

USP



Mc
Graw
Hill
Education

Casarett & Doull's
TOXICOLOGY
The Basic Science of Poisons

8TH EDITION

CURTIS D. KLAASSEN



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

5 chapter

Absorption, Distribution, and Excretion of Toxicants

Lois D. Lehman-McKeeman

Introduction

Cell Membranes

Passive Transport
Simple Diffusion
Filtration
Special Transport
Active Transport
Facilitated Diffusion
Xenobiotic Transporters
Additional Transport Processes

Absorption

Absorption of
Toxicants by the
Gastrointestinal Tract
Absorption of Toxicants
by the Lungs
Gases and Vapors

Aerosols and Particles

Absorption of Toxicants Through
the Skin
Absorption of Toxicants
After Special Routes of
Administration

Distribution

Volume of Distribution
Storage of Toxicants in Tissues
Plasma Proteins as Storage Depot
Liver and Kidney as Storage Depots
Fat as Storage Depot
Bone as Storage Depot
Blood-Brain Barrier
Passage of Toxicants Across
the Placenta
Redistribution of Toxicants

Excretion

Urinary Excretion
Fecal Excretion
Nonabsorbed Ingesta
Biliary Excretion
Exhalation
Other Routes of Elimination
Cerebrospinal Fluid
Milk
Sweat and Saliva

Computational and Experimental Approaches to Assess Xenobiotic Disposition

Absorption
Hepatobiliary Excretion

Conclusion

7 chapter

Toxicokinetics

Danny D. Shen

Introduction

Classic Toxicokinetics

One-Compartment Model
Two-Compartment Model
Apparent Volume of
Distribution
Clearance
Relationship of Elimination
Half-Life to Clearance
and Volume
Absorption and Bioavailability
Metabolite Kinetics
Saturation Toxicokinetics

Accumulation During Continuous
or Intermittent Exposure
Conclusion

Physiological Toxicokinetics

Basic Model Structure
Compartments
Parameters
Anatomic
Physiological
Thermodynamic
Transport
Perfusion-Limited Compartments
Diffusion-Limited Compartments

Specialized Compartments

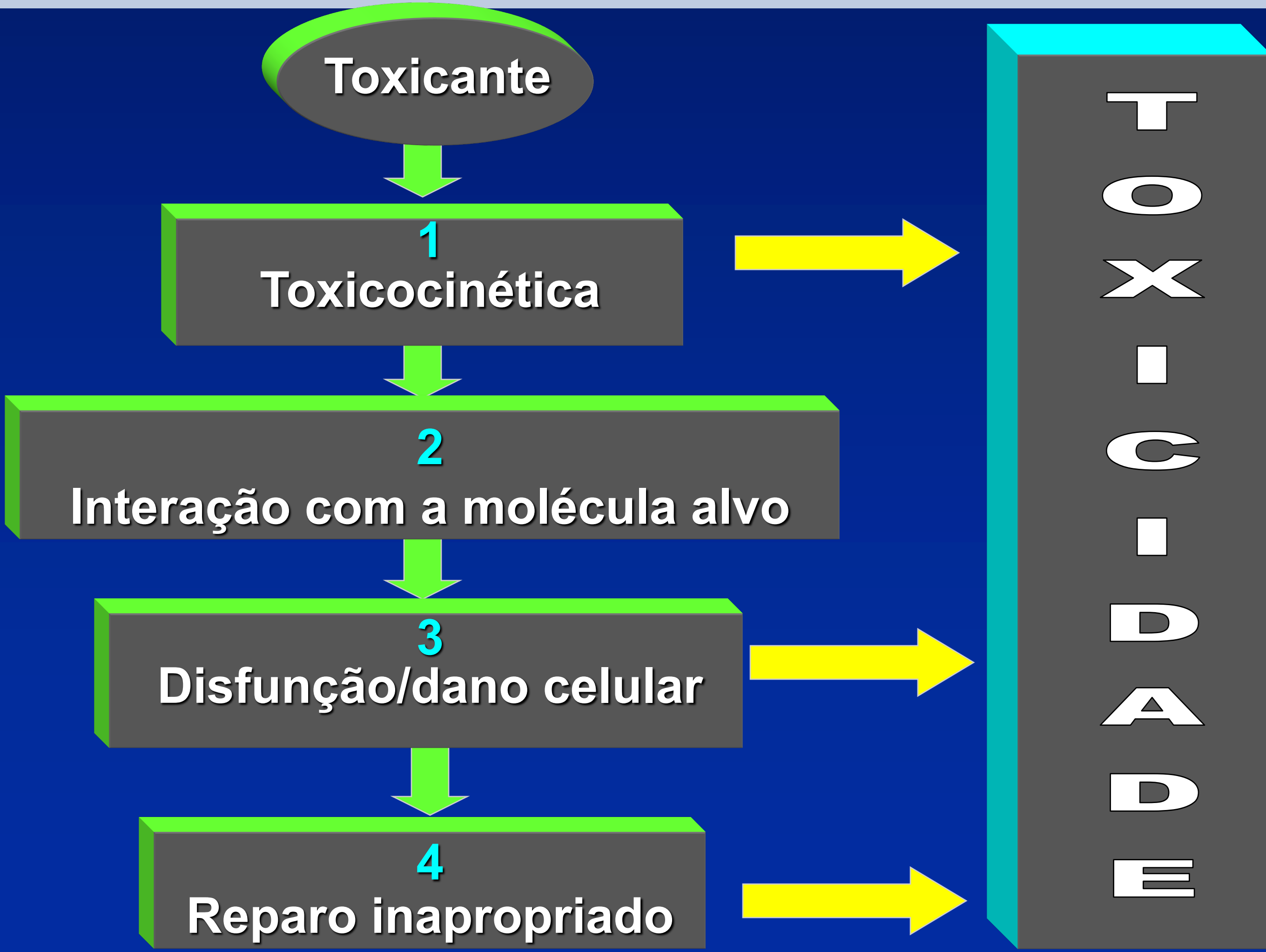
Lung
Liver
Blood

Conclusions

Biological Monitoring

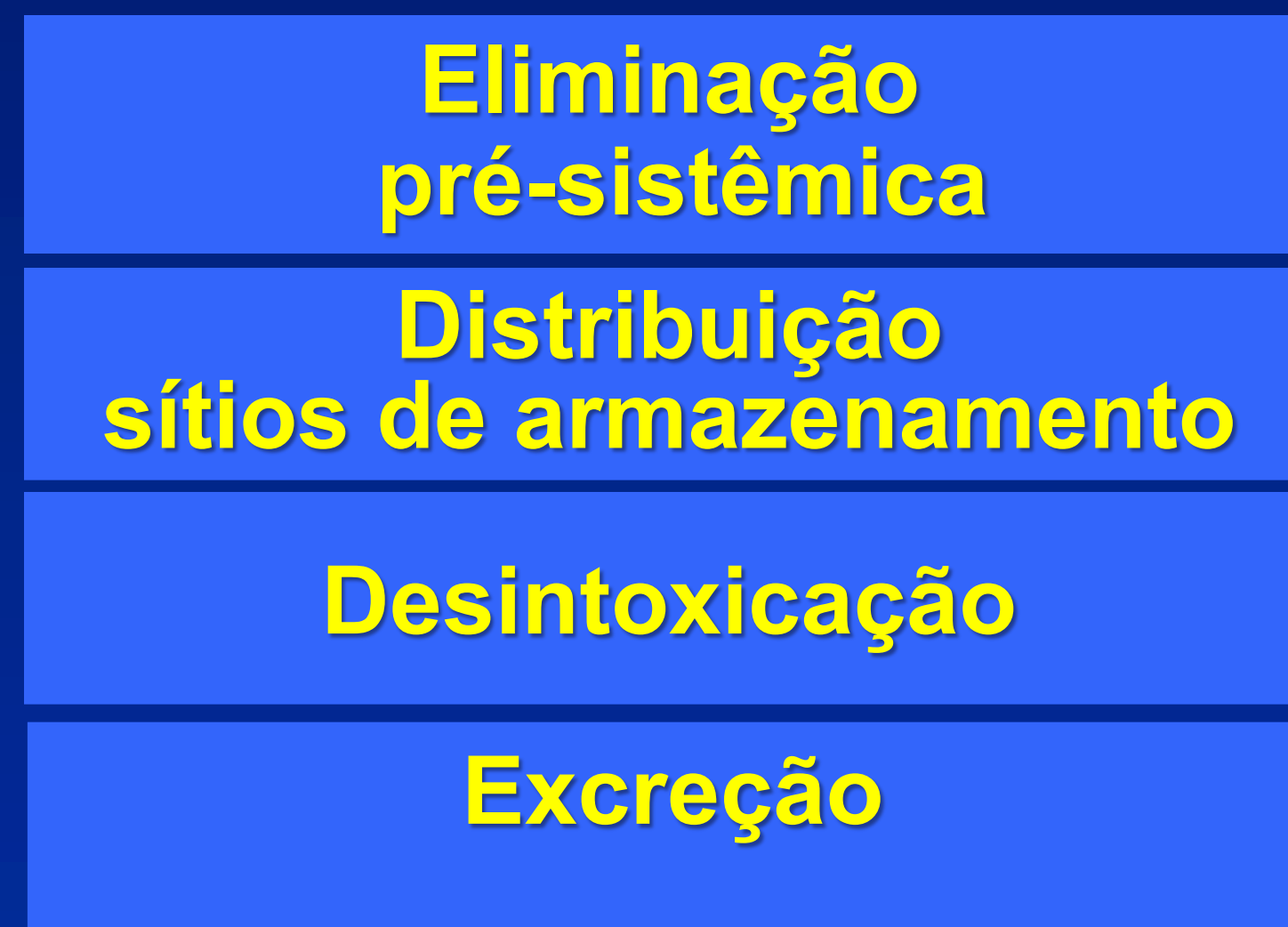
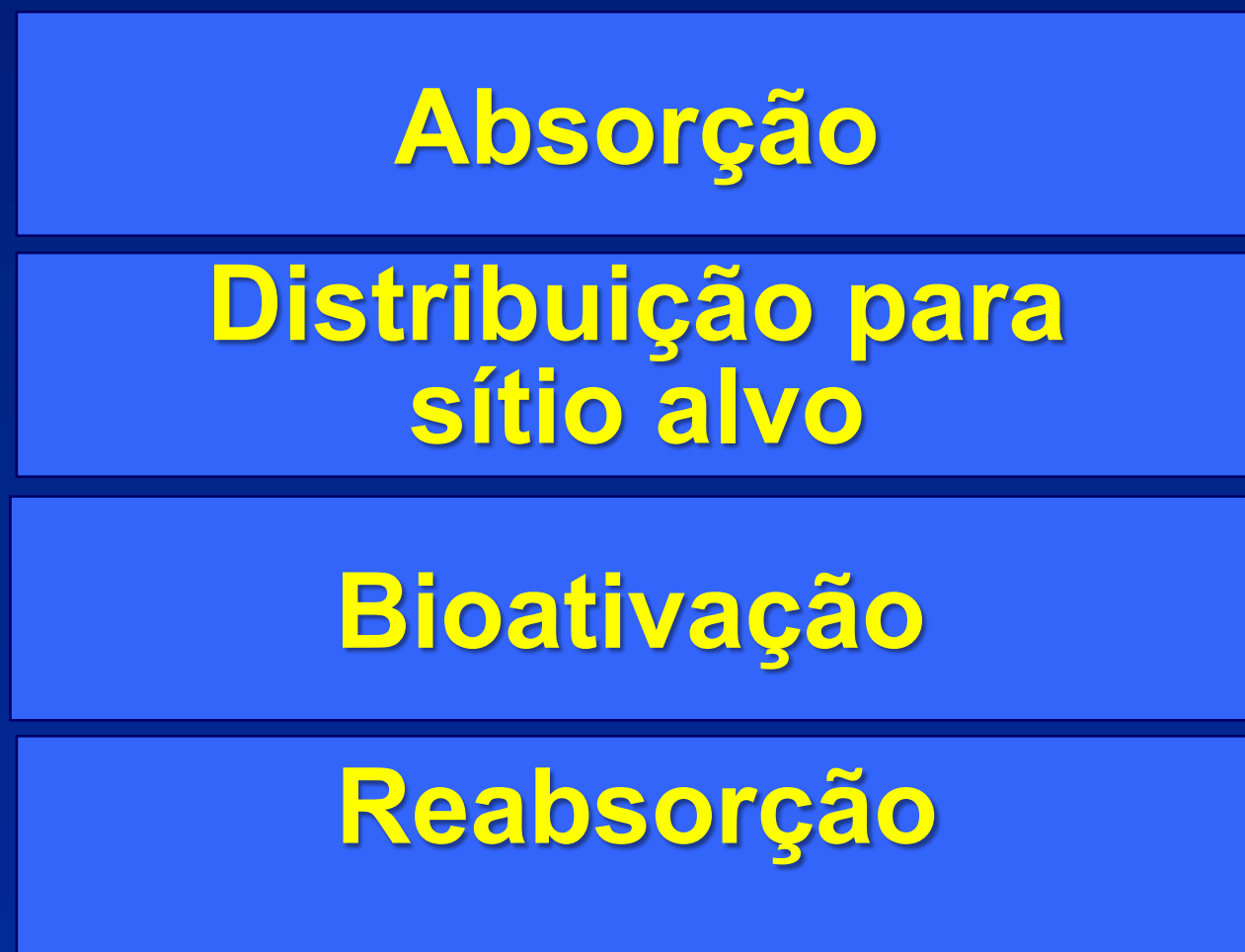
Biomonitoring Reference
Monitoring Strategy
Blood
Urine
Breath
Saliva
Hair

