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Dose / Concentração plasmática

- Medicamento
- Paciente
- Interação de fármacos

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Severity of liver disease Child-Pugh classification

Clinical/biochemical indicator	1 point	2 points	3 points
Serum bilirubin (mg/dL)	<2	2–3	>3
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (s > control)	<4	4–6	>6
Encephalopathy (grade)	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate

Points are summed, and the total score is classified according to severity as follows: 5–6 points = group A (mild), 7–9 points = group B (moderate), 10–15 points = group C (severe)

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Oral bioavailability (F) of drugs in cirrhosis

Drug	Normal	Cirrhosis	Fold increase
Carvedilol	0.19	0.83	4.4
Chlormethiazole	0.10	1.16	11.6
Labetalol	0.33	0.63	1.9
Meperidine	0.48	0.87	1.8
Metoprolol	0.50	0.84	1.7
Midazolam	0.38	0.76	2.0
Morphine	0.47	1.01	2.1
Nifedipine	0.51	0.91	1.8
Nisoldipine	0.04	0.15	3.8
Pentazocine	0.18	0.68	3.8
Propranolol	0.36	0.60	1.7
Verapamil	0.10	0.16	1.6

F is increased in cirrhosis for drugs with moderate to high E_H

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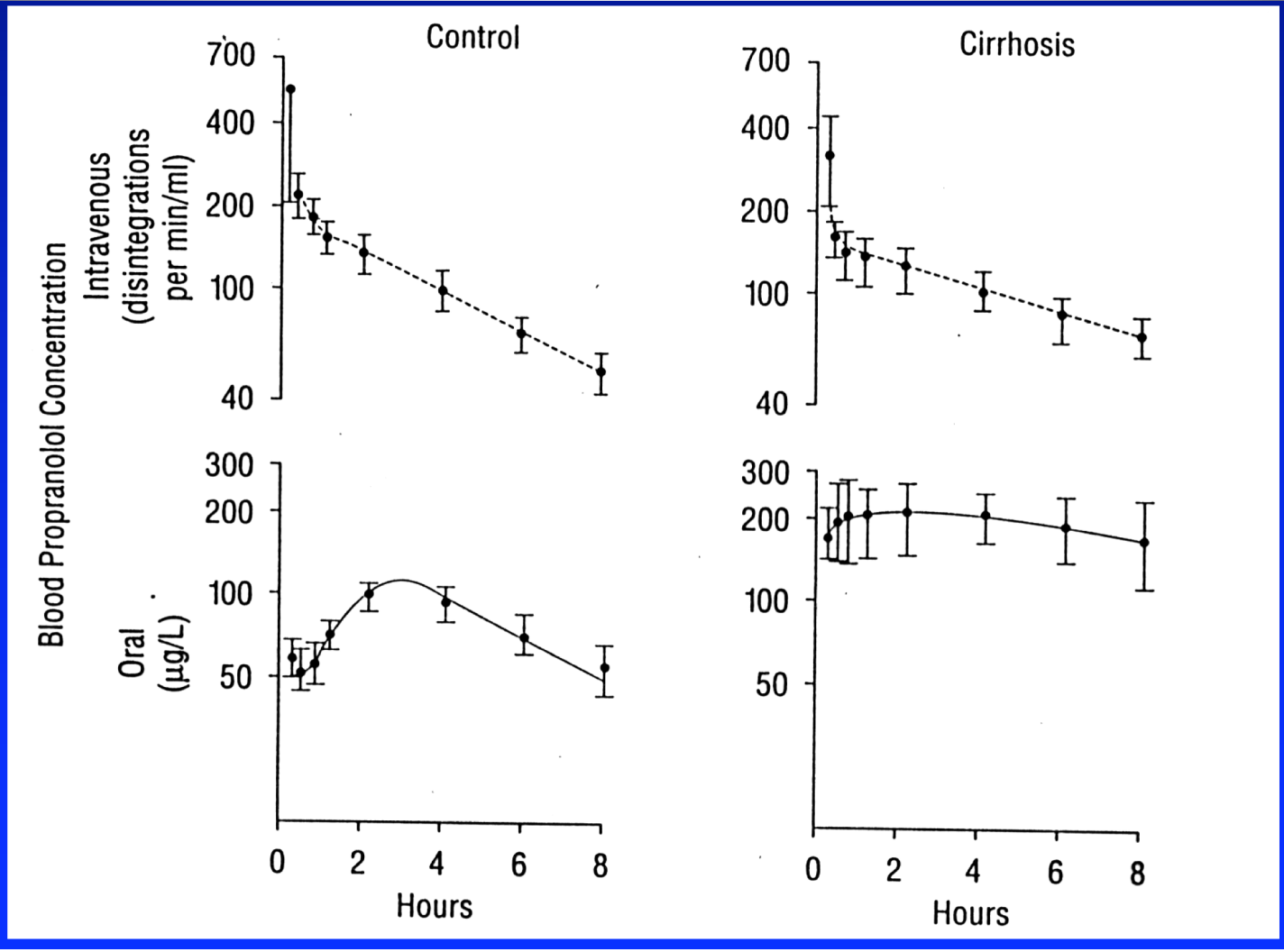
Biodisponibilidade oral (F) do propranolol na cirrose



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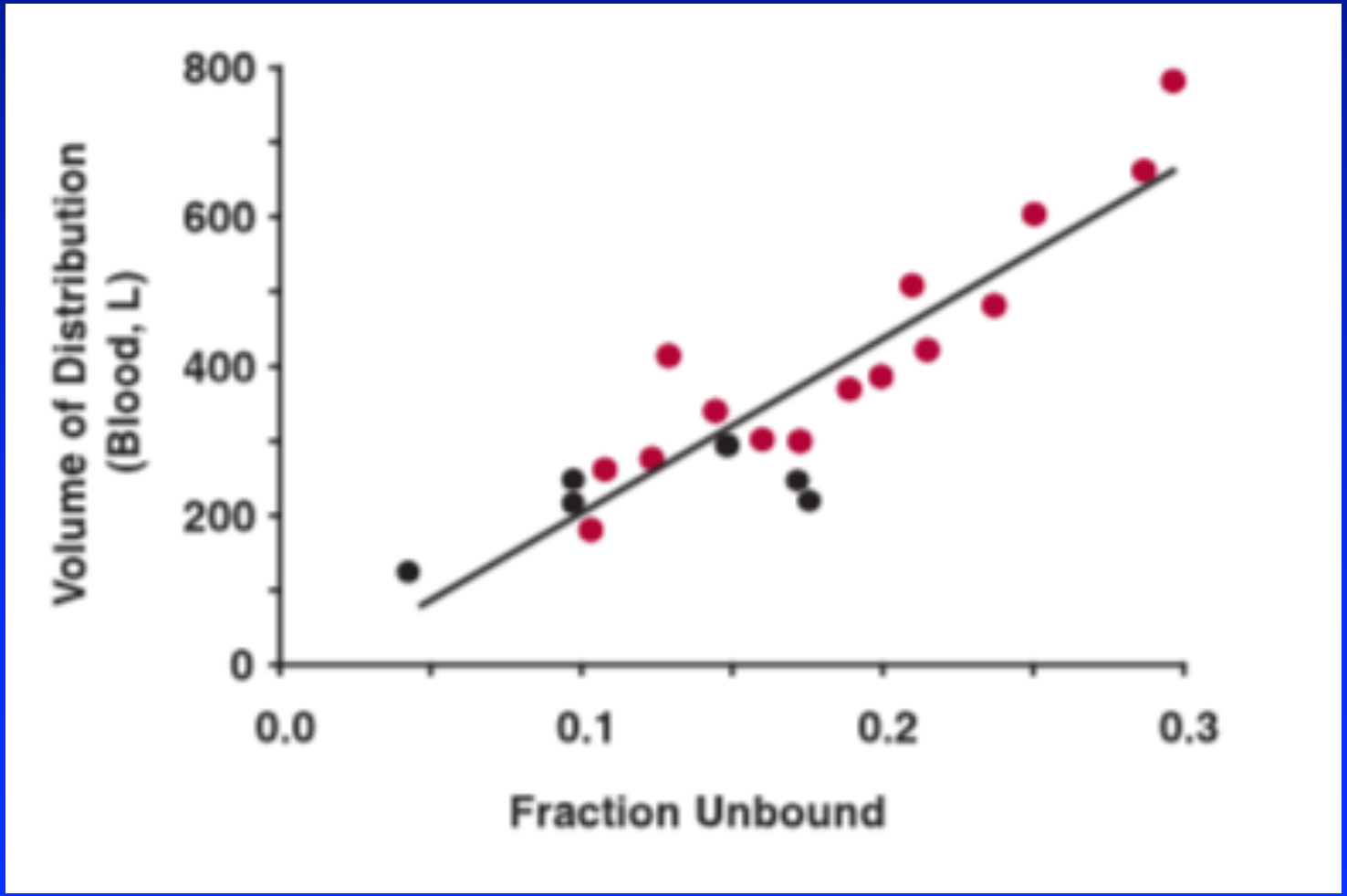
Volume of distribution of (+)-propranolol varies with the fraction unbound in plasma (iv 40 mg bolus dose)



Red circles: chronic hepatic disease

Black circles: healthy volunteers

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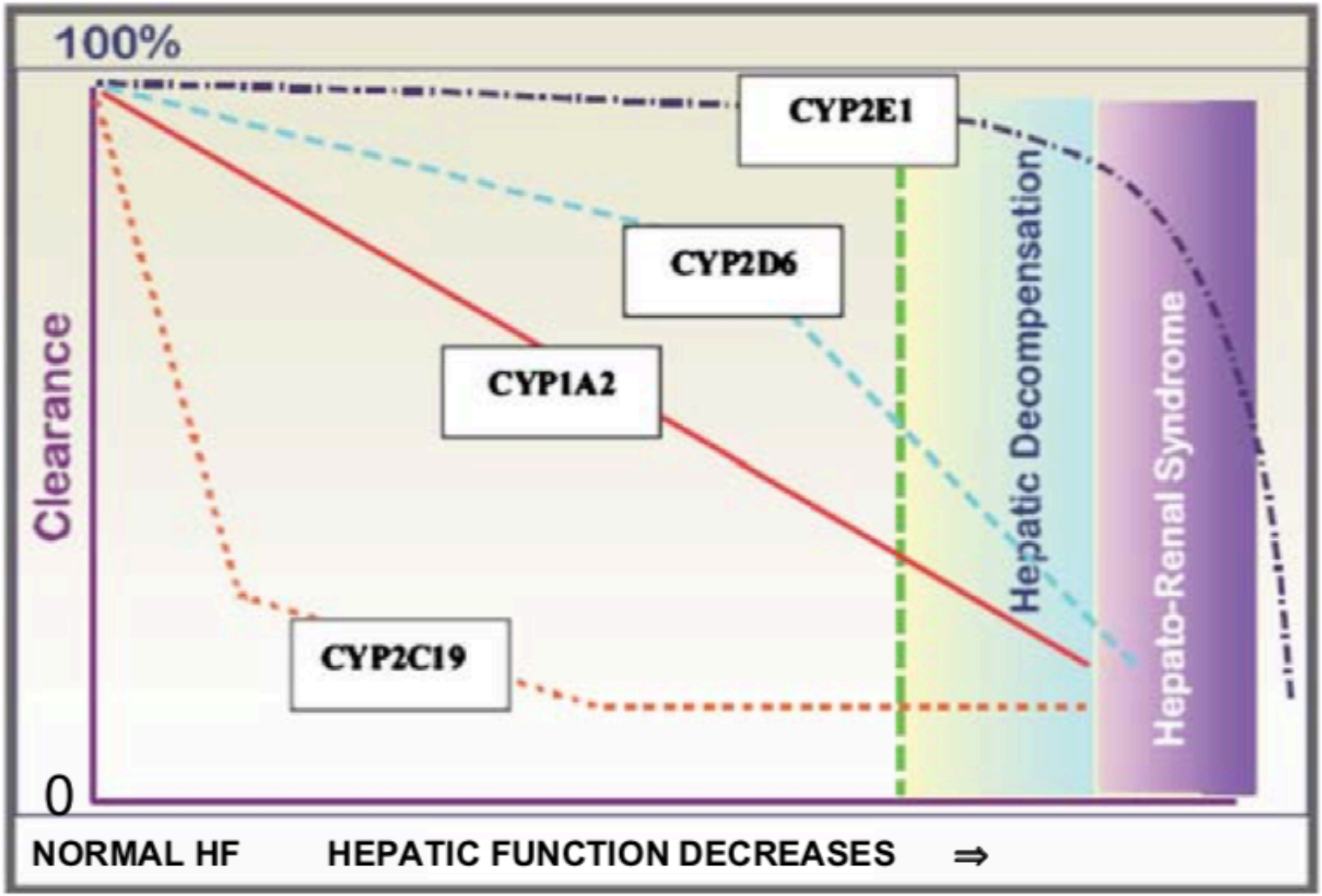
CYP enzymes and hepatic dysfunction



