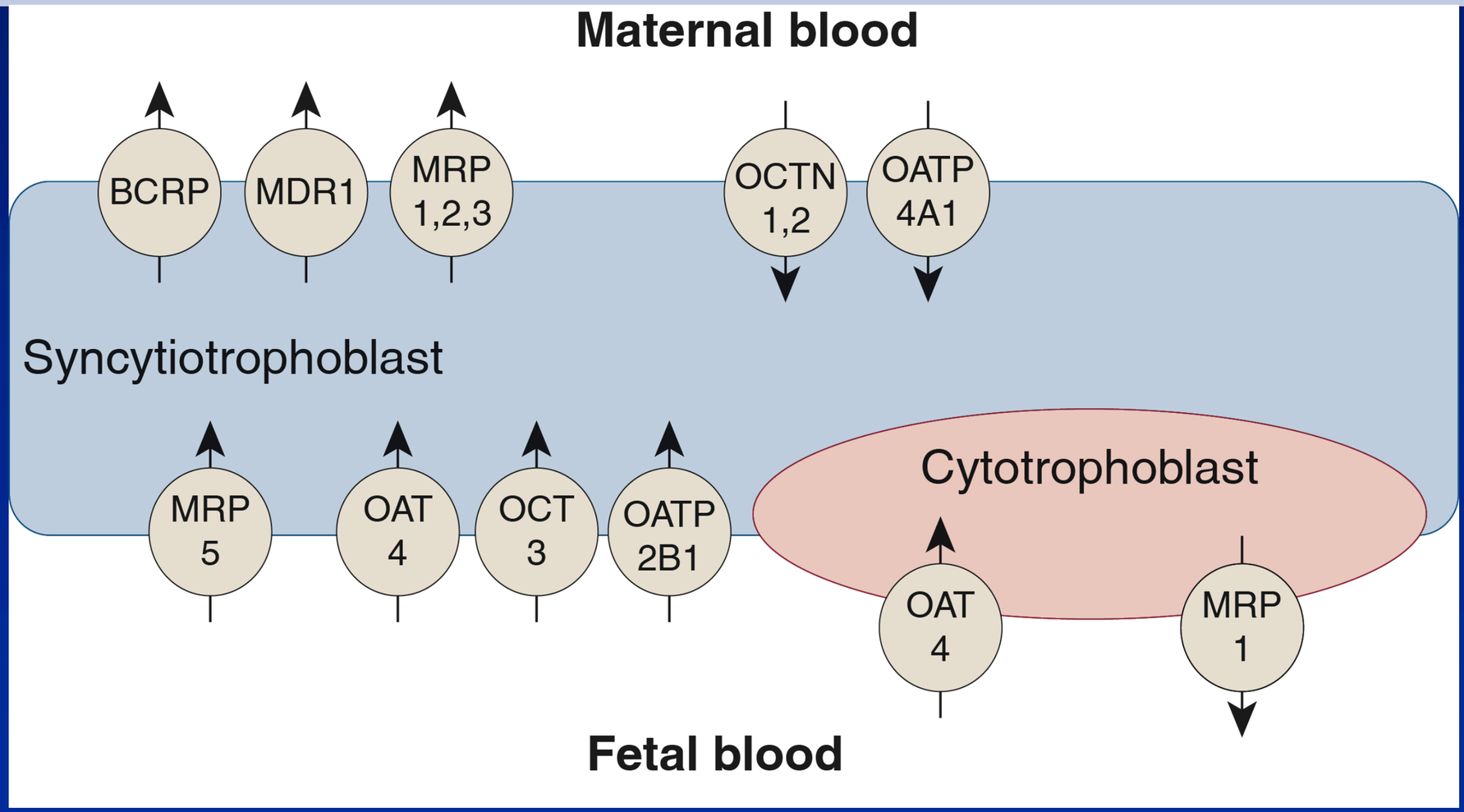
TRANSPORT SYSTEMS THAT CONTRIBUTE TO THE BARRIER FUNCTION OF THE PLACENTA



MDR1/P-gp P-glycoprotein

MRP Multidrug resistance protein

BCRP Breast cancer resistance protein

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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

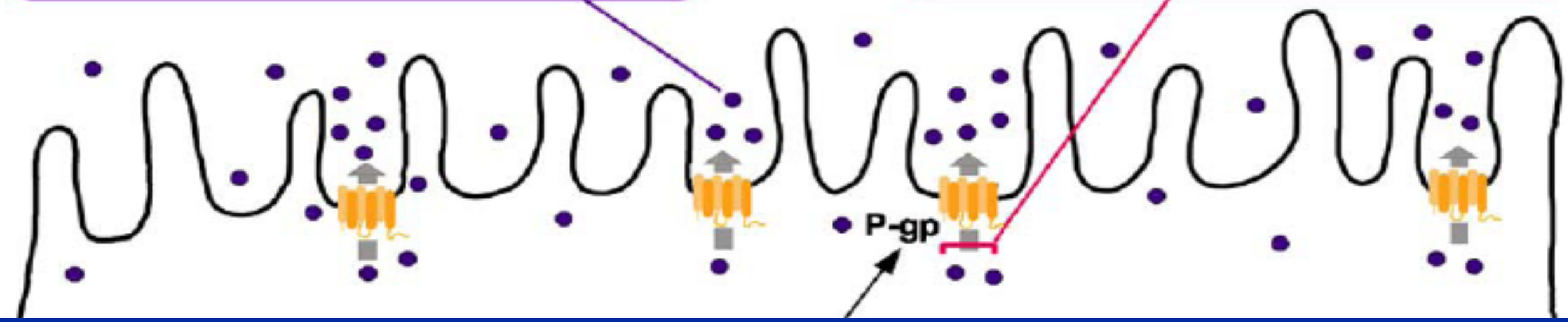
First generation chemosensitizers
verapamil,quinidine
cyclosporine A
progesterone, tamoxifen
trifluoperazine, trifluopromazine,flupentixol

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



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Volume de distribuição (Vd)

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

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

Unidade	volume (mL, L)

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Volume de distribuição (Vd)

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

$$Vd = \frac{Dose\ .F}{AUC.\ Kel}$$

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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