Conclusions

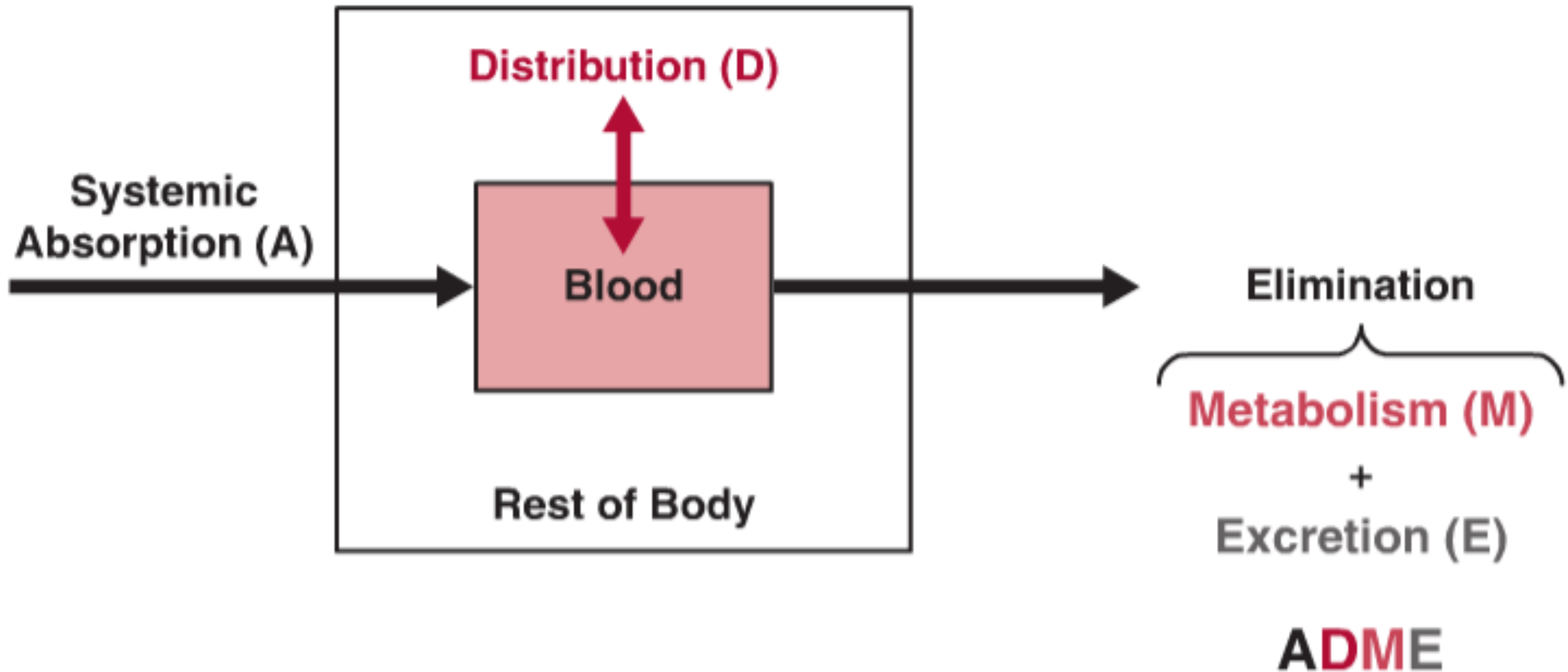


TOXICIDADE

Transporte do sítio de exposição ao sítio alvo
1º estágio

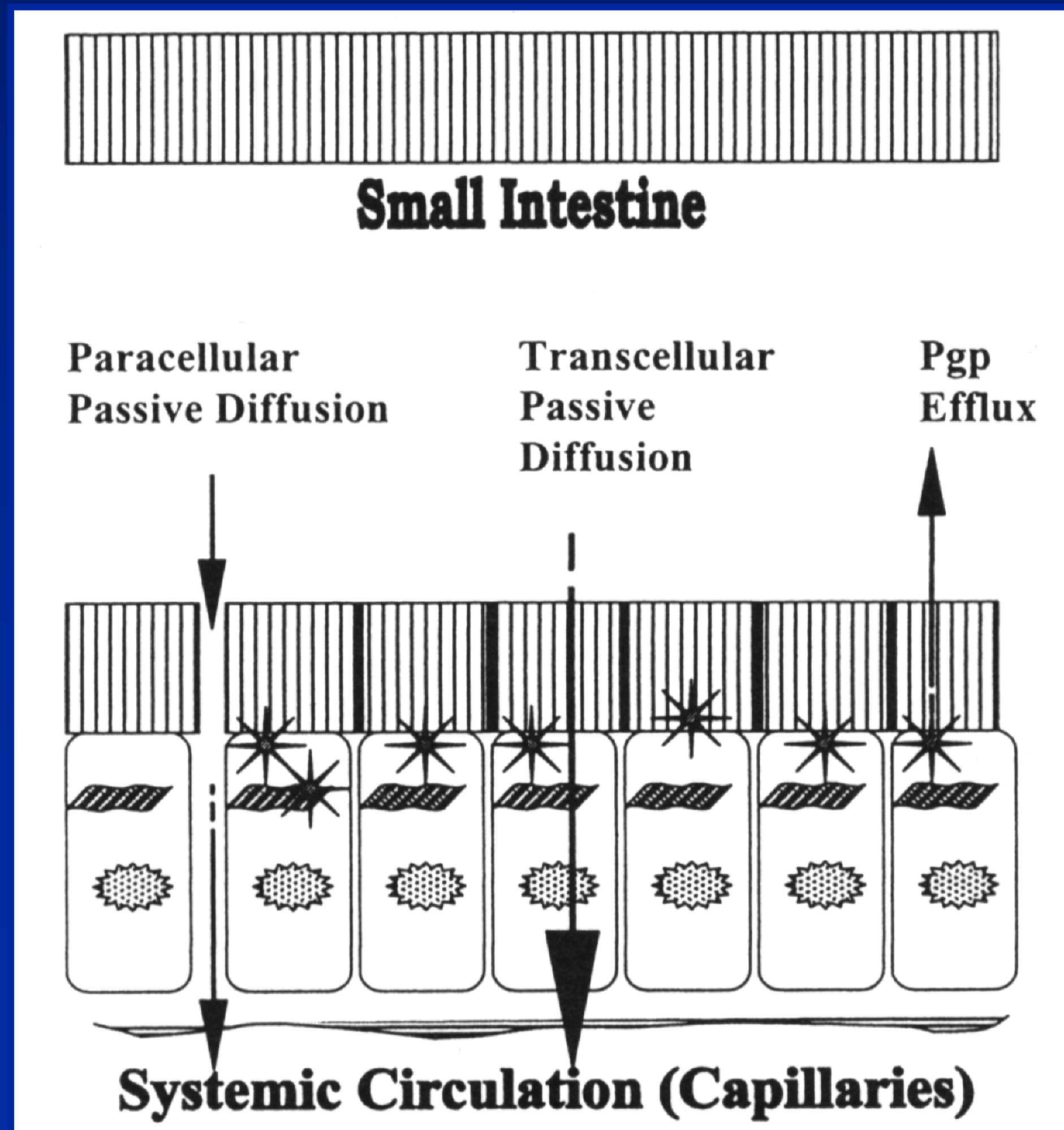


TOXICOCINÉTICA



Passive diffusion

Transcellular and Paracellular



COMPOUND	LOG <i>P</i>
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
<i>p</i> -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.

OCTANOL/WATER PARTITION COEFFICIENTS (*P*)

Log *P*: Physicochemical parameter relative to assessing potential membrane permeability