XENOBIOTIC TRANSPORTING SYSTEMS PRESENT IN THE LIVER

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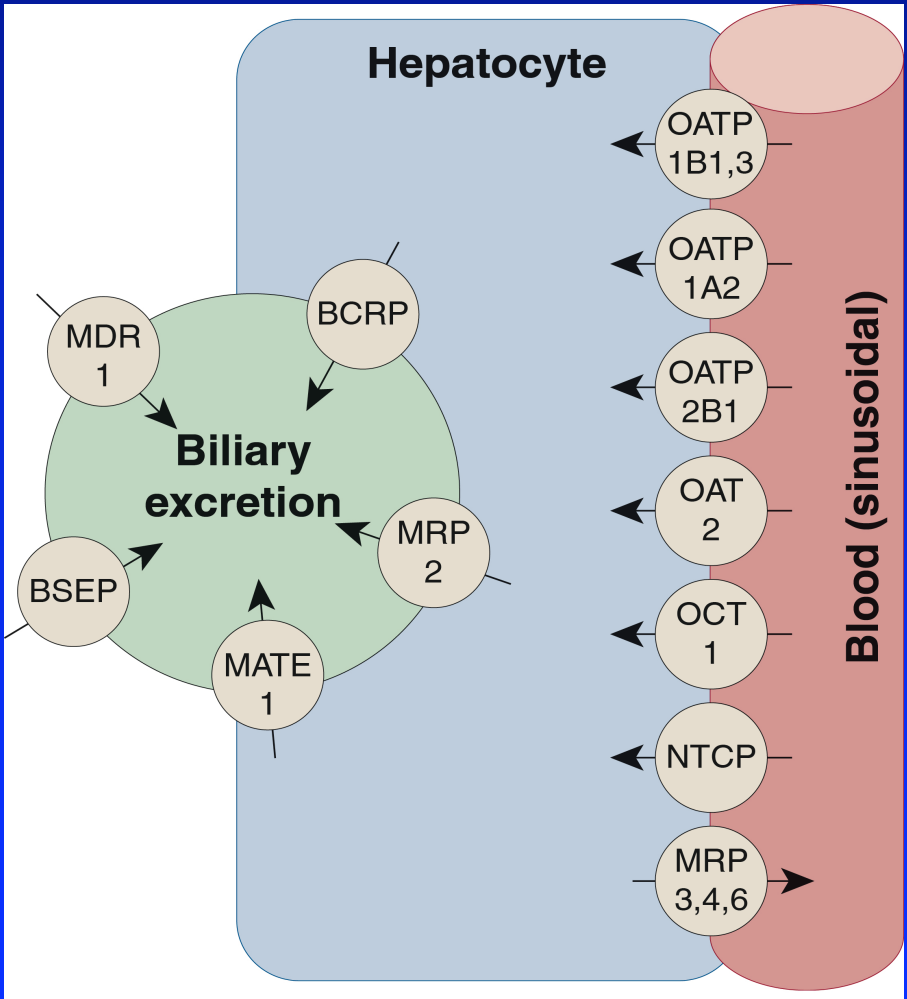

OATP Organic anion transporting polypeptide

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

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CLEARANCE FOR THE ELIMINATING ORGAN

Well-stirred hepatic clearance model

$$Cl_H = \frac{Q \cdot (fu \cdot Cl_{int})}{Q + (fu \cdot Cl_{int})}$$

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

$Cl_H \cong Q$

$\uparrow E_H$

> 0.7

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

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

$\downarrow E_H$

< 0.3

Effects of cirrhosis on clearance of drugs classified according to E_H and f_u

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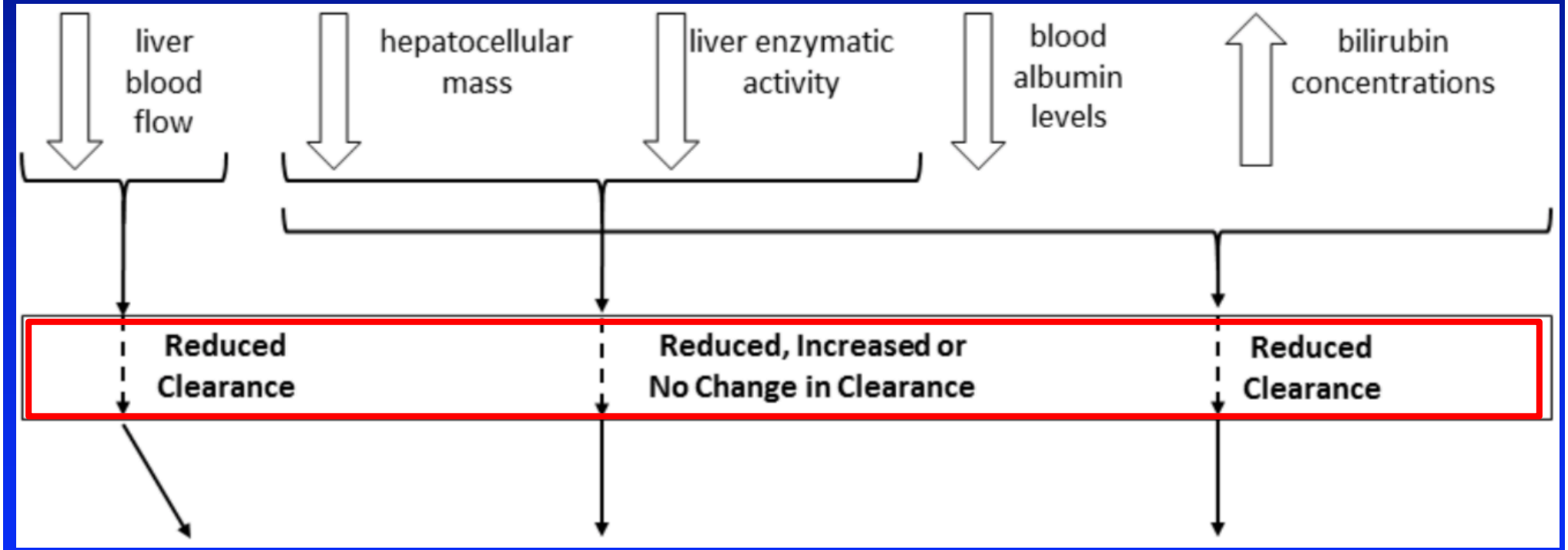

$E_H > 0.7$

$E_H < 0.3$

$fu < 0.1$

$E_H < 0.3$

$fu > 0.1$

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Determinants of systemic clearance (CL_{sys}) and oral clearance (CL_{or})

E_H	CL_{syst}	CL_{or}
$E_H<0.3$	$\sim fu \times CL_{int}$	$fu \times CL_{int}$
$0.3<E_H<0.7$	$CL_H = Q_H \times \frac{fu \times CL_{int}}{Q_H + fu \times CL_{int}}$	$fu \times CL_{int}$
$E_H>0.7$	$\sim Q_H$	$fu \times CL_{int}$

E_H= Hepatic Extraction Ratio

fu= unbound fraction

Q_H= Hepatic blood flow

Cl_{int}= intrinsic clearance

CL_H= Hepatic clearance

Drug	Liver metabolic pathway	Hepatic Extraction Ratio (E_H)	Recommended dosage in cirrhosis
Morphine	Glucuronidation	High	Low doses. Child C: avoid use
Fentanyl	CYP3A4	High	Child A, B: reduce dose by 50% Child C: avoid use
Celecoxib	CYP2C9	Intermediate	Child B: reduce dose by 50% Child C: avoid use
Petidine	N-demethylation	Intermediate	Low doses. Child C: avoid use
Diazepam	CYP2C19, CYP3A	Low	Child A, B: reduce dose by 50% Child C: avoid use
Ibuprofen	CYP2C9, CYP2C8	Low	Child C: avoid use

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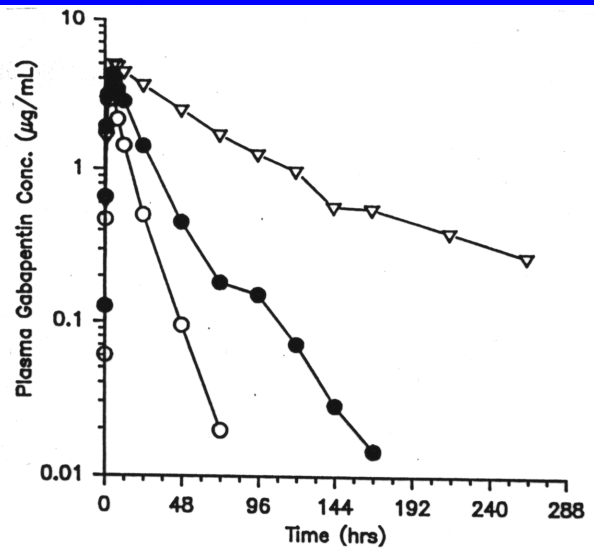
Considerando os parâmetros farmacocinéticos dos medicamentos simvstatina e ácido valpróico, em pacientes com e sem cirrose hepática, responder:

	simvastatina		ácido valpróico	
	controle	cirrótico	controle	cirrótico
Biodisponibilidade (F)	5	10	90	100
% de ligação às proteínas plasmáticas (%pp)	95	85	93	83
Clearance total (Cl/F) (L/h/kg)	0,45	0,22	0,007	0,004
Meia-vida de eliminação ($t_{1/2}$) (h)	2,5	5	14	28
Extração hepática (E)	0,85	0,85	0,005	0,005

9)Considerando que ambos os medicamentos são eliminados principalmente por metabolismo hepático, sugerir os mecanismos envolvidos nas alterações dos parâmetros farmacocinéticos da sinvastatina e do ácido valpróico observados nos pacientes cirróticos.

10) Explicar porque a biodisponibilidade da simvastatina foi alterada em maior extensão do que a do ácido valpróico nos pacientes cirróticos?

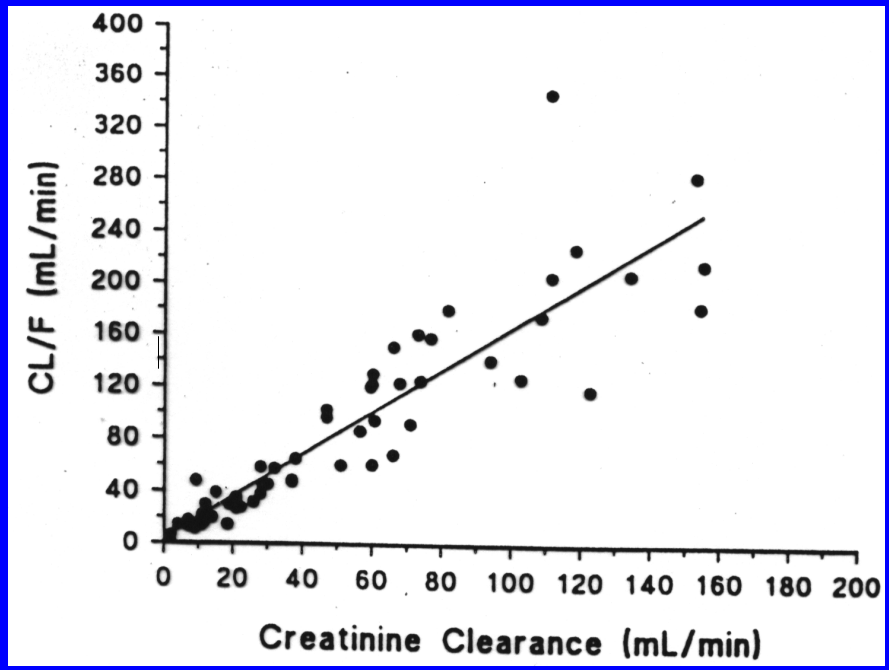
Chronic Kidney Disease (CKD) Gabapentin PK



O $CL_{cr} \geq 60$ mL/min

● CL_{CR} 30-59 mL/min

Δ $CL_{CR} < 30$ mL/min



Chronic Kidney Disease (CKD) Gabapentin PK

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	CL_{CR} (mL/min)		
	≥ 60	30 - 59	< 30
C_{max} (μg/mL)	3,4	4,8	4,8
t½ (h)	9,2	14	40
CL_T (mL/min)	160	63	24
CL_R (mL/min)	79	36	11

