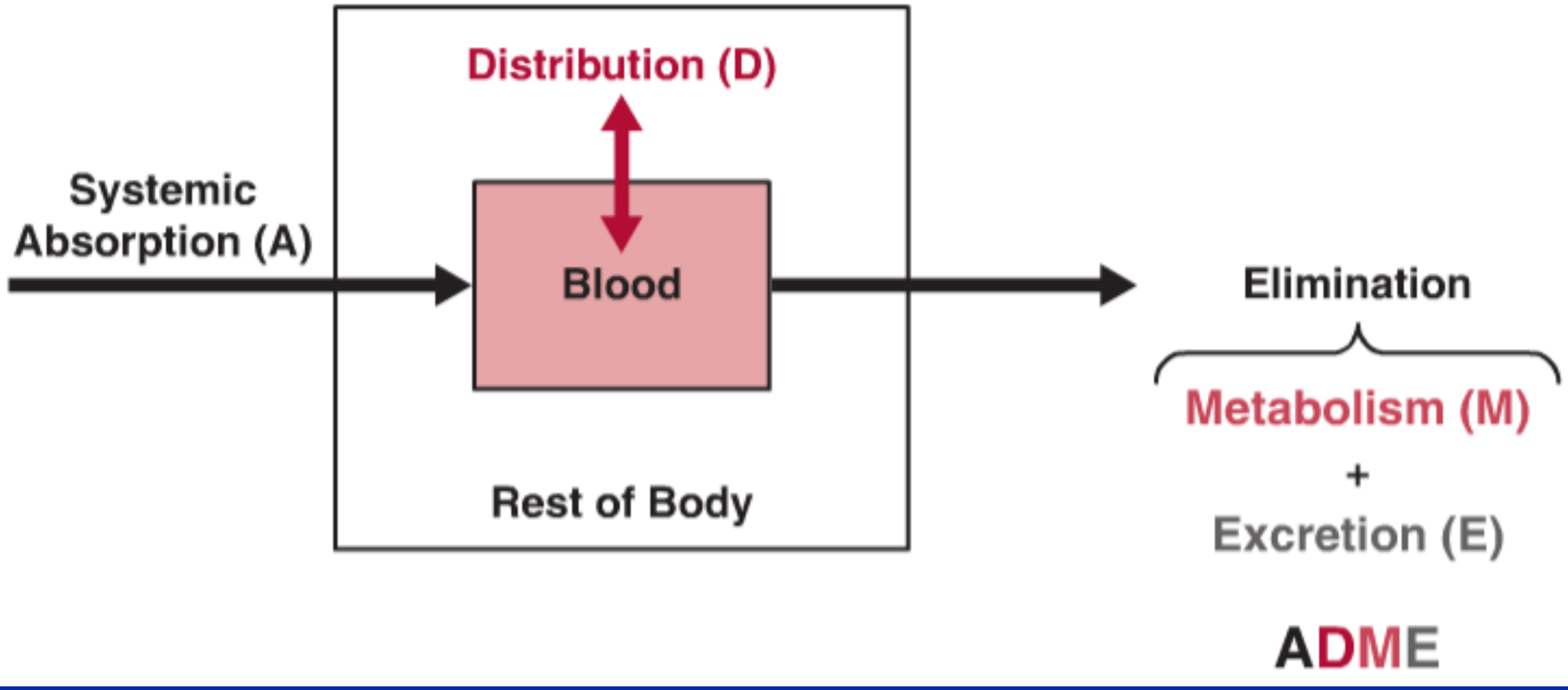
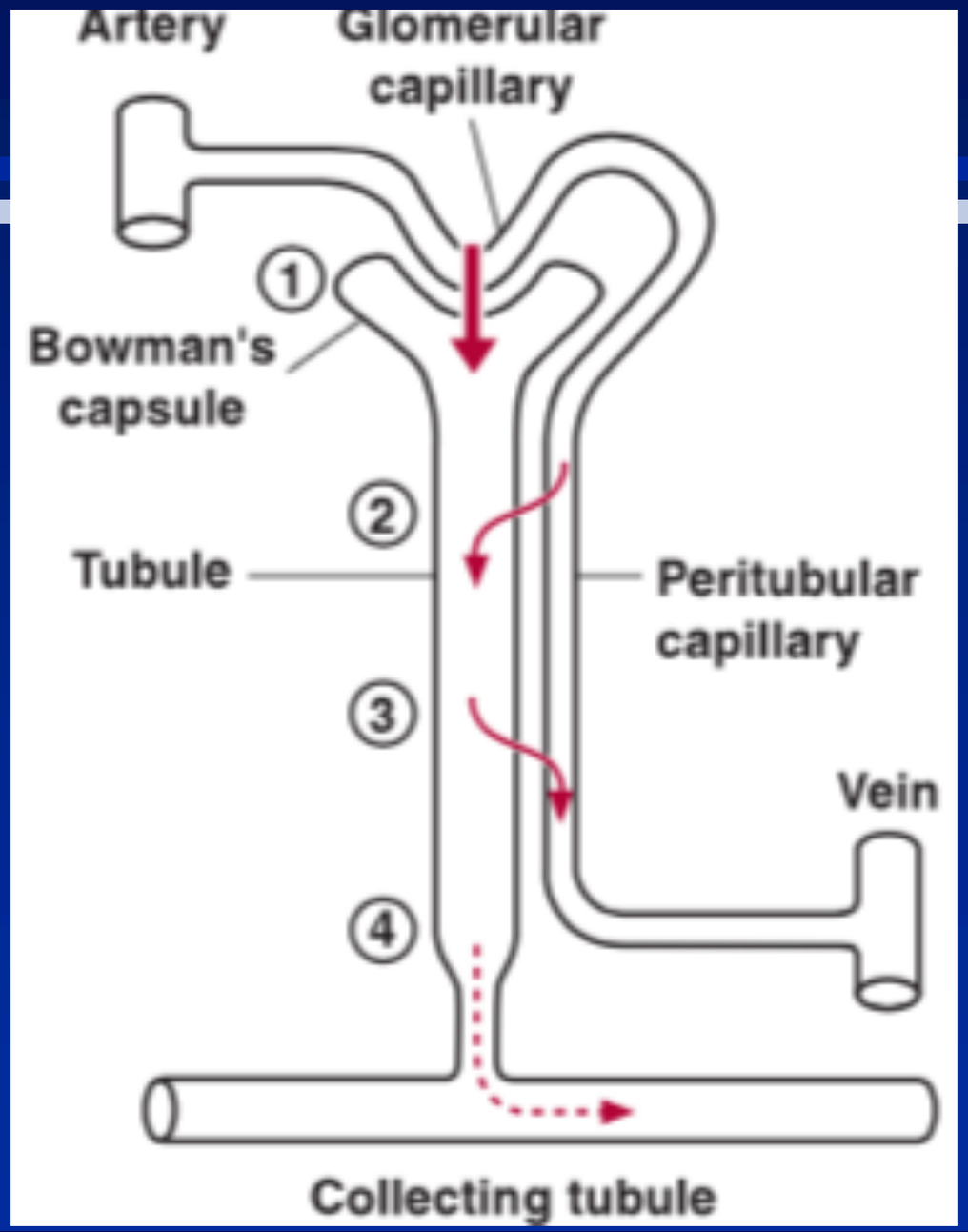
FCFRP-USP

TOXICOCINÉTICA



FCFRP-USP

Excreção renal



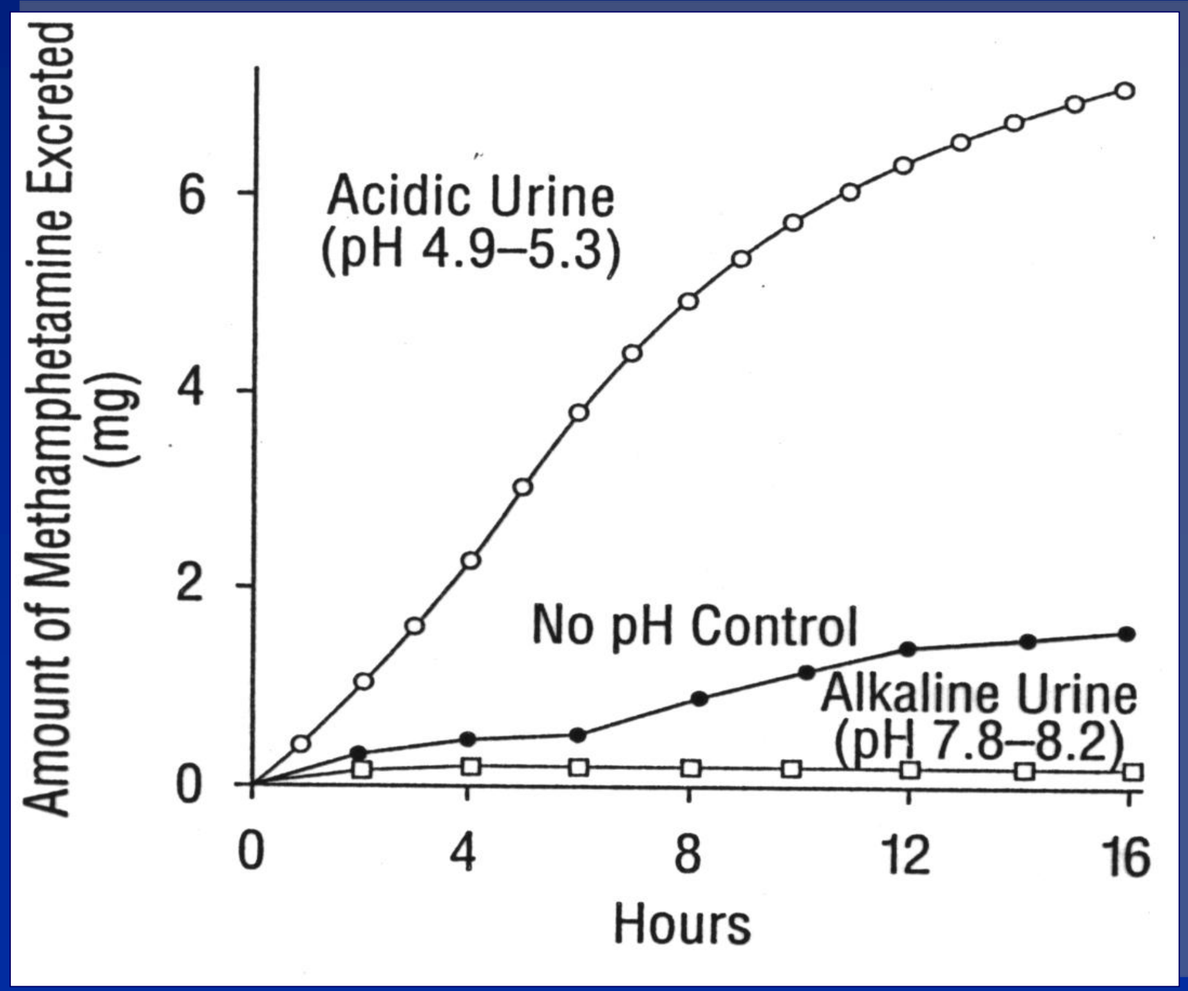
velocidade excreção = (**velocidade filtração** + **velocidade secreção**) **1 – fração reabsorvida**

FCFRP-USP

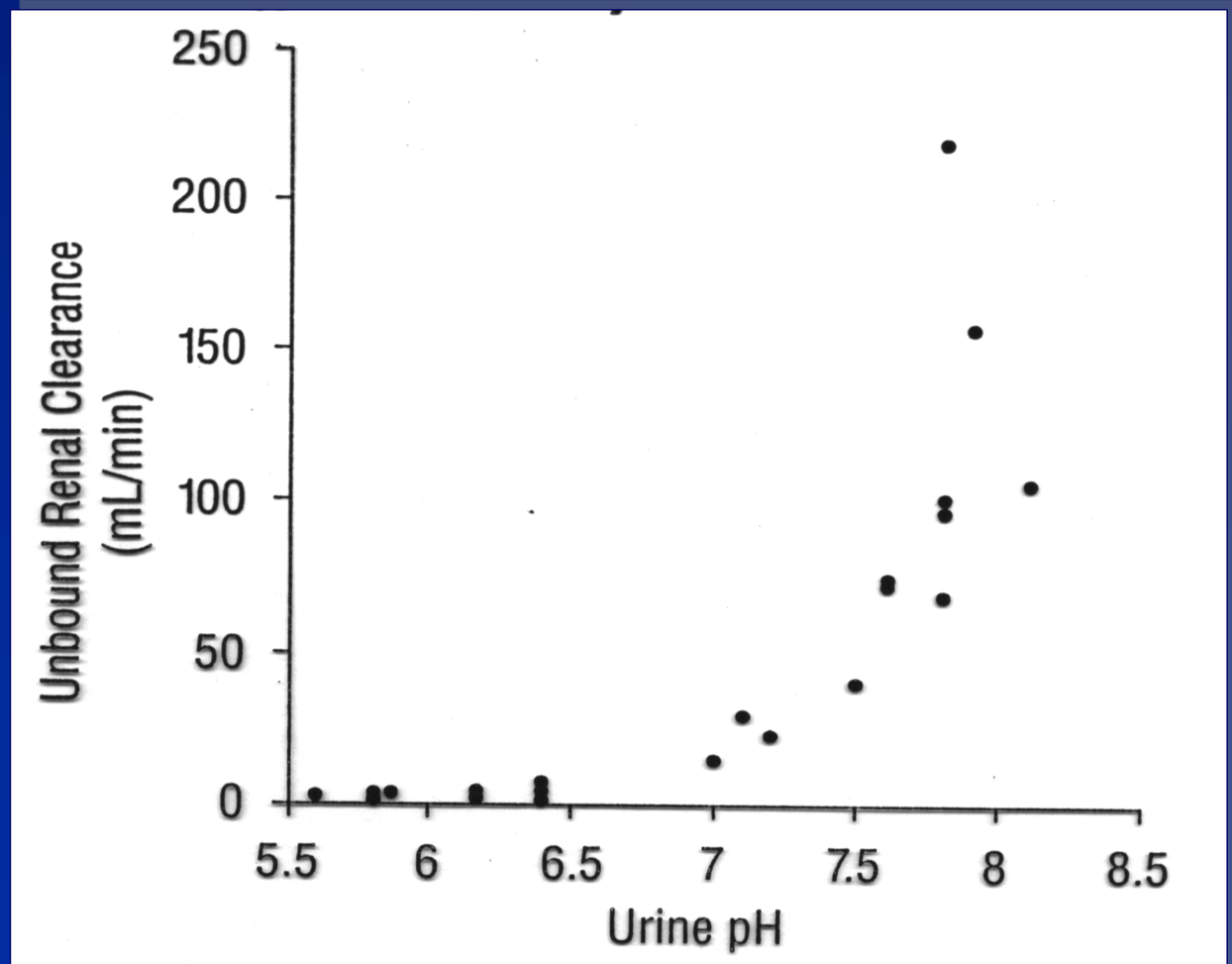
Excreção renal de toxicantes

Influência do pH da urina

Metanfetamina (pKa=10)