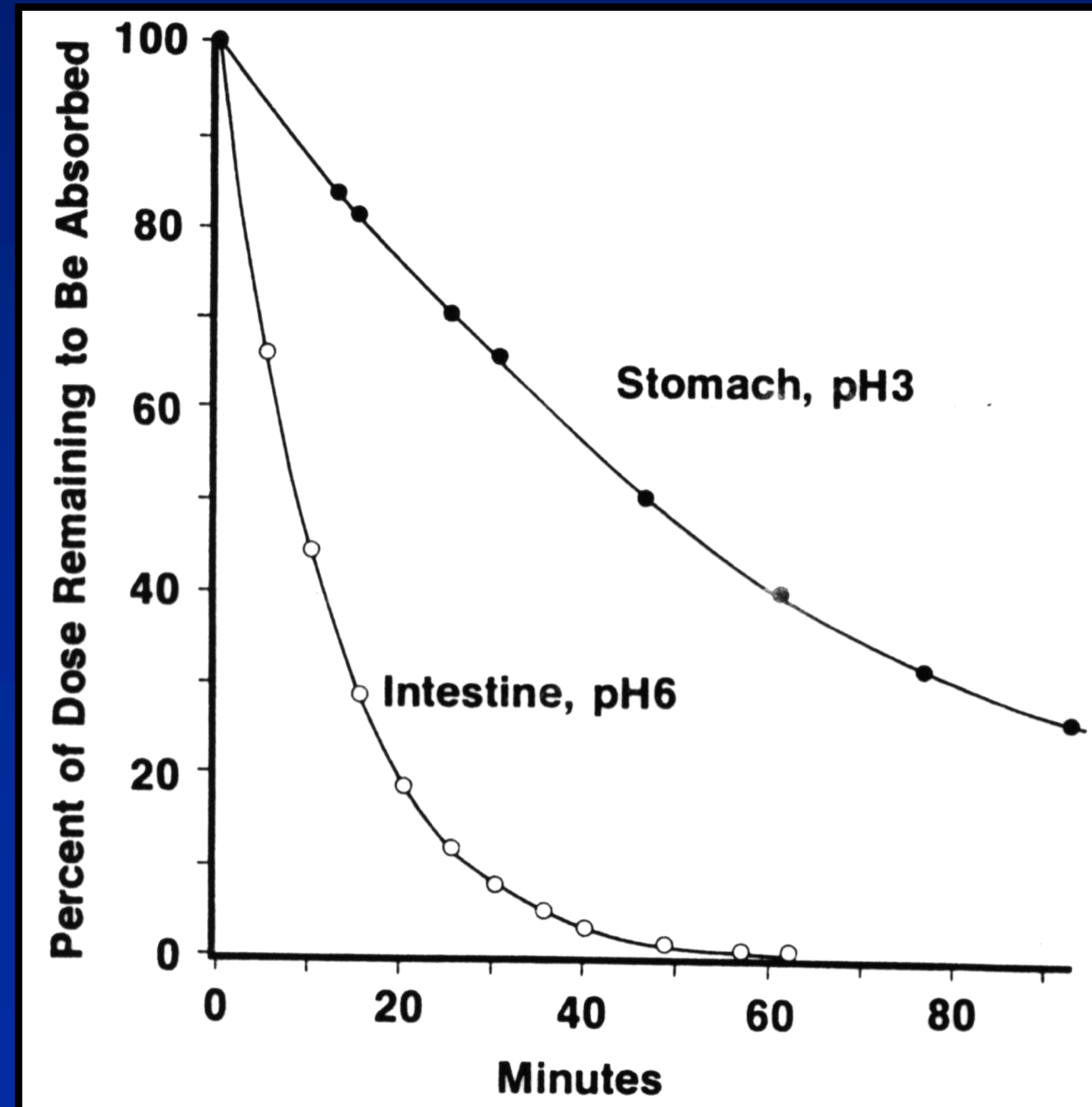


Absorção no trato gastrointestinal

Difusão Passiva

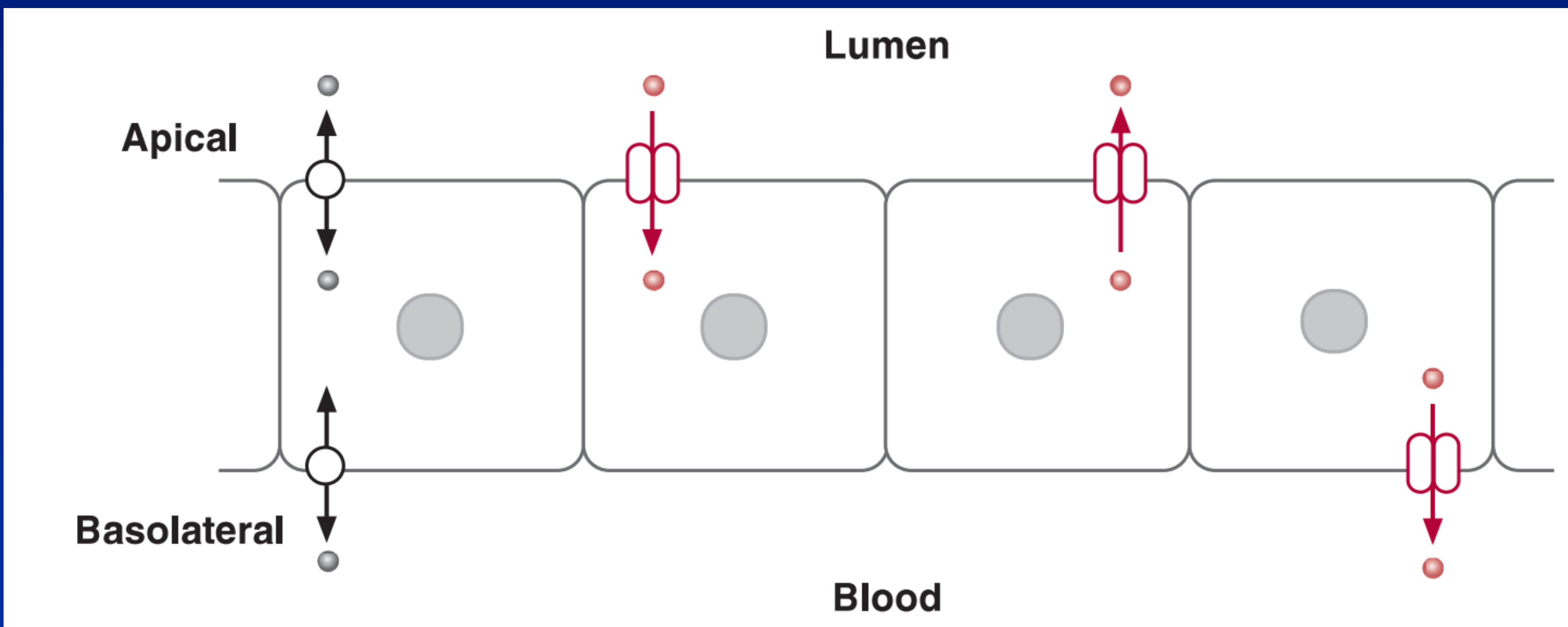
Ácido salicílico (pKa=3)

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

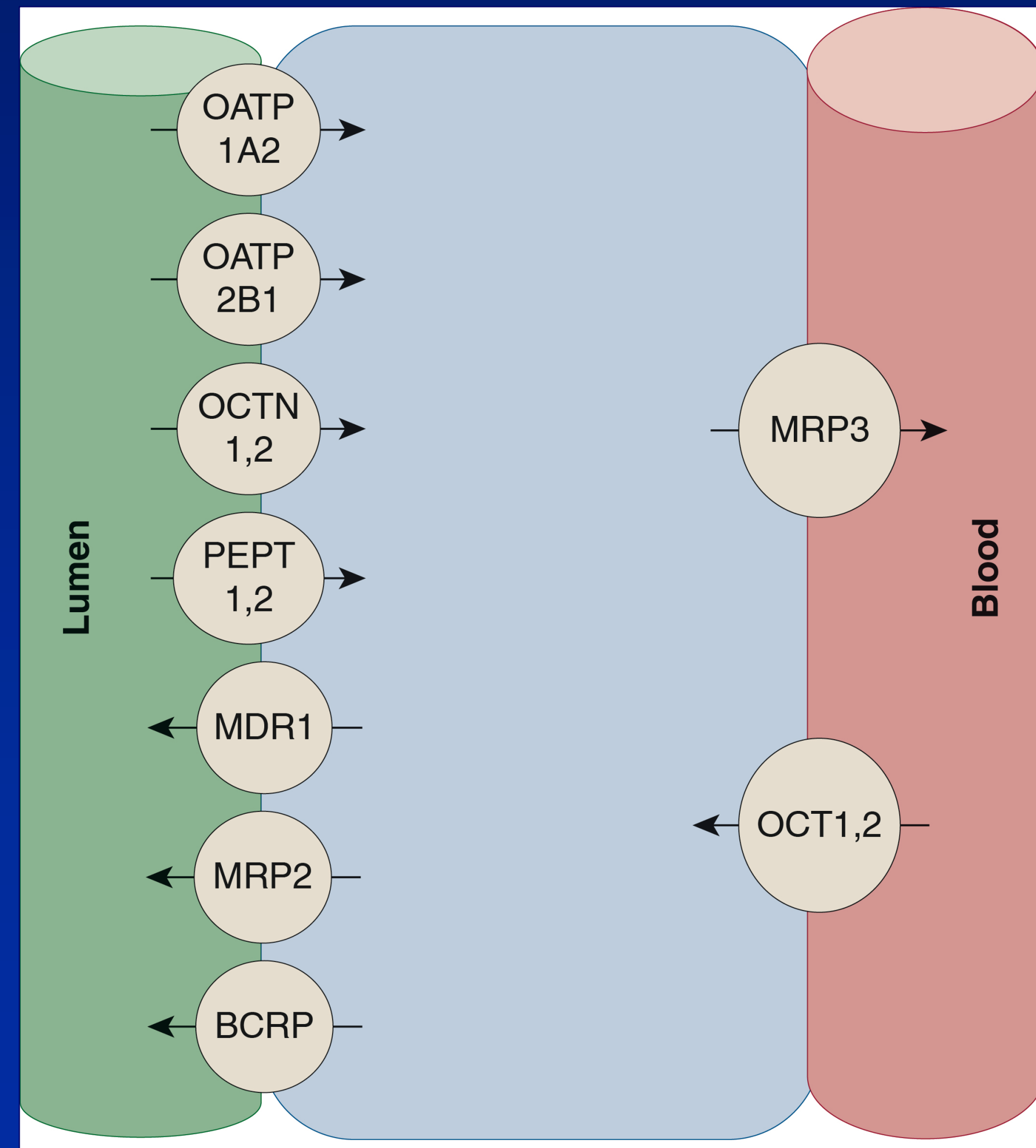


XENOBIOTIC TRANSPORT SYSTEMS PRESENT IN THE GASTROINTESTINAL TRACT

USP



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

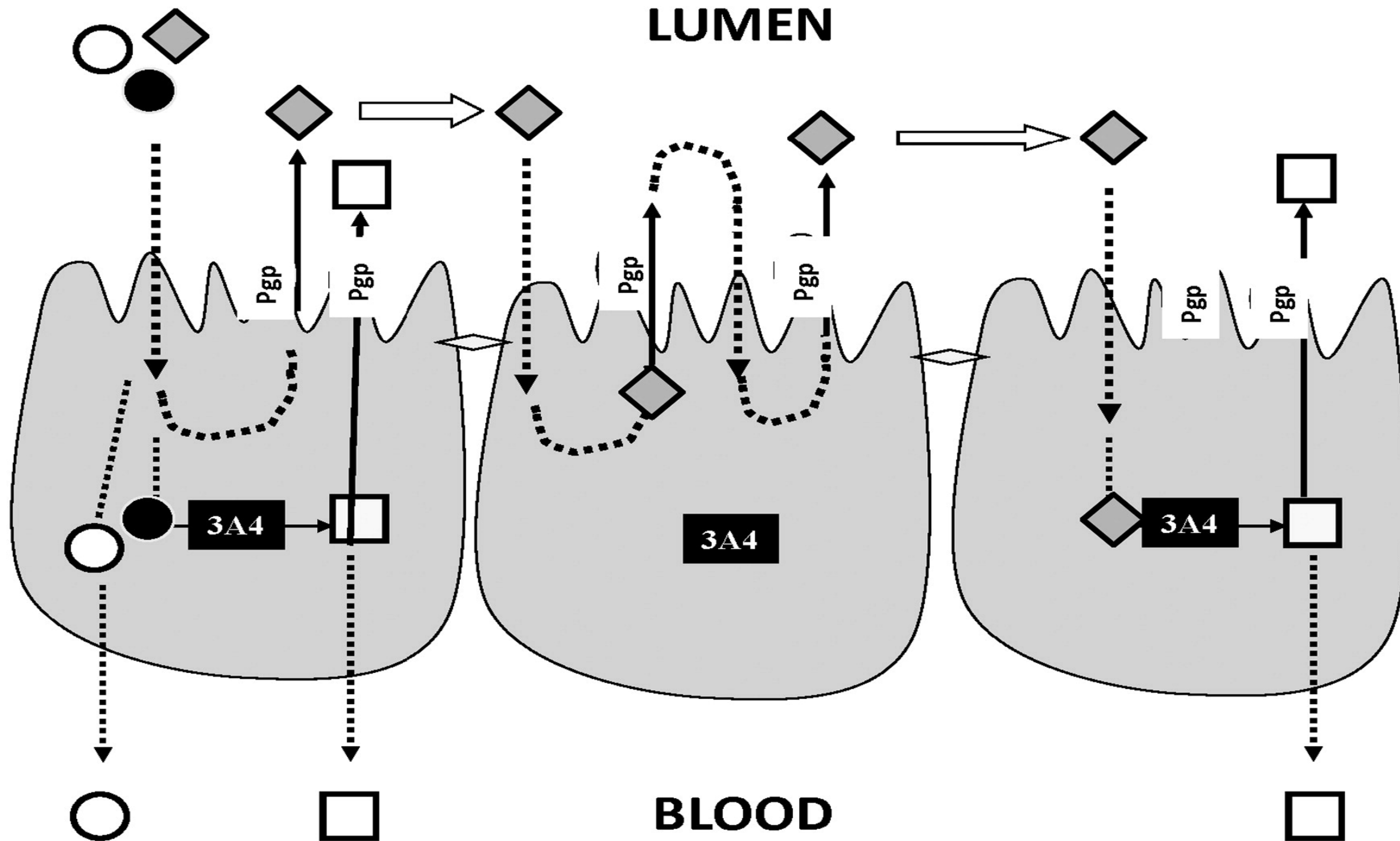
Multidrug resistance-associated protein 2