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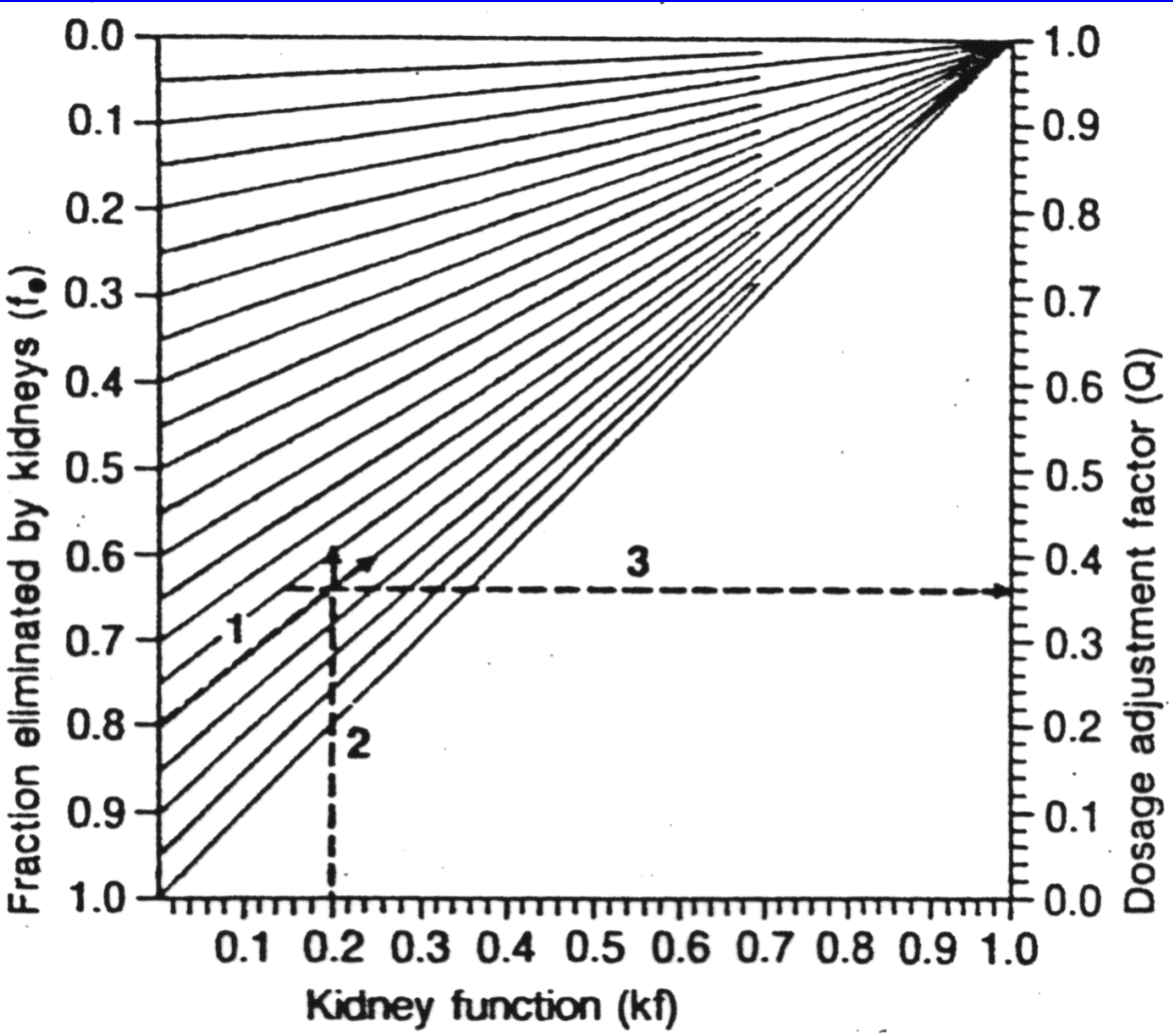
Tubular secretion is the major route of metformin elimination

Subject Groups: GLUCOPHAGE dose[a] (number of subjects)	C_{max}[b] (µg/mL)	T_{max}[c] (hrs)	Renal Clearance (mL/min)
Renal-impaired adults:			
850 mg single dose			
Mild (CL_{cr}[g] 61-90 mL/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CL_{cr} 31-60 mL/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CL_{cr} 10-30 mL/min) (6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

Chronic Kidney Disease (CKD)

Dosage adjustment



Função renal
$K_f = CL_{CR}$ paciente/ CL_{CR} voluntário sadio
Fração eliminada pelos rins fe
Fator de ajuste de dose Q
Intervalo de dose τ/Q Dose manutenção D x Q

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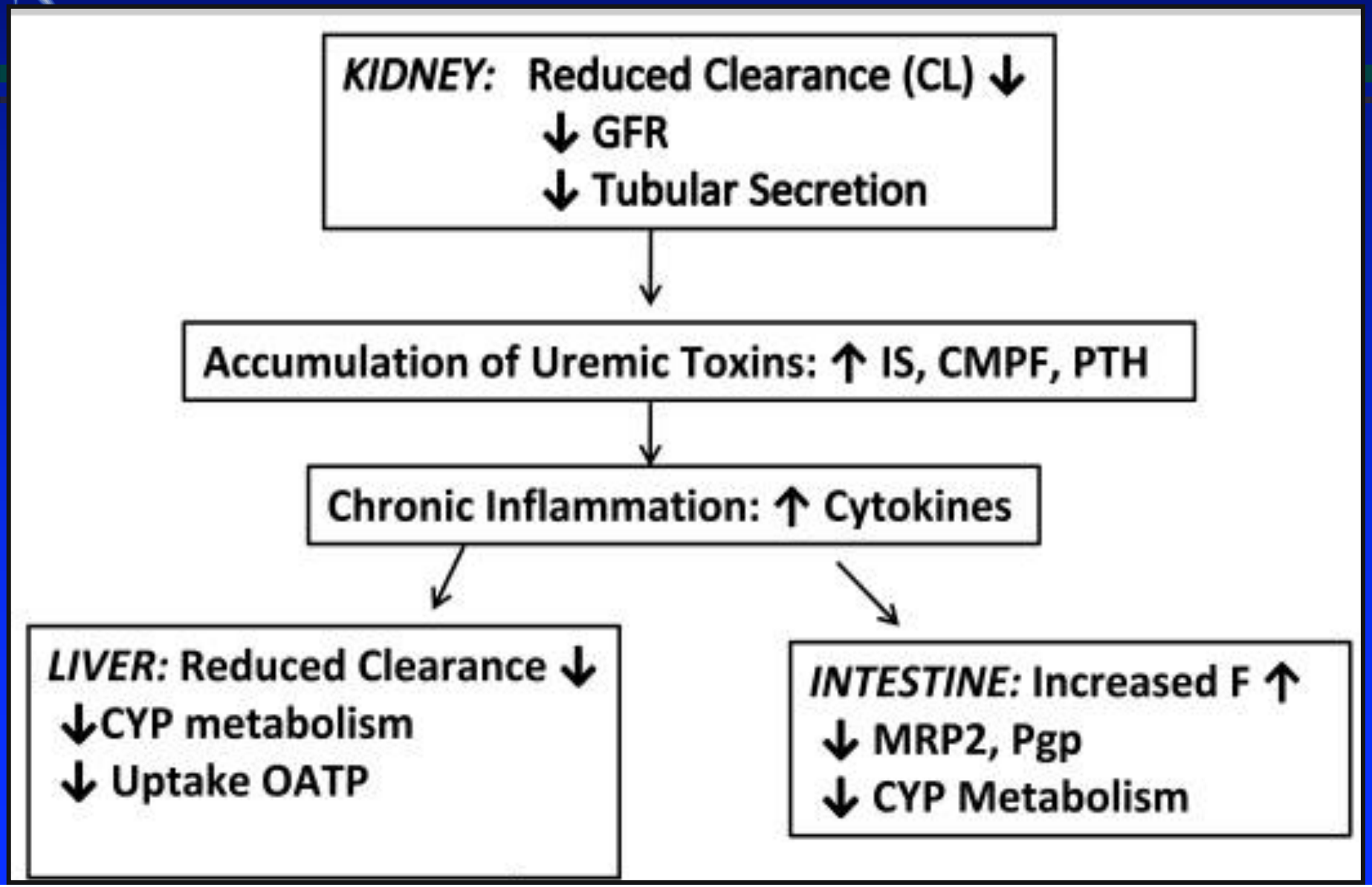
Effect of kidney disease on Drug Metabolism and Transport



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Impact of Chronic Kidney Disease (CKD) on drug clearance

Enzyme/transporter	drug	clearance ratio CKD/controls
CYP2D6	fluoxetine	0.73
	d-nebivolol	0.30
	l-nebivolol	0.52
	paroxetine	0.28
	risperidone	0.47
	sparteine	0.57
UGT2B7	ketoprofen	0.58
	morphine	0.60
	zidovudine	0.48
NAT2	Isoniazid	0.65
	procainamide	0.44
OATP1B	atorvastatin	0.70
	pitavastatin	0.74
	repaglinide	0.37
	rosuvastatin	0.32

Dose adjustment in patients with CKD

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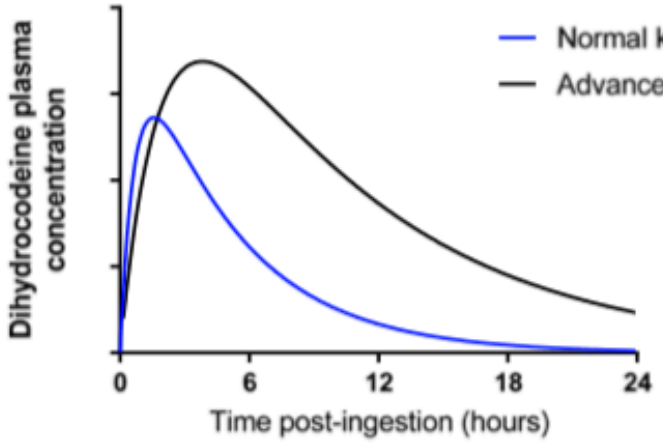

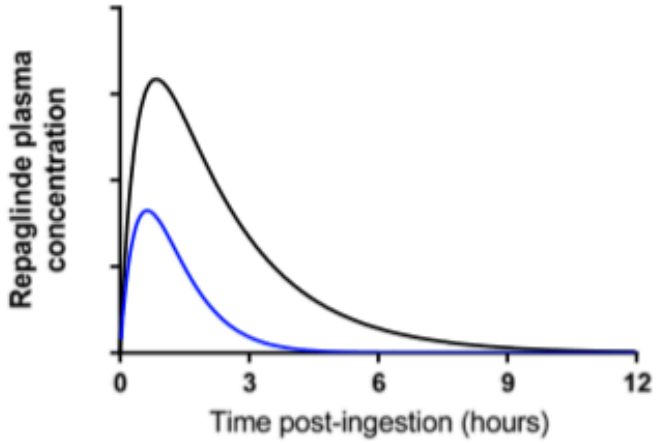

Dihydrocodeine:
substrate of CYP2D6 and CYP3A4

Repaglinide:
Substrate of CYP34, CYP2C8 and OATP1B1

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Nebivolol PK in patients with Chronic Kidney Disease (CKD)

Parameters	*l*-nebivolol			*d*-nebivolol		
	Control (n = 22)	CKD (n = 12)	Haemodialysis (n = 10)	Control (n = 22)	CKD (n = 12)	Haemodialysis (n = 10)
C_{max} (ng ml^{-1})	1.31 (47)	1.98 (47)	1.38 (39)	0.69 (45)*	1.34 (54)*	0.80 (44)*
t_{max} (h)†	1.01 (0.18–2.10)	1.04 (0.68–2.80)	1.15 (0.27–1.54)	1.03 (0.43–2.14)	0.98 (0.61–3.34)	1.13 (0.40–1.86)
$AUC_{0-\infty}$ (ng.h ml^{-1})	6.83 (39)	9.94 (44)	6.41 (35)	4.15 (41)*	7.30 (51)*	4.95 (36)*
t½ (h)	13.79 (35)	12.43 (35)	12.87 (27)	13.19 (47)	11.57 (30)	16.10 (31)
Vd/F (l kg^{-1})	100.19 (66)	59.38 (65)	113.70 (70)	157.60 (83)*	71.95 (64)*	197.49 (65)*
CL/F (l h^{-1} kg^{-1})	10.24 (47)	7.18 (32)	12.45 (35)	16.84 (41)*	9.77 (51)*	15.86 (33)*