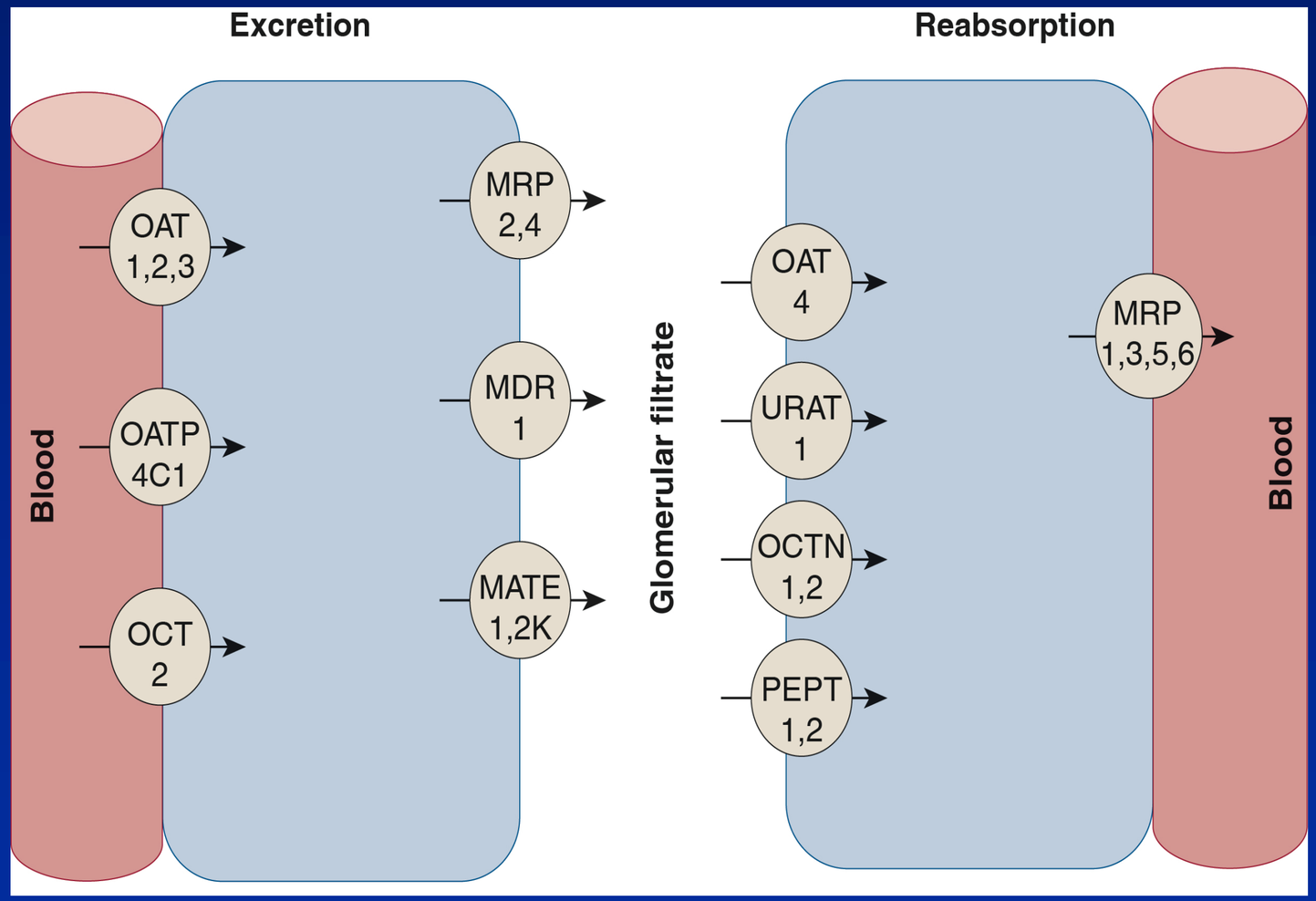


Ácido salicílico (pKa=3,2)



FCFRP-USP

TRANSPORT SYSTEMS IN THE PROXIMAL TUBULE OF THE KIDNEY



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

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

FCFRP-USP

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

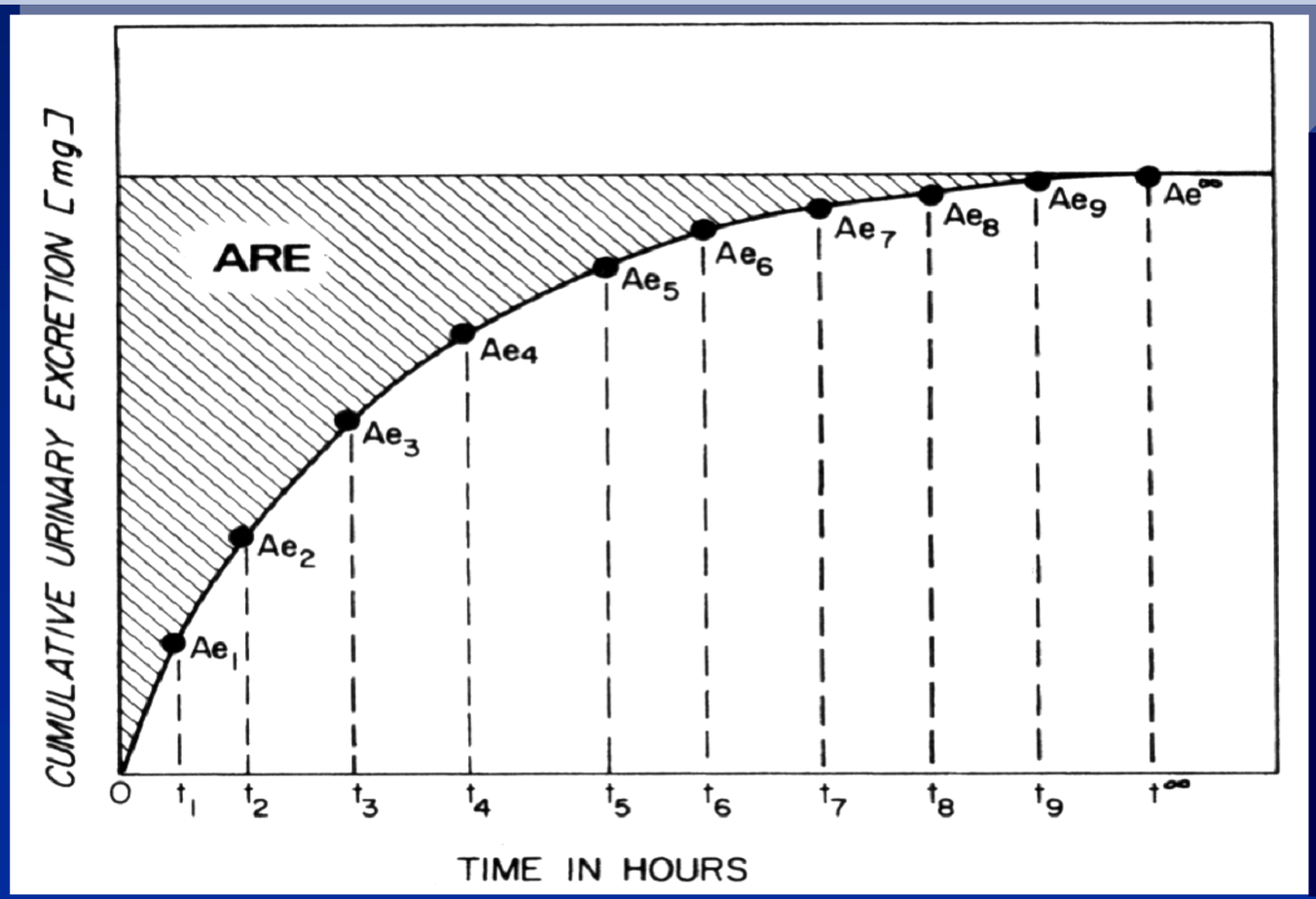
$$Fe = \frac{Ae}{Dose}$$

Fe=fração eliminada na urina

Ae=quantidade excretada

FCFRP-USP

Cumulative urinary excretion



Amount excreted (Ae)

Ae = Cu . V [mg]

Ae= quantidade excretada

Cu=concentração na urina

V=volume da urina

FCFRP-USP

Fraction of dose eliminated by the Kidneys

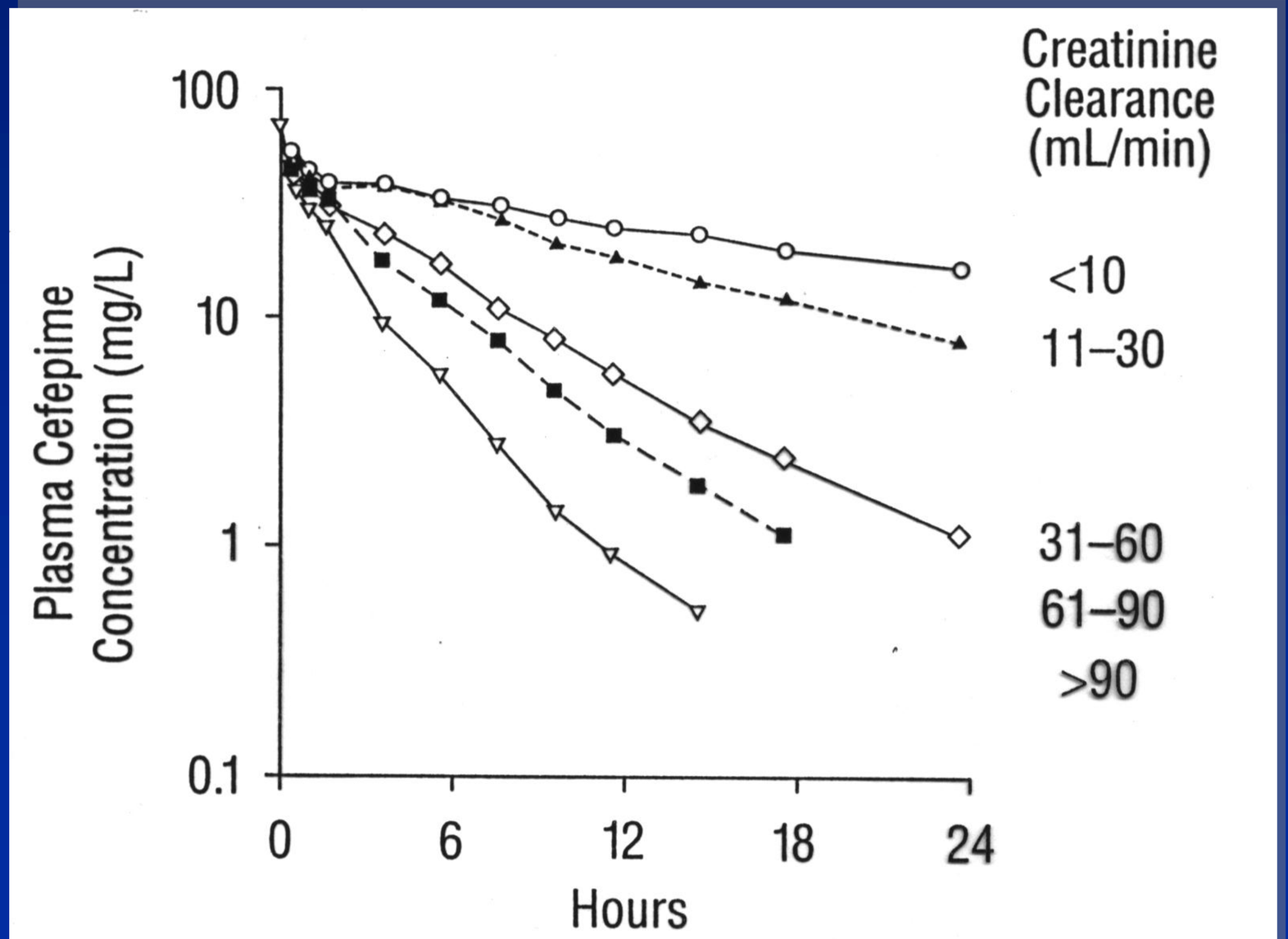
It can be used to compute adjusted drug dosage regimens in patients with reduced renal function