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





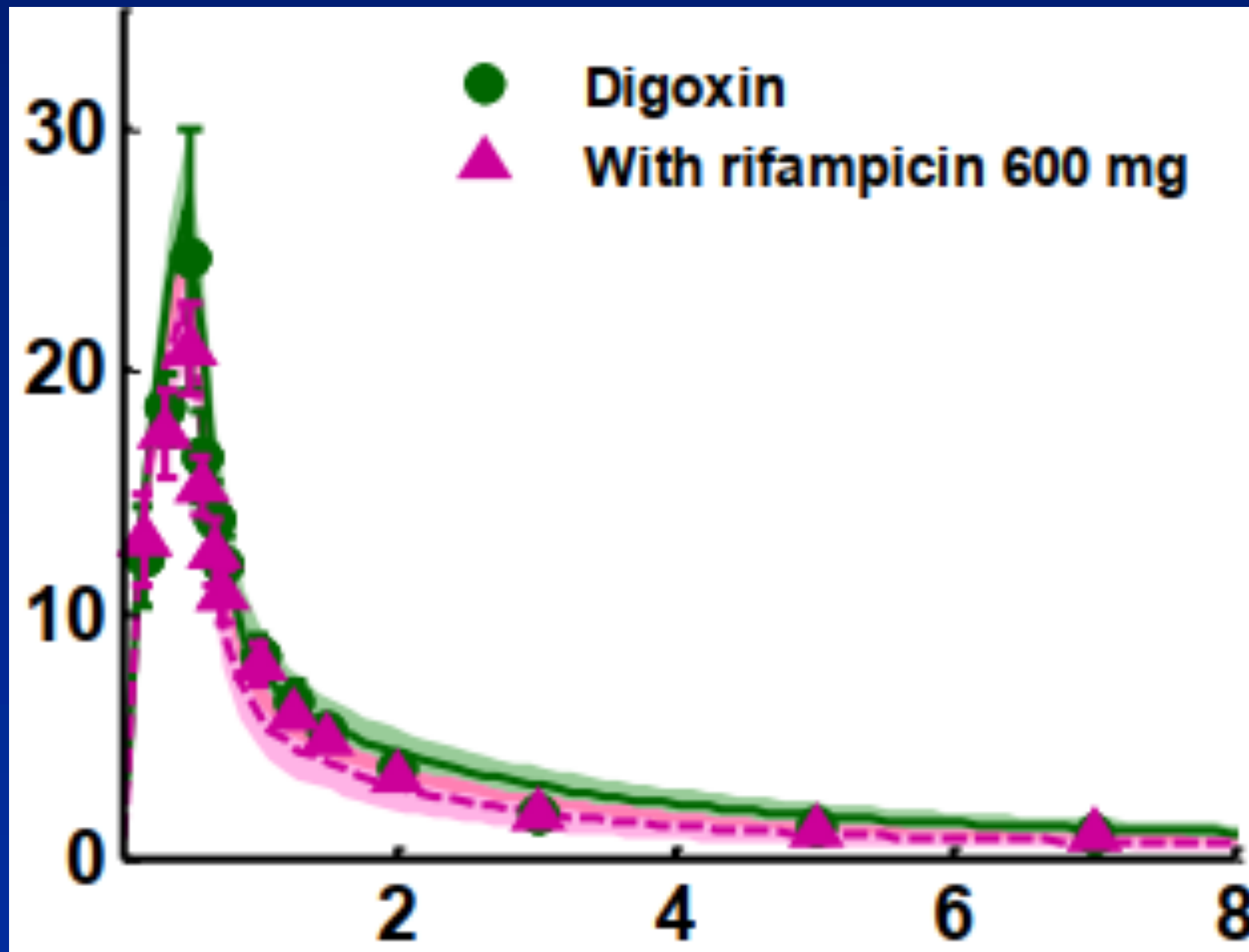
(a) Duodenal biopsy immunostained for P-gp before administration of rifampin (b) Duodenal biopsy after 9 days administration of rifampin (600 mg)



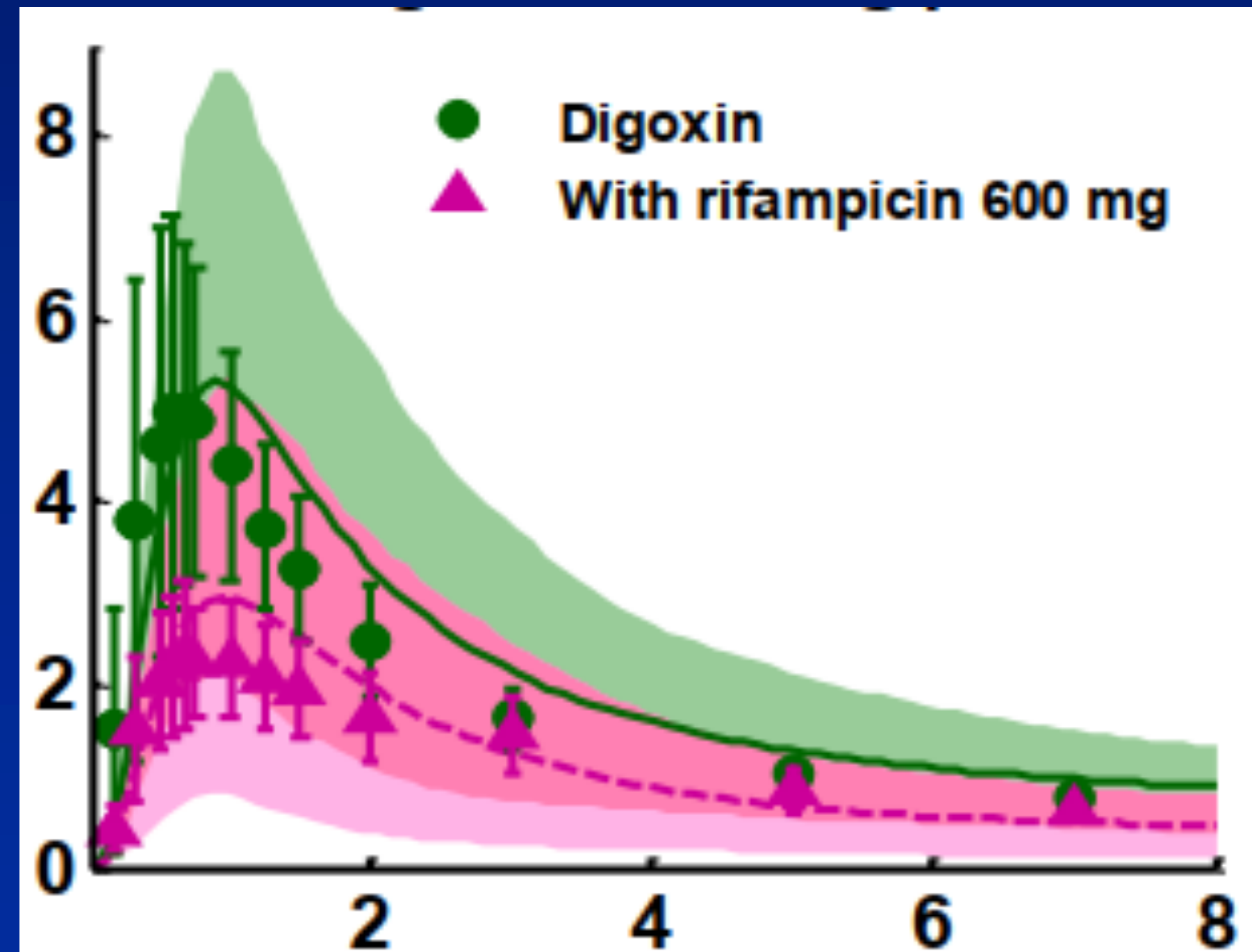


The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin

Plasma conc [ng/ml]



Digoxin - 1.0 mg iv



Digoxin - 1.0 mg po

Biopharmaceutics Drug Disposition Classification System (BDDCS)

	High Solubility	Low Solubility
High Permeability	<p><u>Class 1</u></p> <p>High Solubility High Permeability Rapid Dissolution</p>	<p><u>Class 2</u></p> <p>Low Solubility High Permeability</p>
Low Permeability	<p><u>Class 3</u></p> <p>High Solubility Low Permeability</p>	<p><u>Class 4</u></p> <p>Low Solubility Low Permeability</p>

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

**Absorptive 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
Bupirone	Disopyramide	Ketoprofen	Minocycline	Theophylline
Caffeine	Doxepin	Labetalol	Misoprostol	Valproic Acid
Captopril	Doxycycline	Levodopa	Nifedipine	Verapamil
Chloroquine	Enalapril	Levofloxacin	Phenobarbital	Zodovudine



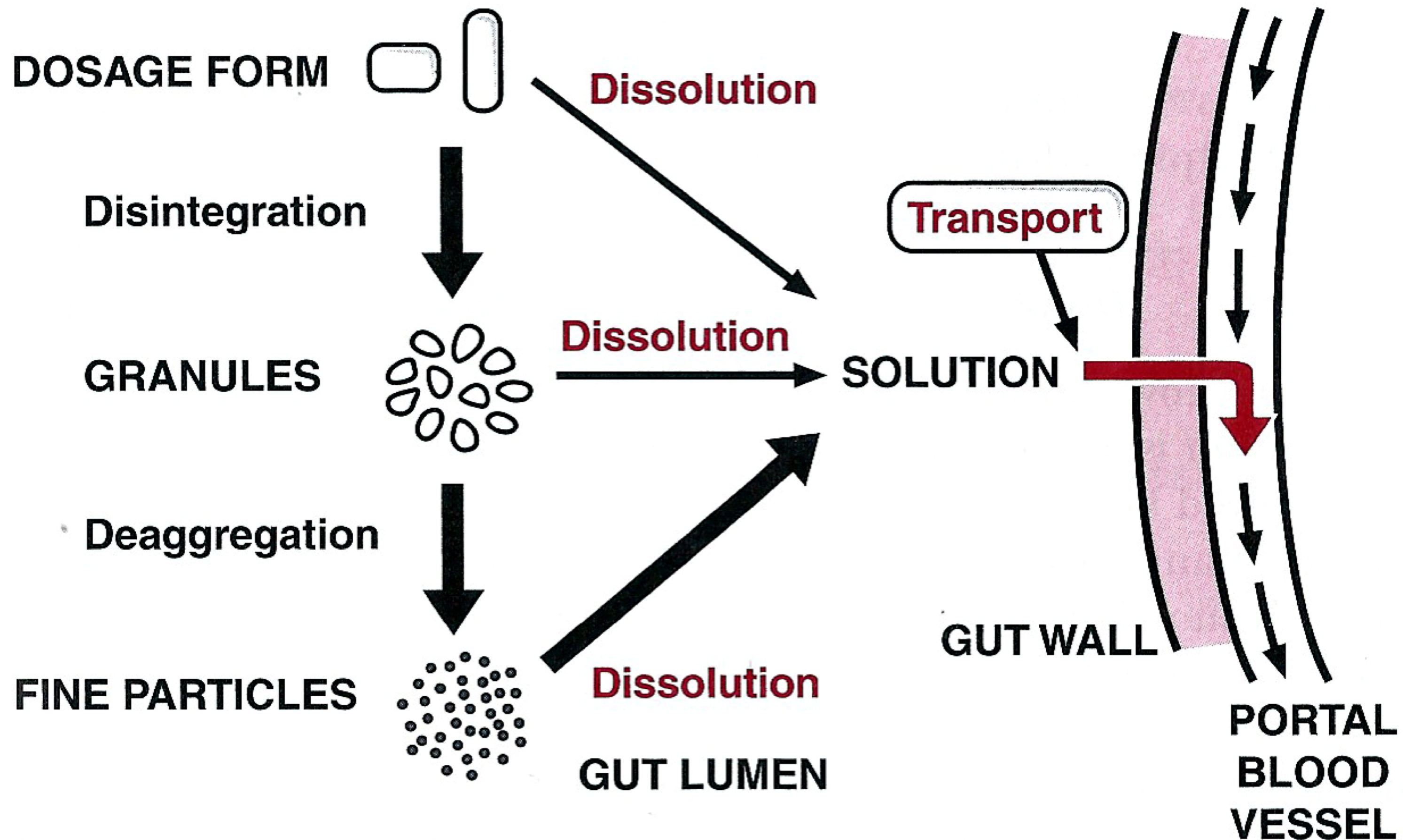
Predicted Effect of Intestinal Drug Transporters on Exposure (AUC) by BDDCS Class

BDDCS Class	1	2	3	4
Inhibition				
Apical Uptake	↔	↔	↓	↓
Apical Efflux	↔	↑	↑	↑
Induction				
Apical Uptake	↔	↔	↑	↑
Apical Efflux	↔	↓	↓	↓