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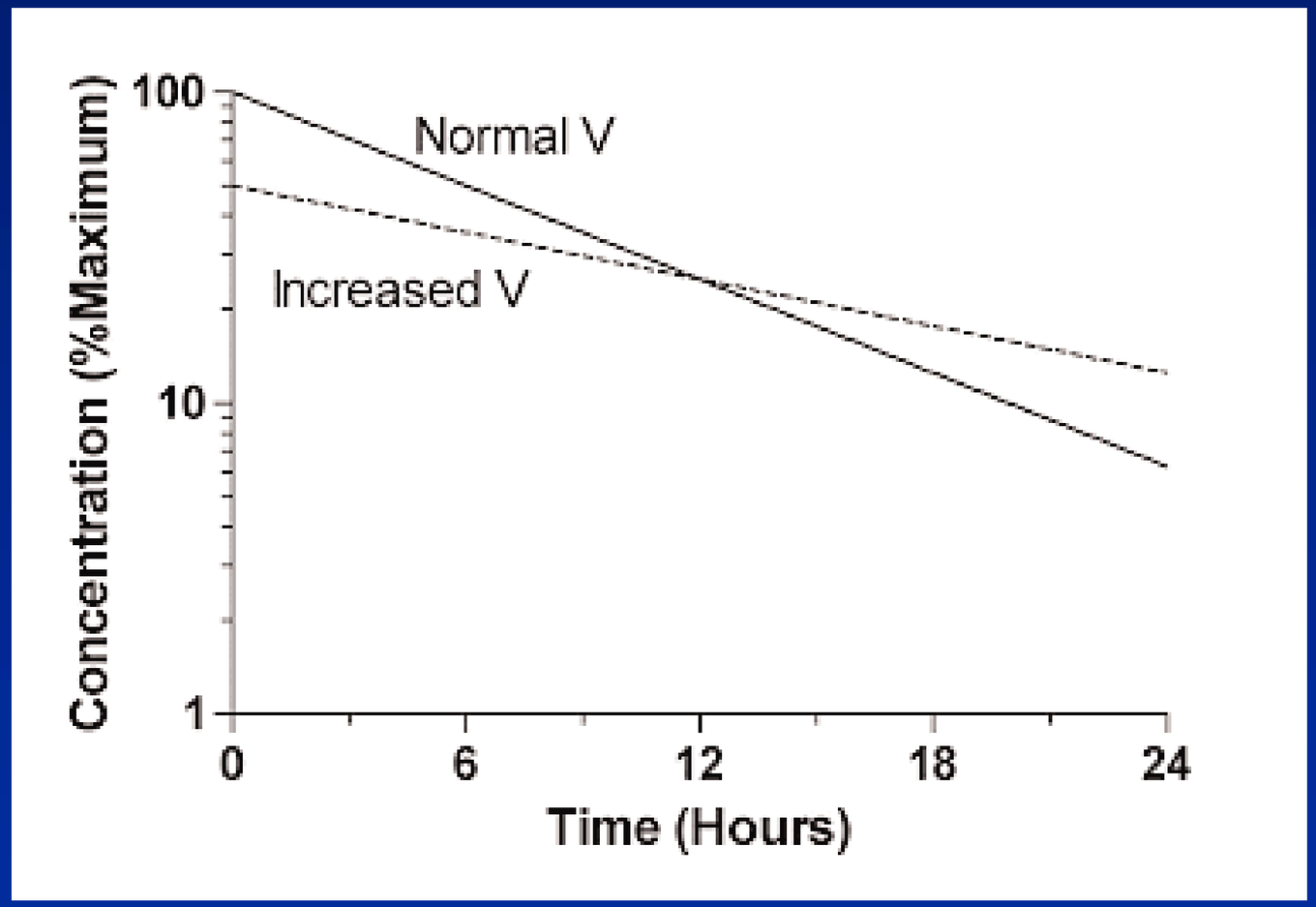
The effects of a two-fold increase in the volume of distribution of a drug on its plasma concentration-time profile

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.

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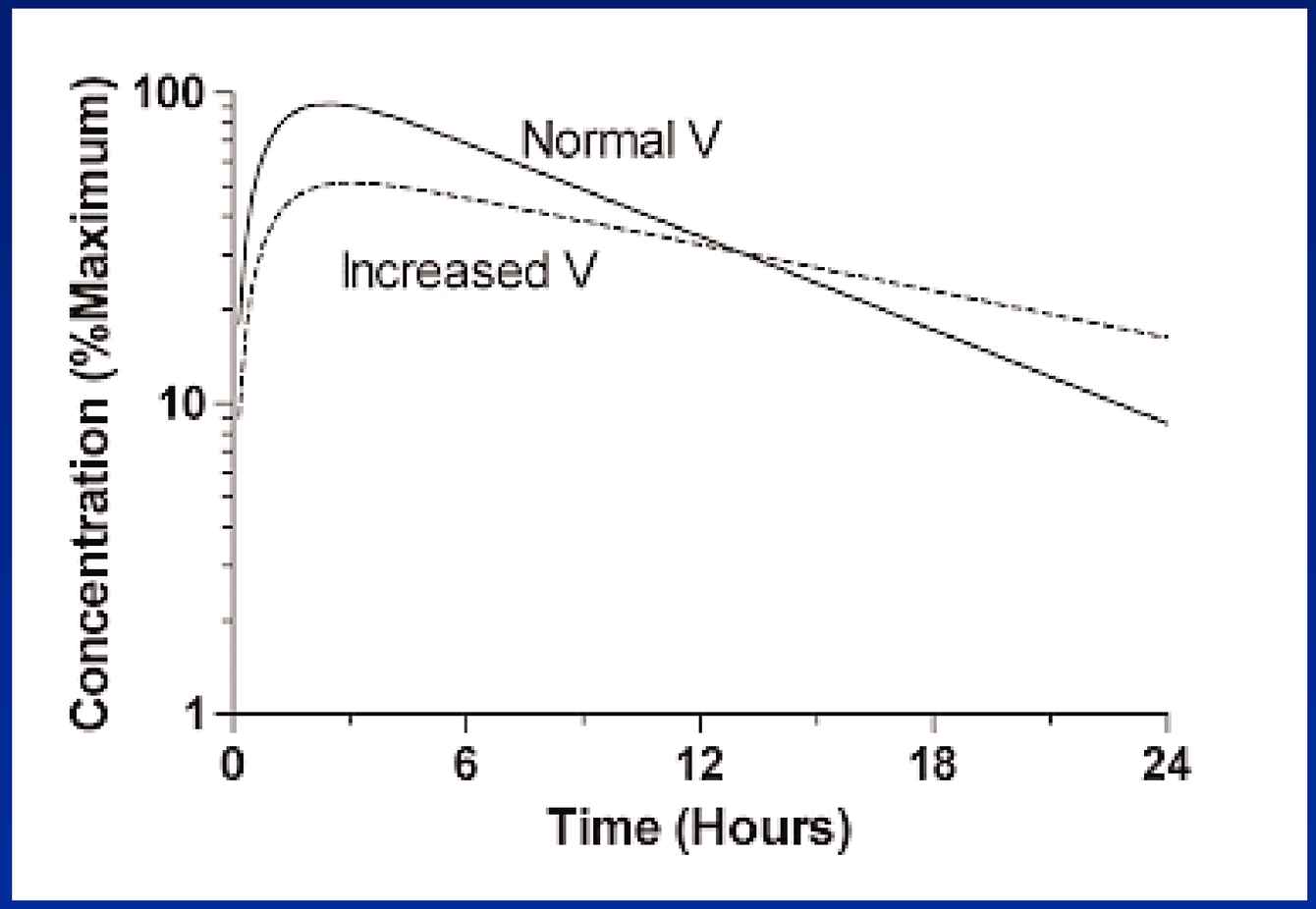
The effects of a two-fold increase in the volume of distribution of a drug on its plasma concentration-time profile

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.

