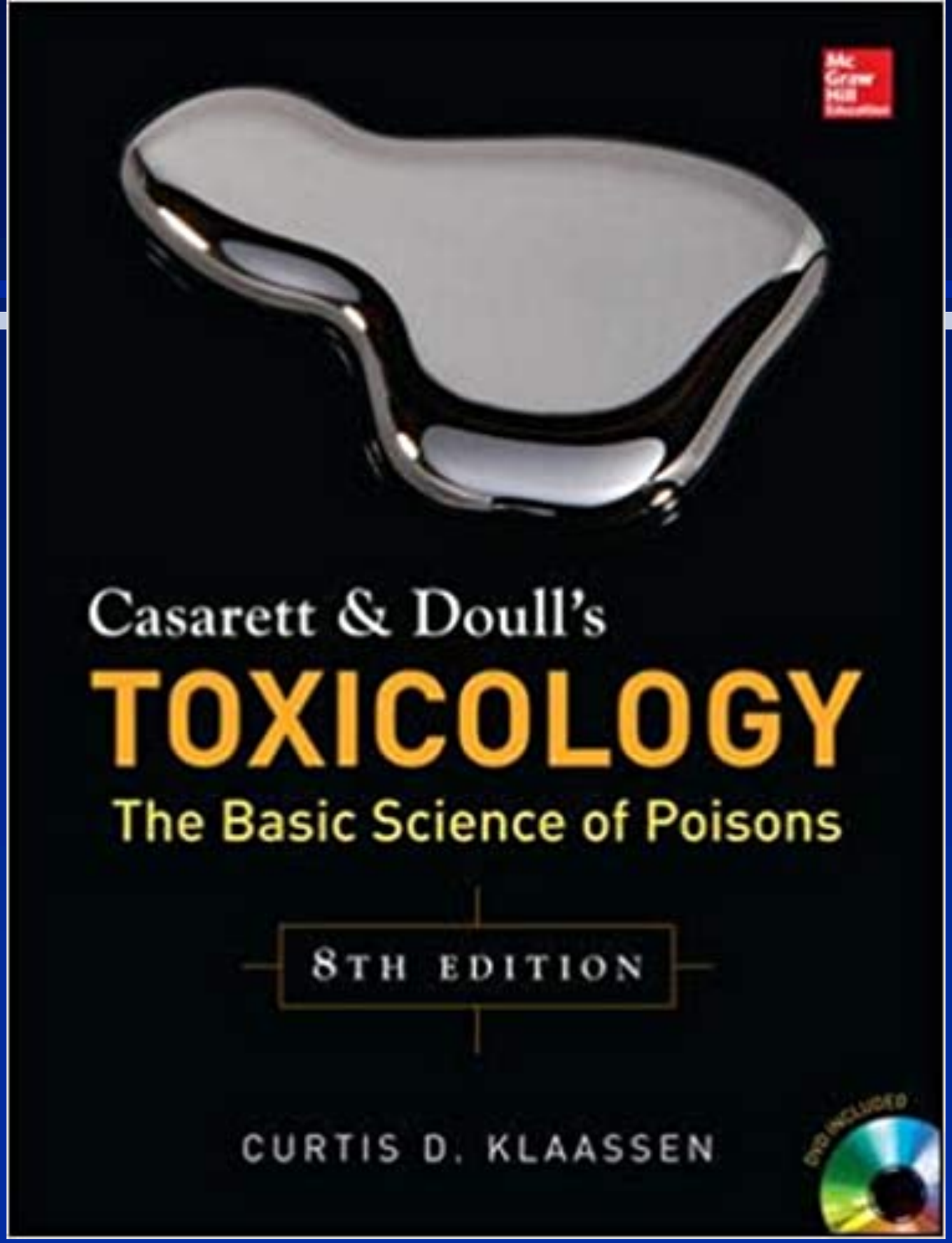

Mc Graw Hill Education
Casarett & Doull's
TOXICOLOGY
The Basic Science of Poisons
8TH EDITION
CURTIS D. KLAASSEN
DVD INCLUDED

KLAASSEN, C.D. (Ed.). Casarett and Doull's TOXICOLOGY: the Basic Science of Poisons. 8th. ed. New York, 2013.

chapter 5

Absorption, Distribution, and Excretion of Toxicants

Lois D. Lehman-McKeeman

chapter 7

Toxicokinetics

Danny D. Shen

Toxicante

1
Toxicocinética

2
Interação com a molécula alvo

3
Disfunção/dano celular

4
Reparo inapropriado

TOXICIDADE

TOXICIDADE

Transporte do sítio de exposição ao sítio alvo

1º estágio

Exposição

Toxicante

TOXICOCINÉTICA

- Absorção
- Distribuição para sítio alvo
- Bioativação
- Reabsorção

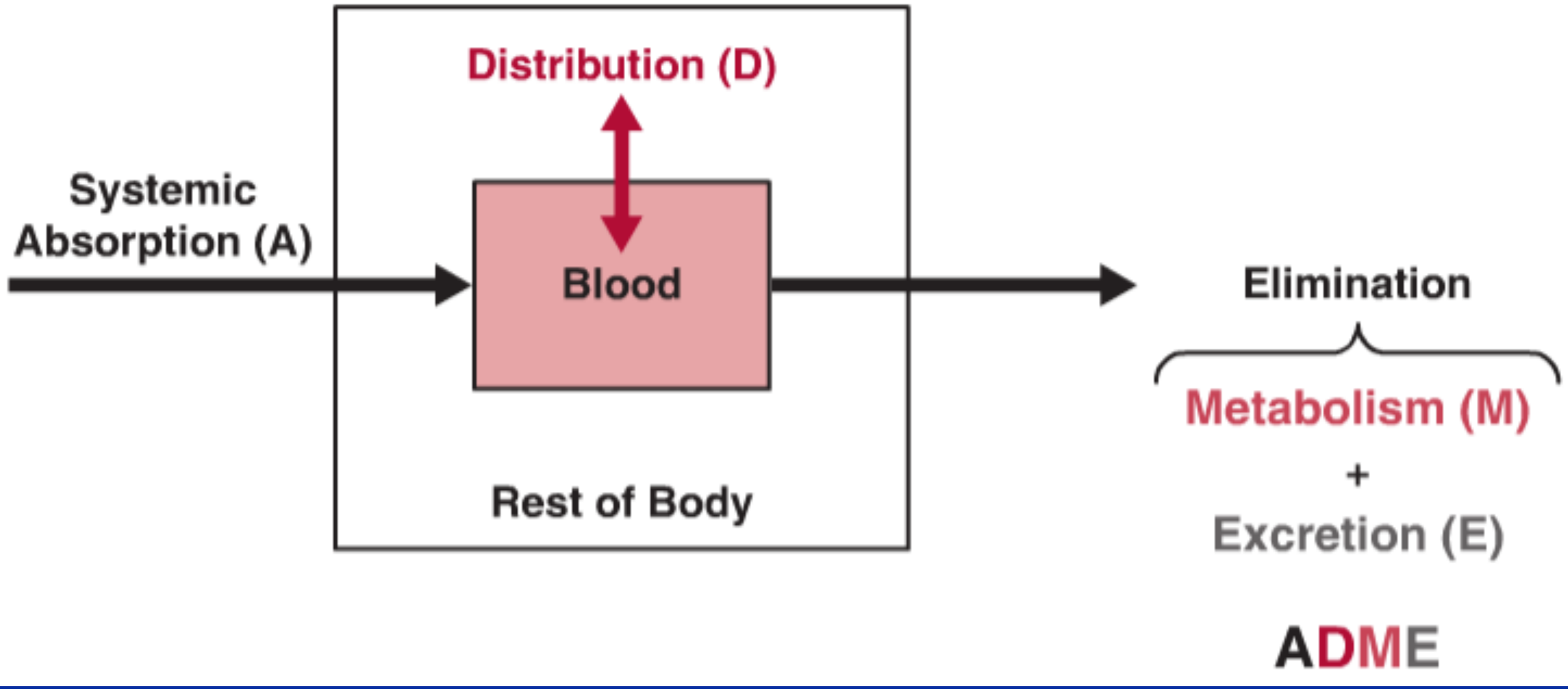
- Eliminação pré-sistêmica
- Distribuição sítios de armazenamento
- Desintoxicação
- Excreção

Toxicante

Molécula alvo

Sítio alvo

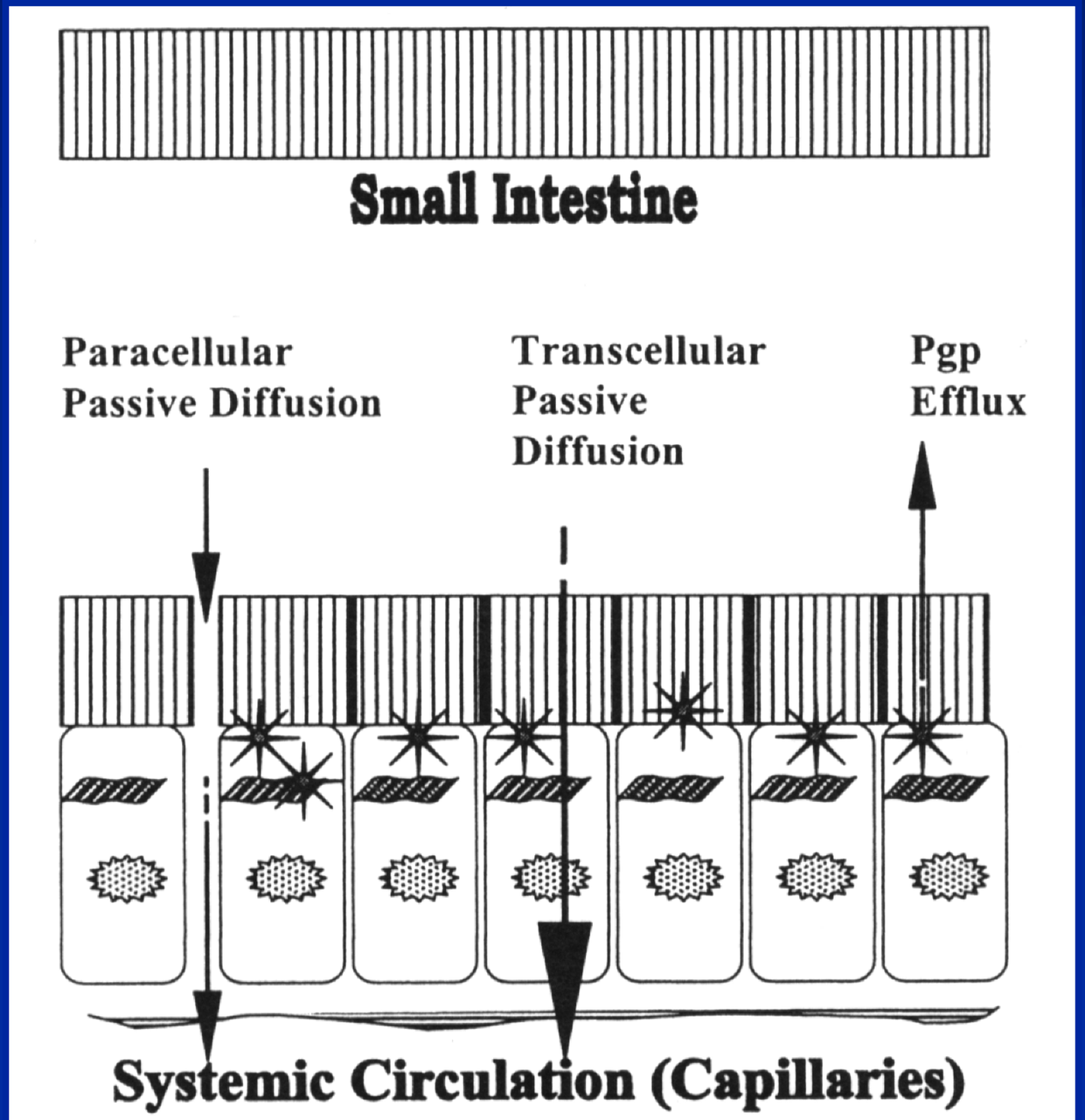
TOXICOCINÉTICA



Clinical pharmacokinetics and pharmacodynamics. 4th edition.