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

Insuficiência renal

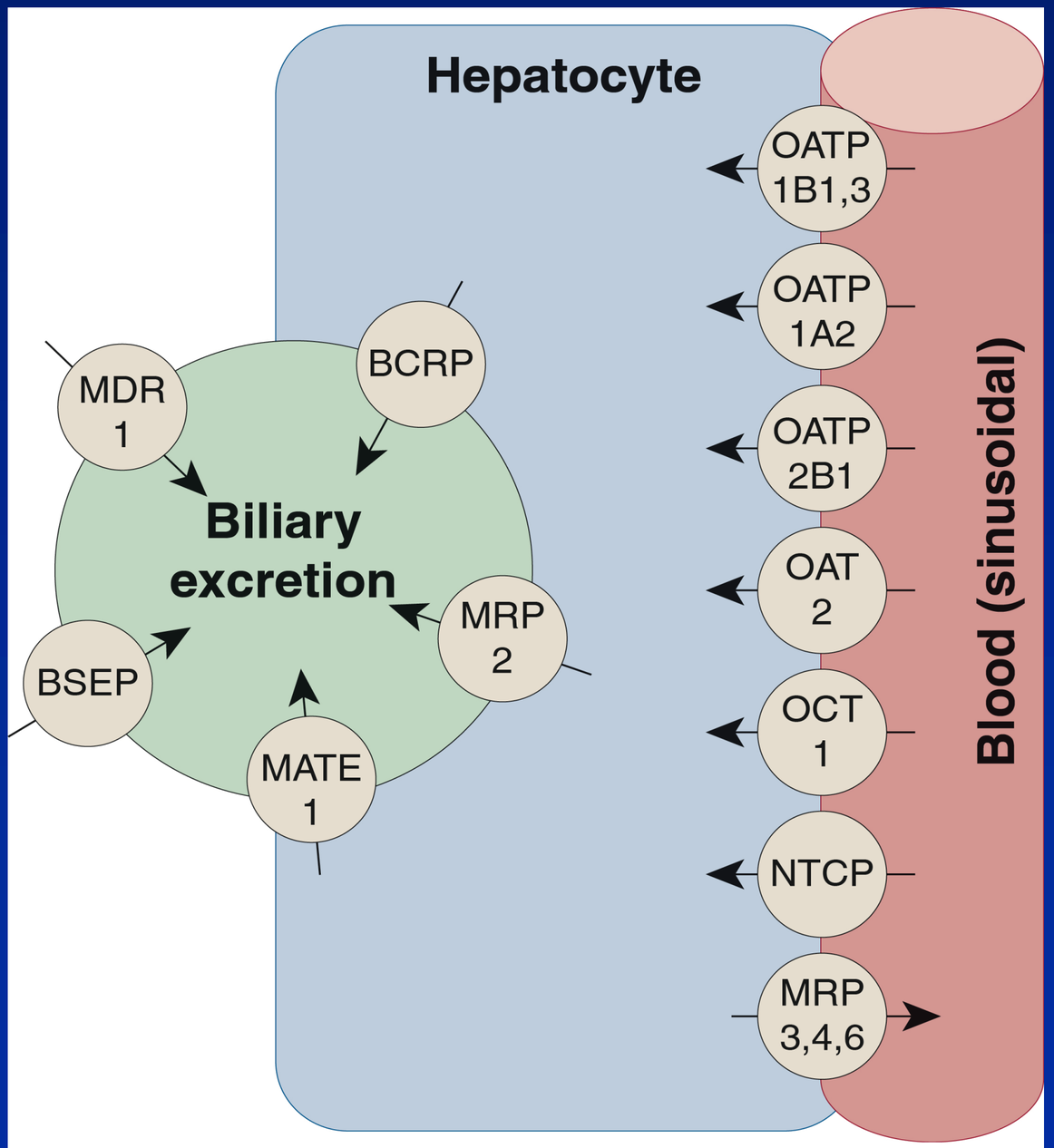
Acúmulo de fármacos de excreção renal

Cefepima



FCFRP-USP

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

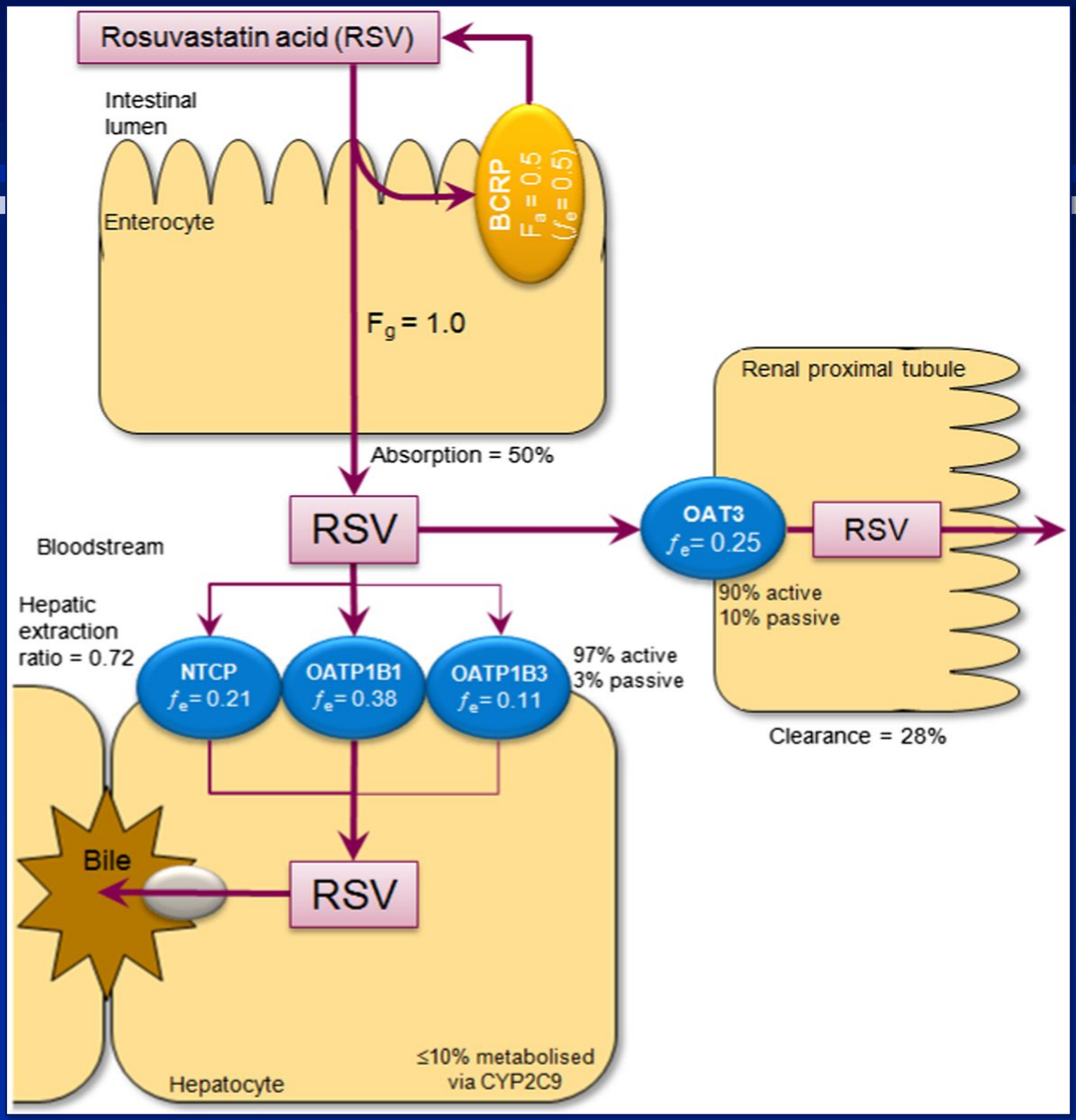
BCRP Breast cancer resistance protein

MRP2 Multidrug resistance protein

BSEP Bile salt excretory protein

FCFRP-USP

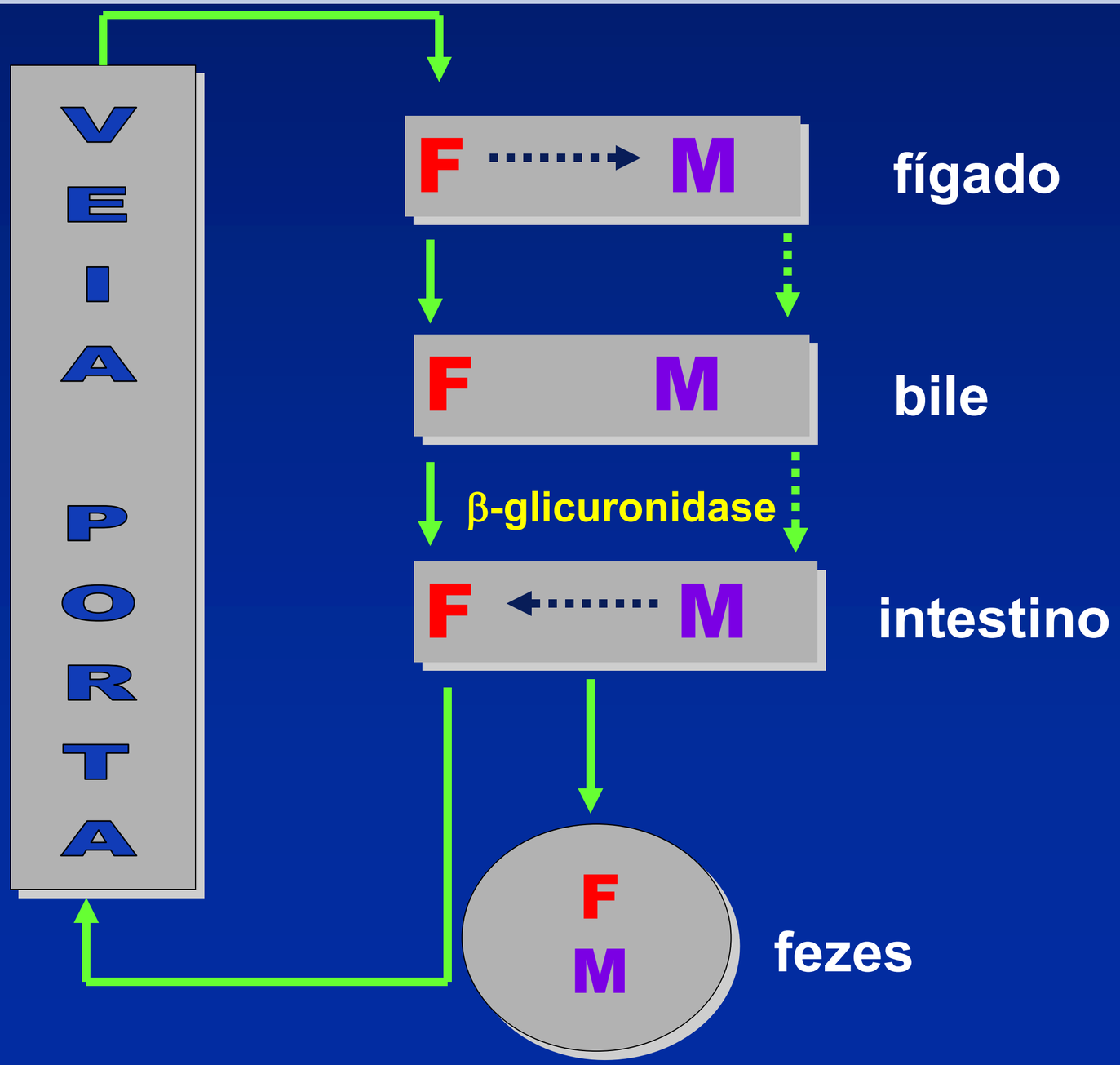
Disposition pathways of rosuvastatin



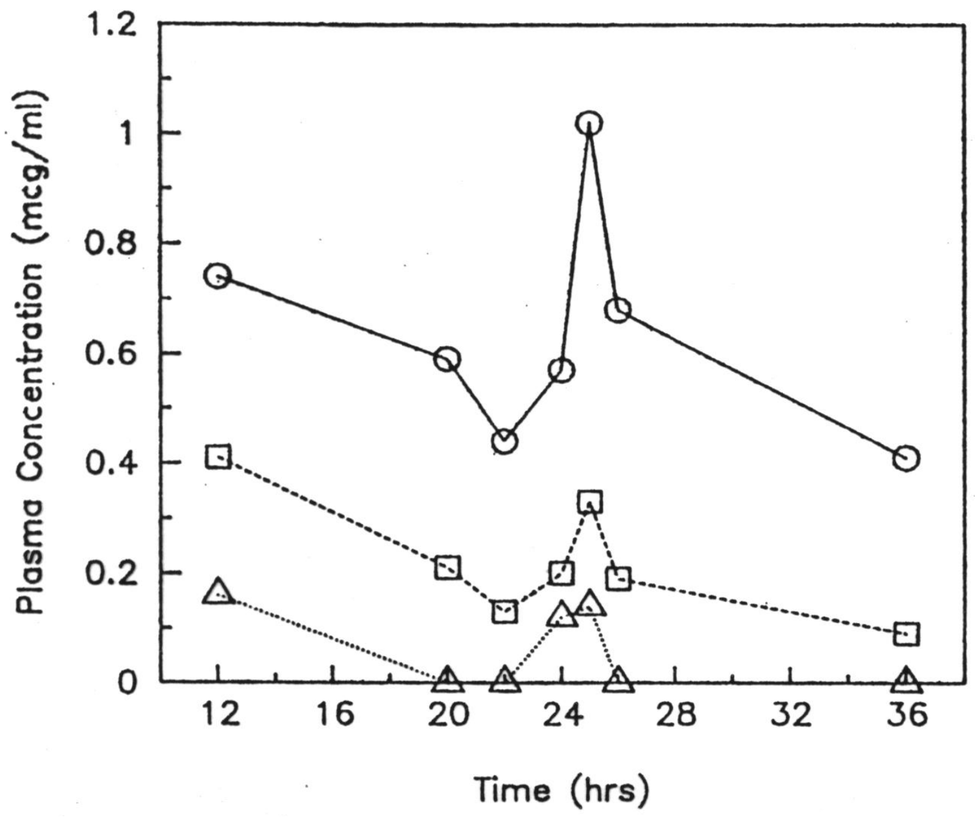
Robert Elsby et al. Drug Metab Dispos 2016;44:398-408