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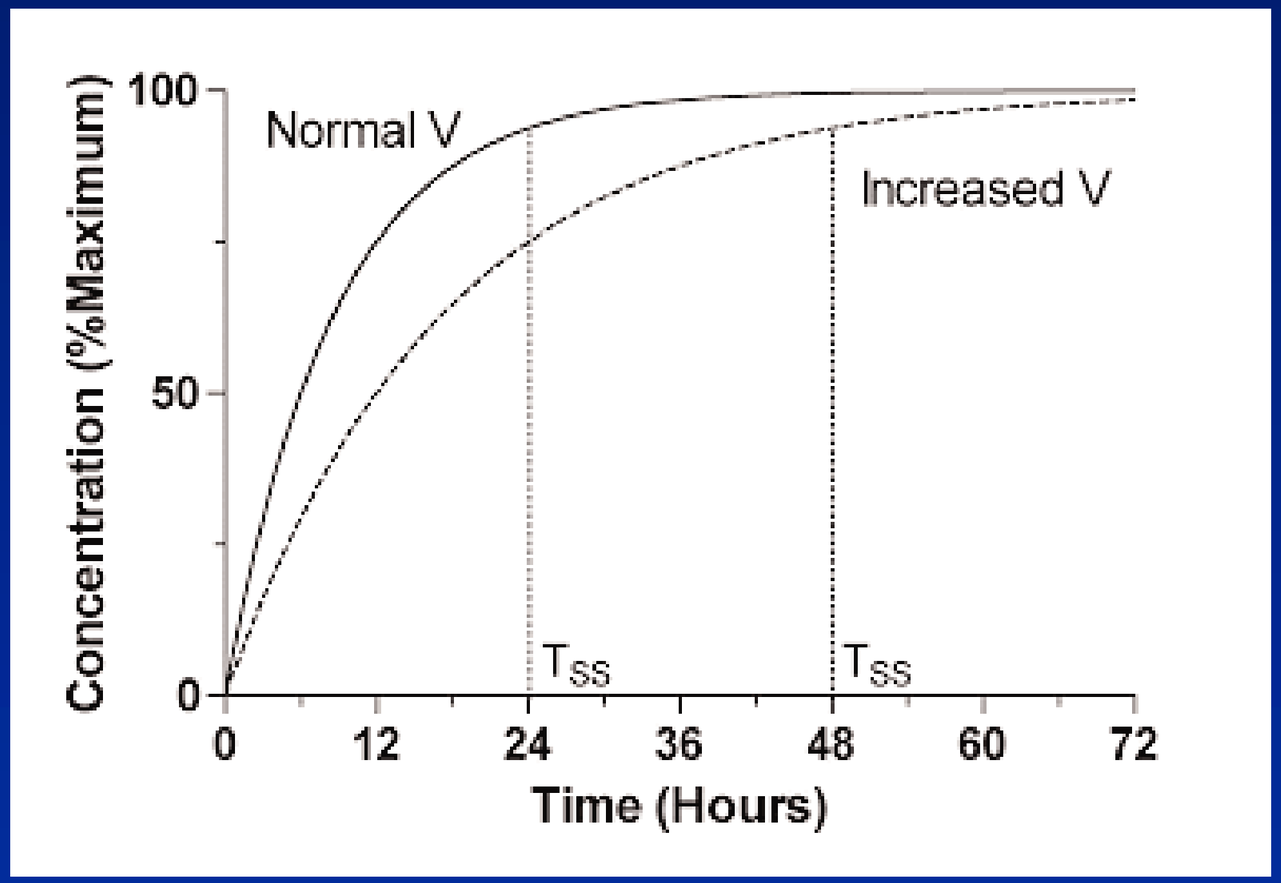
The effects of a two-fold increase in the volume of distribution of a drug on its plasma concentration-time profile

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).

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Volume of distribution

1

It can be used to compute a loading dose

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

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Volume of distribution

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

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

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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

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Central and Peripheral Compartiments

Central COMPARTIMENTS

- Heart
- Liver
- Lungs
- Kidney
- Blood

Examples of Peripheral Compartiments

- Fat Tissue
- Cerebral Fluid
- Muscle Tissue

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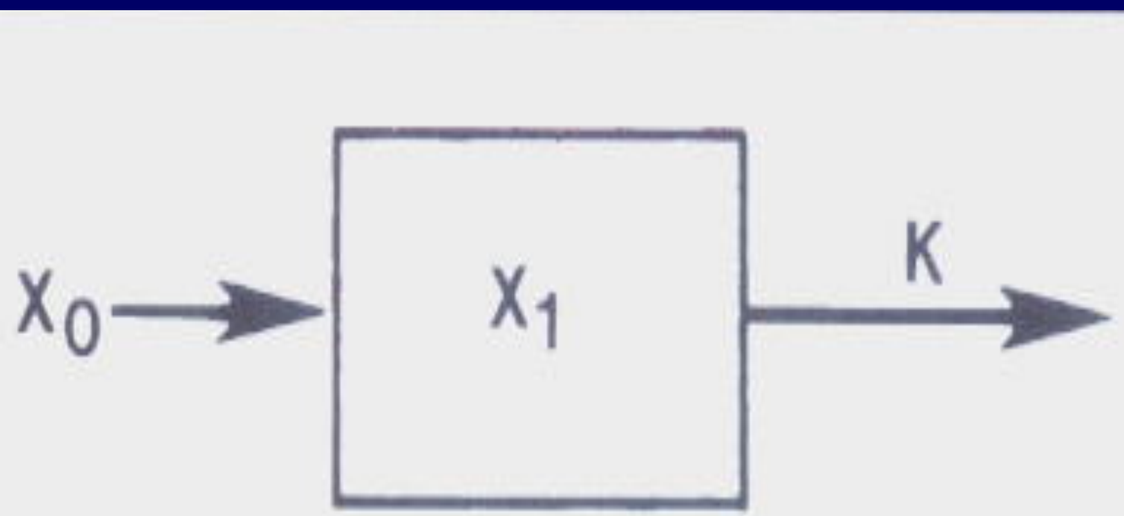
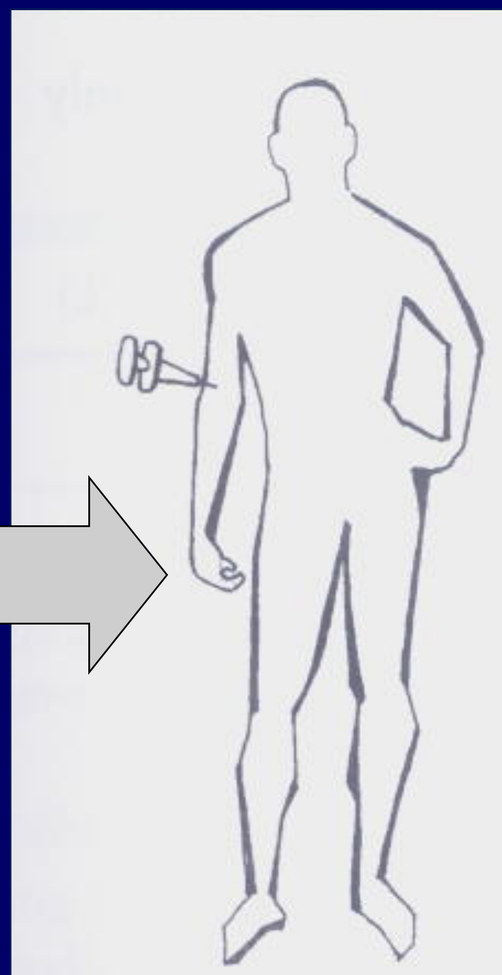
One-compartment model