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.

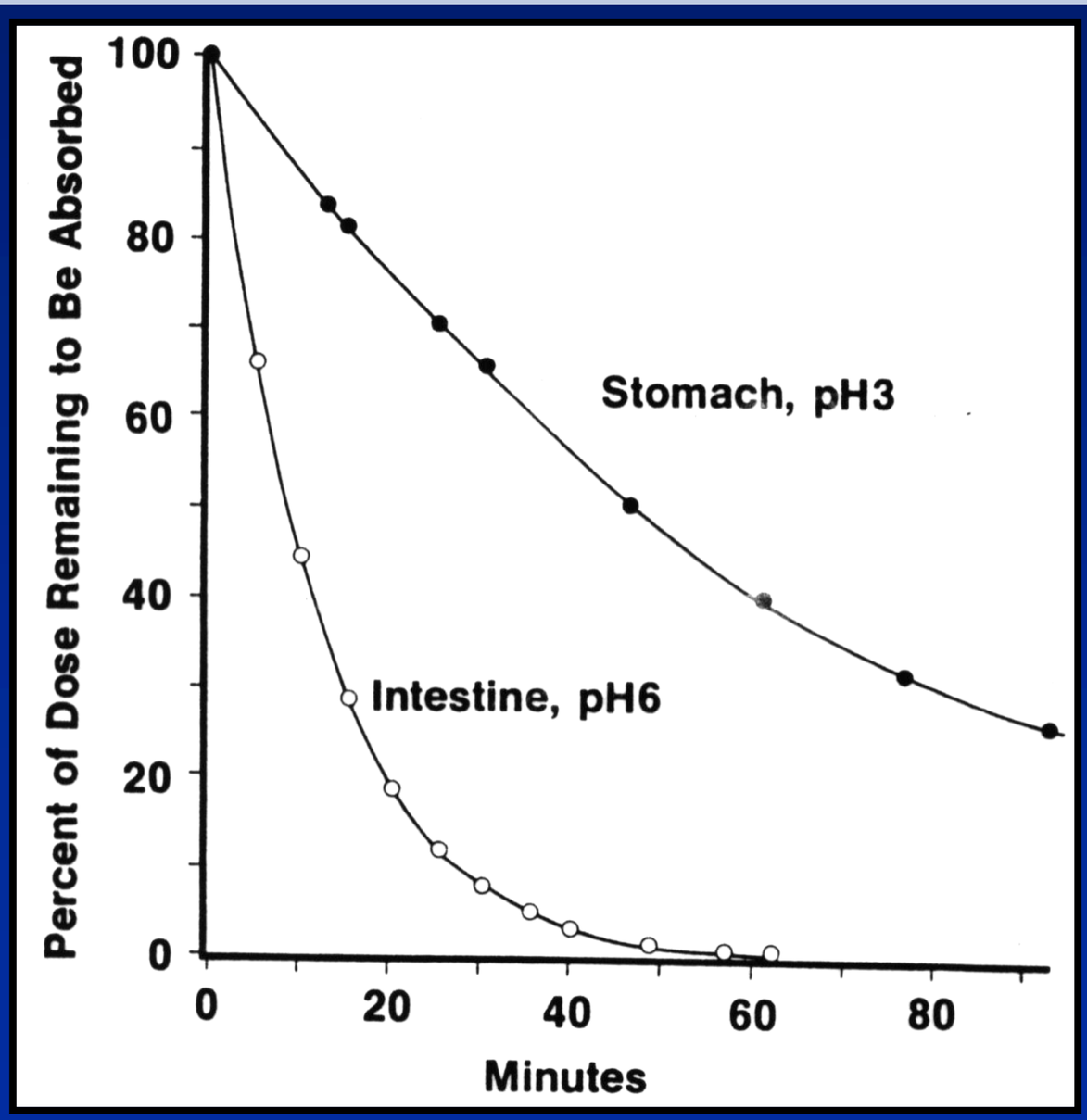
Log P: Physicochemical parameter relative to assessing potential membrane permeability

Absorção no trato gastrintestinal

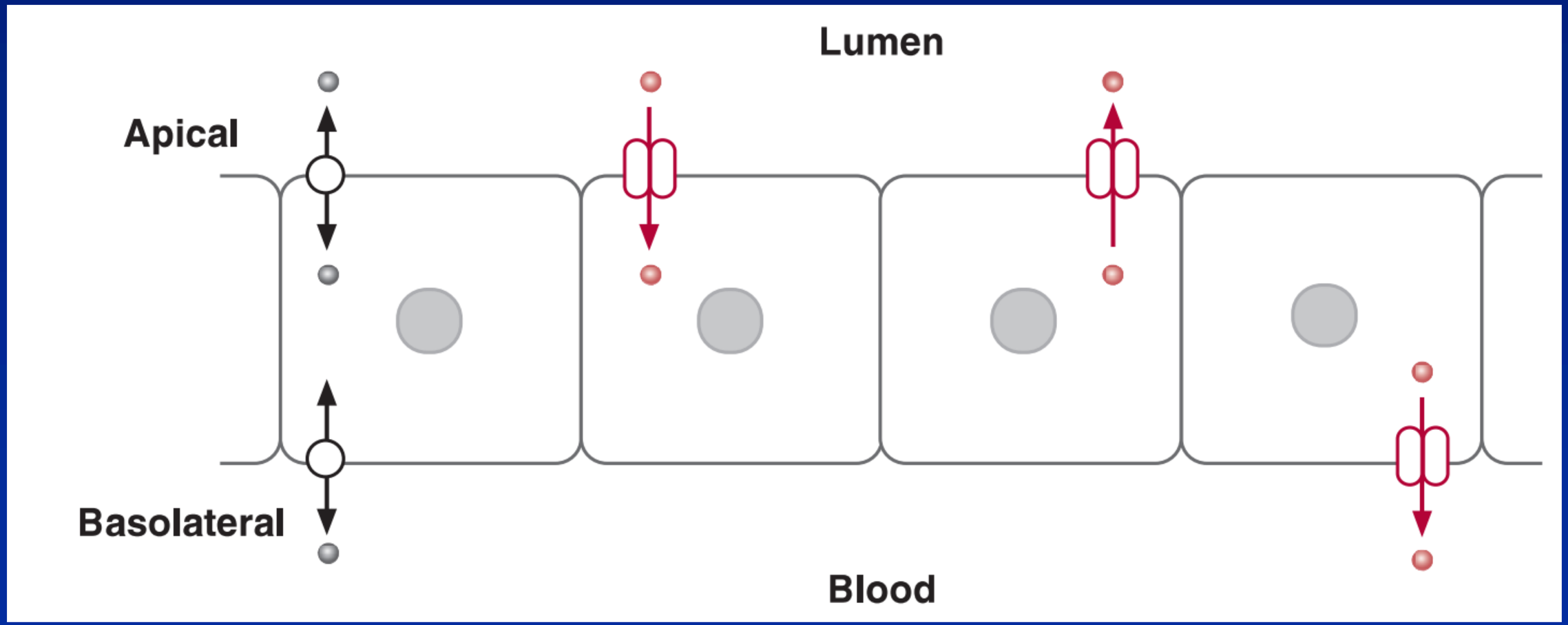
Difusão Passiva

Ácido salicílico (pKa=3)

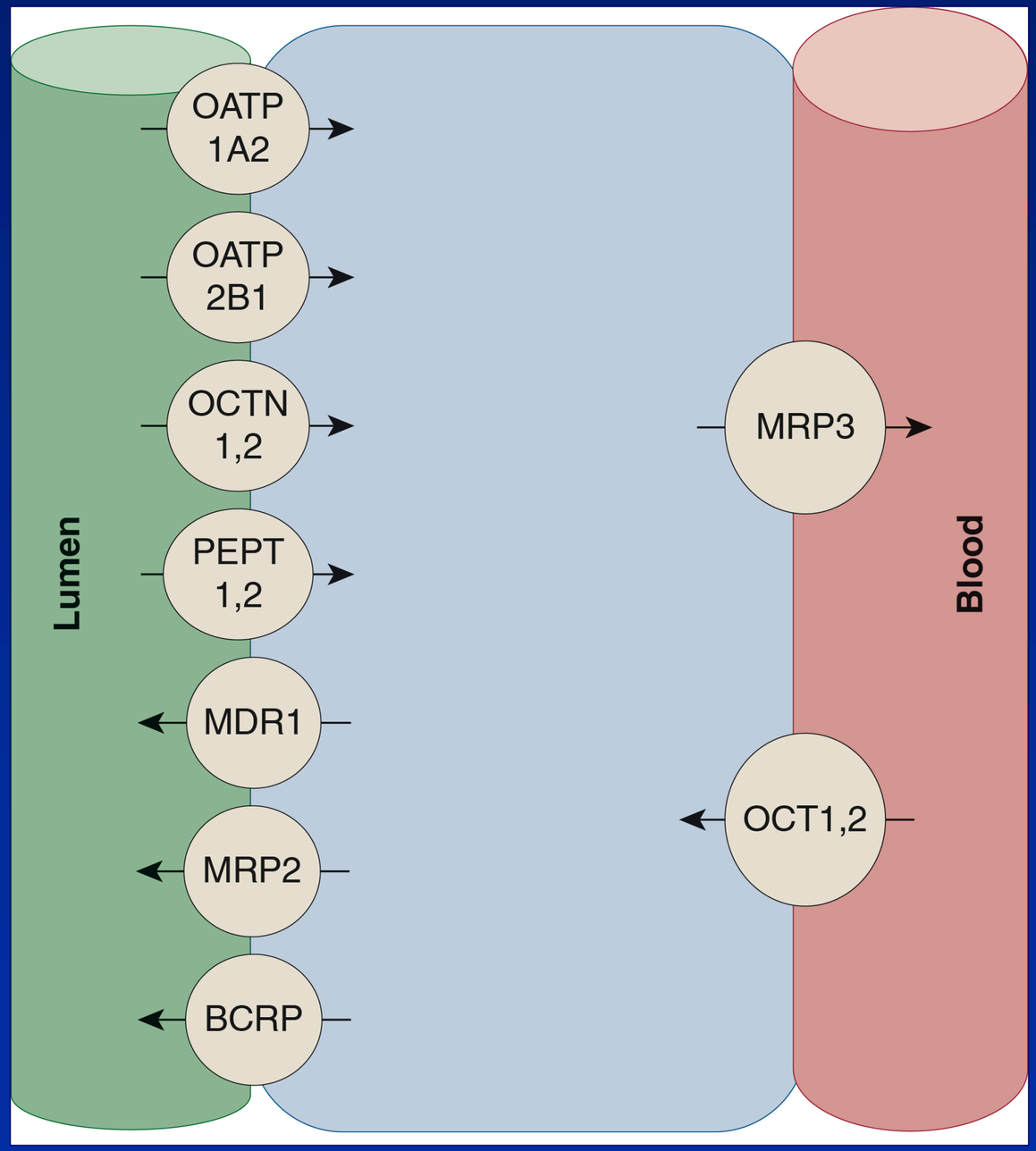
	estômago	intestino delgado
pH	1 – 3,5	5 – 7
área absortiva	1 m^2	200 m^2
perfusão	150 mL/min	1 L/min
permeabilidade	-	+



XENOBIOTIC TRANSPORT SYSTEMS PRESENT IN THE GASTROINTESTINAL TRACT



XENOBIOTIC TRANSPORT SYSTEMS PRESENT IN THE GASTROINTESTINAL TRACT



OATP
Organic anion transporting polypeptide
OCT
Organic cation transporter
PEPT
Peptide transport protein