FCFRP-USP

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 valpróico
- Imipramina e desipramina
- Metabólitos da espironolactona

Total (Cl), renal (Cl_R) and hepatic (Cl_H) clearances

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)

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

$$Cl = Cl_H + Cl_R$$

$$Cl_H = Cl - Cl_R$$

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

FCFRP-USP

Total Clearance

Total clearance can be used to compute the dosing rate (R) required to yeld the desired steady-state plasma concentration (C_{ss})

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

R= dose/intervalo de dose

FCFRP-USP

Total Clearance

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

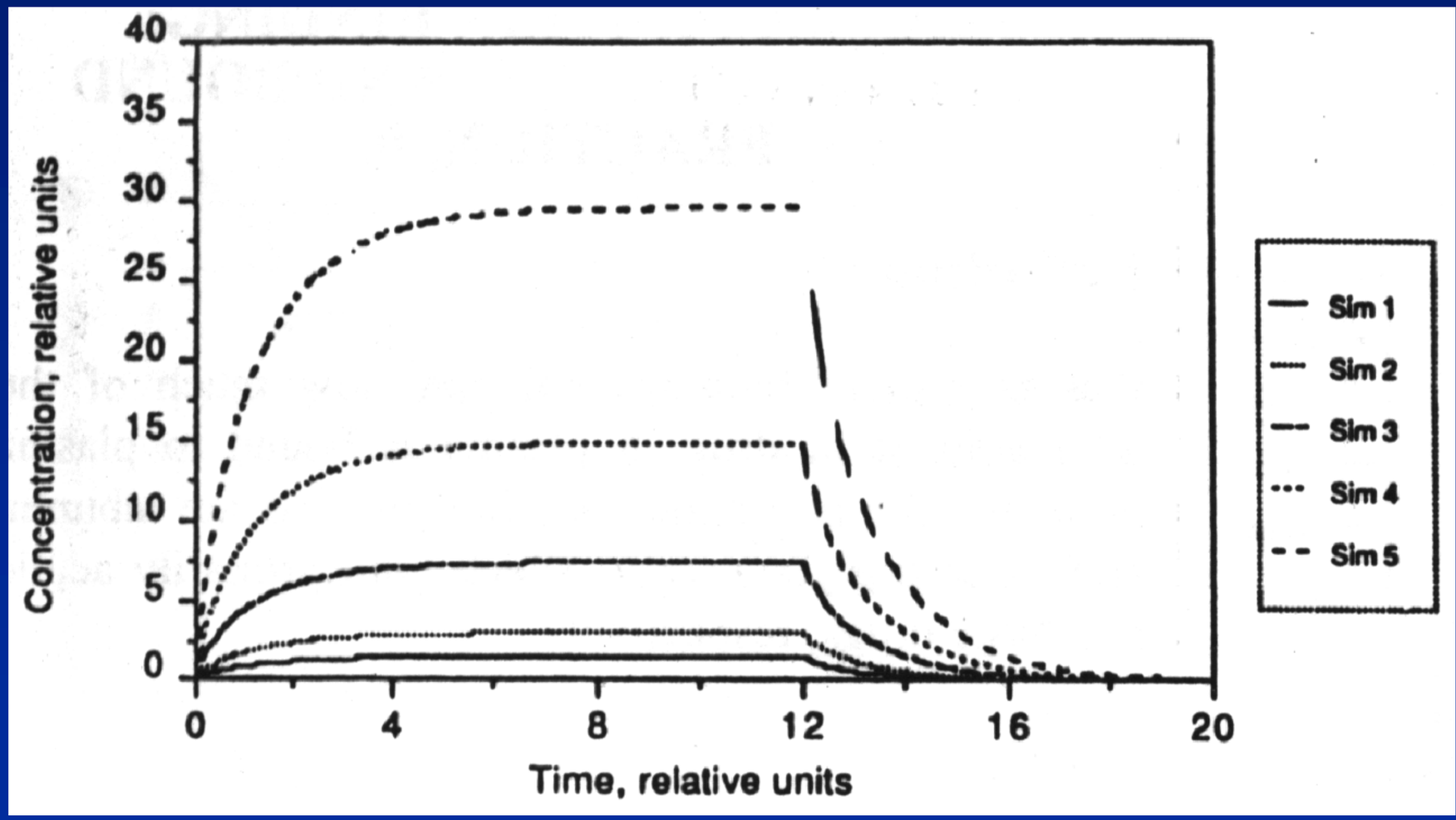
$$\overline{C}_{ss} = \frac{R}{Cl} = \frac{(F)\quad(dose/\tau)}{Cl}$$

R = dosing rate

F = bioavailability

FCFRP-USP

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

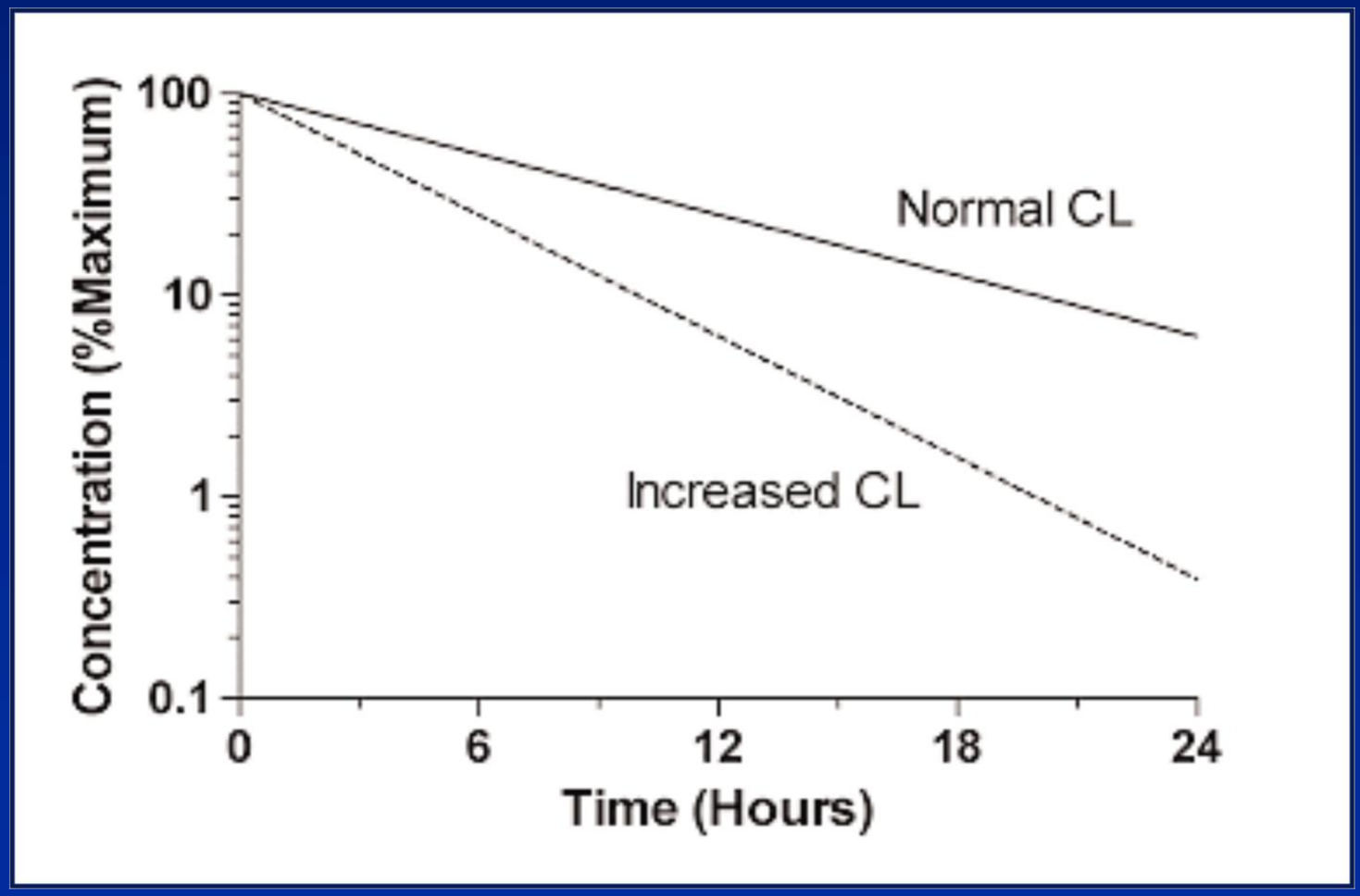


Bjornsson, 1997

FCFRP-USP

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

IV bolus



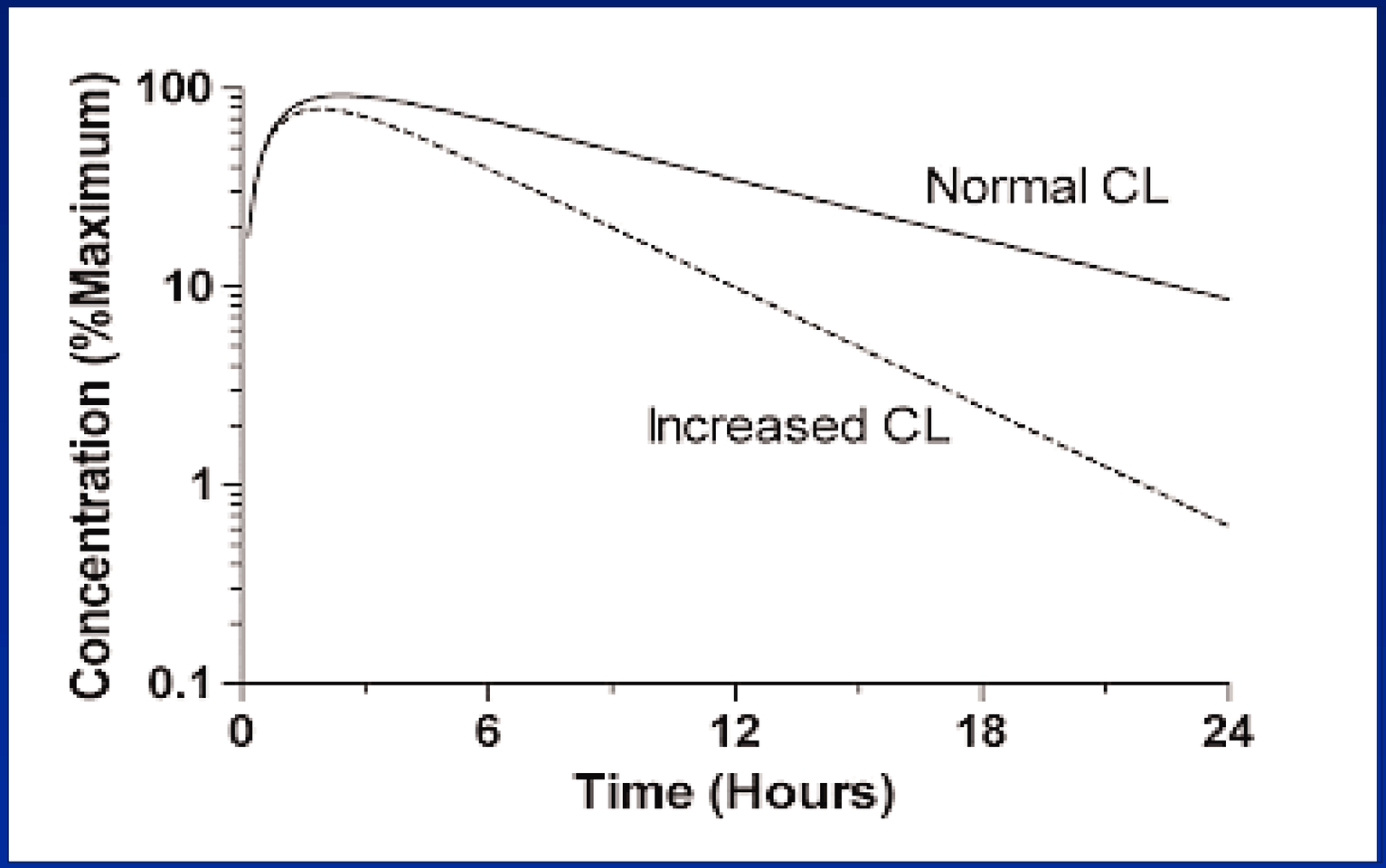
CL of 1.16 L/h and V of 10 L for the “Normal CL” scenario.

