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The aging liver

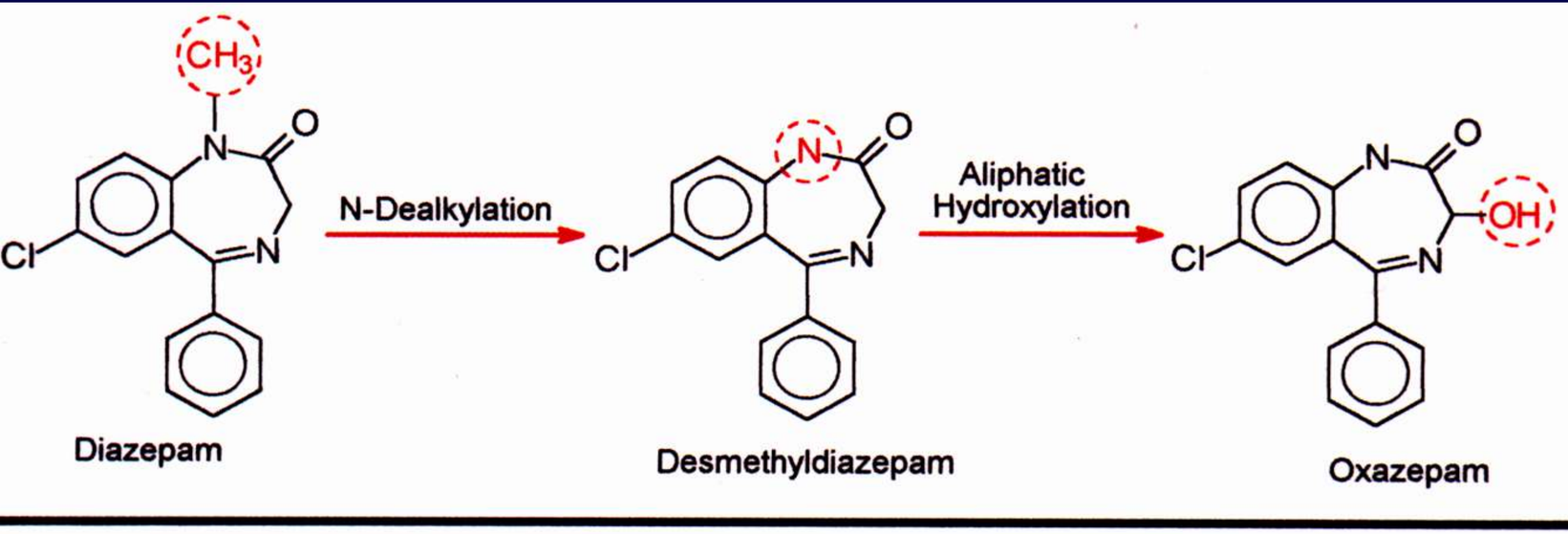
Reduction of liver size is in the order of 25 to 35%

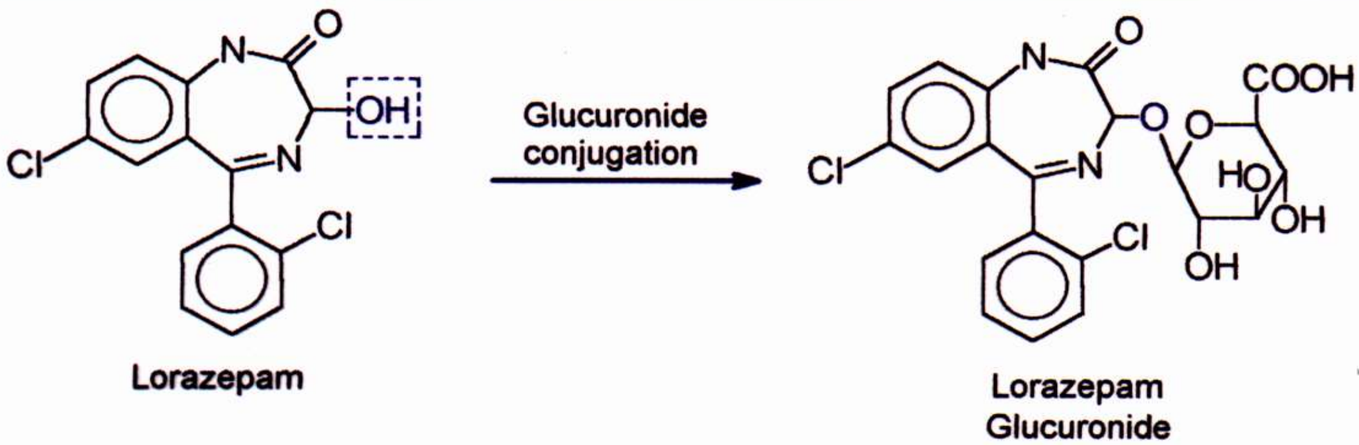
CYP activity is reduced with age, but CYP2D6 and CYP2A are unchanged