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

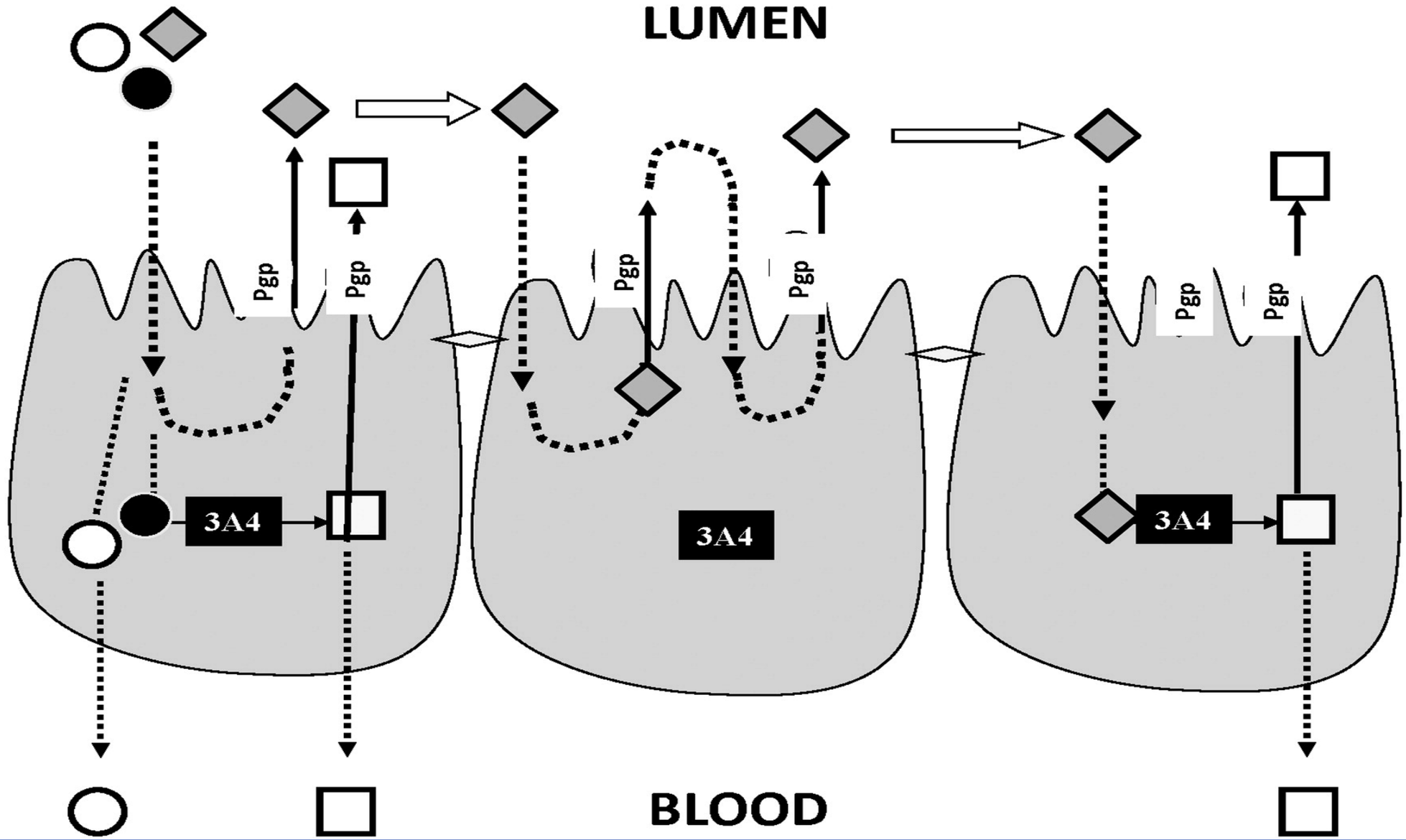
Synergic action of P-gp and CYP3A4 in the enterocytes