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

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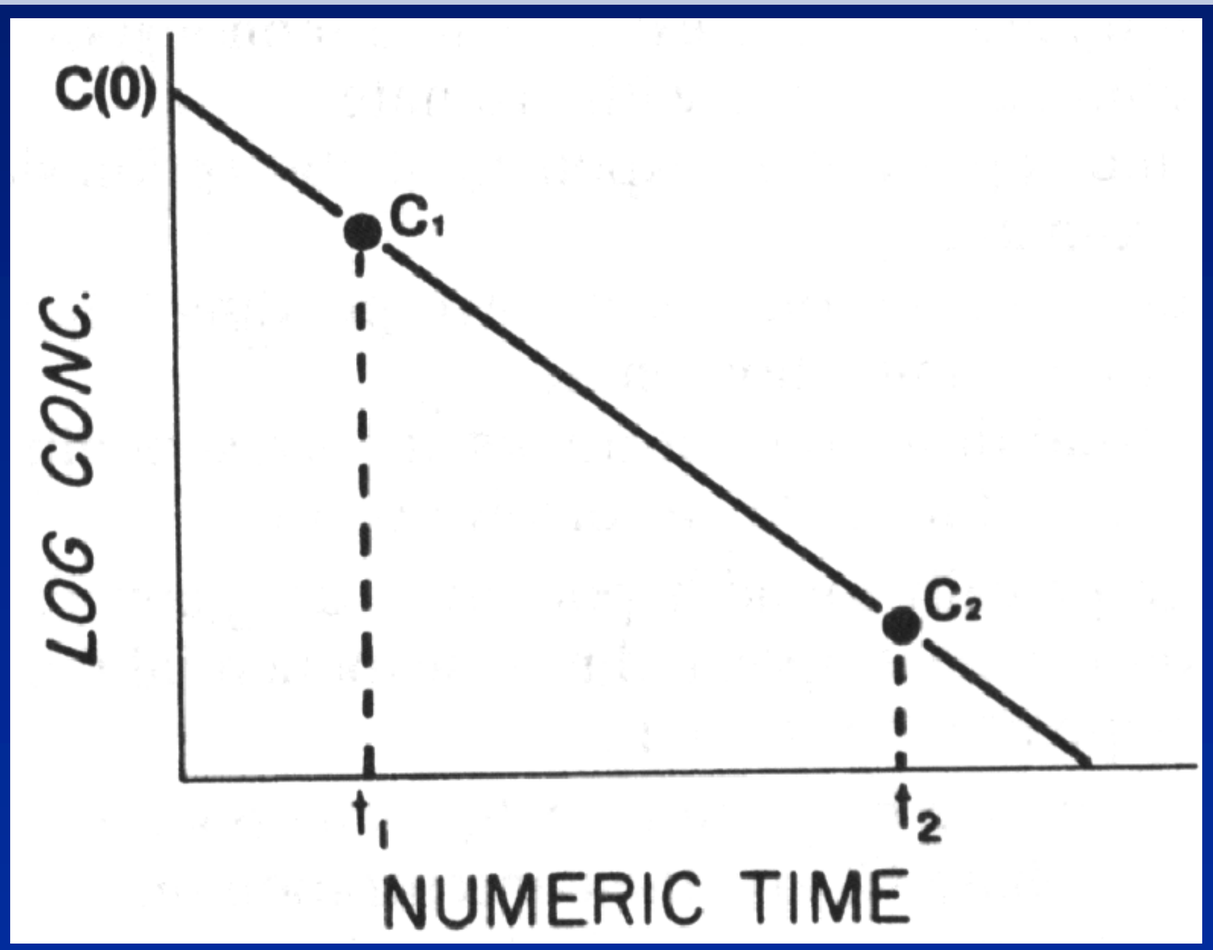
Determination of rate constants

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)