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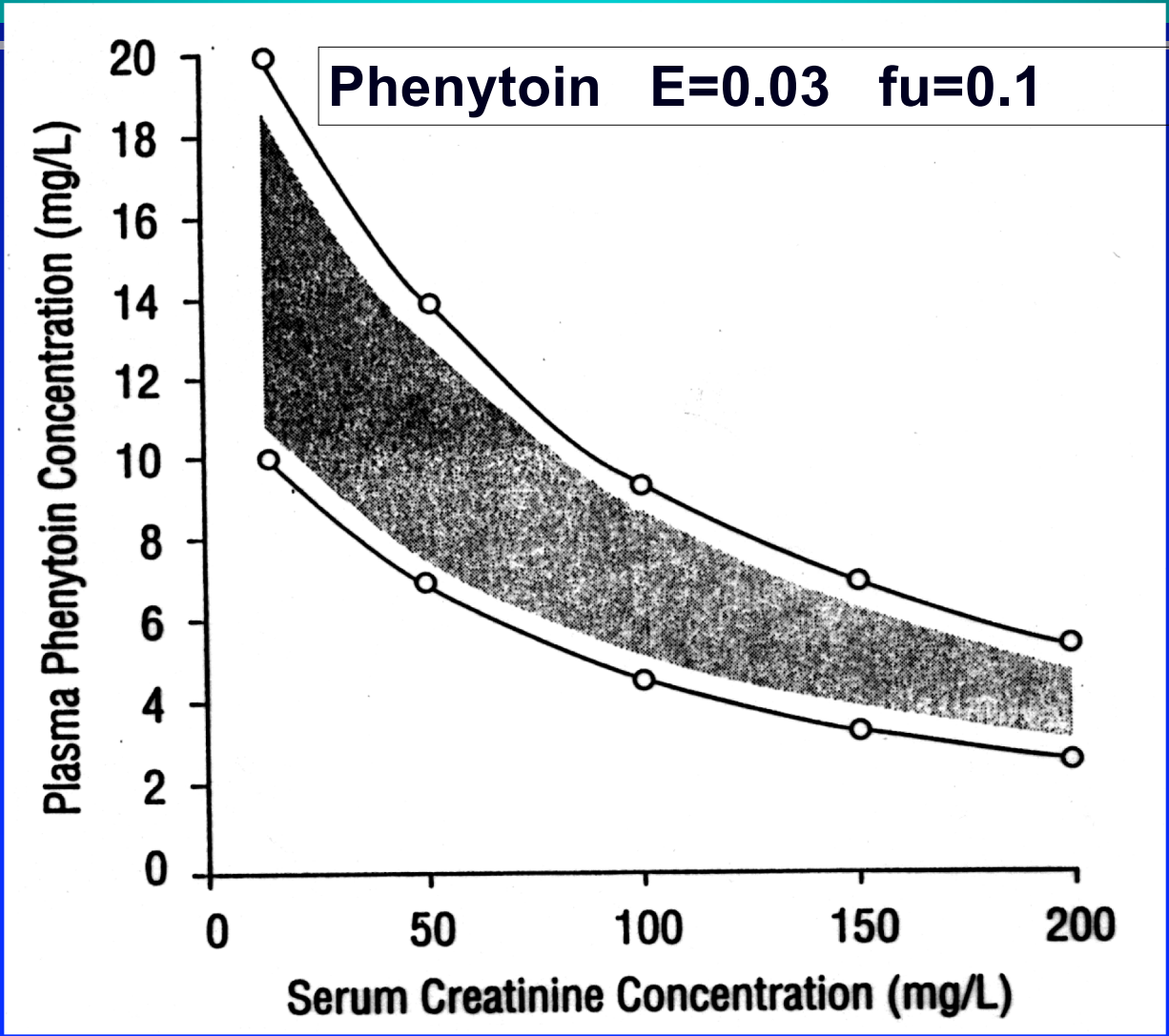
Plasma phenytoin concentrations in patients with CKD



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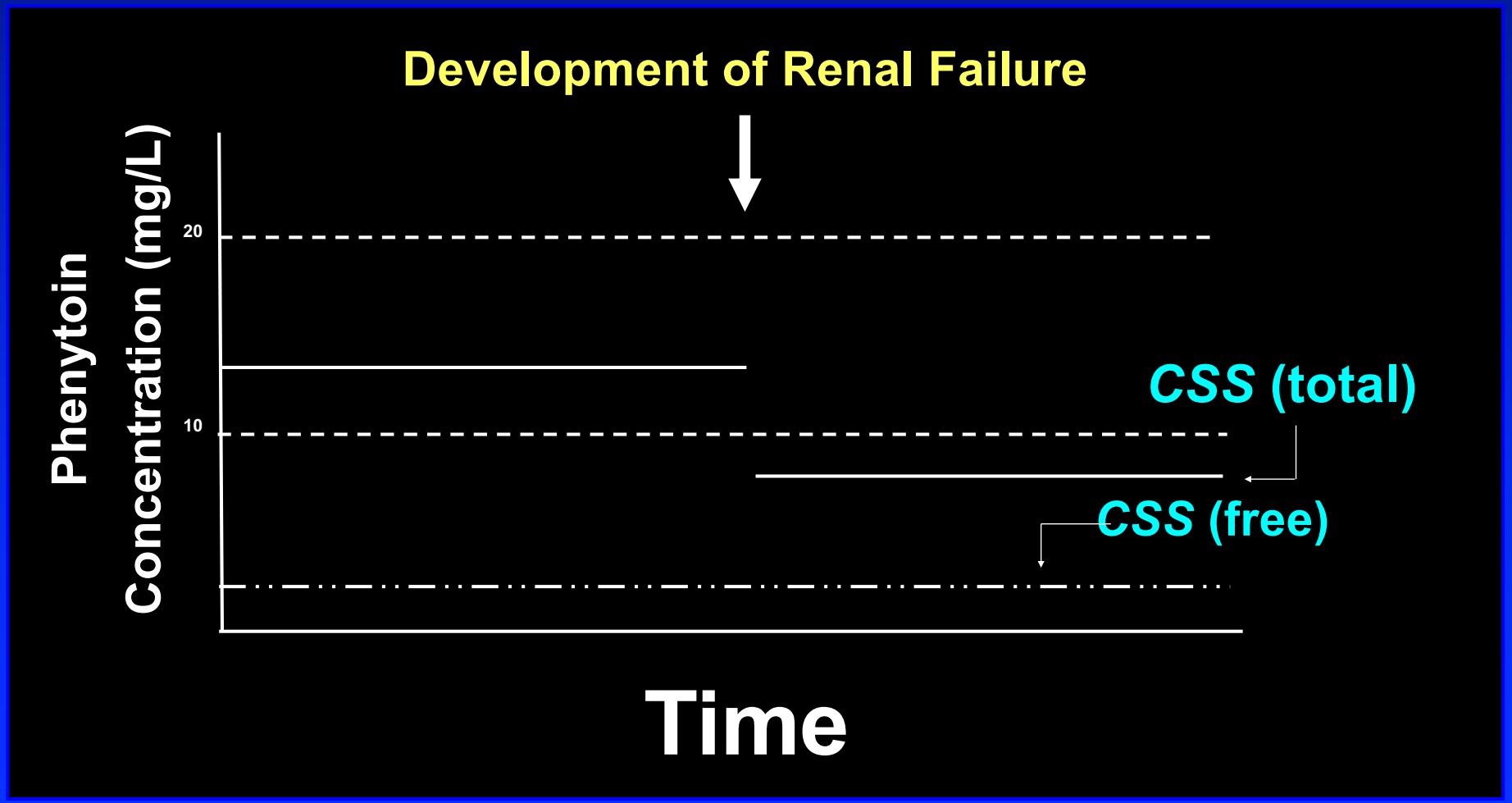
Phenytoin has a low E and possesses high protein binding



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Exercício 2

Um antibiótico foi administrado por via intravascular na dose de 500 mg. A recuperação do antibiótico sob a forma inalterada na urina coletada até 48 h após a administração foi de 400 mg. Considerando a meia-vida de eliminação do antibiótico como 6 h e o volume de distribuição de 21 L, podemos afirmar que:

a) a fração eliminada na urina sob a forma inalterada não pode ser calculada considerando que a biodisponibilidade do fármaco não é conhecida

b) o clearance total do fármaco é de 3,03 L/min

c) o clearance renal do fármaco é de 1,94 L/h

d)os dados apresentados não são suficientes para calcular o clearance total e o clearance renal

e) nenhuma das alternativas está correta

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Classification of Heart Failure

Class	Description
Class I	Mild, no limitations of physical activity
Class II	Mild with slight limitation of physical activity (fatigue, palpitations or dyspnoea with normal activities); no symptoms at rest
Class III	Moderate with marked limitation of physical activity (fatigue, palpitations or dyspnoea with less than normal activities); no symptoms at rest
Class IV	Severe, unable to carry out any physical activity without discomfort; symptoms at rest