Drug not metabolized or transported in the gut

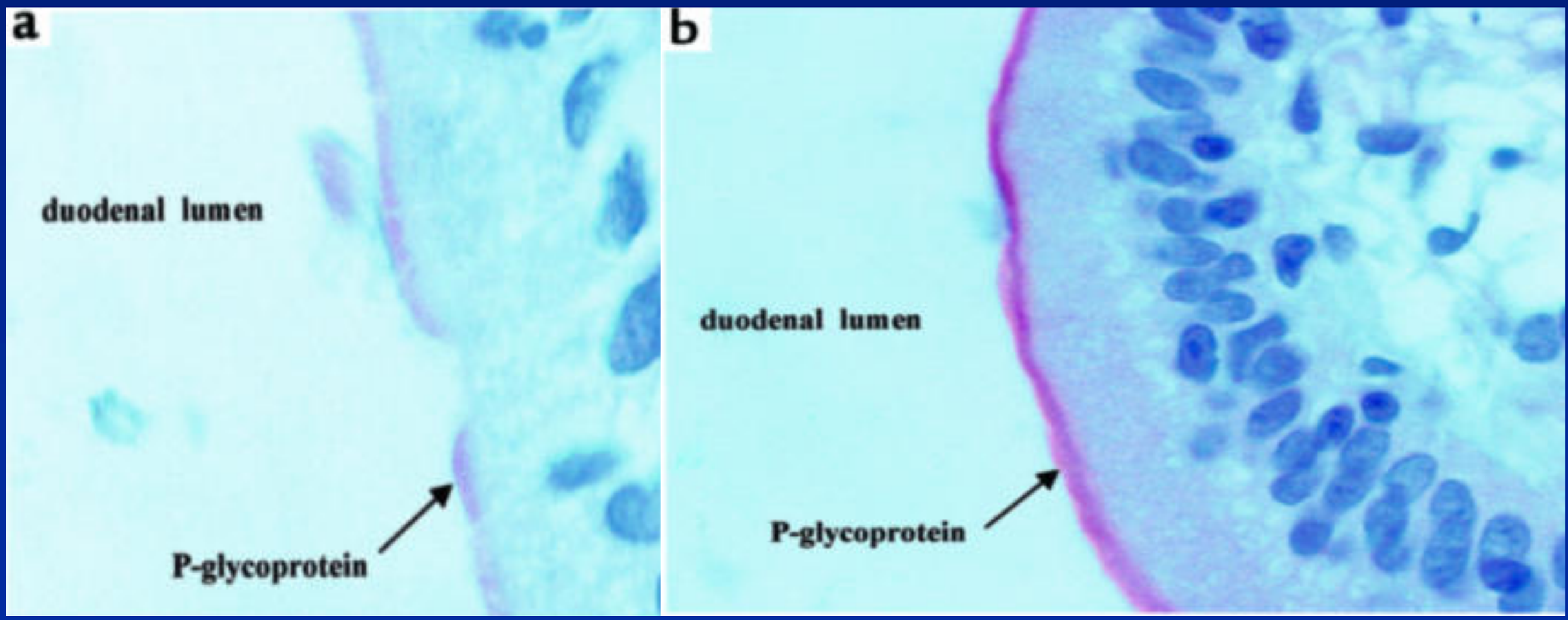
Drug metabolized on first entrance

Drug cycled 4 times before metabolized

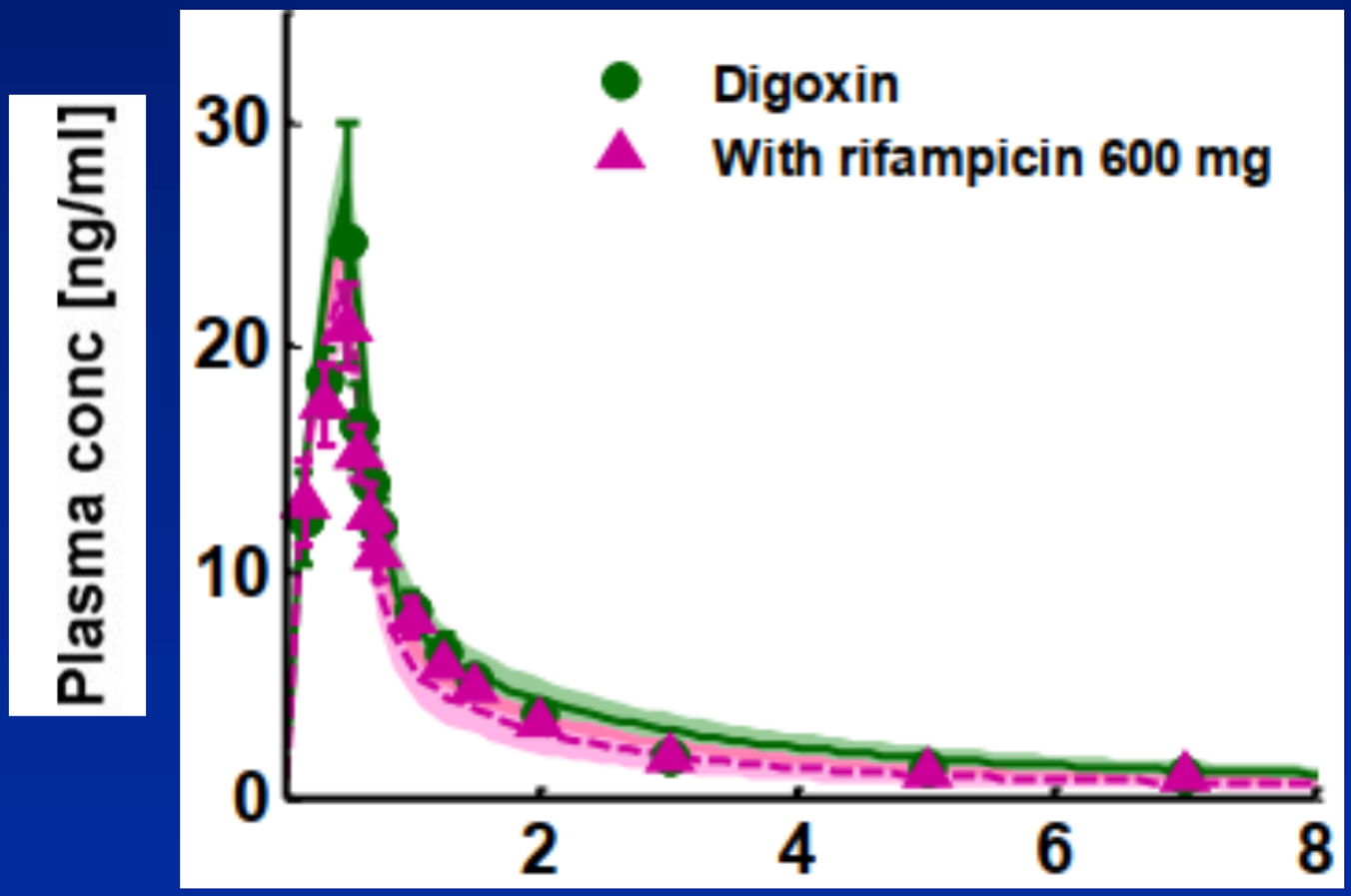
Drug metabolites



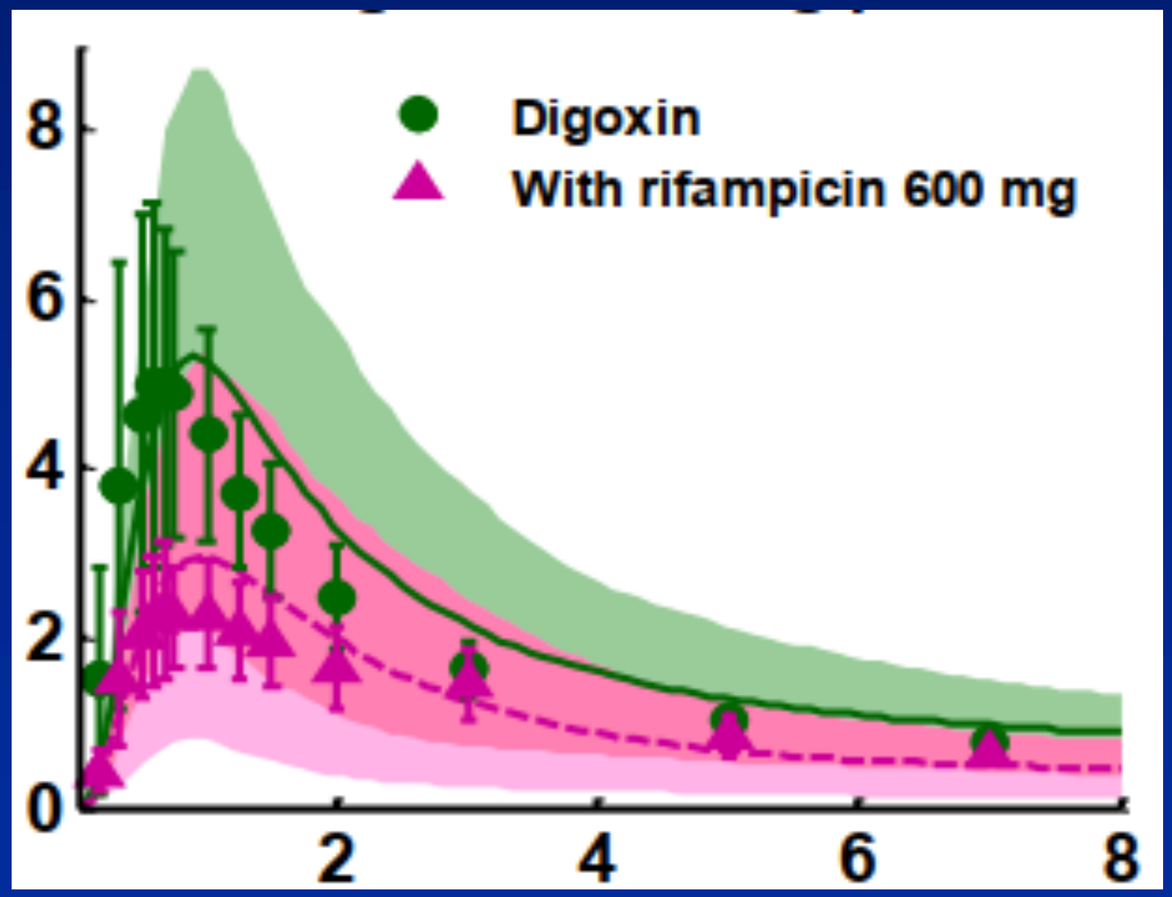
(a) Duodenal biopsy immunostained for P-gp before administration of rifampin (b) Duodenal biopsy after 9 days administration of rifampin (600 mg)



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



Digoxin - 1.0 mg iv



Digoxin - 1.0 mg po

PBPK Models for CYP3A4 and P-gp DDI Prediction: A Modeling Network of Rifampicin, Itraconazole, Clarithromycin, Midazolam, Alfentanil, and Digoxin. CPT Pharmacometrics Syst. Pharmacol. (2018)

Biopharmaceutics Drug Disposition Classification System (BDDCS)

	High Solubility	Low Solubility
High Permeability	**Class 1** High Solubility High Permeability Rapid Dissolution	**Class 2** Low Solubility High Permeability
Low Permeability	**Class 3** High Solubility Low Permeability	**Class 4** Low Solubility Low Permeability

Transporter effects predicted by BDDCS

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**

Examples of Drugs in Class I of the Biopharmaceutics Classification System:

High solubility and High permeability

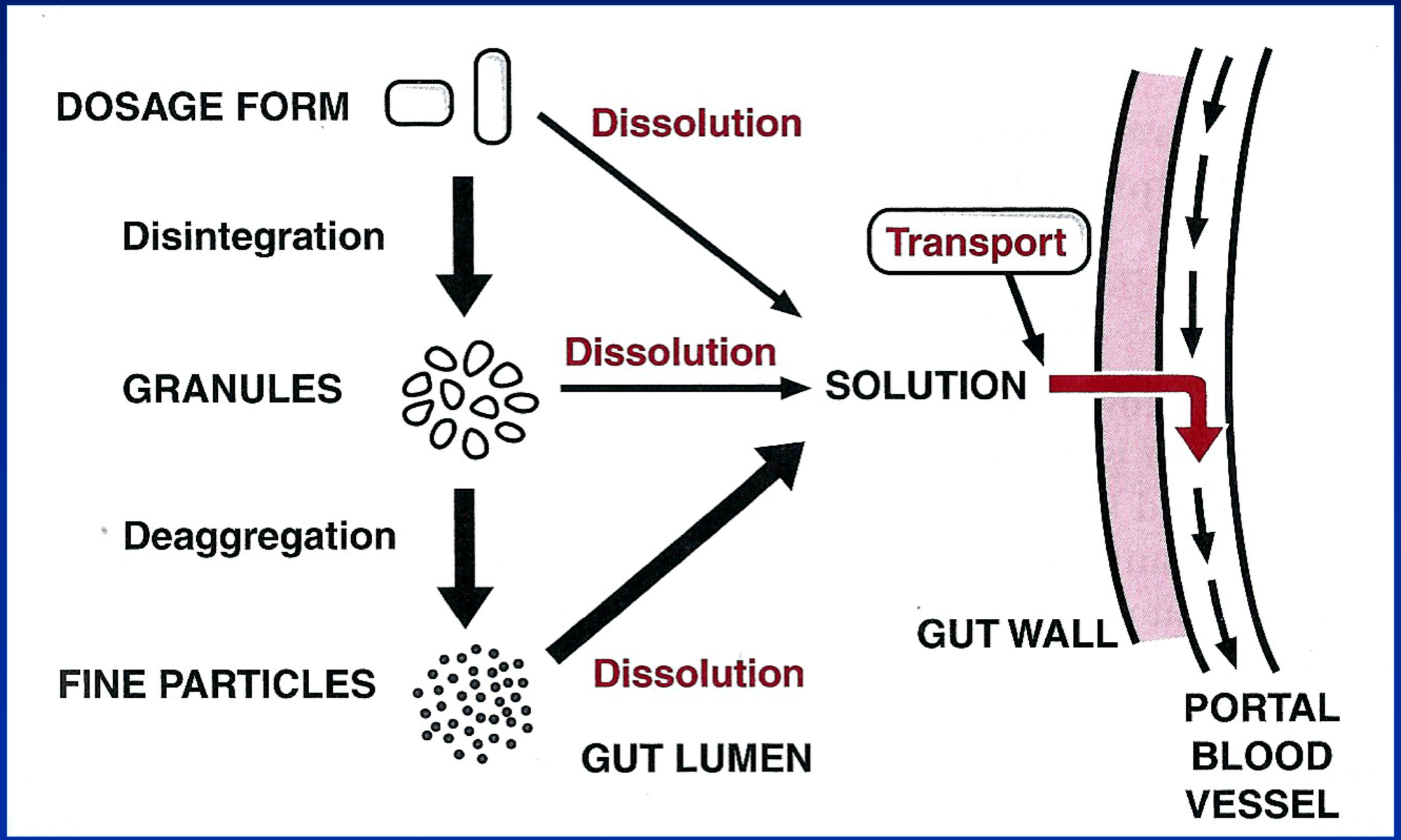
Abacavir	Chlorpheniramine	Ergonovine	Lidocaine	Prednisolone
Acetaminophen	Cyclophosphamide	Ethambutol	Lomefloxacin	Primaquine
Acyclovir	Desipramine	Ethinyl estradiol	Meperidine	Promazine
Amiloride	Diazepam	Fluoxetine	Metoprolol	Propranolol
Amitriptyline	Diltiazem	Imipramine	Metronizadol	Quinidine
Atropine	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

Predicted Effect of Intestinal Drug Transporters on Exposure (AUC) by BDDCS Class

BDDCS Class	1	2	3	4
Inhibition				
Apical Uptake	⇔	⇔	⇩	⇩
Apical Efflux	⇔	⇑	⇑	⇑
Induction				
Apical Uptake	⇔	⇔	⇧	⇧
Apical Efflux	⇔	⇩	⇩	⇩