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

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

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

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

$C_0 = 1$

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

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

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

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

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

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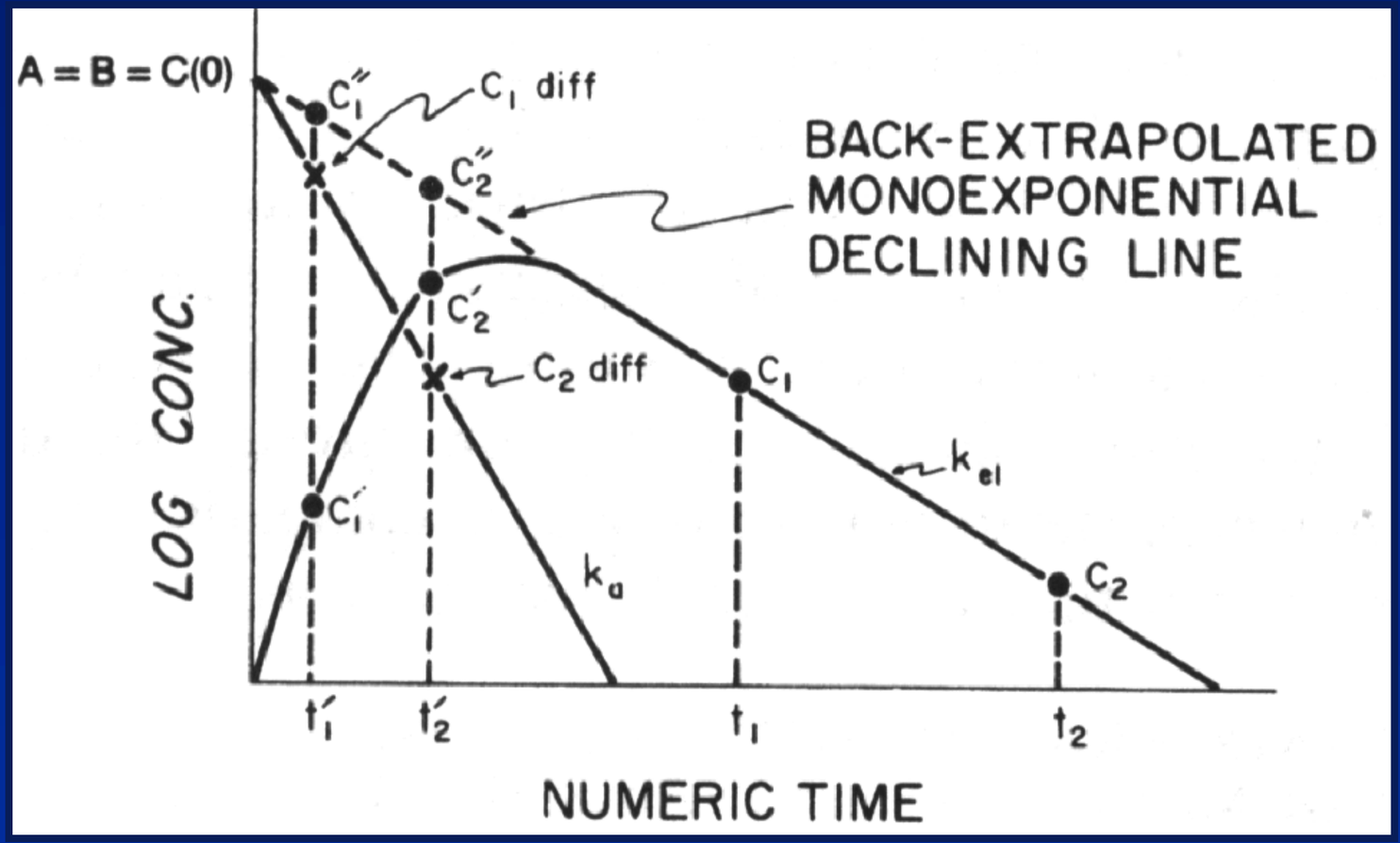
Determination of rate constants