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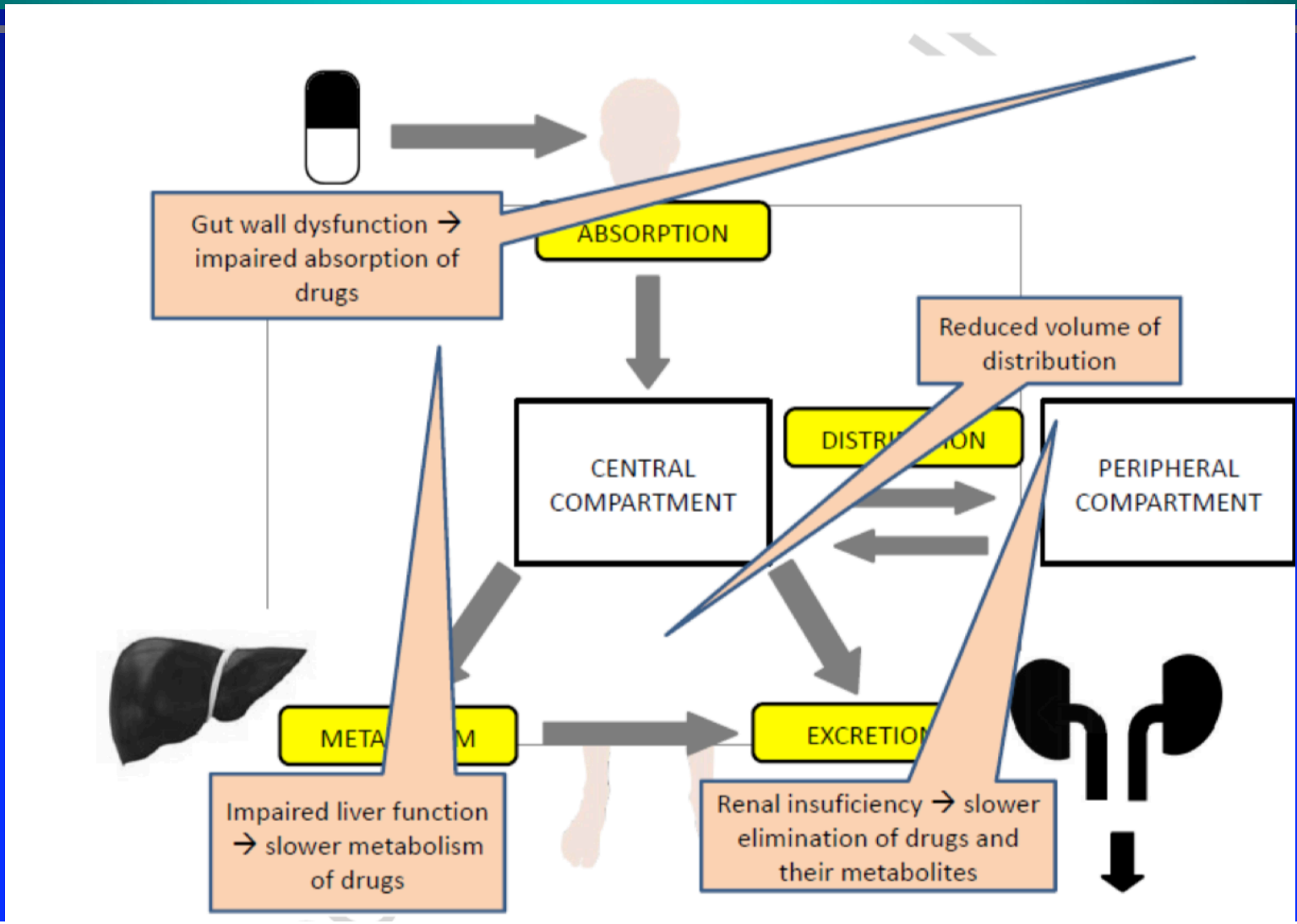
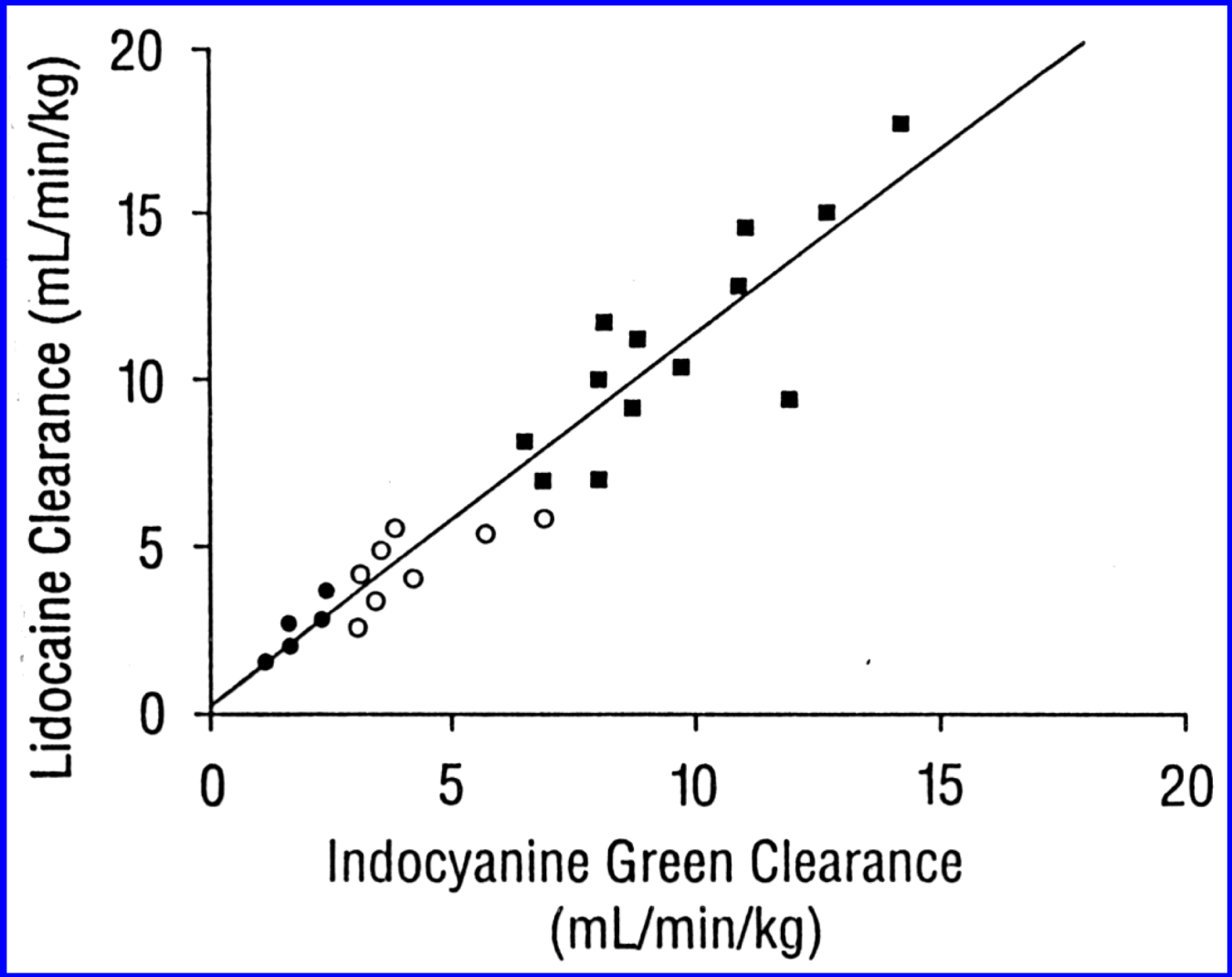
Influence of heart failure on PK





■ voluntários sadios

○ leve ICC

● graveICC

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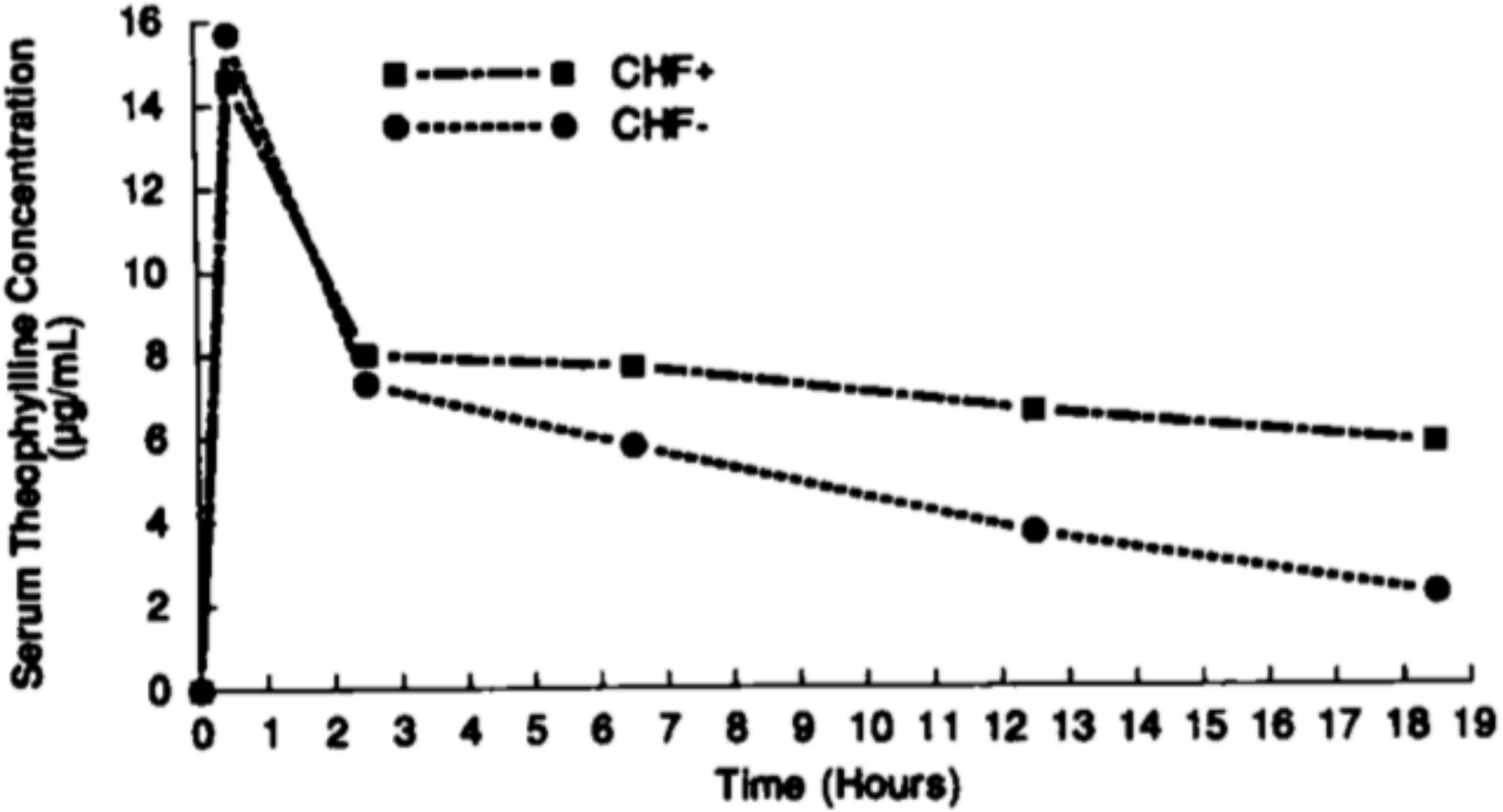
Theophylline serum concentration/time curve after intravenous aminophylline (6 mg/kg over 30 minutes)



Theophylline serum concentration/time curve after intravenous aminophylline (6 mg/kg over 30 minutes)

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Change in Total Clearance of Theophylline after treatment of Congestive Heart Failure

	Decompensated CHF	Compensated CHF
CL (mL/kg/h)	21.66	43.44
Vd (L/kg)	0.52	0.54
t1/2 (h)	18.2	9.1

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Decompensated heart failure Oral administration

In patients with decompensated heart failure, the oral pharmacokinetics of certain drugs may be altered, but the magnitude of changes would be at most a 50 % increase in the oral area under the plasma concentration–time curve as compared with those observed in patients without heart failure.

Body Mass Index (BMI)-based classification for underweight, overweight, and obese subjects

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BMI (kg/m^2)	Classification
<18.5	Underweight
≥18.5 and <25.0	Normal weight
≥25.0 and <30.0	Overweight
≥30.0	Obese (in general)
≥30.0 and <35.0	Obese class I (moderate obesity)
≥35.0 and <40.0	Obese class II (severe obesity)
≥40.0	Obese class III (morbid obesity)

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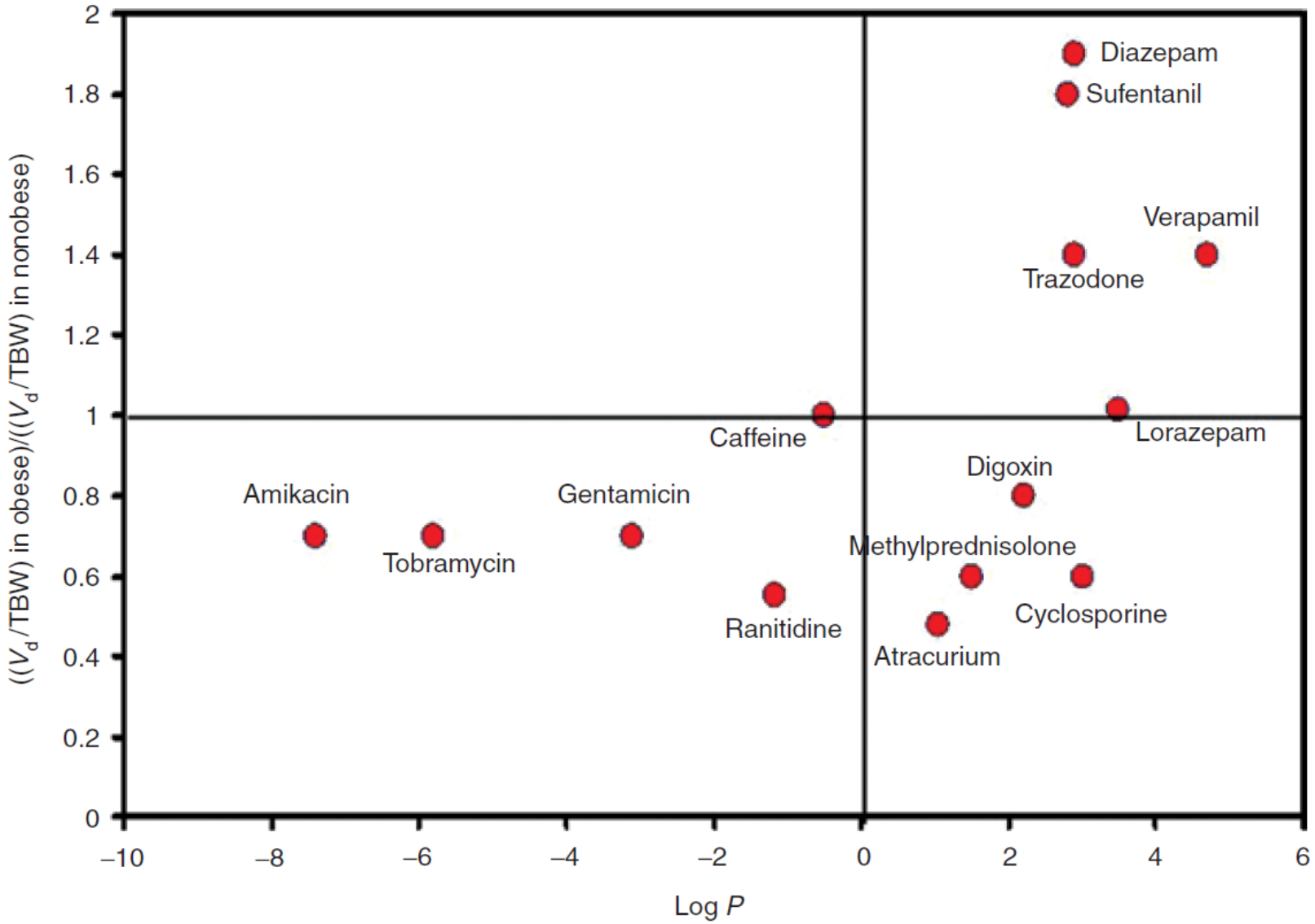
The ratios of the volumes of distribution Vd/TBW OBESE / Vd/TBW NONOBESE