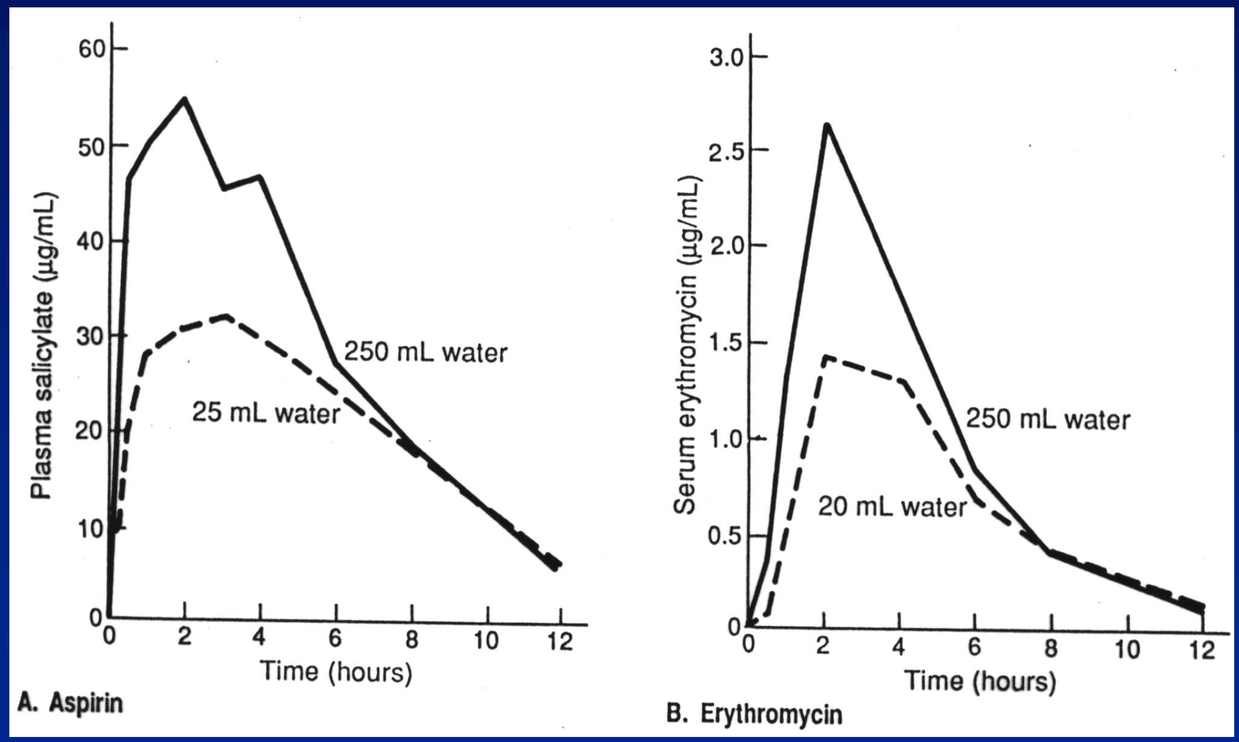
Absorção no trato gastrintestinal

Solubilidade



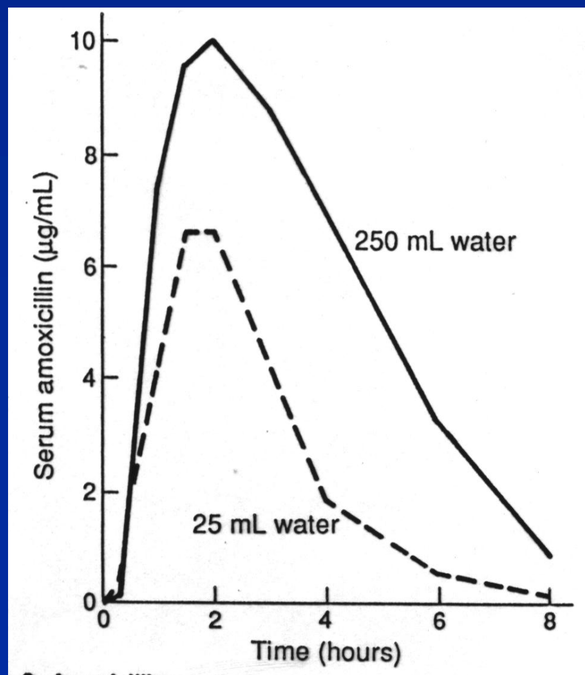
Absorção no trato gastrintestinal

Influência do esvaziamento gástrico

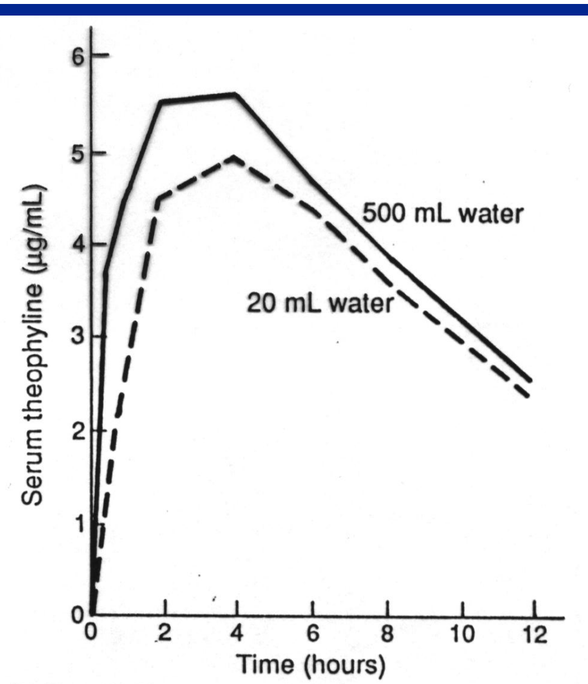


A. Aspirin

B. Erythromycin



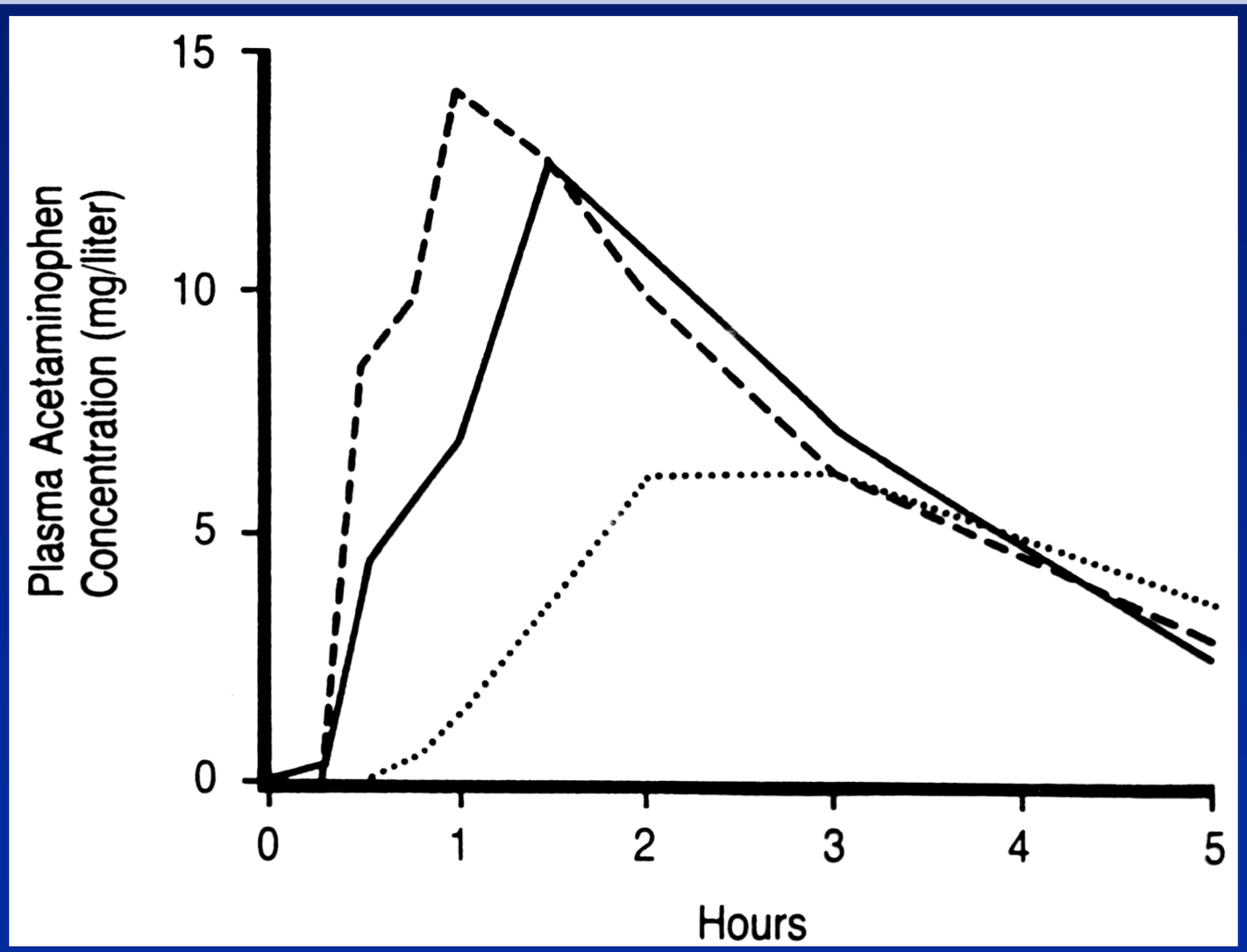
C. Amoxicillin



D. Theophylline

Absorção no trato gastrintestinal

Influência do esvaziamento gástrico



— acetaminofeno

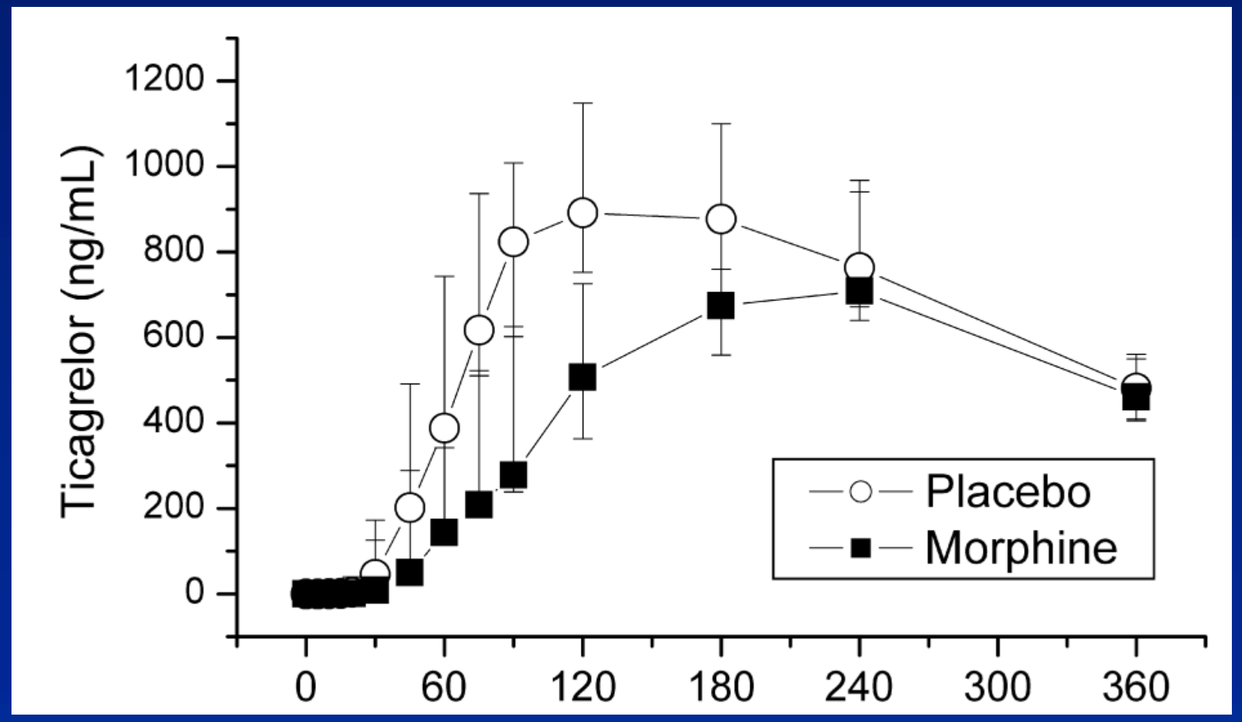
– – acetaminofeno + metoclopramida

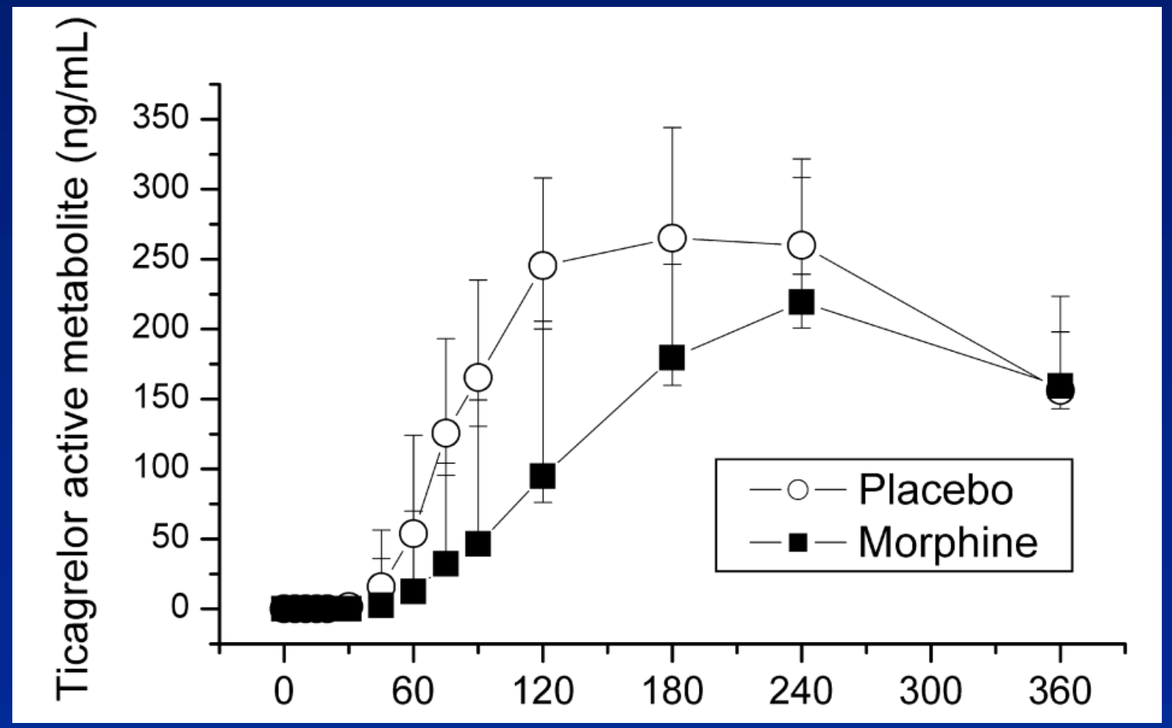
..... acetaminofeno + propantelina

Absorção no trato gastrintestinal

Influência do esvaziamento gástrico

MORPHINE *and* TICAGRELOR





Minutes after co-administration of ticagrelor and placebo/morphine

		AUC_{0-n} (ng.h/mL)	Cmax (ng/mL)	Tmax (min)
Ticagrelor	Placebo	228	1222	120
	Morphine	177	913	180
Ticagrelor metabolite	Placebo	67	325	180
	Morphine	51	242	240

Influência de alimentos na biodisponibilidade de fármacos

ANVISA. Resolução RE nº 1170 de 19 de abril de 2006 atualizada em 10/06/2020

ALIMENTAÇÃO

- Acarbose
- Ácido Ursodesoxicólico
- Acitretina
- Albendazol
- Axetilcefuroxima susp
- Biperideno
- Bromocriptina
- Capecitabina
- Cetoconazol
- Cetoprofeno
- Cinacalcete (cloridrato)
- Darunavir
- Diacereína
- Etionamida
- Exemestano
- Fenofibrato
- Ganciclovir
- Glibenclamida + Metformina
- Glimepirida + Metformina
- Hidroxicloroquina
- Imatinibe
- Isotretinoína
- Itraconazol
- Lercanidipino
- Linagliptina + Metformina
- Lovastatina
- Mefloquina
- Metformina
- Metformina + Pioglitazona
- Metformina + Sitagliptina
- Nelfinavir
- Nitazoxanida
- Nitrendipino
- Nitrofurantoína
- Ornidazol
- Pentoxifilina
- Pinavério
- Propafenona
- Ritonavir
- Rivastigmina
- Rosiglitazona + Glimepirida
- Saquinavir
- Selegilina
- Ticlopidina
- Trazodona
- Valganciclovir
- Ziprasidona