Absorção no trato gastrintestinal

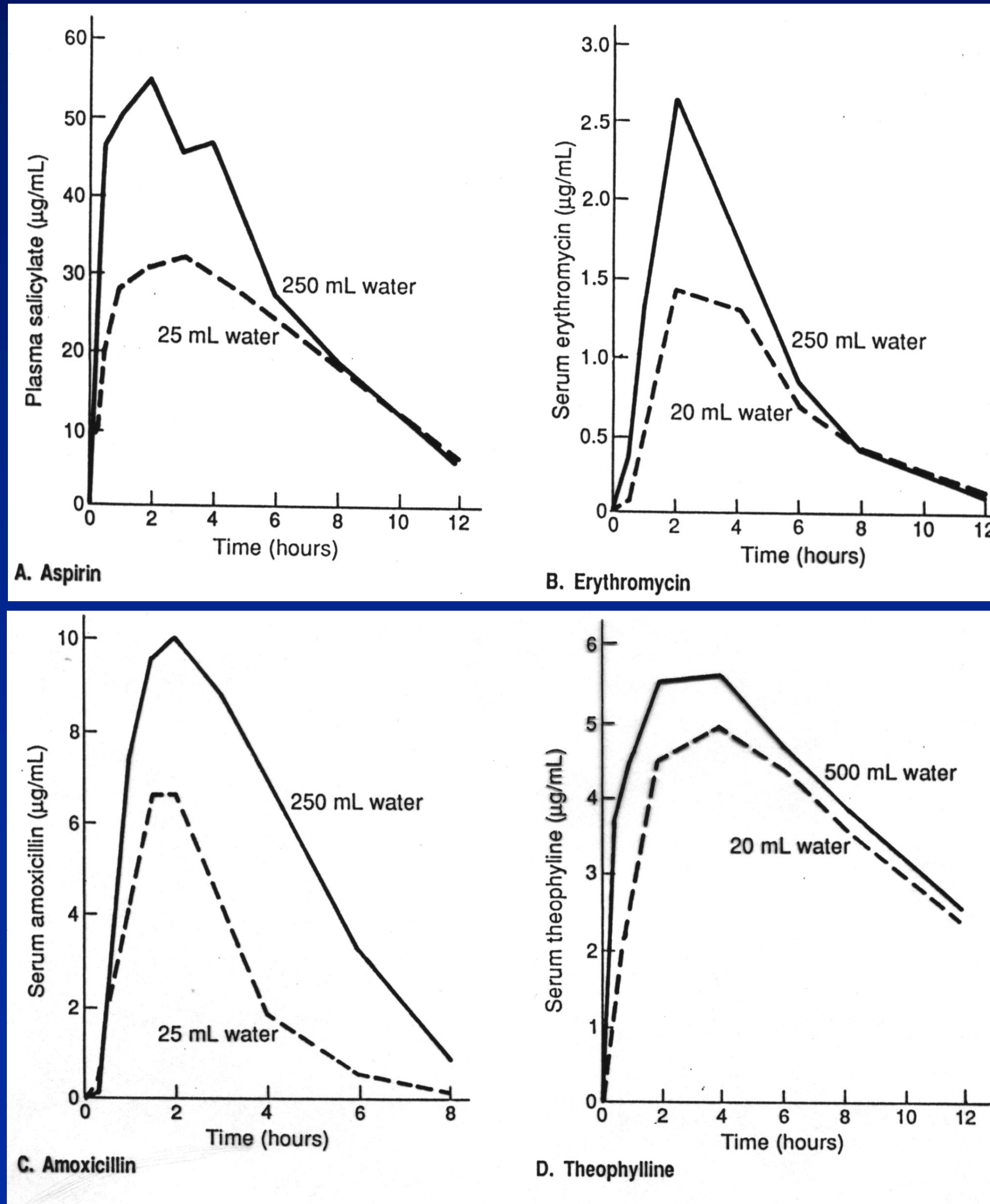
Solubilidade

USP



Absorção no trato gastrintestinal

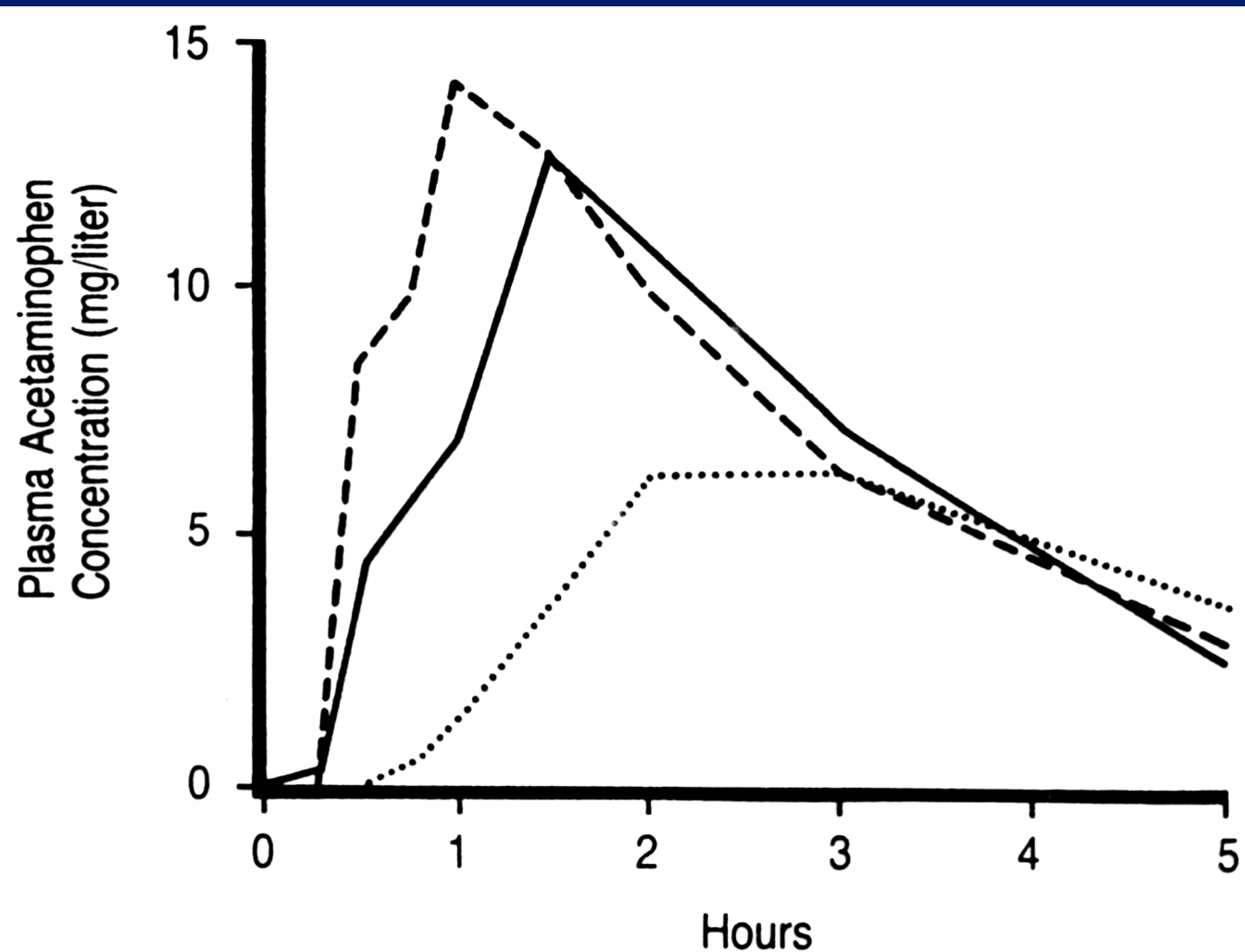
Influência do esvaziamento gástrico





Absorção no trato gastrointestinal

Influência do esvaziamento gástrico



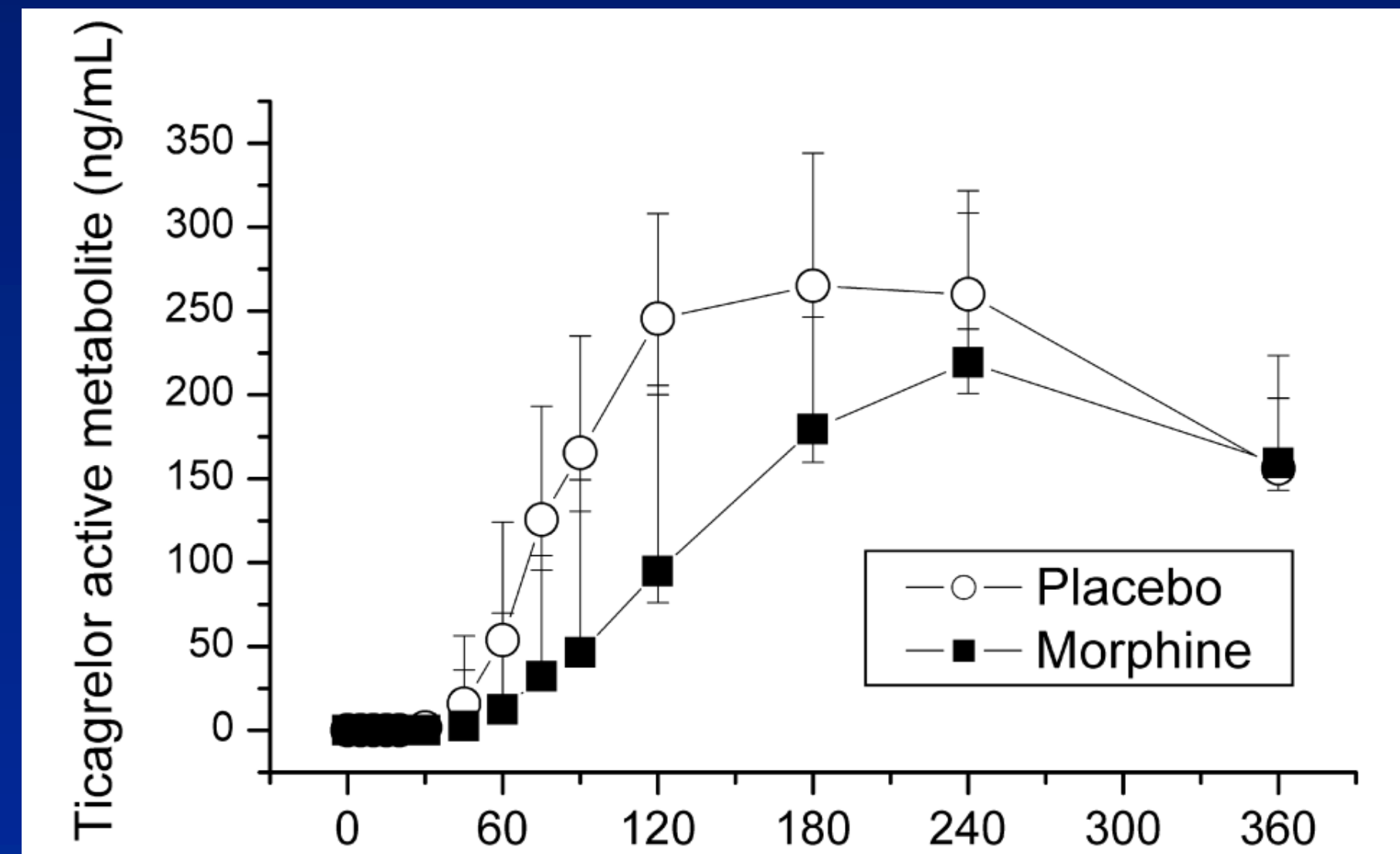
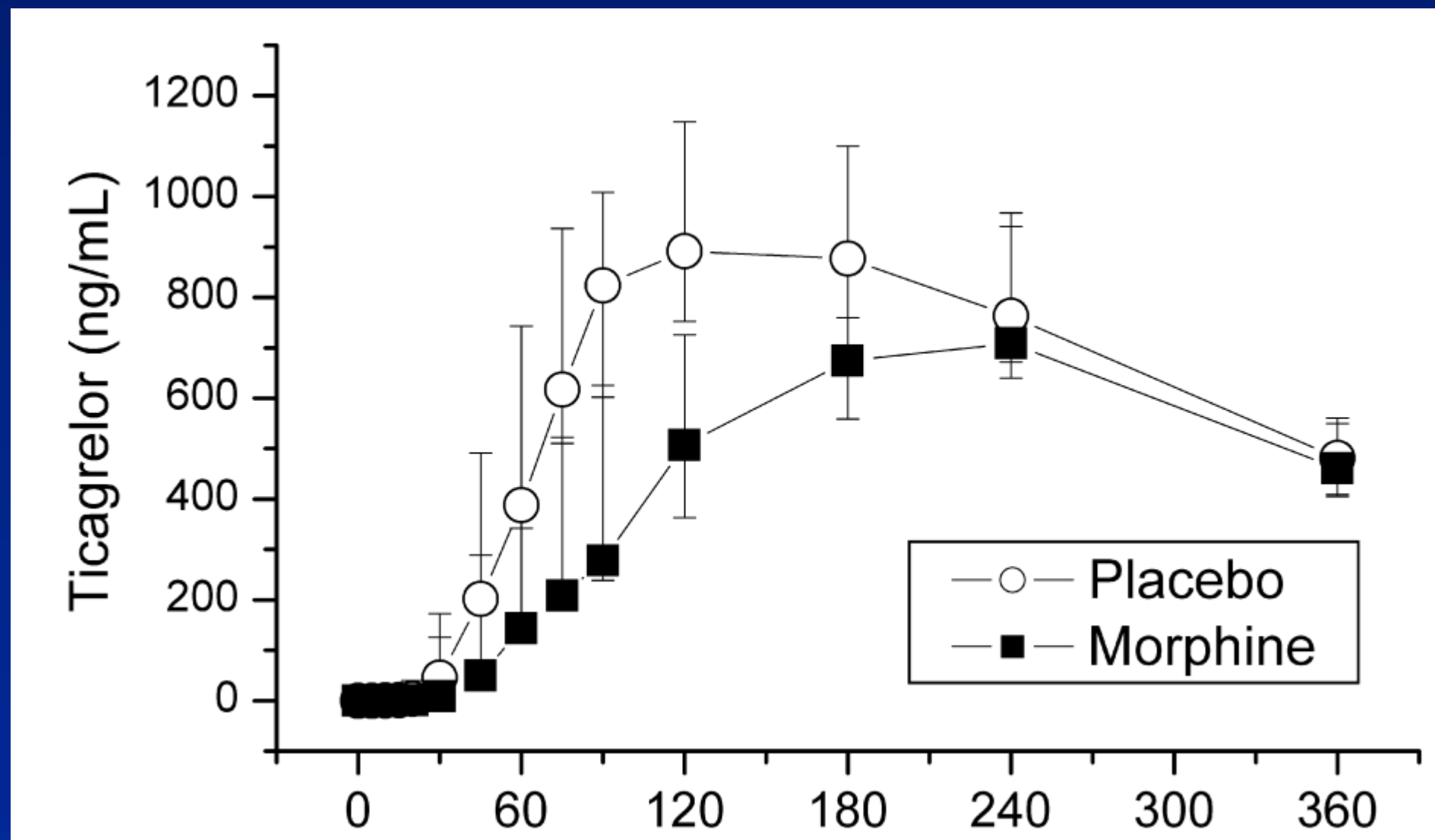
- acetaminofeno
- - acetaminofeno + metoclopramida
- acetaminofeno + propantelina