One - compartment model Extravascular route

Step 1



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

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

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

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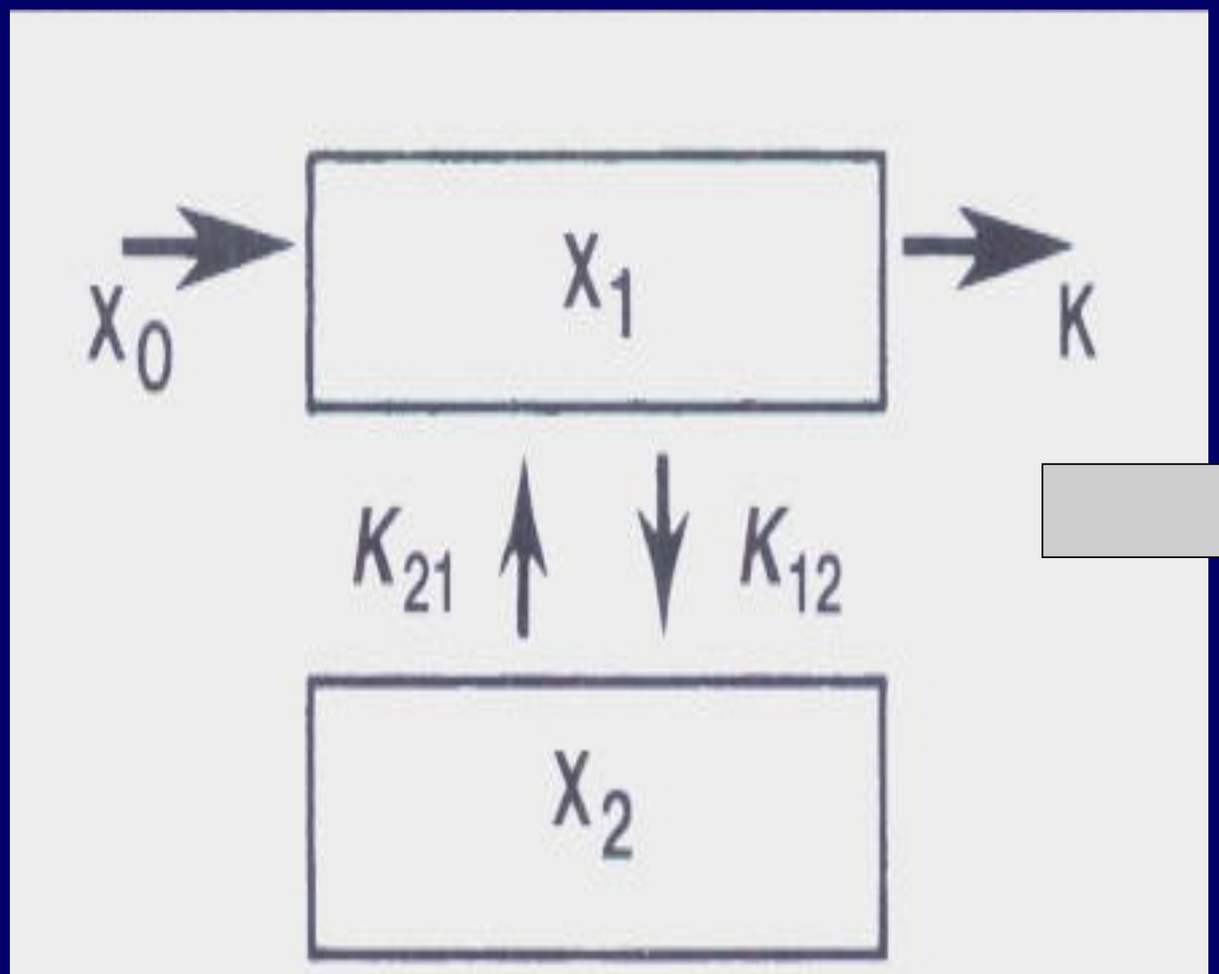
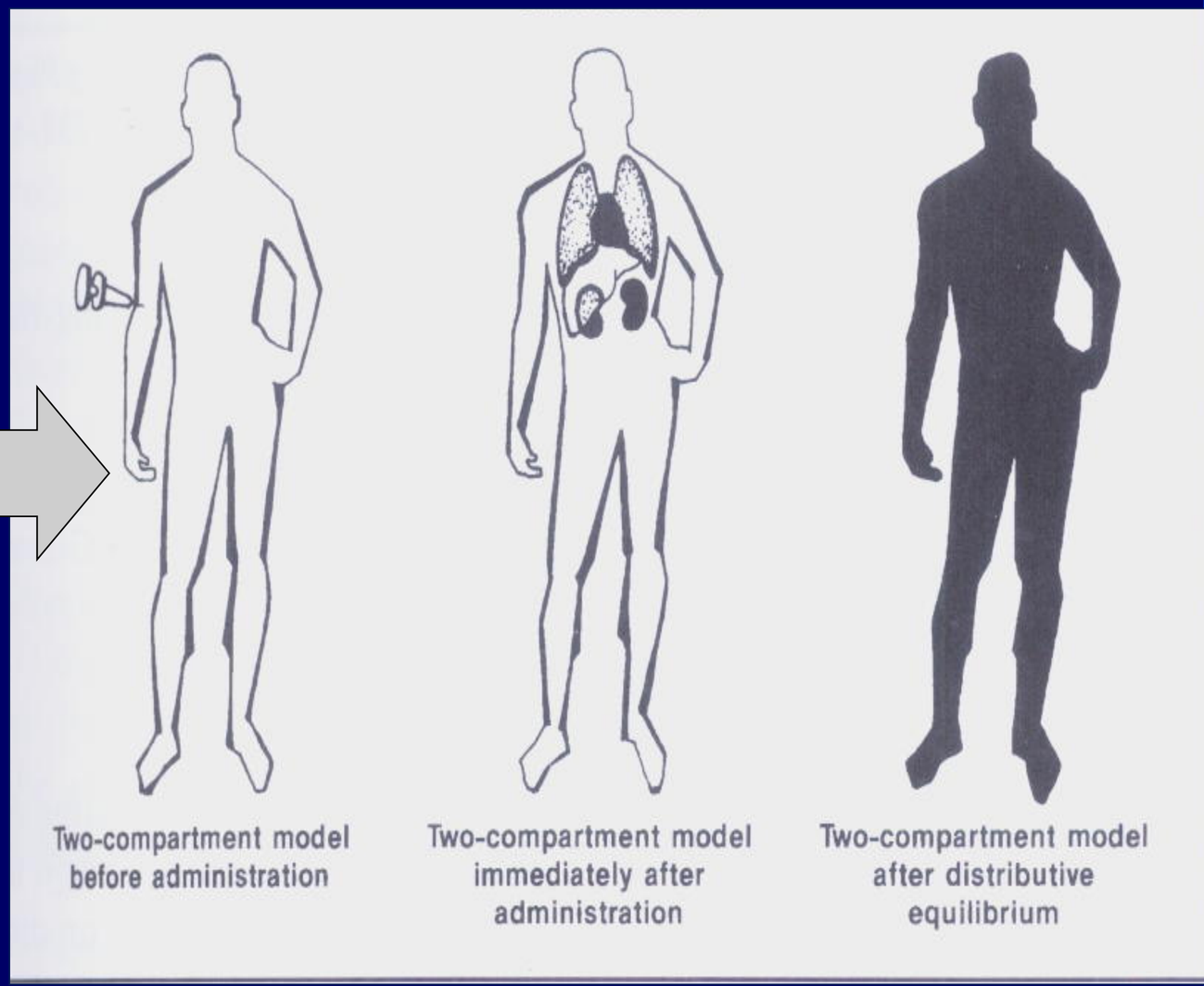
Two-compartment model