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

FCFRP-USP

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

Oral

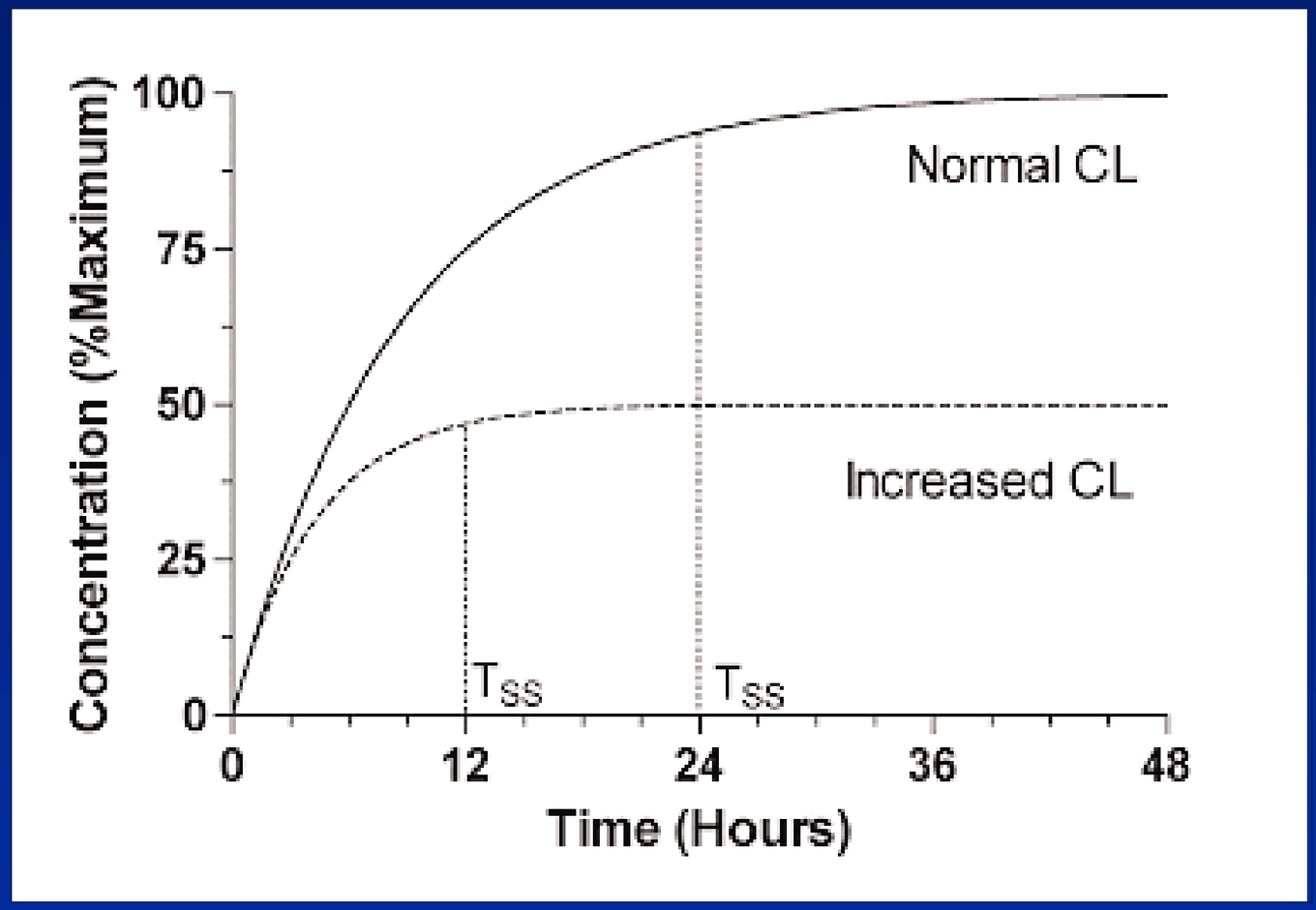


CL of 1.16 L/h, V of 10 L, absorption rate constant of 1 hr -1 , and F of 1 for the “Normal CL” scenario. CL was increased to 2.32 L/h for the “Increased CL” scenario.

FCFRP-USP

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

constant IV infusion



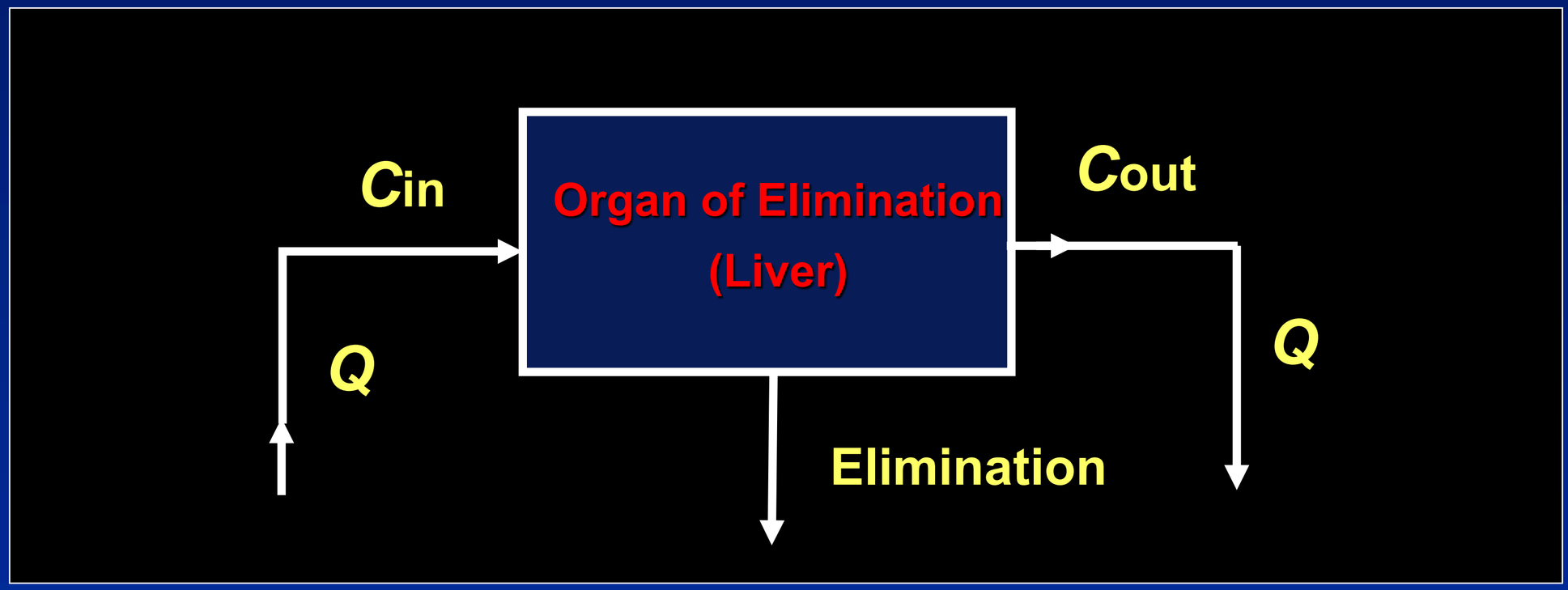
CL of 1.16 L/h and V of 10 L for the “Normal CL” scenario.

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).

FCFRP-USP

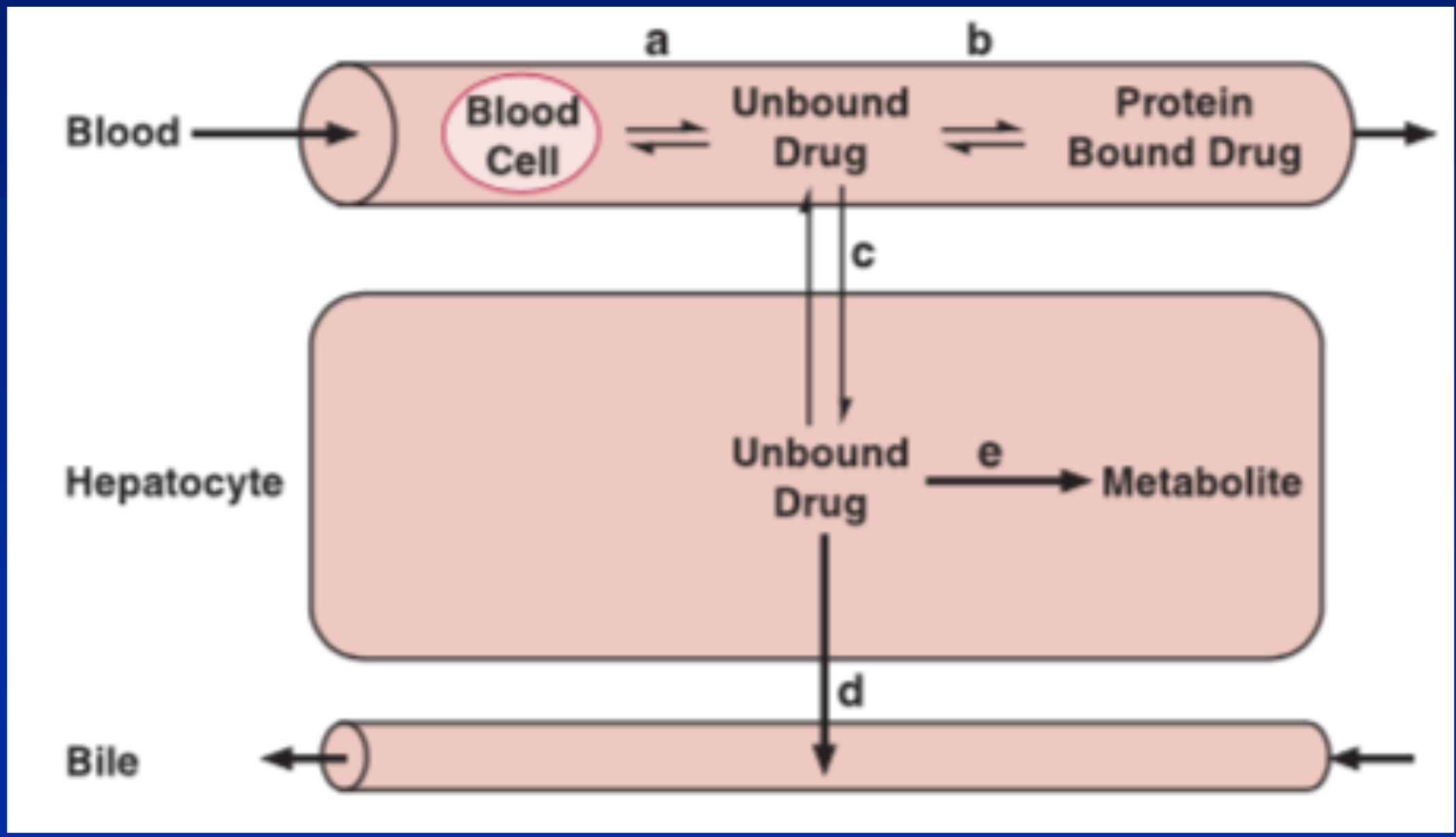
Model for hepatic clearance of a drug



$$Cl_H = Q \times \frac{Cin - Cout}{Cin} = Q \,.\, E$$

Q= blood flow through the liver is about 1.5 L/min

Well-Stirred Hepatic clearance Model (WSHM)



FCFRP-USP

CLEARANCE FOR THE ELIMINATING ORGAN

Well-stirred hepatic clearance model

$$Cl_H = \frac{Q \cdot (fu_b \cdot Cl_{met} + Cl_{bile})}{Q + (fu_b \cdot Cl_{met} + Cl_{bile})}$$

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

$Cl_H \cong Q$

↑E

> 0.7

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

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

↓E

≤ 0.3

FCFRP-USP

Effect of blood flow (Q) on hepatic clearance (Cl_H)

Extraction Ratio (*E*)	Blood Flow (*Q*)	Clearance (Cl_H)
High (0.7-1.0)	Low	Low
Low (<0.3)	High	Low
High (0.7-1.0)	High	High
Low (<0.3)	Low	Low

FCFRP-USP

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%

FCFRP-USP

E is independent of the fraction of the dose eliminated by liver

Diazepam

CL = 27 mL/min (Low E)