Absorção no trato gastrointestinal

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

ALIMENTAÇÃO e JEJUM

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

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)

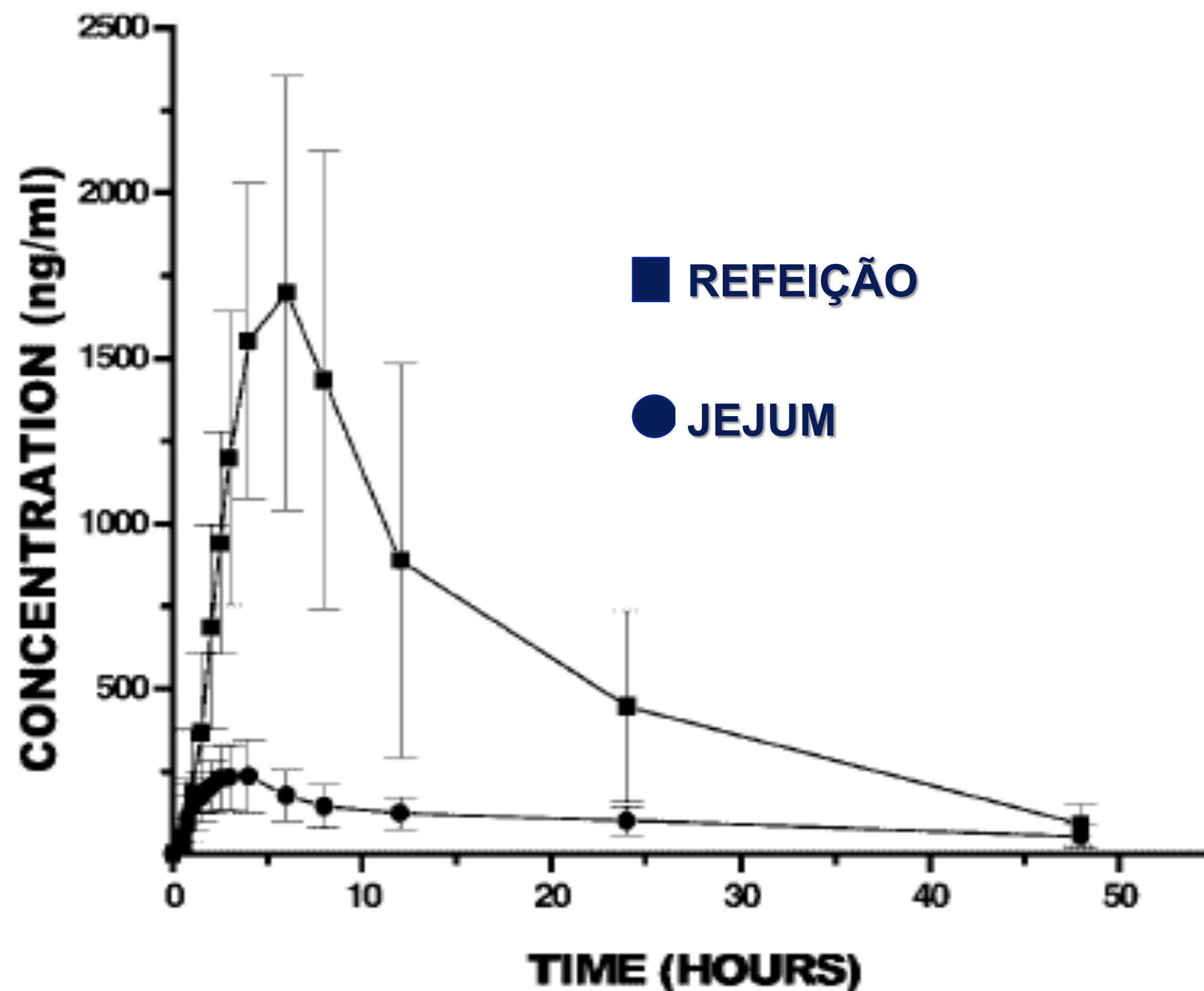
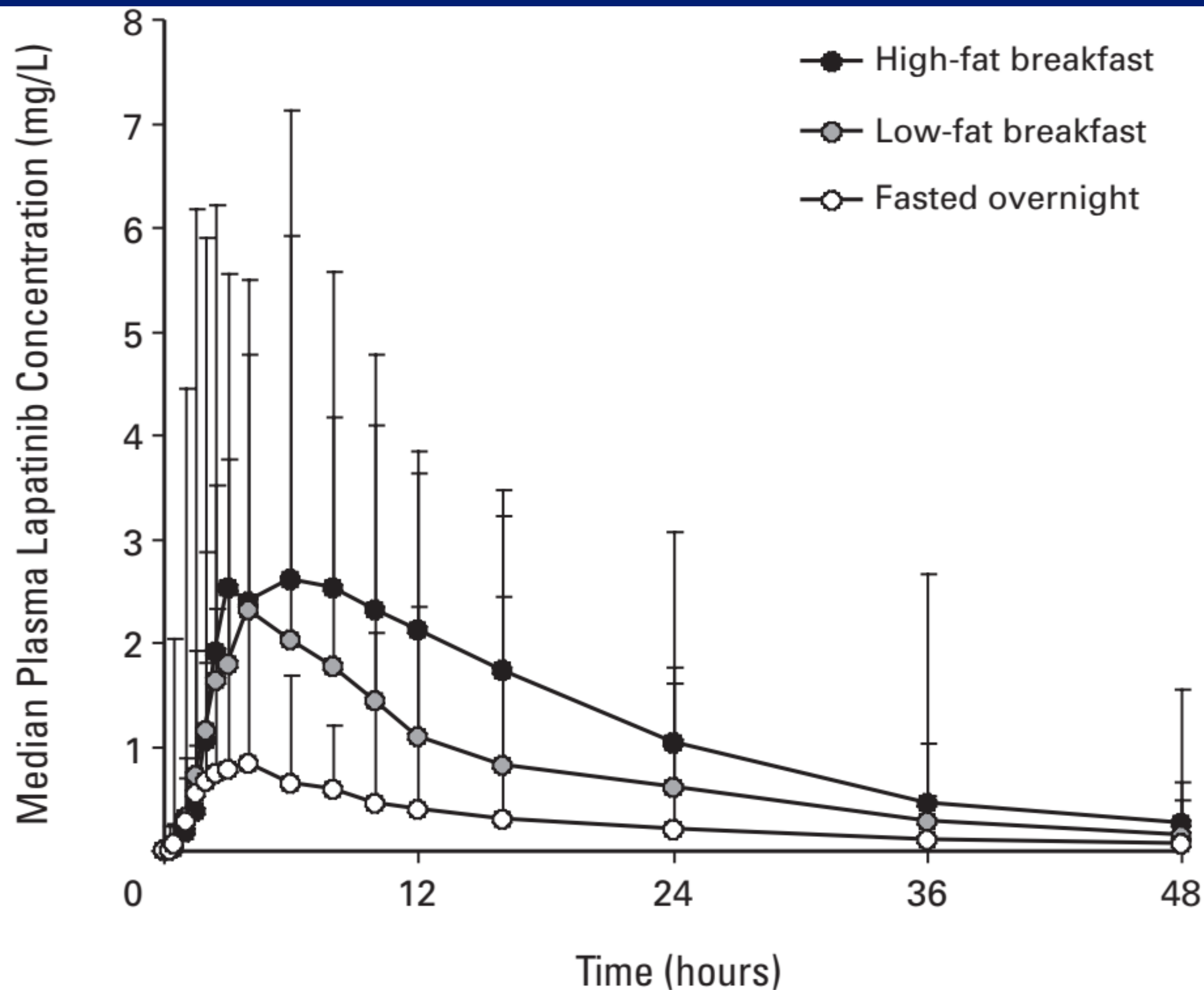


Fig. 1. Mean plasma concentration of albendazole sulfoxide after a single oral dose of 800 mg of albendazole in fasting state (●) and after a fatty meal (■).

Food effect of lapatinib PK in patients with cancer



LOW-FAT breakfast:

1 xíc. cereal matinal; leite desnatado; torrada com geléia, suco de maçã 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.