Two-compartment model before administration

Two-compartment model immediately after administration

Two-compartment model after distributive equilibrium

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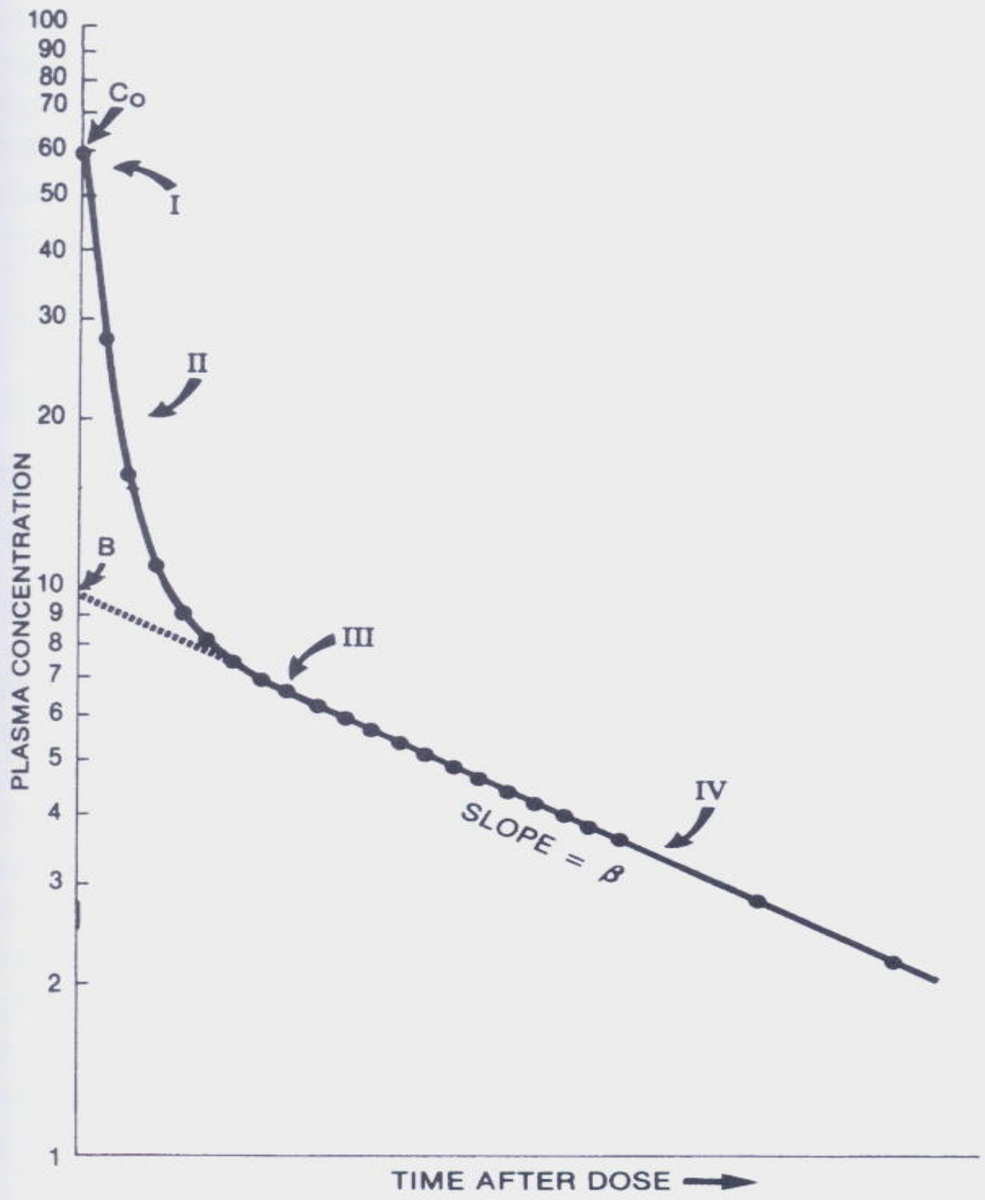
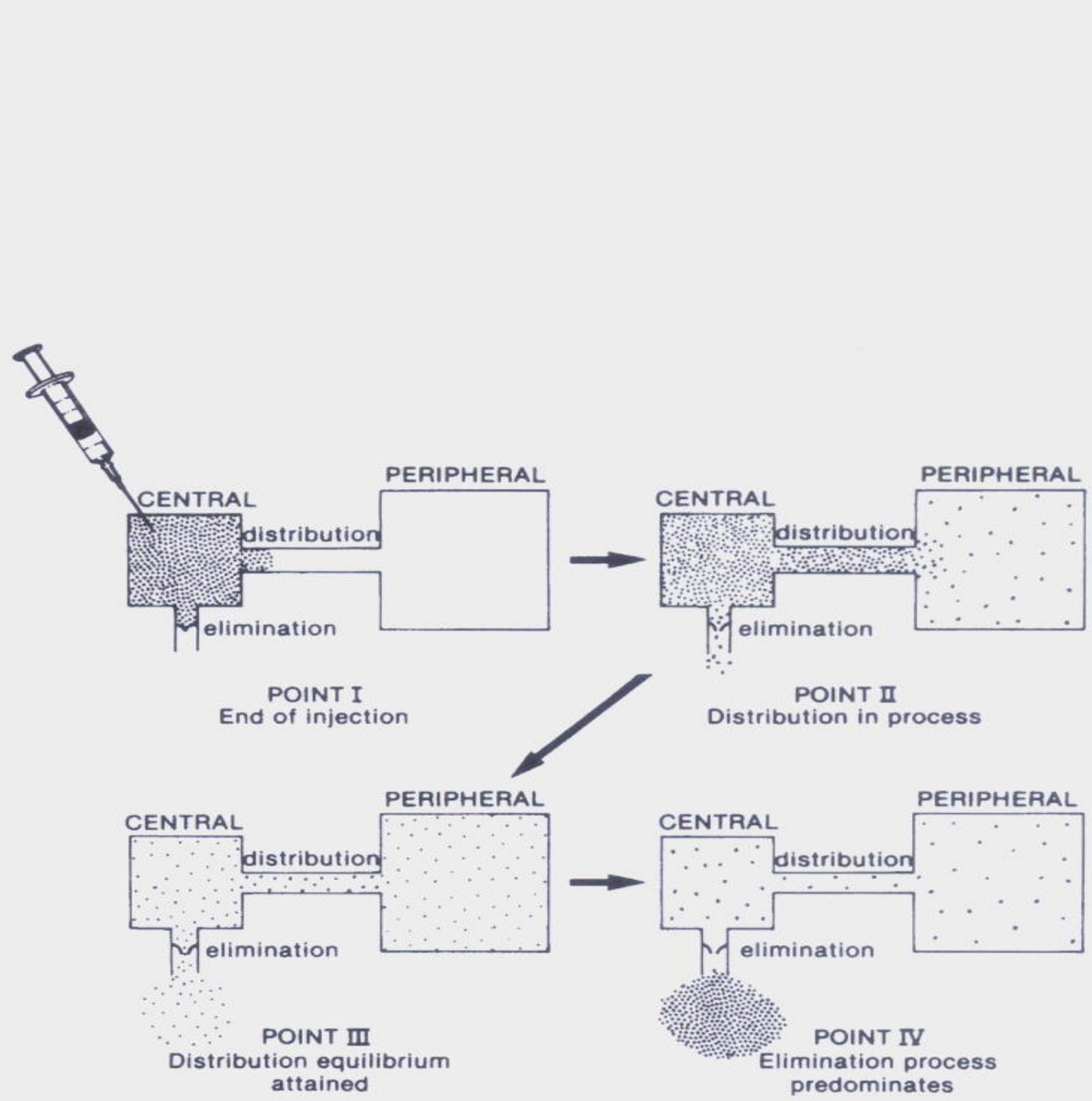
Two-compartment model