ALIMENTAÇÃO e JEJUM

- Alfuzosina
- Amiodarona
- Buspirona
- Ciclosporina
- Darifenacina
- Divalproato sódico
- Everolimo
- Fampridina
- Medroxiprogesterona
- Piridoxina
- Pitavastatina
- Propiltiouracil
- Rivaroxabana 20 mg
- Sirolimo
- Sulpirida
- Tacrolimo
- Talidomida
- Trimetazidina

Influence of a mexican diet on the bioavailability of albendazole

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)**

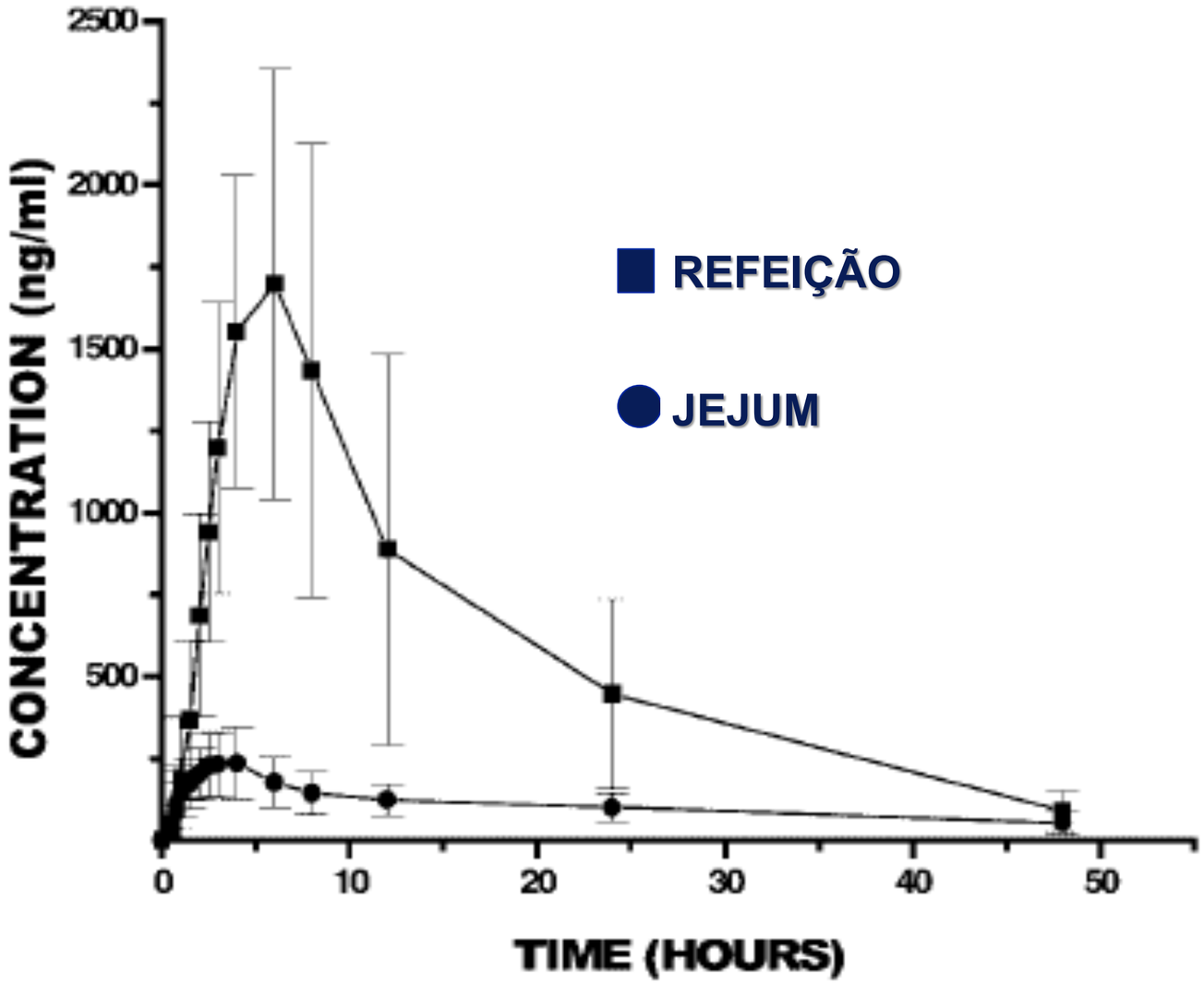
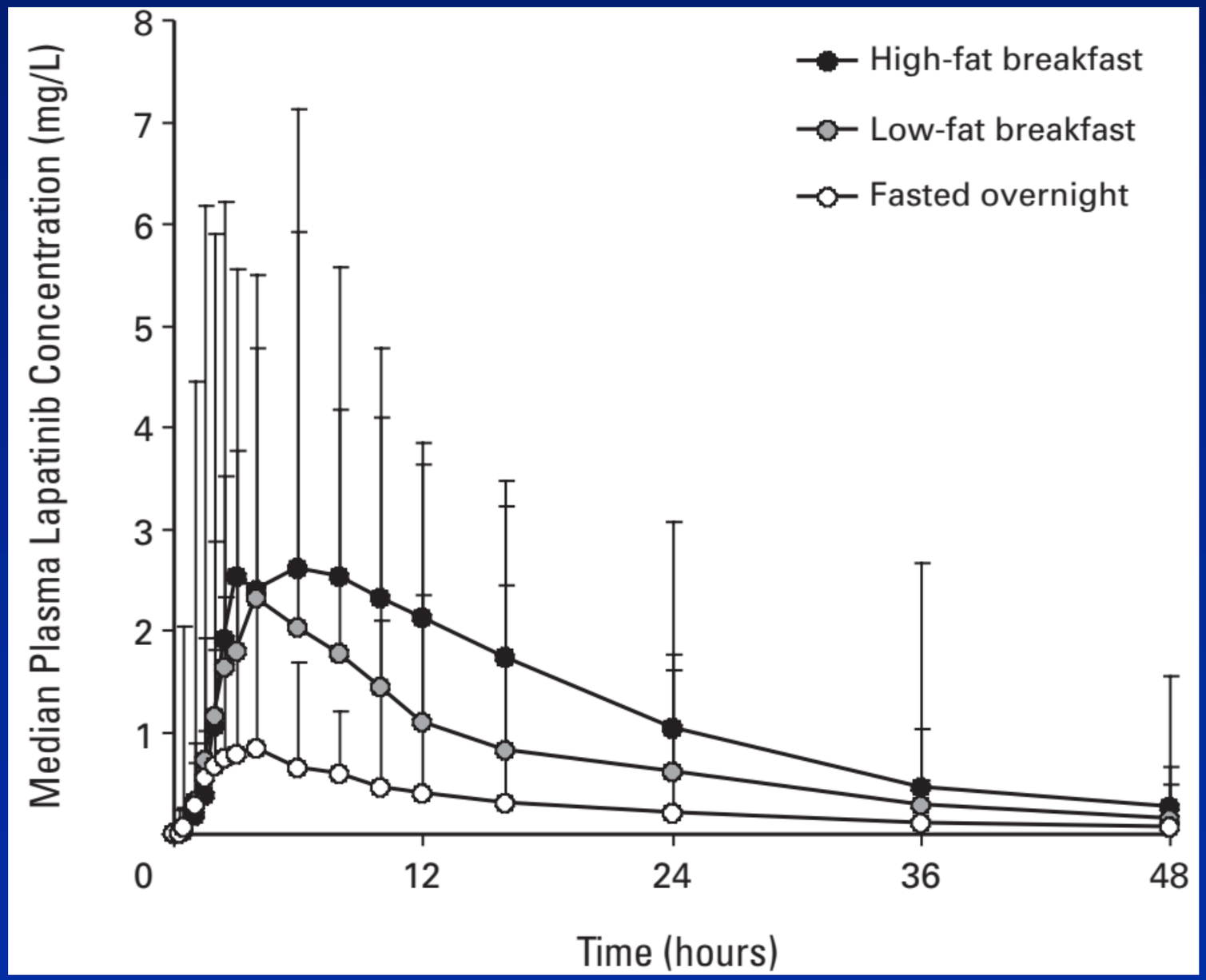


Fig. 1. Mean plasma concentration of albendazole sulfoxide after a single oral dose of 800 mg of albendazole in fasting state (●) and after a fatty meal (■).

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

Food effect of lapatinib PK in patients with cancer



LOW-FAT breakfast:

1 xíc. cereal matinal; leite **desnatado**; torrada com geléia, suco de maça e café ou chá.

HIGH-FAT breakfast:

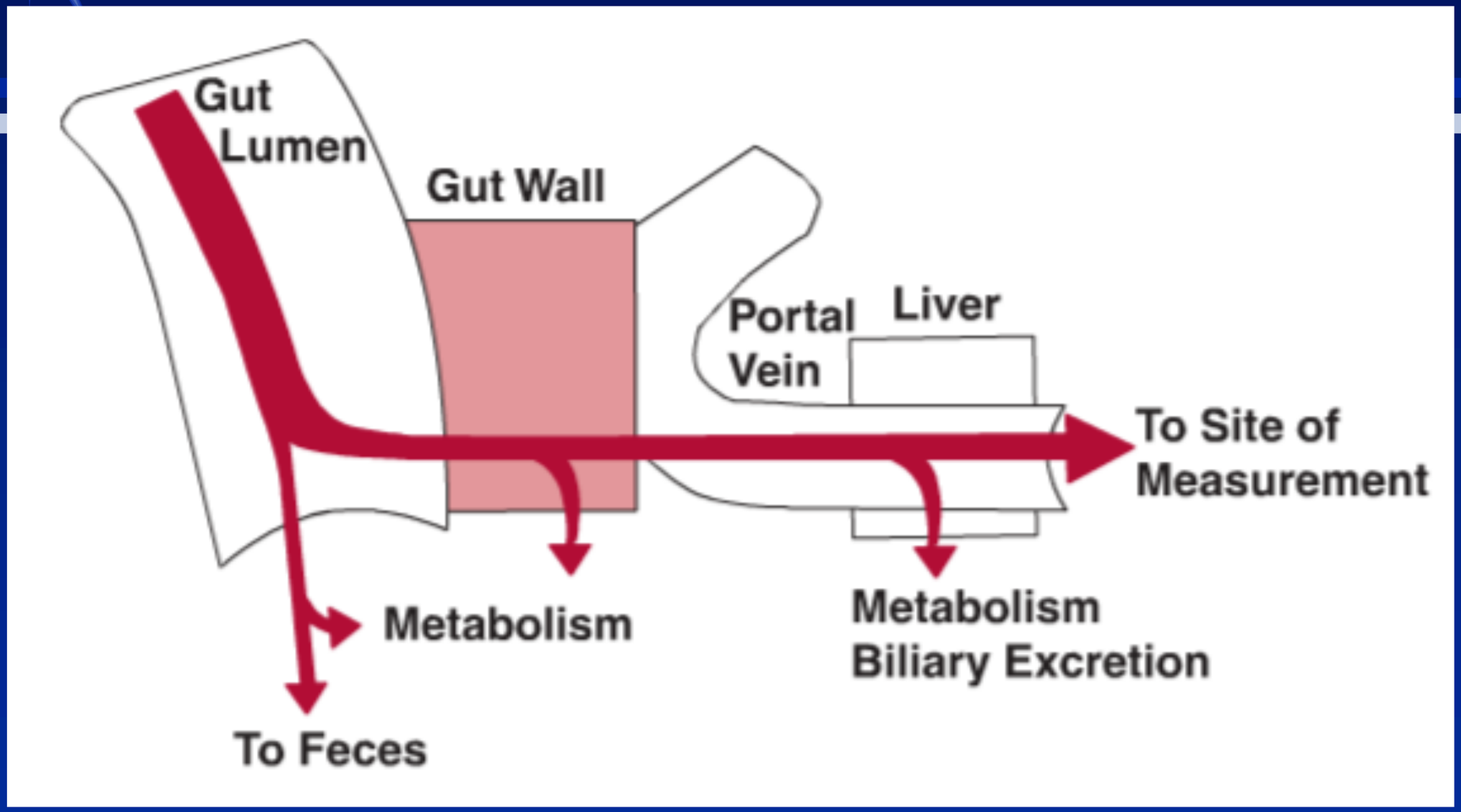
Ovos fritos em manteiga, tiras de bacon, torradas com manteiga, batata picada frita, leite **integral** e café ou chá.