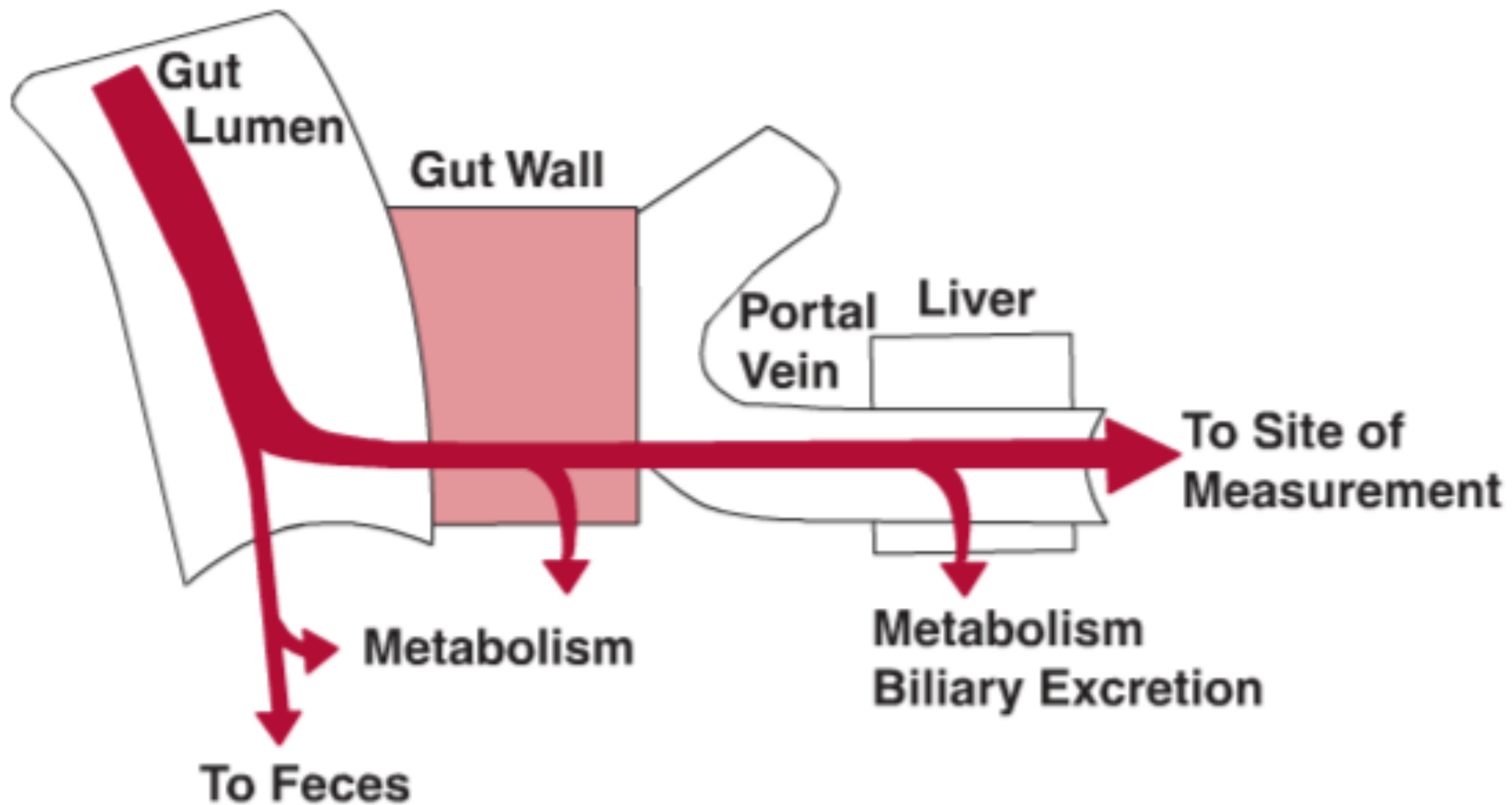


Bioavailability (F): Amount of drug absorbed or reaching systemic circulation

$(F) \cdot (\text{Dose})$

$$F = F_a \cdot F_G \cdot F_H$$

Eliminação pré-sistêmica



Eliminação pré-sistêmica: $F \leq 0,5$

Amitriptilina

Nifedipina

Lidocaina

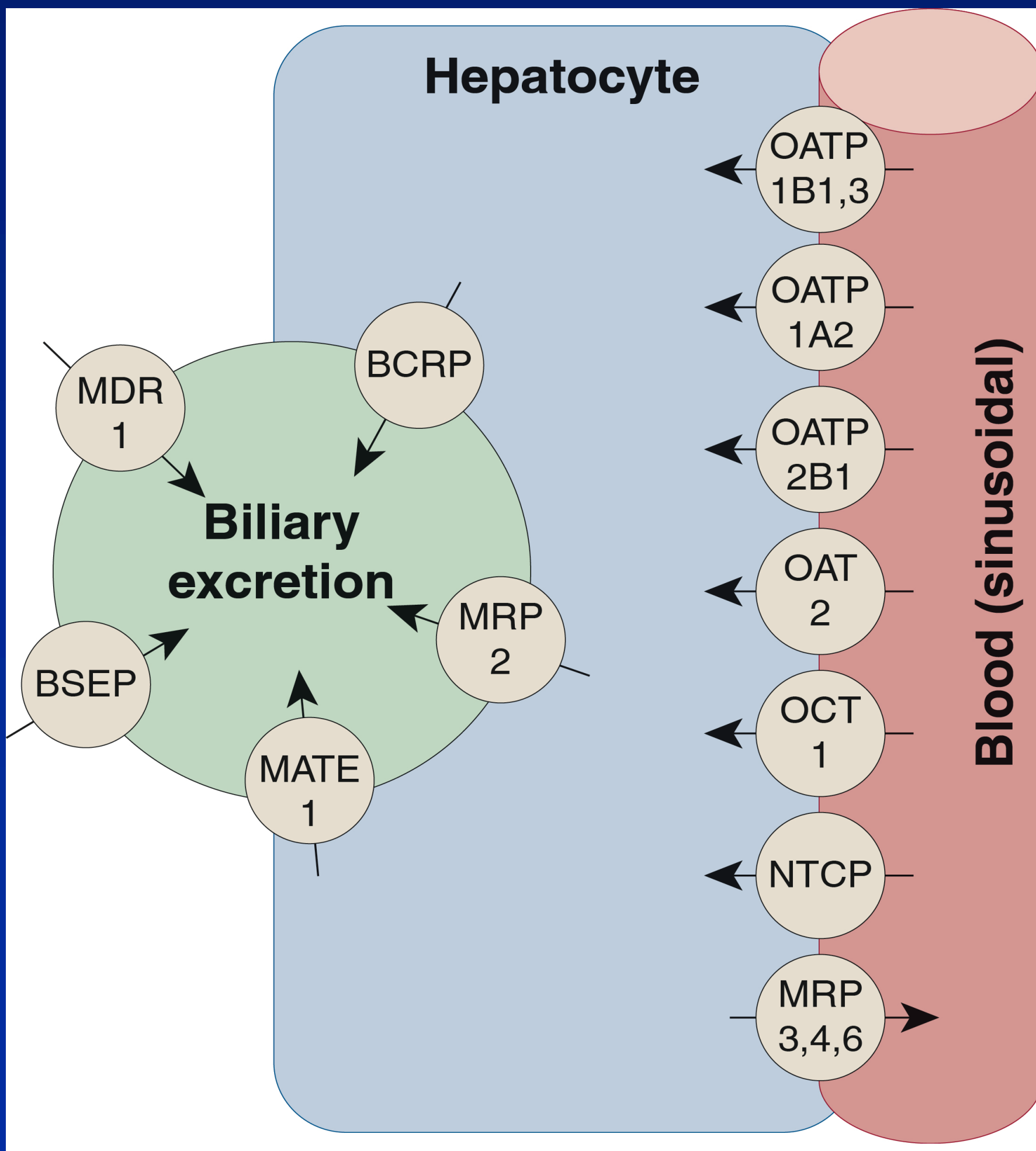
Propranolol

Morfina

5-fluorouracila

XENOBIOTIC TRANSPORTING SYSTEMS PRESENT IN THE LIVER

USP



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
<i>C_{max}</i> ($\mu\text{g/L}$)	9.3	112	14.2	12.4	
<i>AUC</i> ($\mu\text{g}\cdot\text{hr/L}$)	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

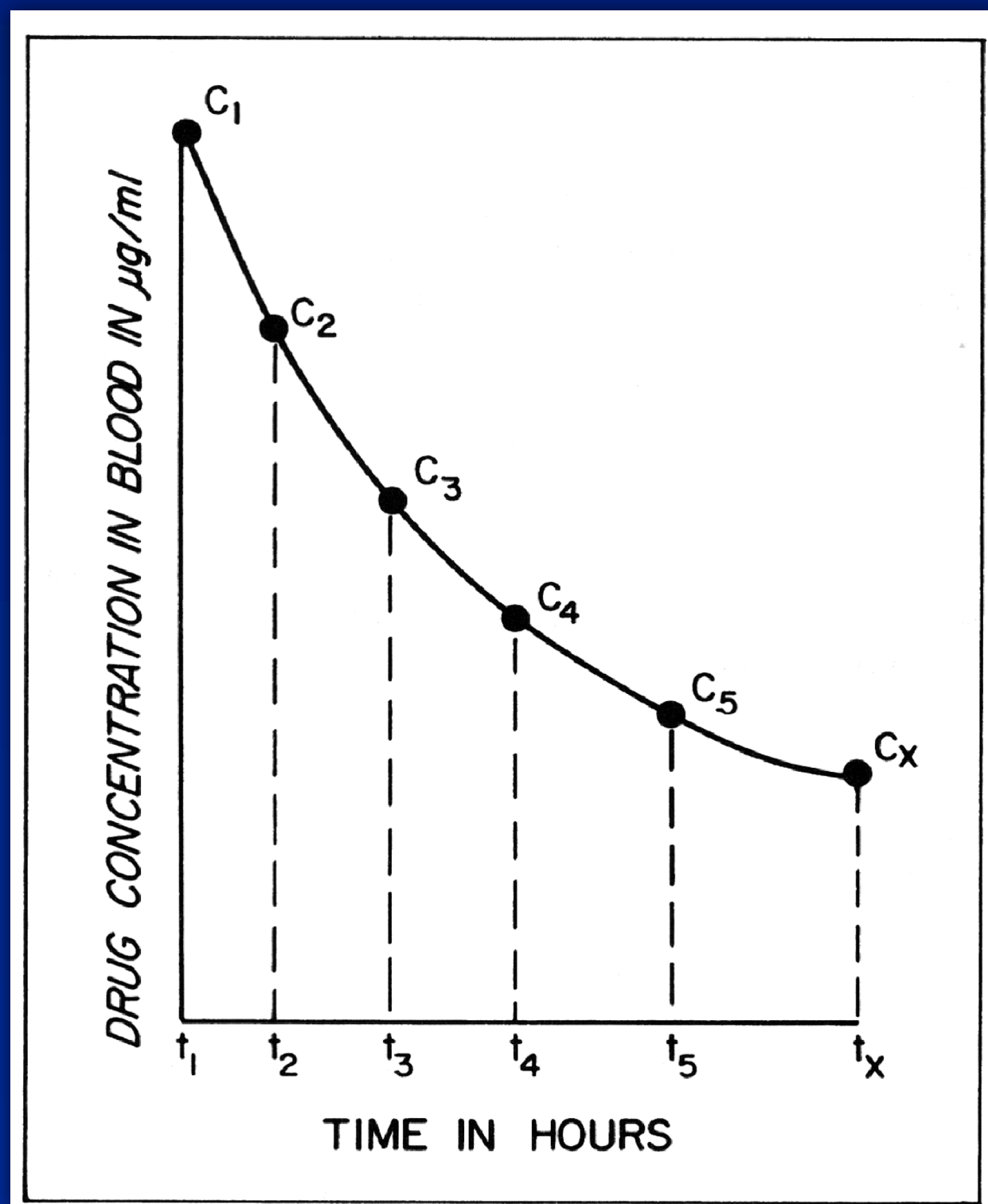


Como calcular a biodisponibilidade (F)?

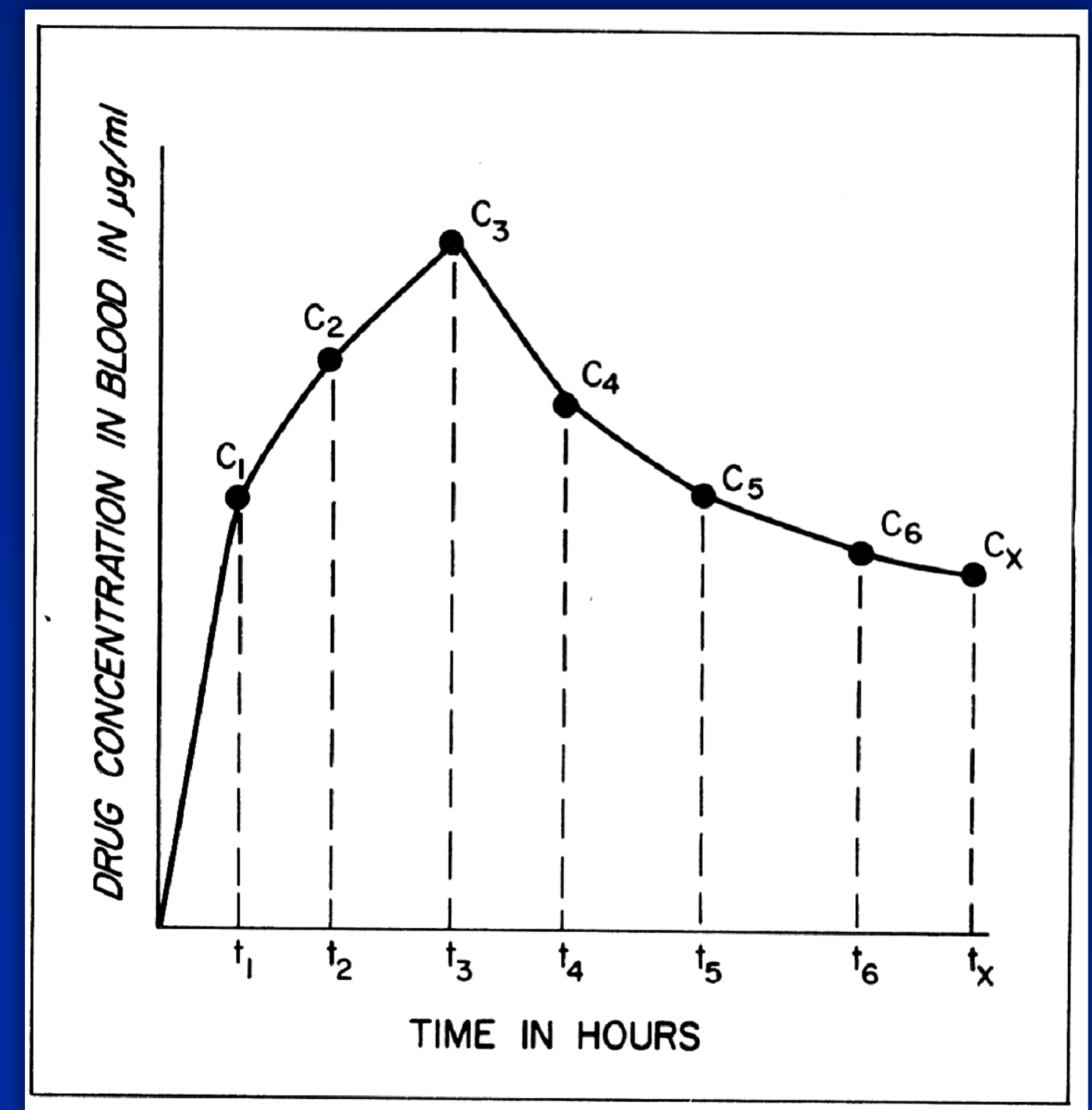
$$F = \frac{AUC\ ev \cdot dose\ iv}{AUC\ iv \cdot dose\ ev}$$