Effect of obesity on the PK
Loading dose adjustment

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Loading dose = Vd. Cp

fármaco	Vd (L)		ajuste de dose
	controle	obeso	
diazepam	91	292*	peso corporal total
sufentanil	346	547*	peso corporal total
metil-prednisolona	122	104	peso corporal ideal
ciclosporina	280	230	peso corporal ideal

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Effect of obesity on the PK

Dose / τ = Cp^{ss} . CL

fármaco	CL (L/h)		ajuste de dose
	controle	obeso	
diazepam	1,6	2,3*	peso corporal total
nitrazepam	4	6*	peso corporal total
verapamil	75	80	peso corporal ideal
ciclosporina	47	42	peso corporal ideal

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Pharmacokinetic parameters of dexfenfluramine

Parameter	Obese patients n=10	Control subjects n=10
Cl ($L.h^{-1}$)	43.9	37.3
V_{ss} (L)	969.7•	668.7
V_{ss} ($L.kg^{-1}$)	10.2	11.3
t½ (h)	17.8	13.5

A tabela abaixo mostra os parâmetros farmacocinéticos da digoxina, um fármaco empregado no tratamento da insuficiência cardíaca congestiva e fibrilação atrial, avaliado nas situações de monoterapia e administração concomitante com quinidina. Com base nos dados apresentados, responder:

	biodisponibilidade (%)	clearance total (mL/min)	clearance renal (mL/min)	volume de distribuição (L)	fração livre
digoxina	0,75	140	101	500	0,78
digoxina + quinidina	0,75	72	51	240	0,78

Considerando que o intervalo terapêutico da digoxina é de 1-3 µg/L, calcular a dose de ataque da digoxina administrada por via oral (biodisponibilidade de 75%) na situação de monoterapia para um paciente de 70 kg.

Avaliar o tempo necessário para a observação de concentrações plasmáticas de digoxina no estado de equilíbrio na situação de monoterapia para um paciente de 70 kg.

Considerando que o intervalo terapêutico da digoxina é de 1-3 µg/L, avaliar se a dose de manutenção diária (intervalo de dose=24h) da digoxina administrada por via oral (biodisponibilidade de 75%) deve ser alterada na situação de administração concomitante com quinidina, ou seja, calcular as doses diárias de manutenção da digoxina nas situações de monoterapia e associação com quinidina.

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Dose / Concentração Plasmática

- medicamento
- paciente
- Interação de fármacos

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REAÇÕES DE DESLOCAMENTO DE RELEVÂNCIA CLÍNICA

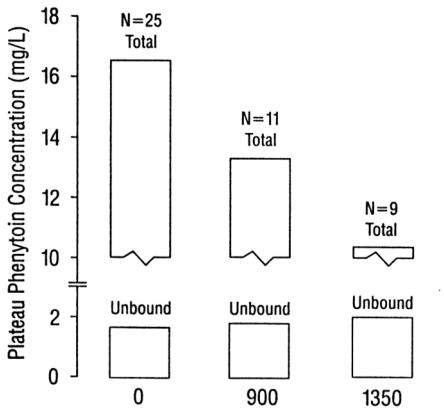
↑E, via i.v. lidocaina ⇨ Interação de relevância clínica

↓E, ↓IT, ↓Vd, ↑%pp

Warfarina: fu = 0,01 ; Vd = 9L
Tolbutamida: fu = 0,04 ; Vd = 10L
Fenitoina: fu = 0,04 ; Vd = 35L

⇨ ↑ transitório na concentração livre é de relevância clínica?

Interação fenitoina - ácido valproico



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%

Drugs for which changes in protein binding are not clinically relevant

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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

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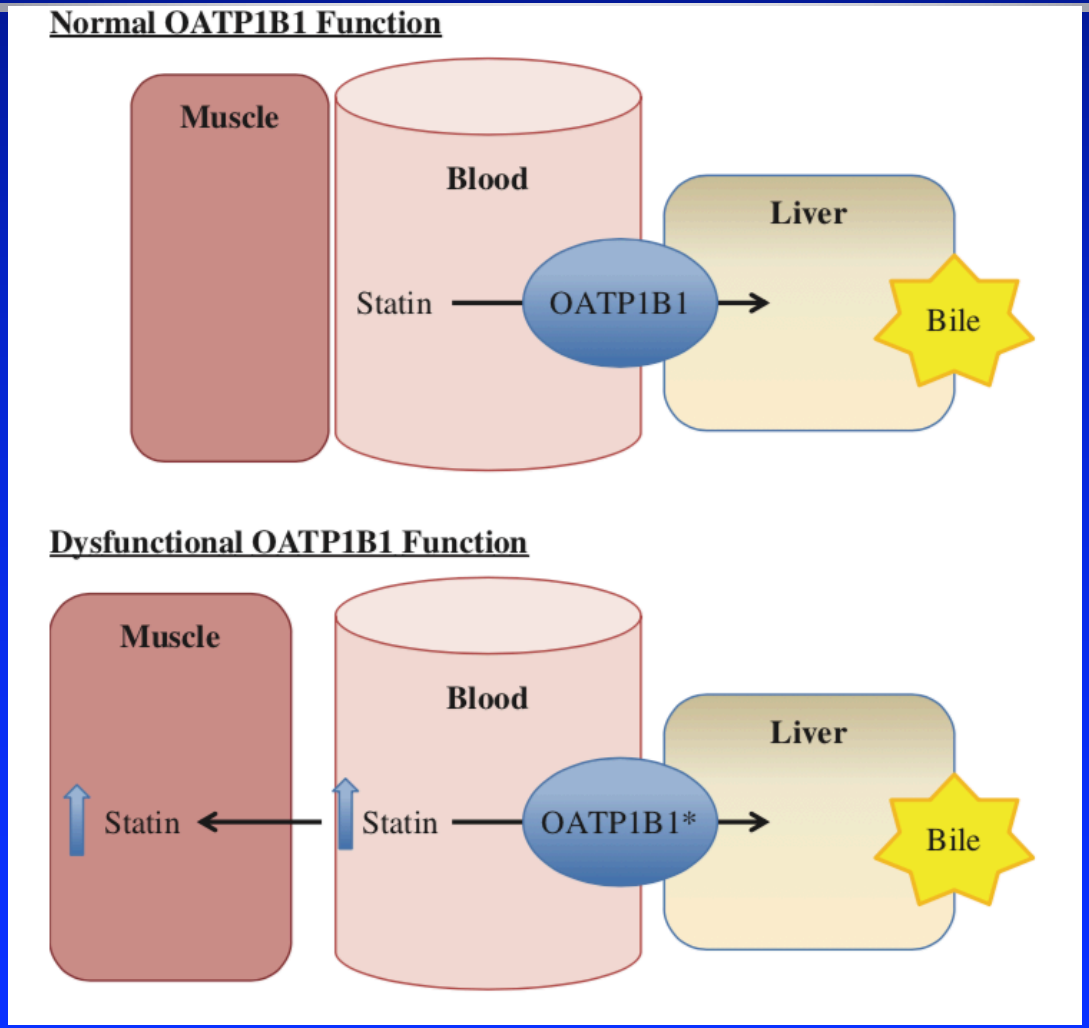
Inhibition of hepatic OATP1B1 (Organic Anion Transporting Polypeptide)



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Recent Labeling on Drug-Drug Interactions (Rosuvastatin)

Rosuvastatin dose range for adults: 5-40 mg daily

	Change in AUC	Change in Cmax	Dose (mg/day)
cyclosporine	7.1	11	5
atazanavir/ritonavir	3.1	7	10
simeprevir	2.8	3.2	10
lopinavir/ritonavir	2.1	5	10
gemfibrozil	1.9	2.2	10

Patients taking atazanavir and ritonavir, lopinavir and ritonavir, or simeprevir: Initiate CRESTOR therapy with 5 mg once daily. The dose of CRESTOR should not exceed 10 mg once daily

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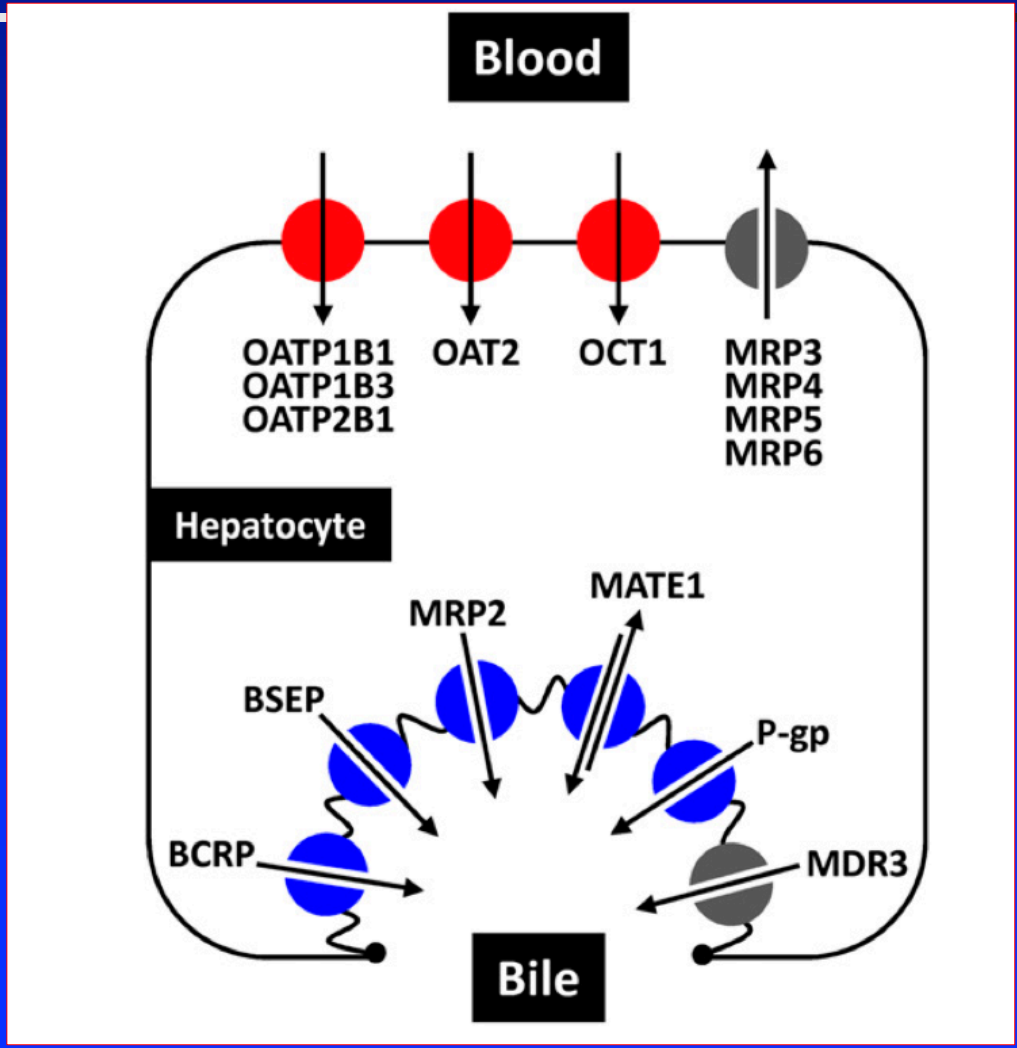
Inhibition of canalicular BSEP (Bile Salt Export Pump)