Bioavailability (F): Amount of drug absorbed or reaching systemic circulation

(F) . (Dose)

$$F = F_a . F_G . F_H$$

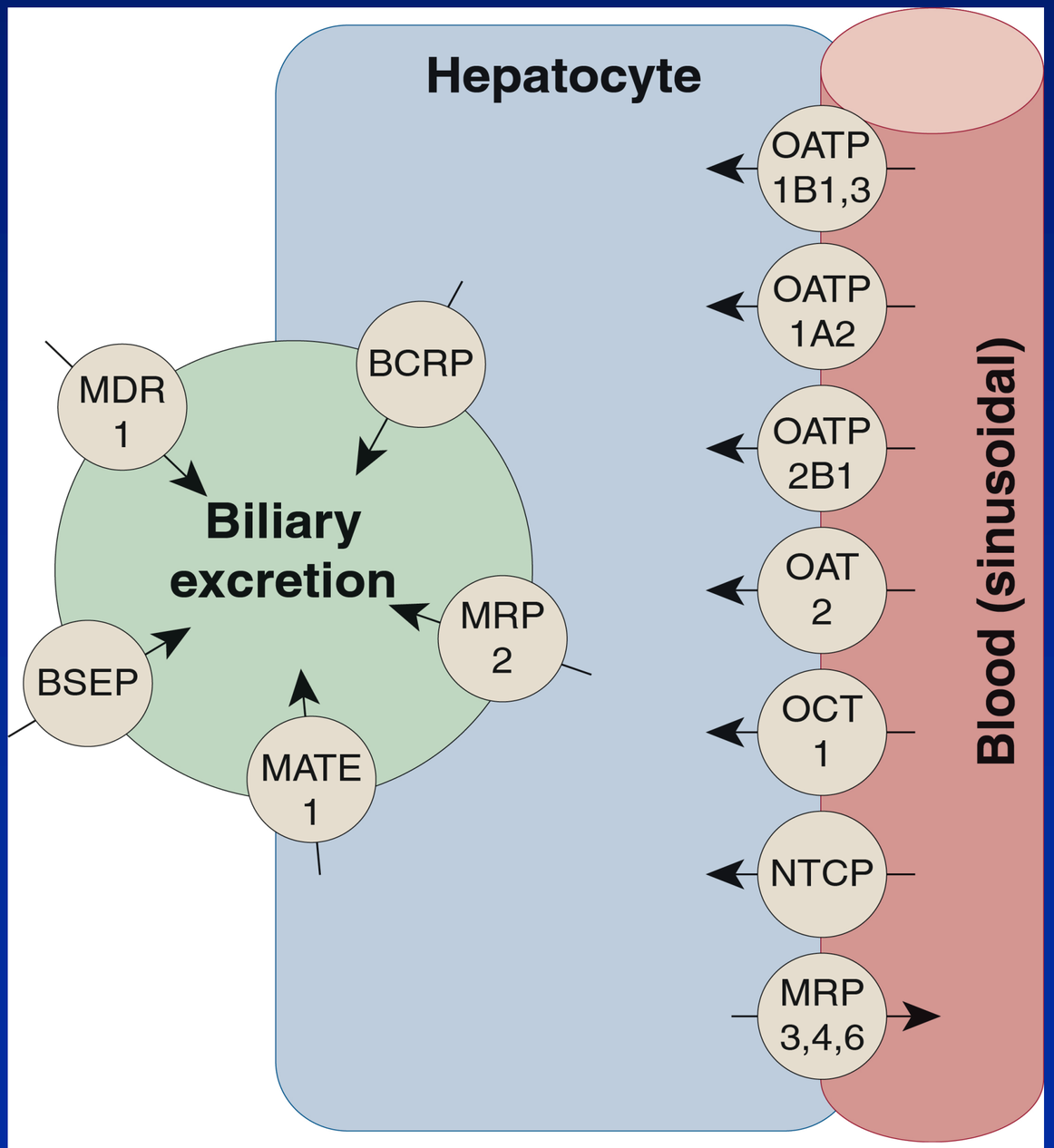
Eliminação pré-sistêmica



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

Clinical pharmacokinetics and pharmacodynamics. 4th edition.

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

Predicted Hepatic Effect of Drug Transporters on Exposure (AUC) by BDDCS Class

BDDCS Class	1	2	3	4
Inhibition				
Basolateral Uptake	⇔	⇧	⇧	⇧
Basolateral Efflux	⇔	⇩	⇩	⇩
Induction				
Basolateral Uptake	⇔	⇩	⇩	⇩
Basolateral Efflux	⇔	⇧	⇧	⇧

Simvastatin with and without Grapefruit Juice

Changes in oral bioavailability

	Water	Grapefruit juice	time after discontinuing GFJ		
			24 h	3 days	7 days
Cmax (µg/L)	9.3	112		14.2	12.4
AUC (µg.hr/L)	28.9	390	59.4	39.6	30.6

Grapefruit juice is a potent inhibitor of CYP3A

Uses of Bioavailability

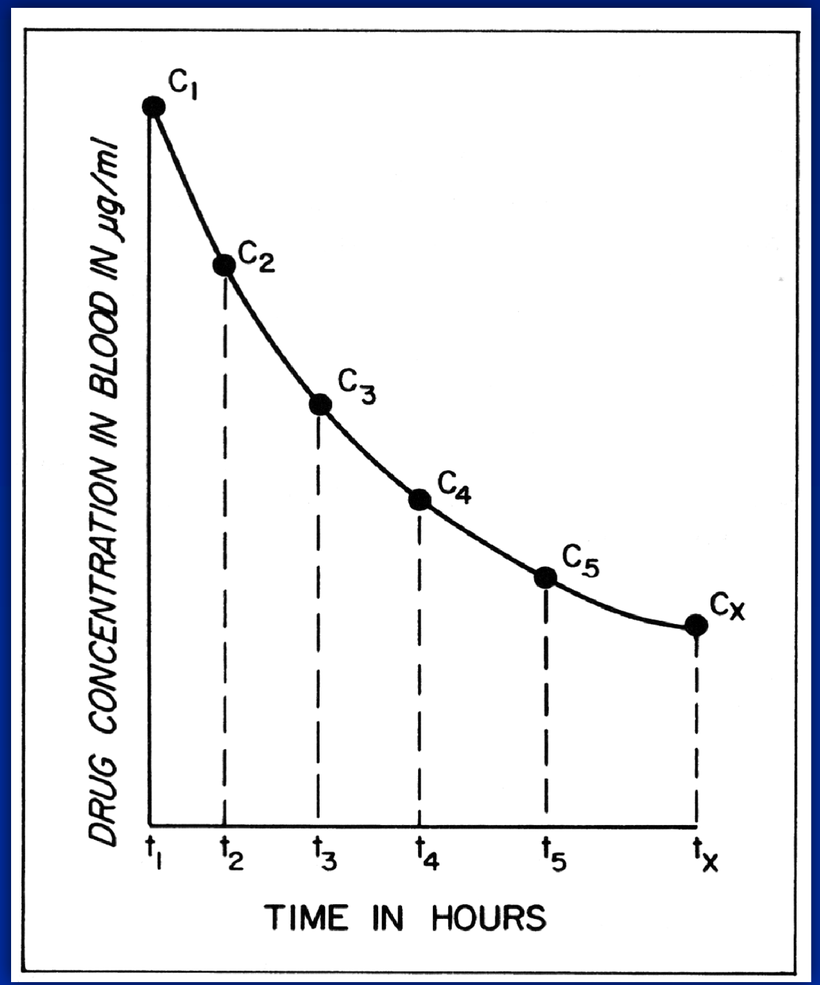
- Bioavailability is a key determinant in the difference in dose sizes between intravenous and oral preparations

Como calcular a biodisponibilidade (F)?

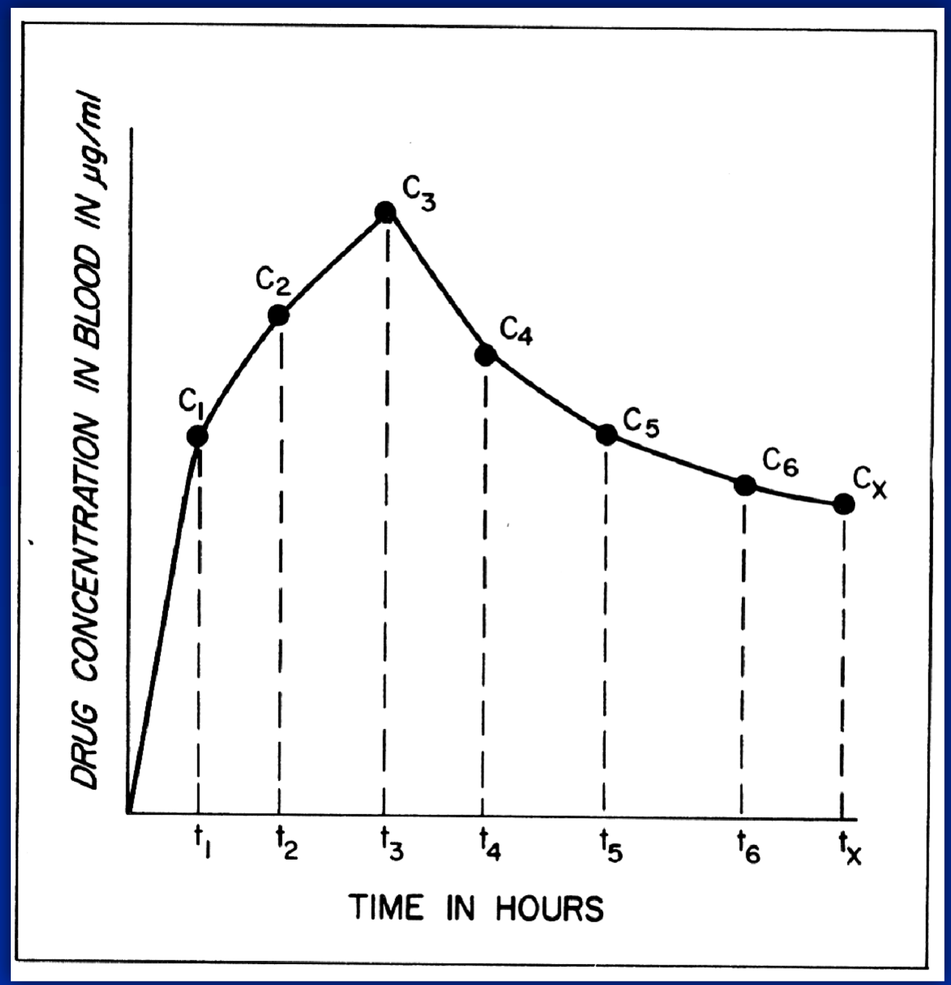
$$F = \frac{AUC\ ev\ .\ dose\ iv}{AUC\ iv\ .\ dose\ ev}$$