Area under the blood level-time curve

Intravascular route



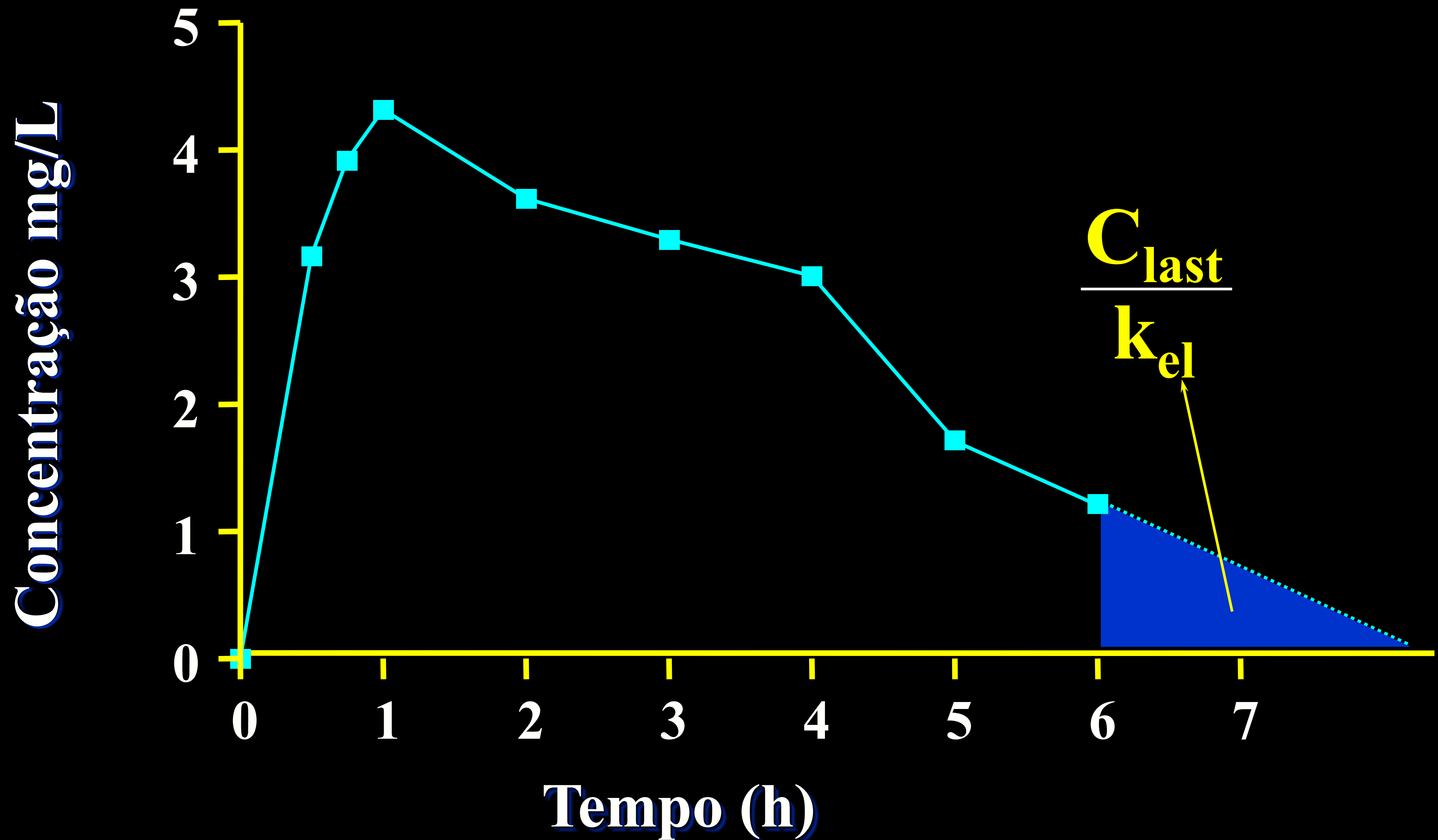
Extravascular route





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.

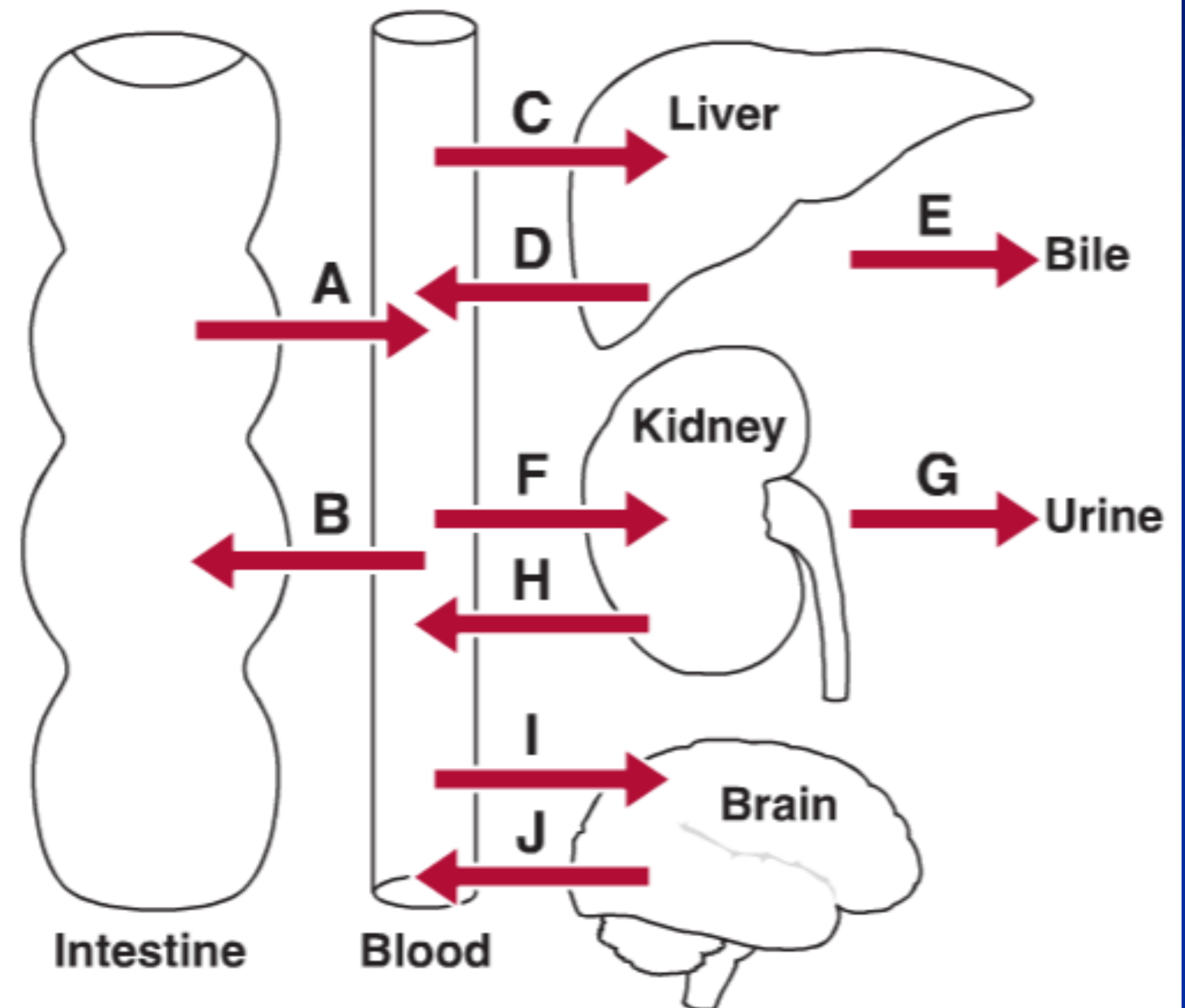
Via	Dose (mg)	AUC (mg.h/L)
I.V	500	13,1
Oral	1000	19,9

Exercício 2 – Biodisponibilidade

Comente a influência de transportadores de fármacos na biodisponibilidade.

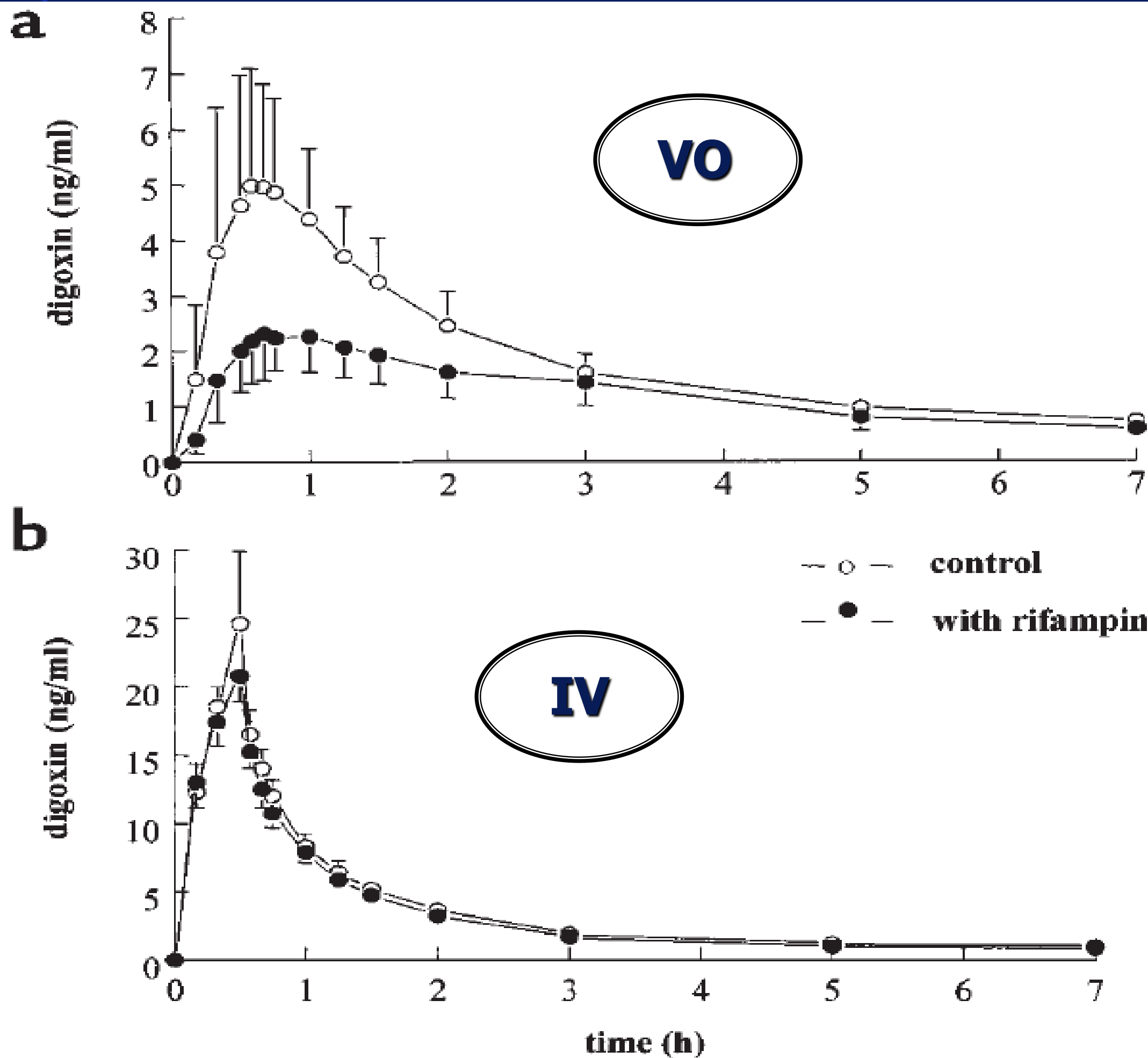
Key	Process	Example Transporter
A	Intestinal Uptake	OATPs
B	Intestinal Efflux	MDR1*, BCRP
C	Hepatic Uptake	OATPs
D	Hepatic Efflux	MRP3
E	Biliary Secretion	MDR1, MRP2
F	Renal Uptake	OAT3
G	Renal Secretion	MDR1, MRP2
H	Renal Reabsorption	SVCT1
I	Brain Uptake	LAT1
J	Brain Efflux	MDR1, BCRP

*Commonly called P-glycoprotein



Exercício 3 – Absorção e biodisponibilidade

USP



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.