< 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

FCFRP-USP

INFLUENCE OF EXTRACTION RATIO ON DRUG AVAILABILITY

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

Labetalol

- CL_H = 1,29 L/min
- E_H = 0.86
- F = 14%

FCFRP-USP

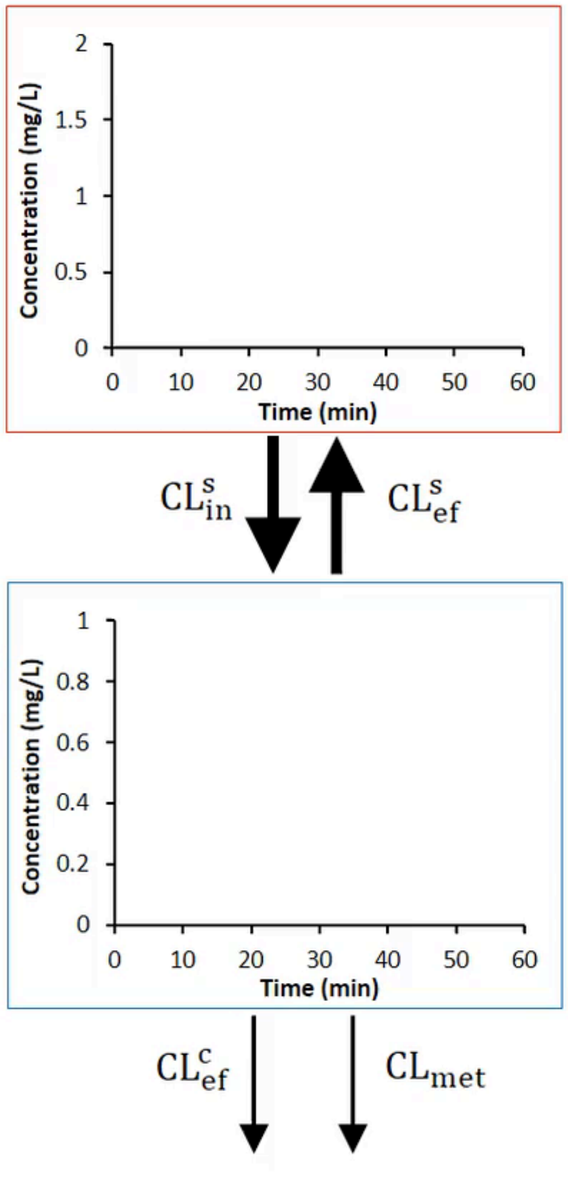
midazolam (CYP3A)

docetaxel (CYP3A, GST, Pgp, MRP2)

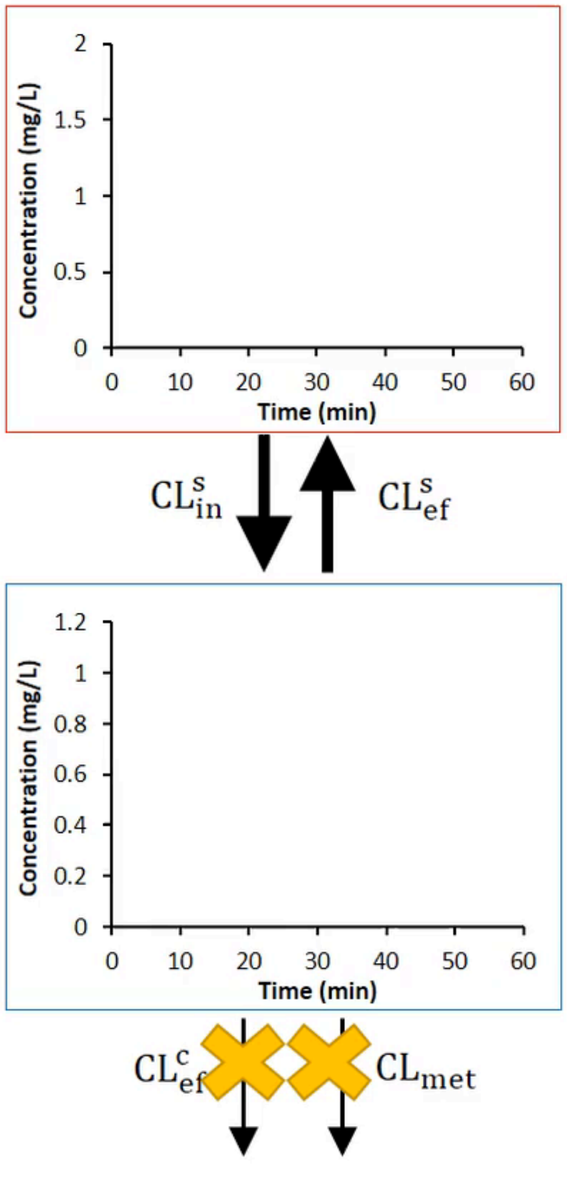
Scenario 2/3: Metabolism and canalicular efflux are the rate-determining steps in hepatic CL

Condition: $CL_{in}^{s} = CL_{ef}^{s} >> (CL_{met} + CL_{ef}^{c})$

No inhibition



Inhibition of metabolism and canalicular efflux CL



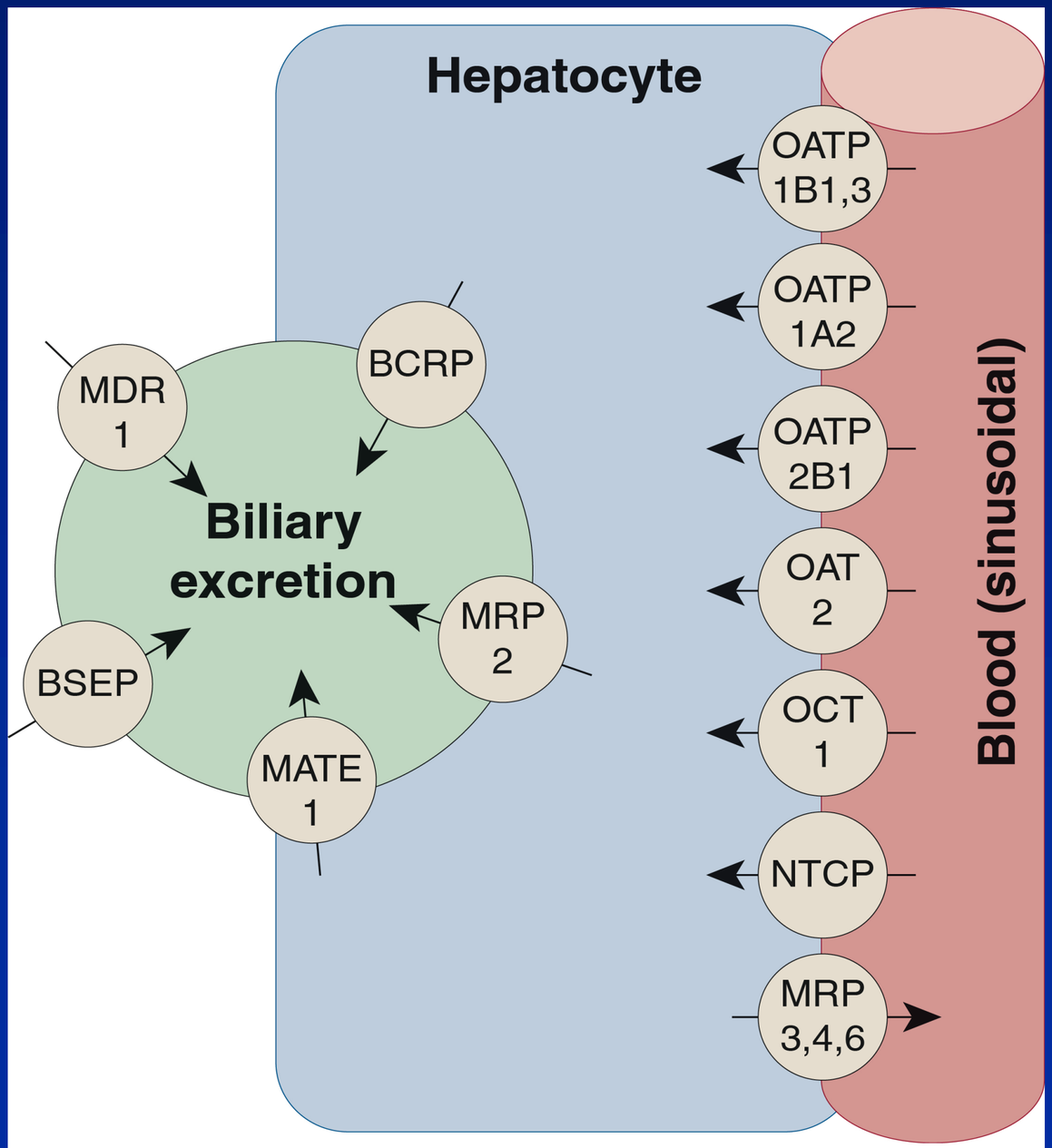
Extended clearance model (ECM) (drug transportes)

- Sinusoidal influx clearance (CL^{s}_{in})
- Sinusoidal efflux clearance (CL^{s}_{ef})
- Canalicular efflux (biliary) clearance (CL_{bile})
- Metabolic clearance (CL_{met})
- Hepatic blood flow (Q_{h})
- Fraction unbound in the blood (fu_{b})

$$CL_h = \frac{Q_h fu_b CL^s_{in}(CL_{met} + CL_{bile})}{Q_h\left(CL^s_{ef} + CL_{met} + CL_{bile}\right) + fu_b CL^s_{in}(CL_{met} + CL_{bile})}$$

FCFRP-USP

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

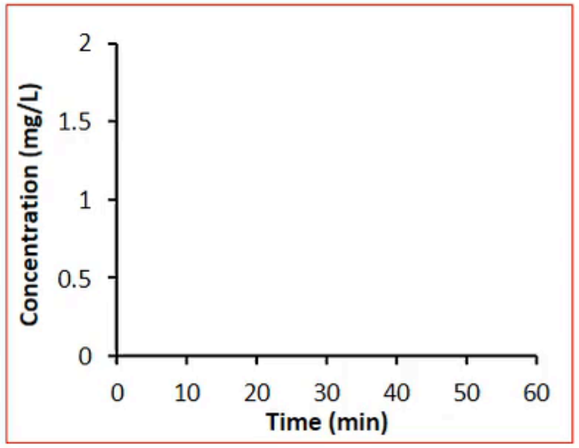
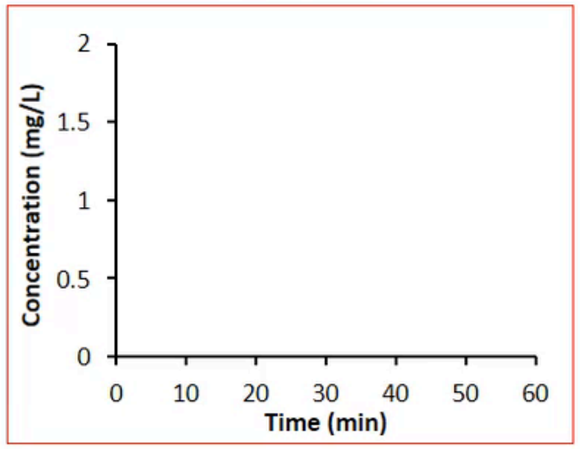
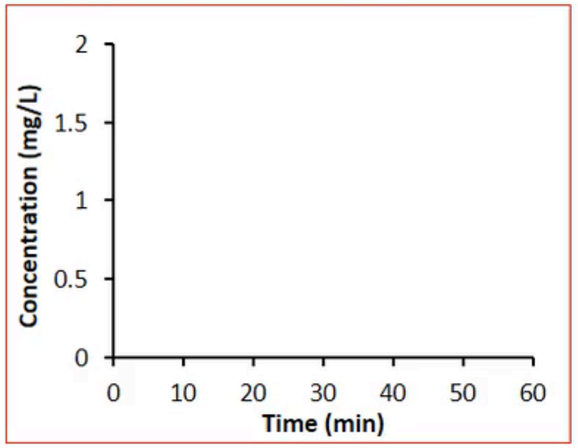
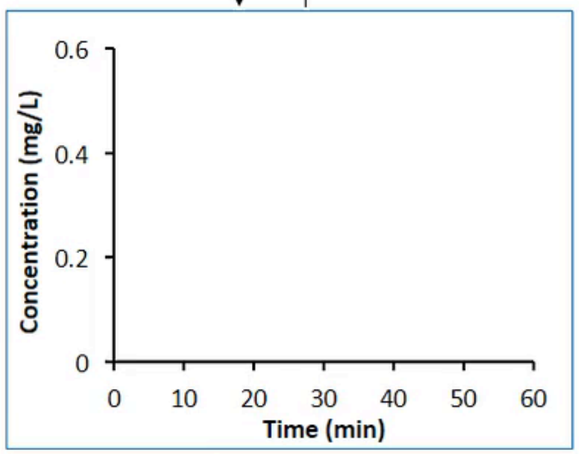
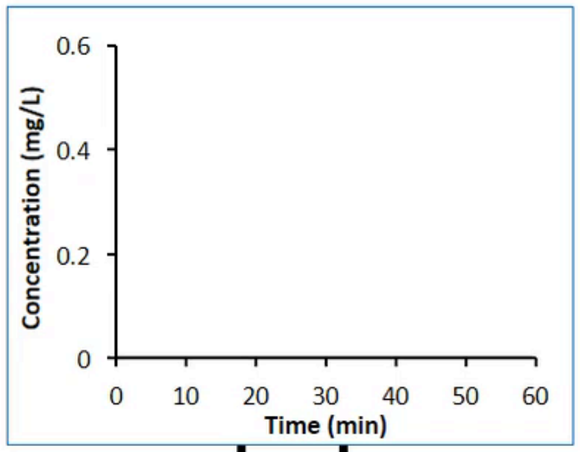
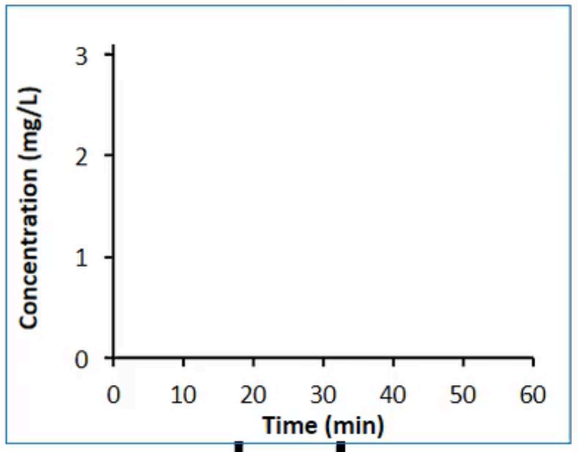
BSEP Bile salt excretory protein