- bosentan
- cyclosporine
- glibenclamide
- rifampin



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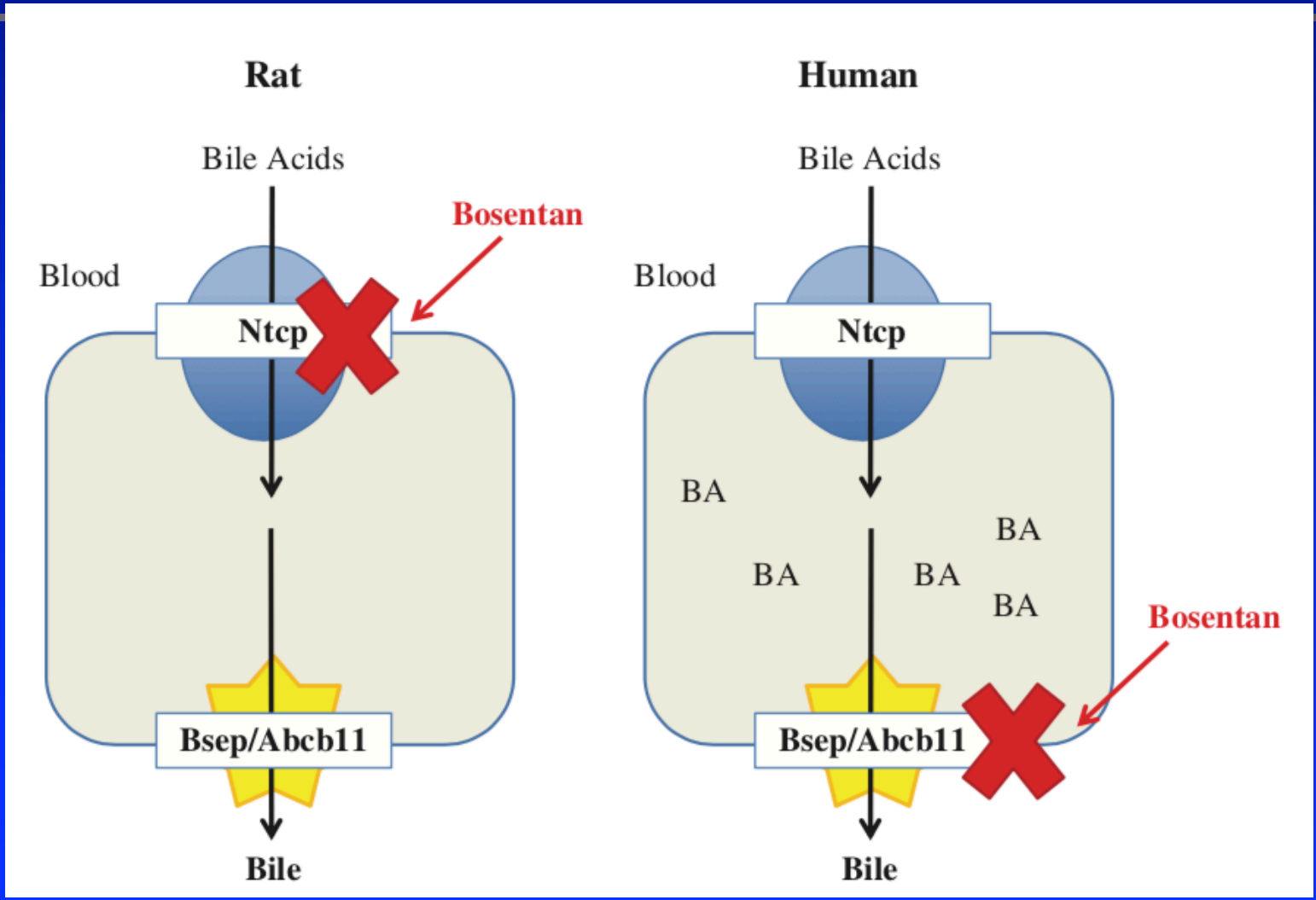
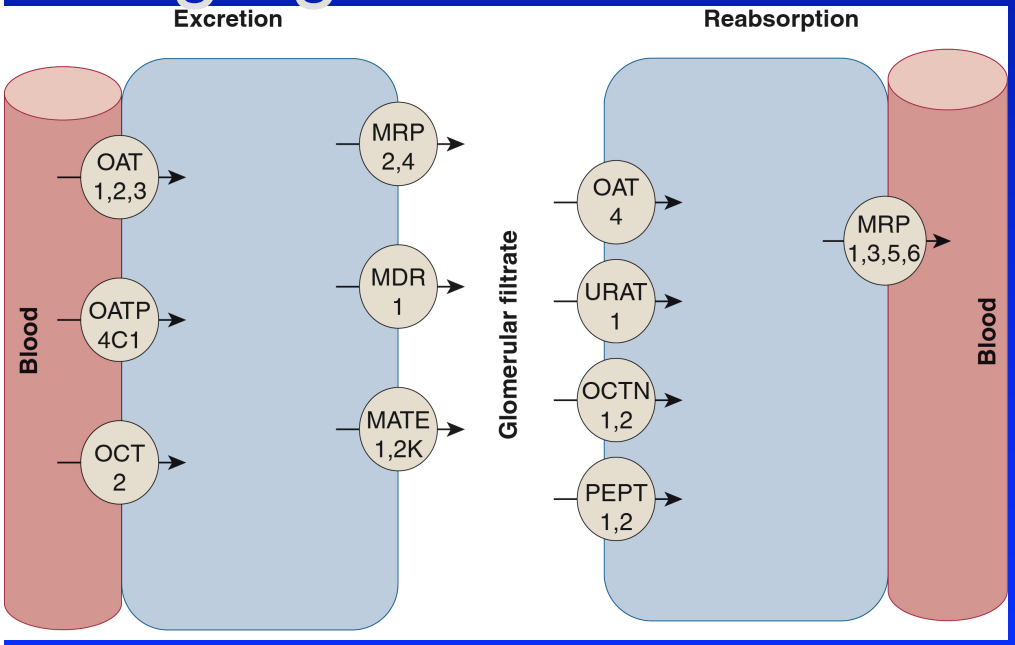
Inhibition of canalicular BSEP (Bile Salt Export Pump)



Renal OATs (Organic Anion Transporters)

FCFRP-USP

500 mg probenecid orally, 8 and 2 h before 1mg/kg furosemide iv



	F	F + P
CL_T (mL/min)	155	85*
CL_R (mL/min)	134	63*
CL_{NR} (mL/min)	21	17
$CL_{creatinine}$ (mL/min)	124	129

Probenecid is known to be a potent competetive inhibitor of secreted weak organic acids

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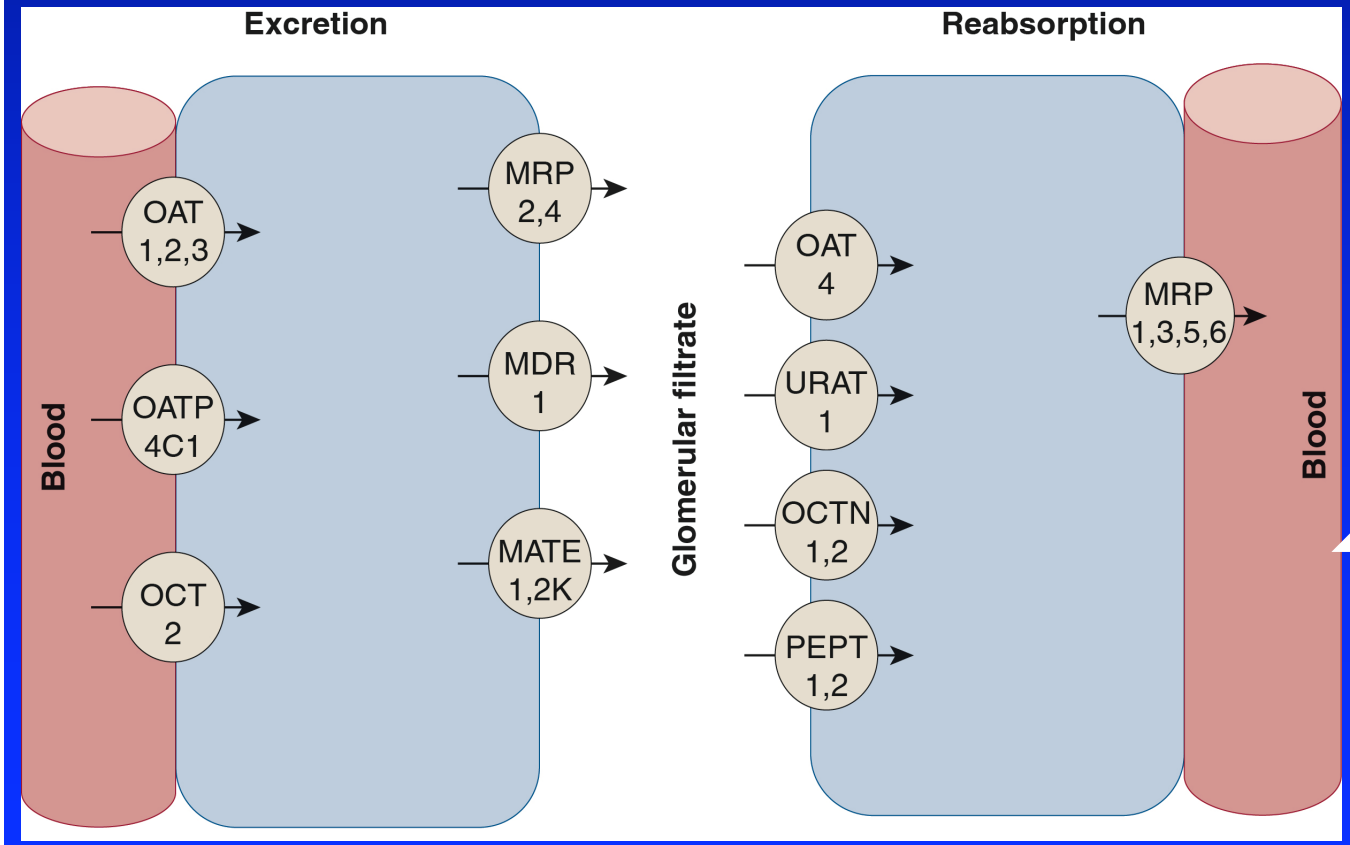
Inhibition of renal OCT2/MATE

(Organic Cation Transporter/Multidrug and Toxin Extrusion)

OCT2/MATE inhibitors: ranolazine, vandetanib, dolutegravir, cimetidine



METFORMIN

⇧ AUC

⇩ CL_R

⇧ Risk for lactic acidosis

Inhibition of intestinal/renal P-gp (P-glycoprotein): digoxin DDI

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Inhibition of intestinal P-gp

Precipitant	AUC/AUC ratio
Quinidine	2.65
Quinidine	1.76
Amiodarone	1.68
Ranolazine	1.6
Carvedilol[a]	1.56
Verapamil	1.51
Amiodarone	1.63
Diltiazem	1.44
Conivaptan	1.43
Captopril[b]	1.39
Mibefradil	1.31

Inhibition of renal P-gp

Precipitant	CL_r/ CL_{renal} ratio
Valspodar[a]	0.25
Valspodar[b]	0.35
Ranolazine	0.54

For digoxin, a 25% increase in exposure is clinically relevant because untoward toxicity may occur as a result of increased drug levels.