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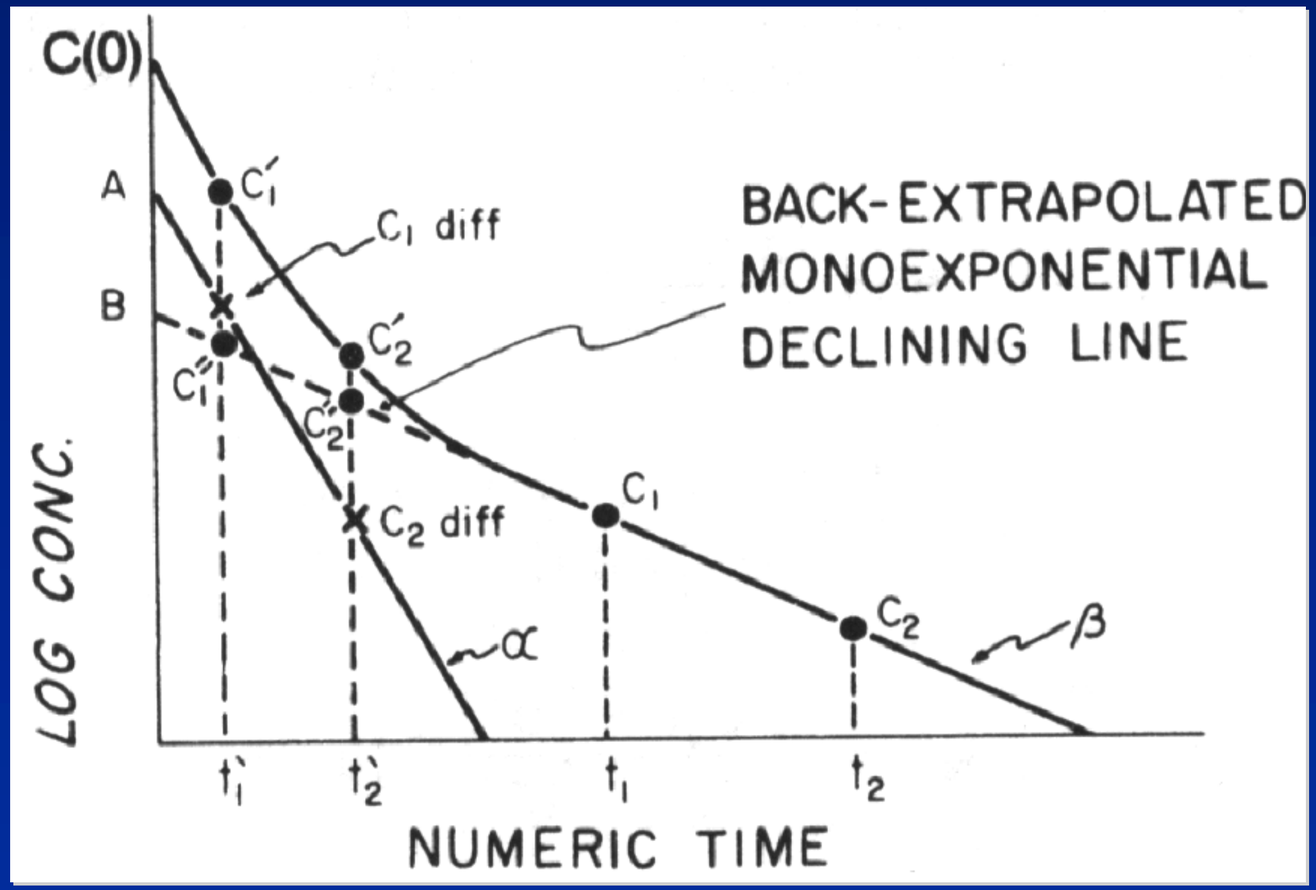
Determination of rate constants

Two - compartment model Intravascular route



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

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

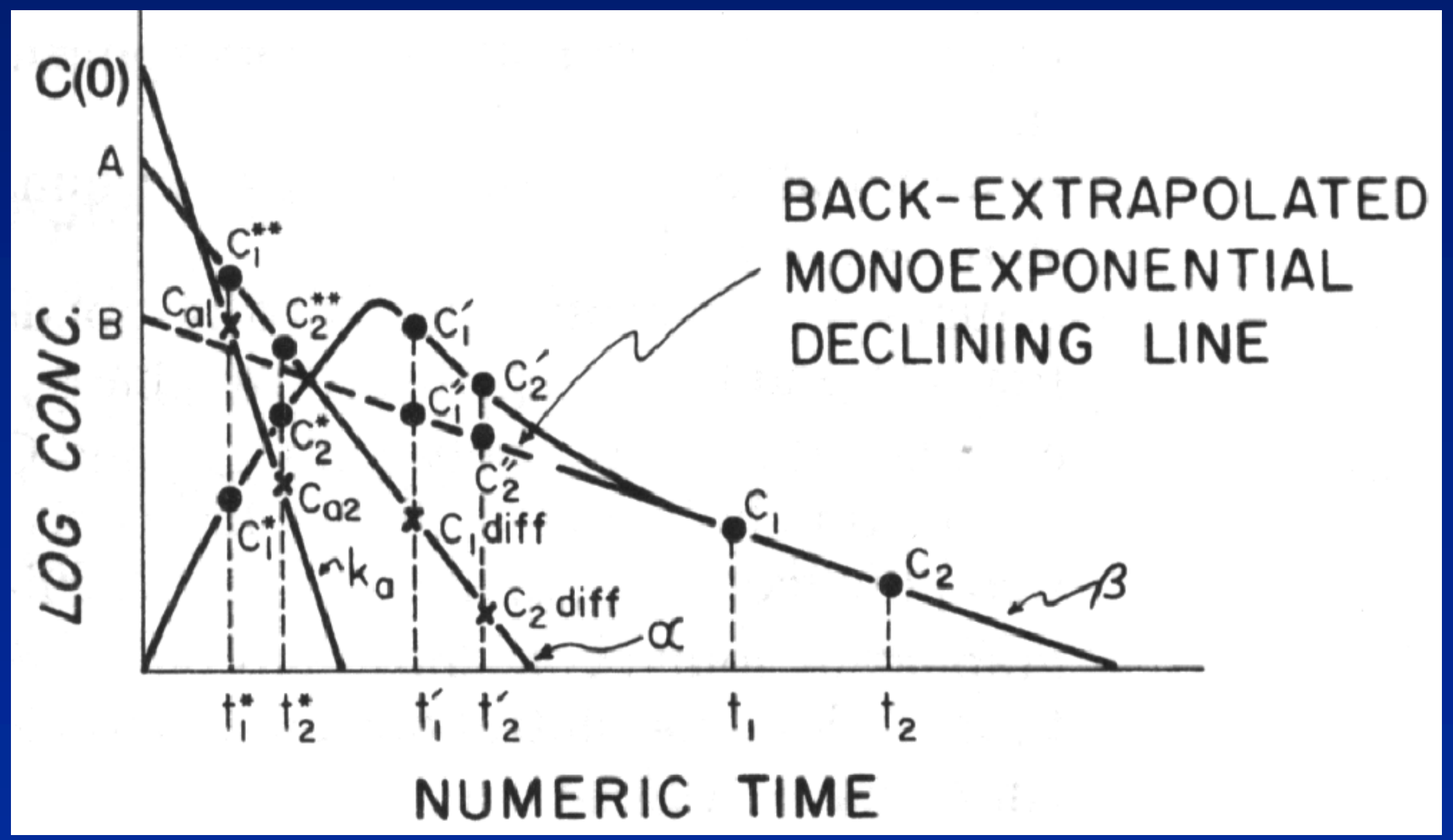
$$Cp = B.e^{-\beta.t} + A.e^{-\alpha.t}$$

FCFRP-USP

Determination of rate constants

Two - compartment model Extravascular route

Step 1



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

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

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

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Exercício 1

A Figura abaixo mostra o decaimento das concentrações plasmáticas de teofilina em função do tempo após a administração de uma dose única iv de 500 mg a um paciente de 70 kg. Considerando que a AUC (tempo zero ao infinito) é 125 mg.h/L, calcular o volume de distribuição da teofilina.