Exemplo: atorvastatina (OATP1B1 e CYP3A)

FCFRP-USP

Scenario 1: Sinusoidal uptake is the rate-determining step in hepatic clearance

Condition: $CL^{s}_{ef} << (CL_{met} + CL^{c}_{ef})$

No inhibition	Inhibition of sinusoidal uptake CL	Inhibition of metabolism and canalicular efflux CL
		
CL^{s}_{in} ↓ ↑ CL^{s}_{ef}	CL^{s}_{in} ✕ ↑ CL^{s}_{ef}	CL^{s}_{in} ↓ ↑ CL^{s}_{ef}
		
CL^{c}_{ef} ↓ ↓ CL_{met}	CL^{c}_{ef} ↓ ↓ CL_{met}	CL^{c}_{ef} ✕ ✕ CL_{met}

FCFRP-USP

Uptake transporter-based interactions at the liver

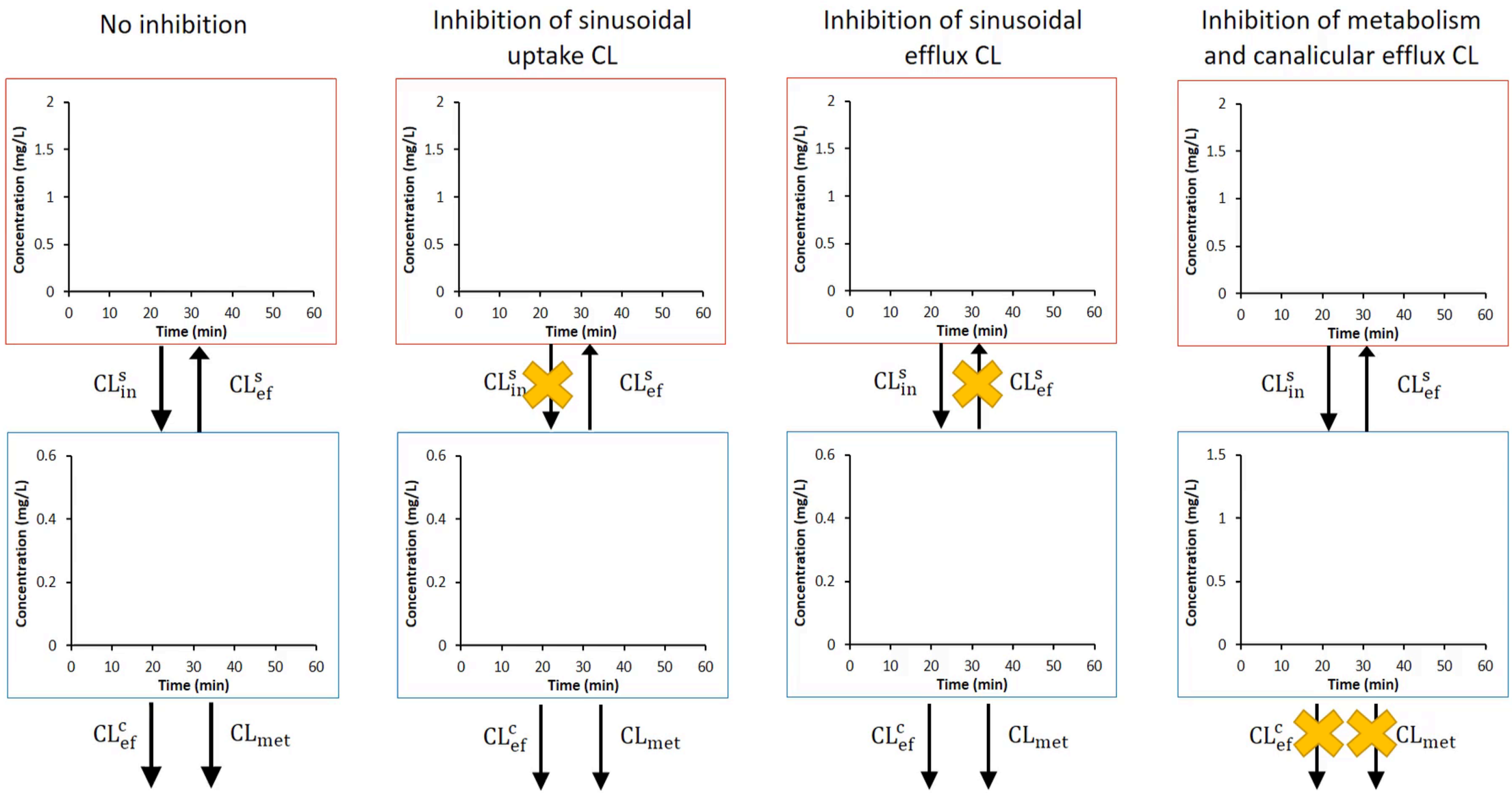
HEPATIC INTERACTION			
Drug	**Interaction**	**Mechanism**	**CL/F**
Atorvastatin	Rifampin	Inhibition of OATP1B1 uptake	↓ 87.0%
Cerivastatin	Cyclosporine	Inhibition of OATP1B1 uptake	↓ 73.3%
Glyburide	Rifampin	Reduced OATP2B1 uptake	↓ 54.6%
Metformin	OCT1 reduced function allele	Reduced OCT1 uptake	↓ 37.5%
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

Exemplo: repaglinida é substrato do CYP2C8, CYP3A e OATP1B1

FCFRP-USP

Scenario 4: All hepatobiliary clearance pathways determine hepatic clearance

Condition: $CL^{s}_{ef} \leq$ or $\geq (CL_{met} + CL^{c}_{ef})$ and $CL^{s}_{in} \neq CL^{s}_{ef}$



FCFRP-USP

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

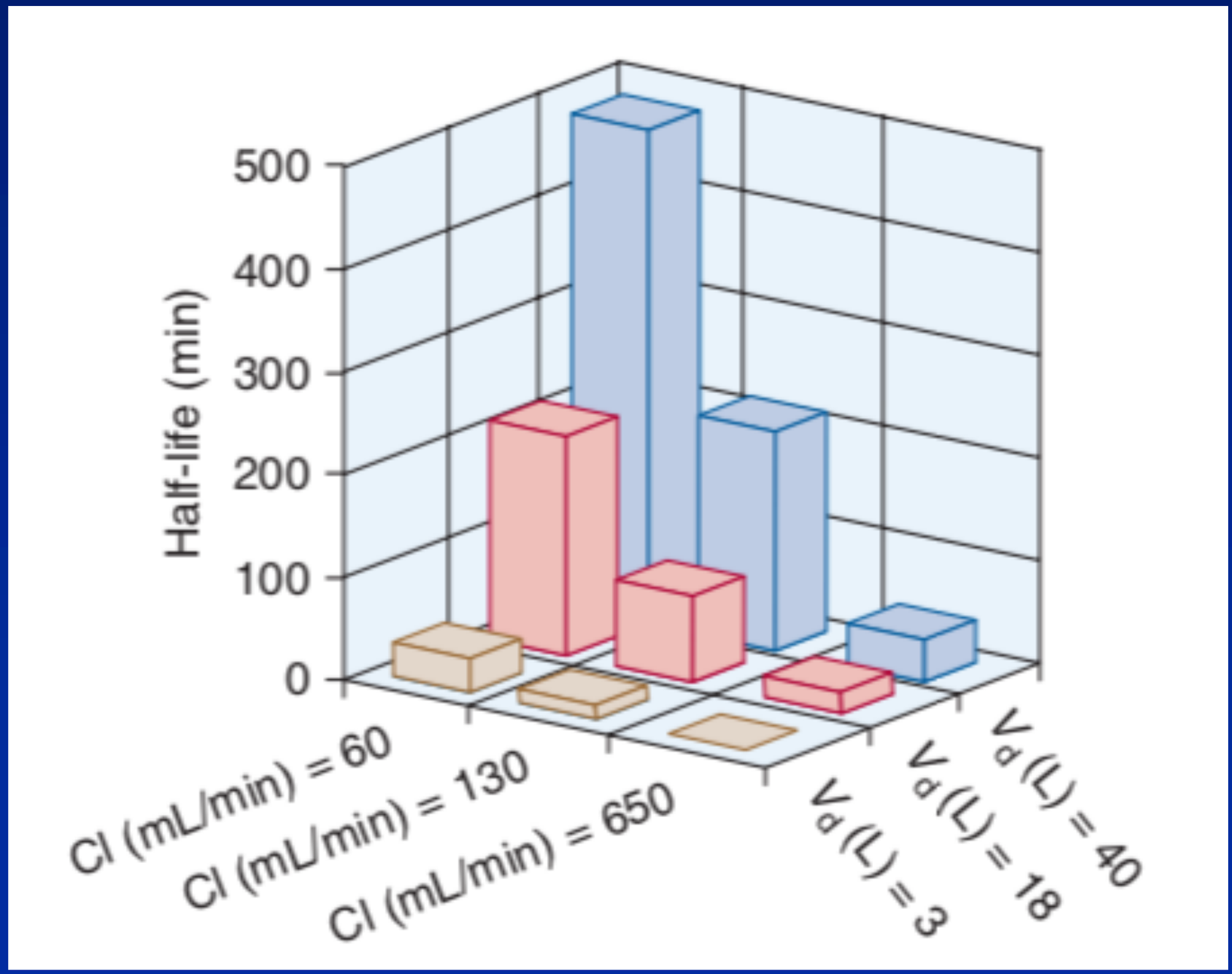
$$t_{1/2} = \frac{0.693}{Kel} = \frac{0.693 \times Vd}{Cl}$$

Unit	time (min, h, day)