The individualized dosing of digoxin for patients with cardiac insufficiency: serum creatinine, coadministration, and SLCO4C1 genotypes

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	Serum creatinine <85 µmol/L			
	Spironolactone		None spironolactone	
	rs3114660 CC	rs3114660 CG/GG	rs3114660 CC	rs3114660 CG/GG
	Serum creatinine <85 mmol/L			
rs rs3114661 GG	0.1875 mg QD (91.4)	0.25 mg QD (89.9)	0.25 mg QD (94.6)	0.5 mg QD (95.7)
rs rs3114661 GA/AA	0.25 mg QD (92.1)	0.3125 mg QD (90.0)	0.5 mg QD (93.6)	0.3125 mg BID (96.3)
	Serum creatinine >85 µmol/L			
rs rs3114661 GG	0.125 mg QD (92.3)	0.1875 mg QD (91.9)	0.1875 mg QD (95.2)	0.25 mg QD (90.5)
rs rs3114661 GA/AA	0.1875 mg QD (92.6)	0.25 mg QD (90.3)	0.3125 mg QD (92.5)	0.5 mg QD (95.2)

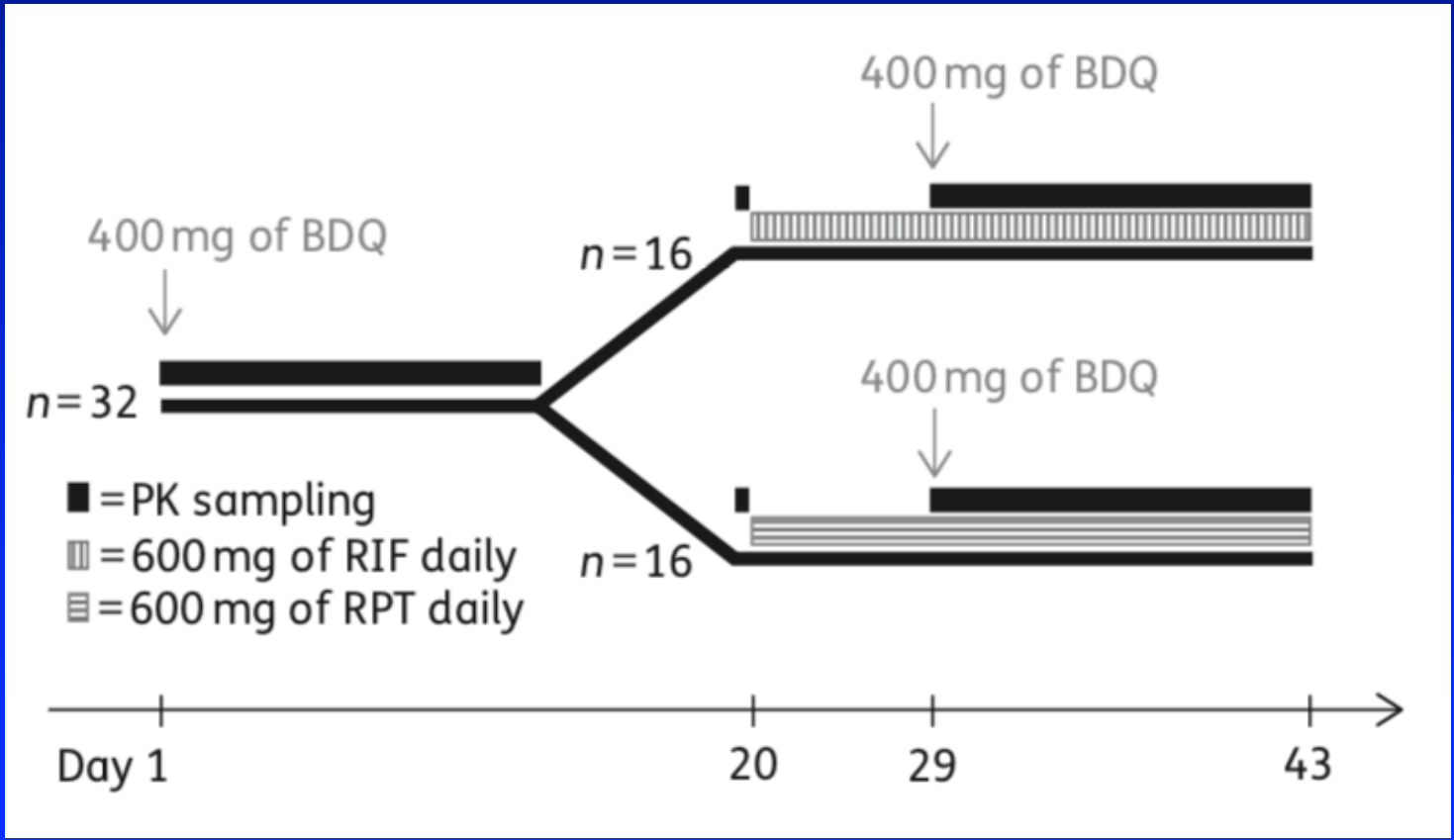
Classification of CYP Inducers

FCFRP-USP

CYP Enzymes	**Strong Inducers** ≥ 80% decrease in AUC	**Moderate Inducers** 50-80% decrease in AUC	**Weak Inducers** 20-50% decrease in AUC
CYP1A2		Montelukast, phenytoin, smokers versus non-smokers	Moricizine, omeprazole, phenobarbital,
CYP2B6		Efavirenz, rifampin	Nevirapine
CYP2C8		Rifampin	
CYP2C9		Carbamazepine, rifampin	Aprepitant, bosentan, phenobarbital, St. John's wort
CYP2C19		Rifampin	Artemisinin
CYP3A	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, clobazamechinacea, pioglitazone, prednisone, rufinamide, vemurafenib
CYP2D6	None known	None known	None known

Bedaquiline is metabolized by CYP3A4

Rifampicin and rifapentine are potent inducers of CYP3A4



BDQ, bedaquiline; RIF, rifampicin; RPT, rifapentine

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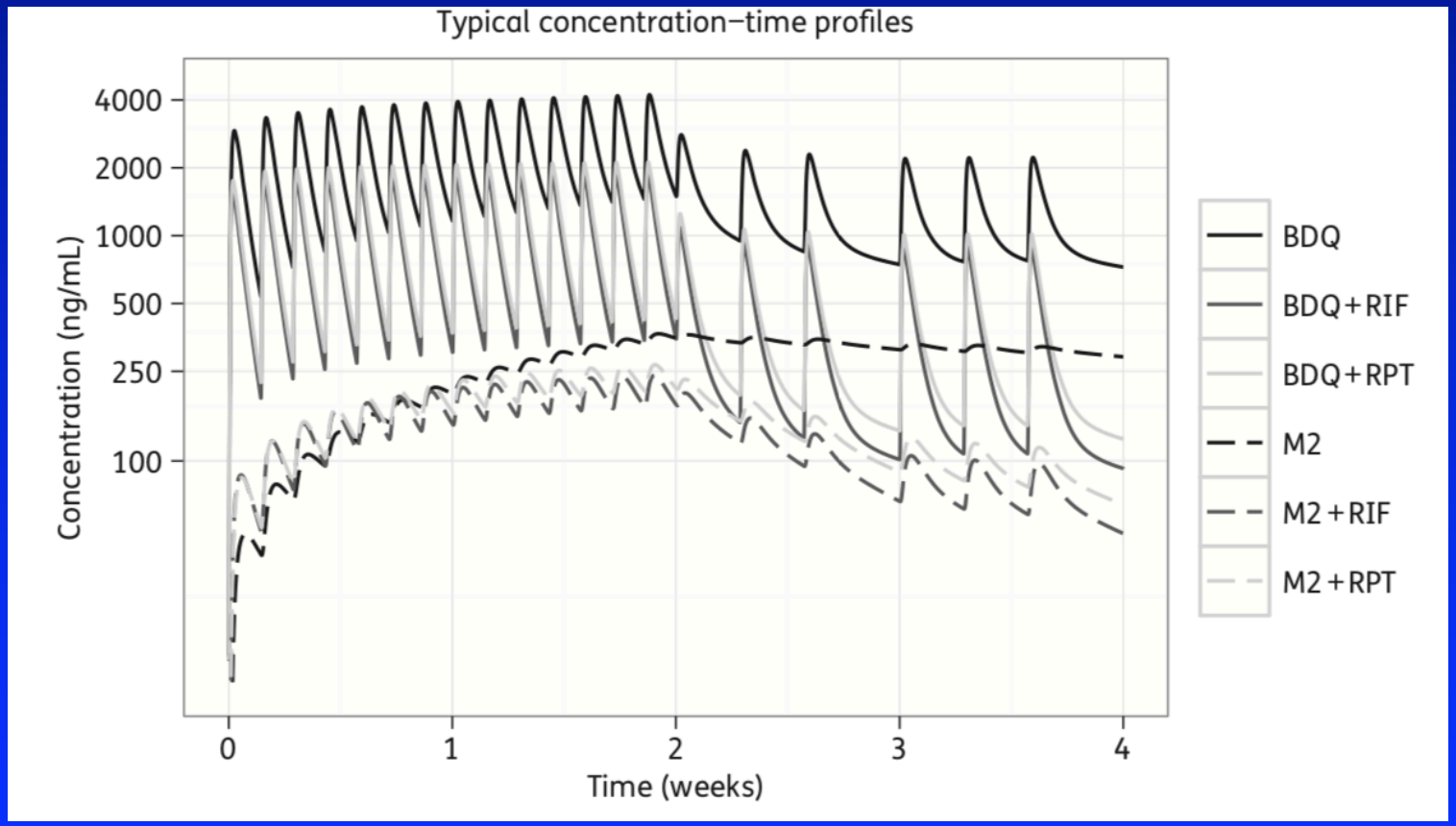
Rifamycin co-administration increased bedaquiline clearance 4.78-fold

Rifapentine co-administration increased bedaquiline clearance 3.96-fold



BDQ, bedaquiline; RIF, rifampicin; RPT, rifapentine

SIRTURO™ (bedaquiline) Tablets

FCFRP-USP

Rifampin (strong CYP3A4 inducer)

Due to the possibility of a reduction of the therapeutic effect of bedaquiline because of the decrease in systemic exposure, co-administration of bedaquiline and rifamycins (e.g., rifampin, rifapentine and rifabutin) or other strong CYP3A4 inducers used systemically should be avoided

Classification of CYP Inhibitors

FCFRP-USP

CYP Enzymes	Strong Inhibitors ≥ 5-fold increase in AUC or > 80% decrease in CL	Moderate inhibitors ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL	Weak inhibitors ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL
CYP1A2	Ciprofloxacin, enoxacin, fluvoxamine	Methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, vemurafenib, zileuton	Acyclovir, allopurinol, caffeine, cimetidine, Daidzein, , disulfiram, Echinacea' famotidine, norfloxacin, propafenone, propranolol, terbinafine, ticlopidine, verapamil
CYP2B6			Clopidogrel, ticlopidine prasugrel
CYP2C8	Gemfibrozil		Fluvoxamine, ketoconazole, trimethoprim

Classification of CYP Inhibitors

FCFRP-USP

CYP Enzymes	Strong Inhibitors ≥ 5-fold increase in AUC or > 80% decrease in CL	Moderate inhibitors ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL	Weak inhibitors ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL
CYP2C9		Amiodarone, fluconazole, miconazole, oxandrolone	Capecitabine, cotrimoxazole, etravirine, fluvastatin, fluvoxamine, metronidazole, sulfinpyrazone, tigecycline, voriconazole, zafirlukast
CYP2C19	Fluconazole, fluvoxamine, ticlopidine	Esomeprazole, fluoxetine, moclobemide, omeprazole, voriconazole	Allicin (garlic derivative), armodafinil, carbamazepine, cimetidine, etravirine, human growth hormone (rhGH), felbamate, ketoconazole, oral contraceptives

Classification of CYP Inhibitors

CYP2D6	Bupropion, fluoxetine, paroxetine, quinidine	Cinacalcet, duloxetine, terbinafine	Amiodarone, celecoxib, clobazam, cimetidine, desvenlafaxine, diltiazem, diphenhydramine, Echinacea, escitalopram, febuxostat, gefitinib, hydralazine, hydroxychloroquine, imatinib, methadone, oral contraceptives, pazopanib, propafenone, ranitidine, ritonavir, sertraline, telithromycin, verapamil, vemurafenib
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole,	Amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole,	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo,

Recent Labeling on Drug-Drug Interactions

Vardenafil- doses 10-20 mg

FCFRP-USP

vardenafil is metabolized by CYP3A4/5, and to a lesser degree by CYP2C9. CYP inhibitors are expected to reduce vardenafil clearance.

Drug	vardenafil AUC fold-change	vardenafil Cmax fold-change	vardenafil labeling mg/day
erytromycin (200 mg daily)	4	3	≤ 5
ketoconazole (200 mg daily)	10	4	≤ 5
indinavir 800 mg tid	16	7	≤ 2.5
ritonavir 600 mg bid	49	13	≤ 2.5

Concomitant Drug	Effect on Concentration of Lamotrigine or Concomitant Drug	Clinical Comment
Estrogen-containing oral contraceptive preparation containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel	↓ lamotrigine	Decreased lamotrigine levels approximately 50%.
	↓ levonorgestrel	Decrease in levonorgestrel component by 19%.
Carbamazepine (CBZ) and CBZ epoxide	↓ lamotrigine	Addition of carbamazepine decreases lamotrigine concentration approximately 40%.
	? CBZ epoxide	May increase CBZ epoxide levels
Phenobarbital/Primidone	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Phenytoin (PHT)	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Rifampin	↓ lamotrigine	Decreased lamotrigine AUC approximately 40%.
Valproate	↑ lamotrigine	Increased lamotrigine concentrations slightly more than 2-fold.
	? valproate	Decreased valproate concentrations an average of 25% over a 3-week period then stabilized in healthy volunteers; no change in controlled clinical trials in epilepsy patients.

Glucuronidation

UGT1A4 and UGT2B7

Ex: lamotrigine

↓= Decreased (induces lamotrigine glucuronidation)

↑= Increased (inhibits lamotrigine glucuronidation)

FCFRP-USP

Dose / Concentração plasmática

- Medicamento
- Paciente
- Interação de fármacos