Area under the blood level-time curve

Intravascular route

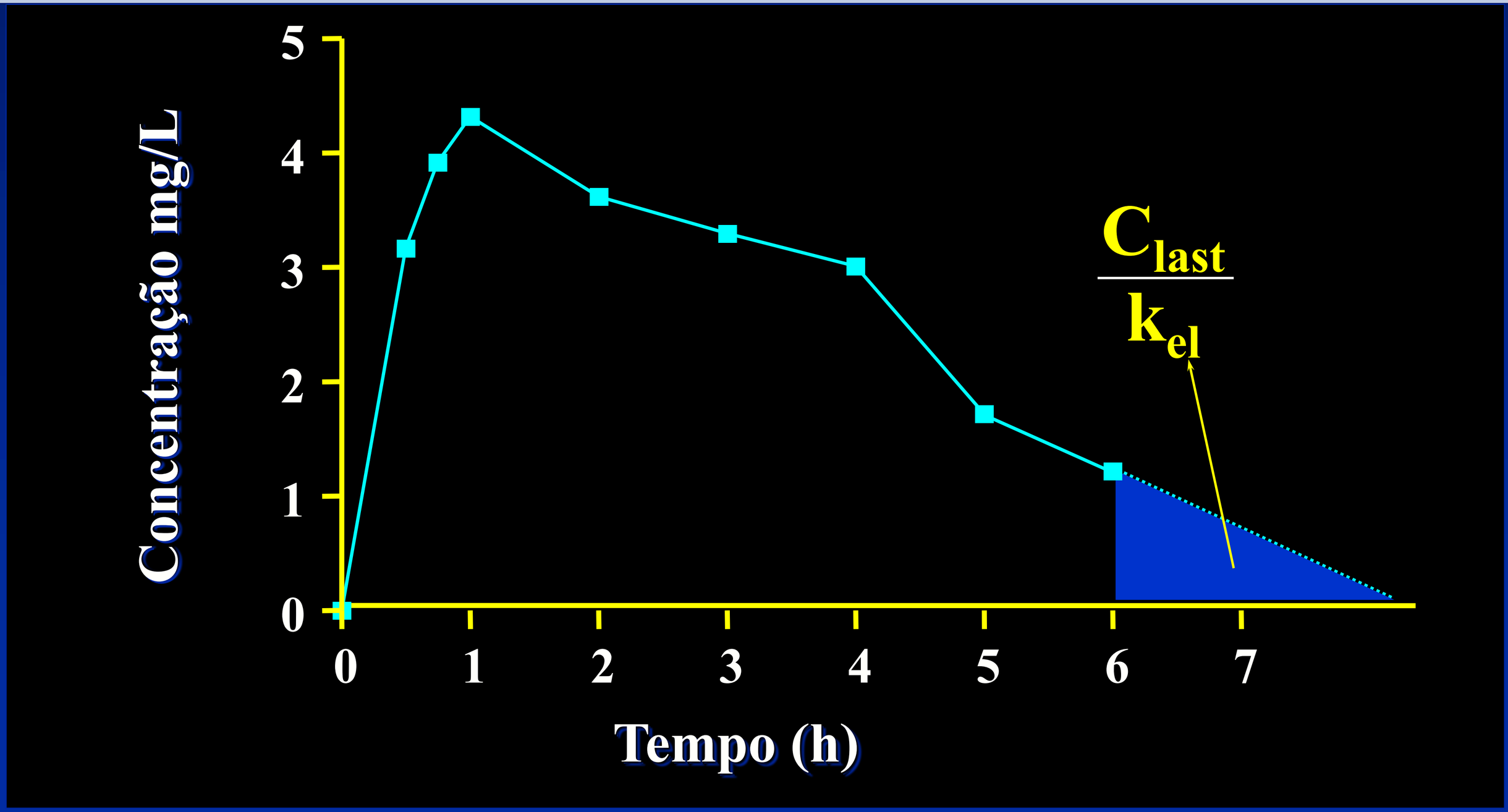


Extravascular route



Area extrapolada até o infinito

(∞)



Exercício 1 –Biodisponibilidade (F)

Você está avaliando a biodisponibilidade oral (F) de uma nova formulação de procainamida, um fármaco utilizado no tratamento da arritmia cardíaca. A Tabela apresenta os dados obtidos em um estudo clínico com voluntários. Calcule o F da formulação oral.

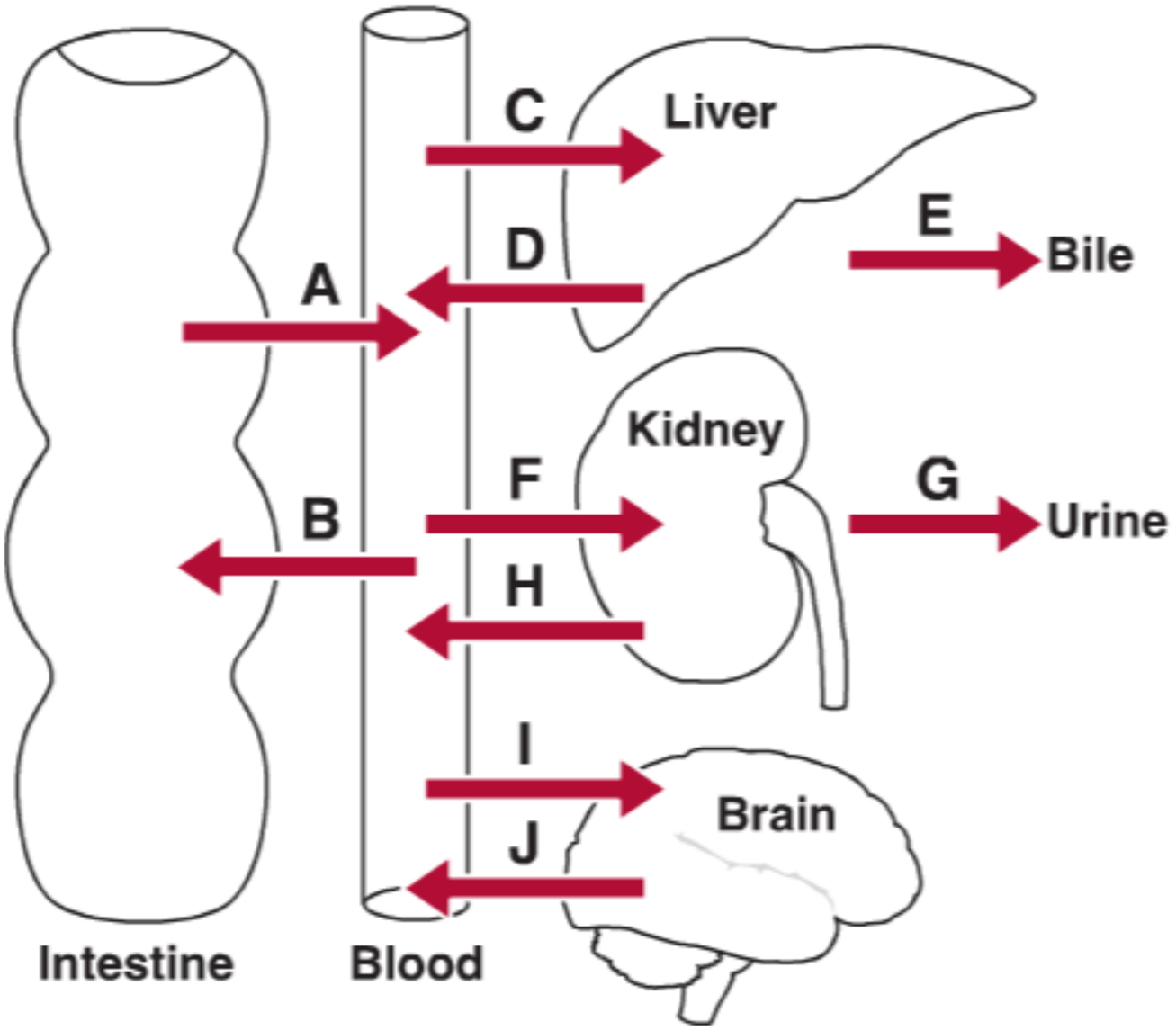
Via	Dose (mg)	AUC (mg.h/L)
I.V	500	13,1
Oral	1000	19,9

Exercício 2 – Biodisponibilidade

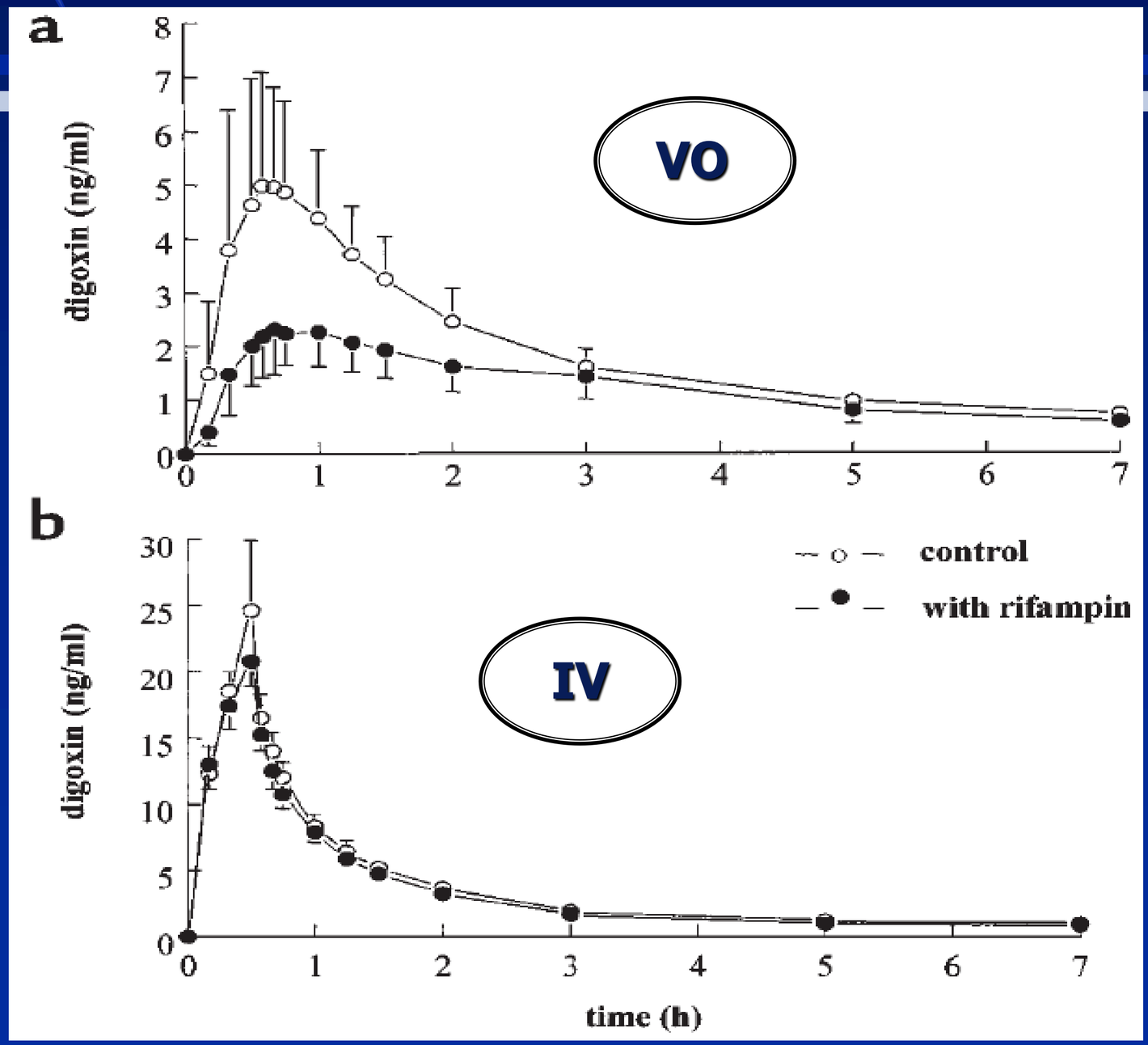
Comente a influência de transportadores de fármacos na biodisponibilidade.

Key	Process	Example Transporter
A	Intestinal Uptake	OATPs
B	Intestinal Efflux	MDR1*, BCRP
C	Hepatic Uptake	OATPs
D	Hepatic Efflux	MRP3
E	Biliary Secretion	MDR1, MRP2
F	Renal Uptake	OAT3
G	Renal Secretion	MDR1, MRP2
H	Renal Reabsorption	SVCT1
I	Brain Uptake	LAT1
J	Brain Efflux	MDR1, BCRP

*Commonly called P-glycoprotein



Exercício 3 – Absorção e biodisponibilidade



Considerando que a digoxina é um substrato do transportador de efluxo P-gp, explique as diferenças observadas nas concentrações plasmáticas da digoxina administrada pela via oral (VO) ou endovenosa (IV) com ou sem uso de rifampicina.