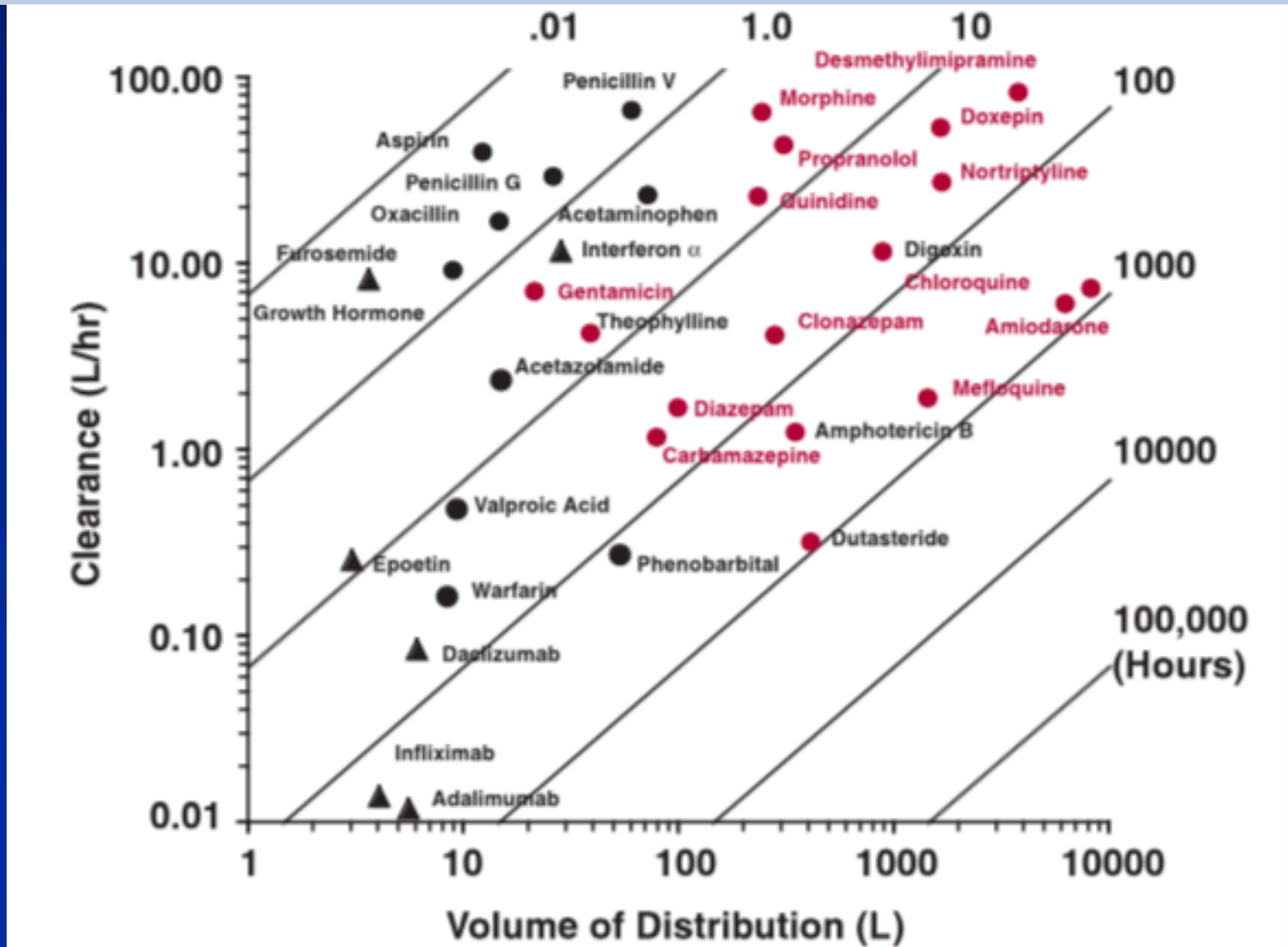
FCFRP-USP

$$T_{1/2} = \frac{0.693 \cdot V_d}{Cl}$$

Elimination half-life



Half-life, Clearance and Volume of distribution



FCFRP-USP

Elimination half-life

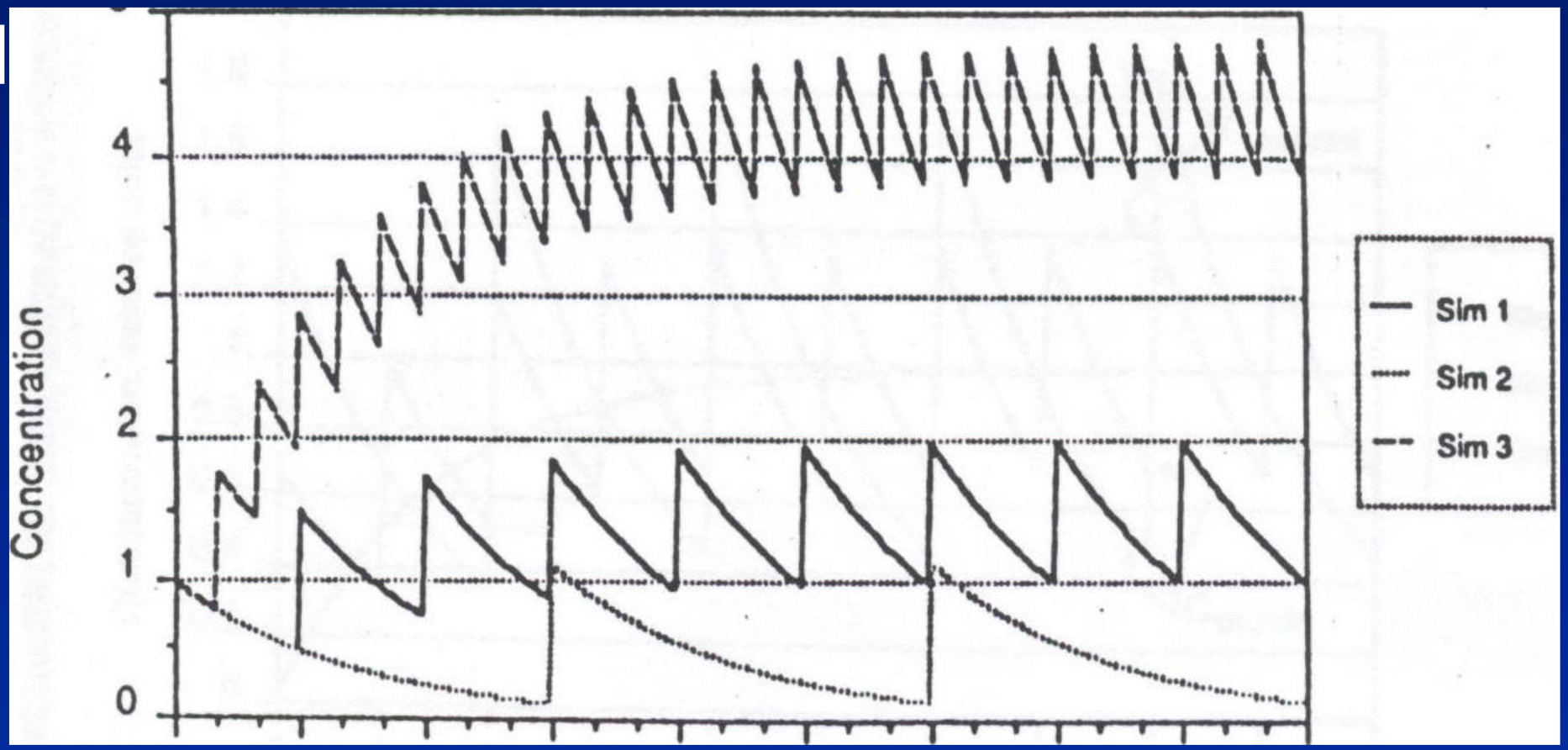
It is used to select lenghts of dosing intervals of drugs

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

FCFRP-USP

Relationship between elimination half-life and dosing interval

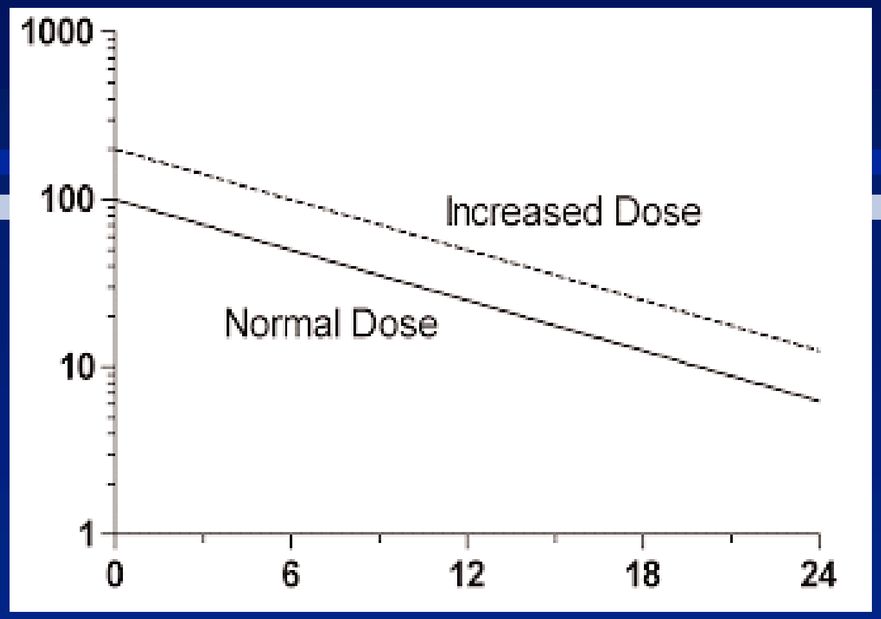
Step 1

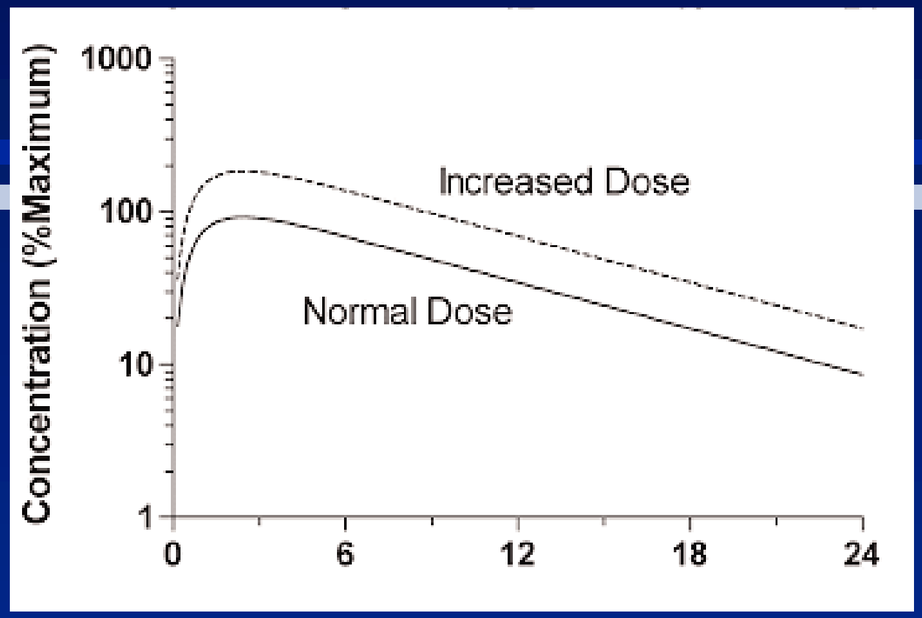


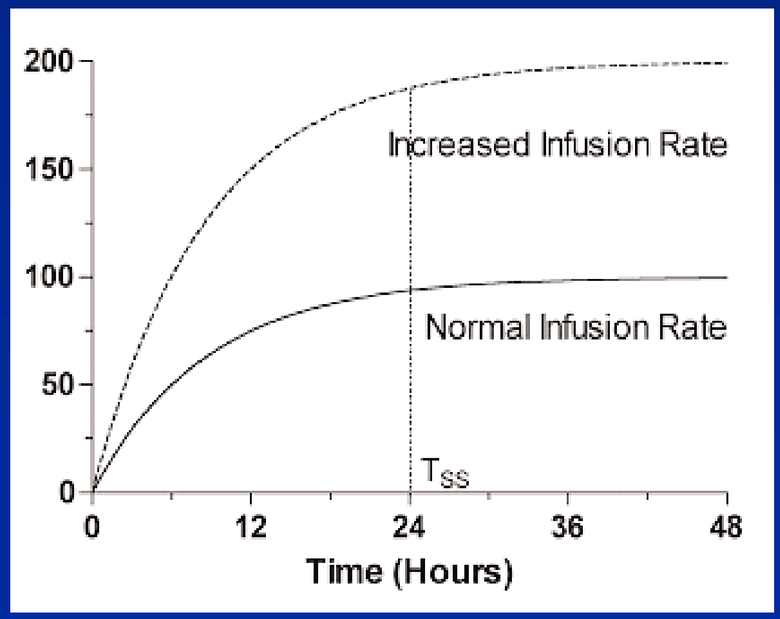
The elimination half-life is the same for all three simulations

FCFRP-USP

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 h^{-1}, and F of 1.

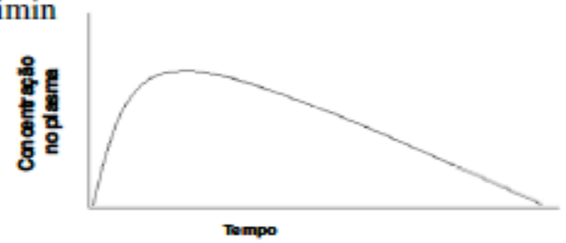
The dose or infusion rate constant was doubled for the “Increased Dose” or “Increased Infusion Rate”

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

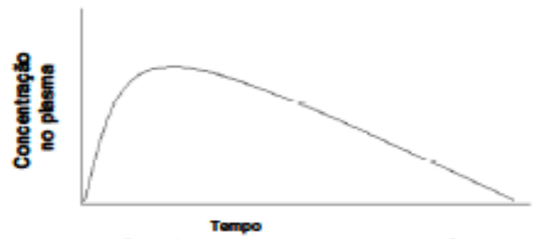
FCFRP-USP

1- As curvas abaixo mostram as concentrações plasmáticas de um fármaco obtidas em função do tempo, seguindo a administração de dose única oral. Para cada uma das situações abaixo, desenhar uma nova curva (assinalada com asterisco) capaz de mostrar as alterações ocorridas.

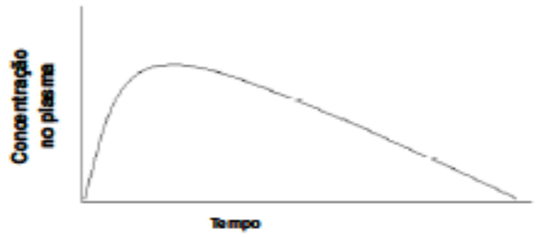
a) aumento do volume de distribuição e redução da constante de velocidade de elimin



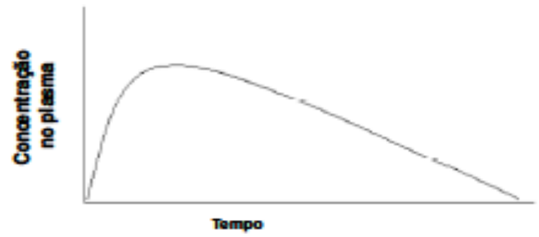
b) aumento da constante de velocidade de absorção



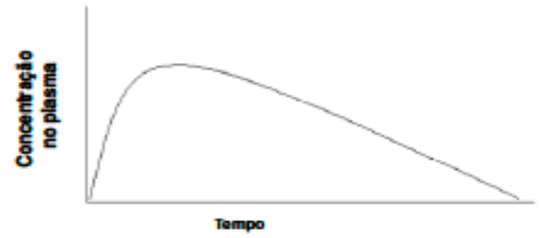
c) aumento do clearance e aumento da constante de velocidade de eliminação



d) redução do clearance e redução da constante de velocidade de eliminação



e) redução da biodisponibilidade



FCFRP-USP

Exercício 2

Um paciente de 60 kg recebeu dose única oral de 60 mg de fexofenadina. As amostras seriadas de sangue foram coletadas até 24 h após a administração do fármaco. Com base nas concentrações plasmáticas de fexofenadina, calcular:

tempo (h)	concentração (ng/mL)
0	0
0,5	4,1
1	7,4
2	53,7
3	88,2
4	72,5
6	50,7
8	36,1
12	18,2
16	9,1
24	2,4

a) **A concentração plasmática máxima (Cmax)**
b) **O tempo para atingir a Cmax (tmax)**
c) **O clearance total (Cl/F)**
d) **O volume de distribuição aparente (Vd/F)**