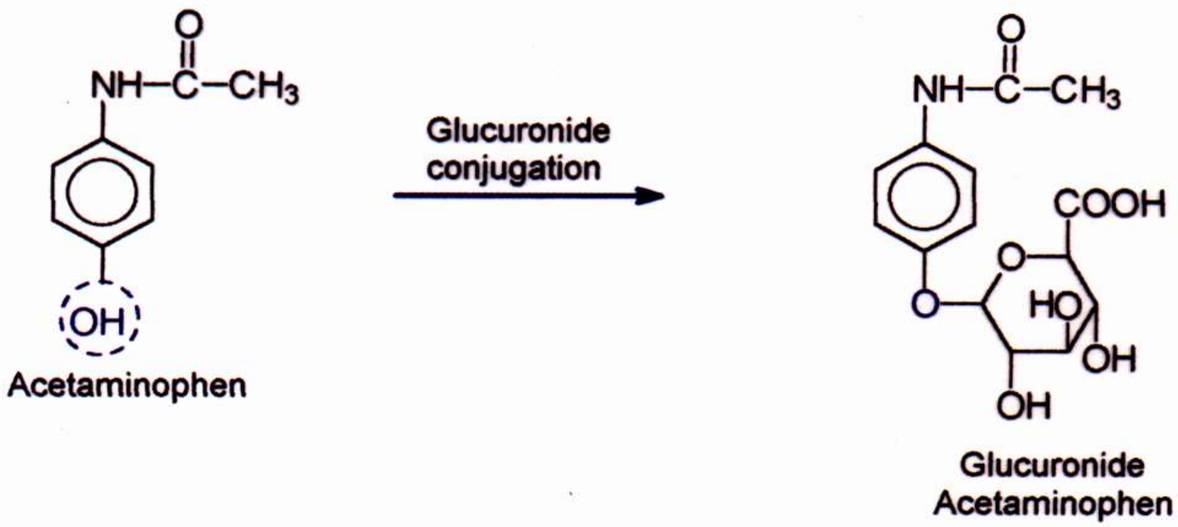
Reduction in blood flow of about 40%

Bile flow and bile salt formation are reduced by about 50%

WOODHOUSE K. biopharmaceutics & drug disposition, 1992, v.13, p.311-320



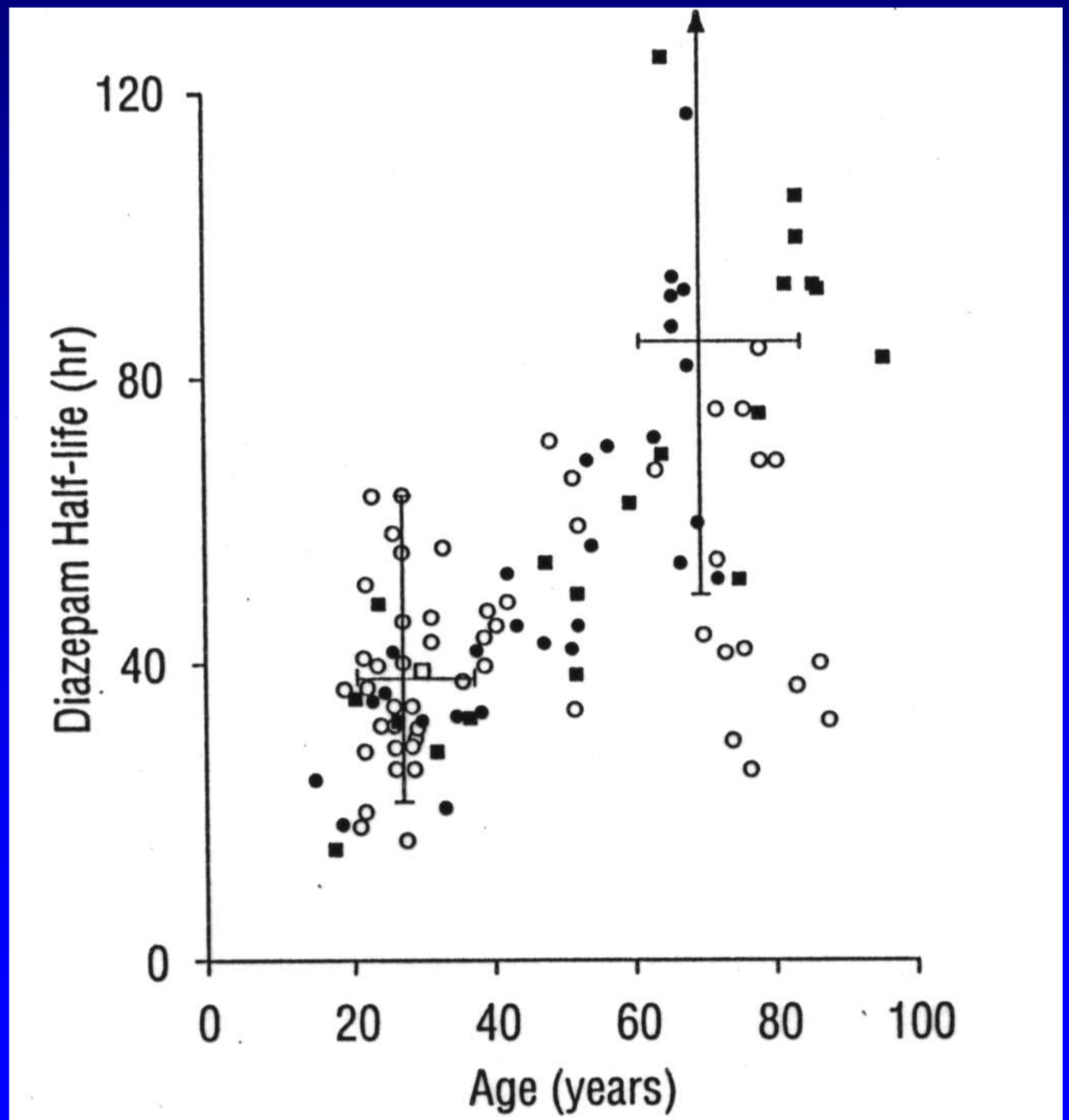




Influência da idade no metabolismo

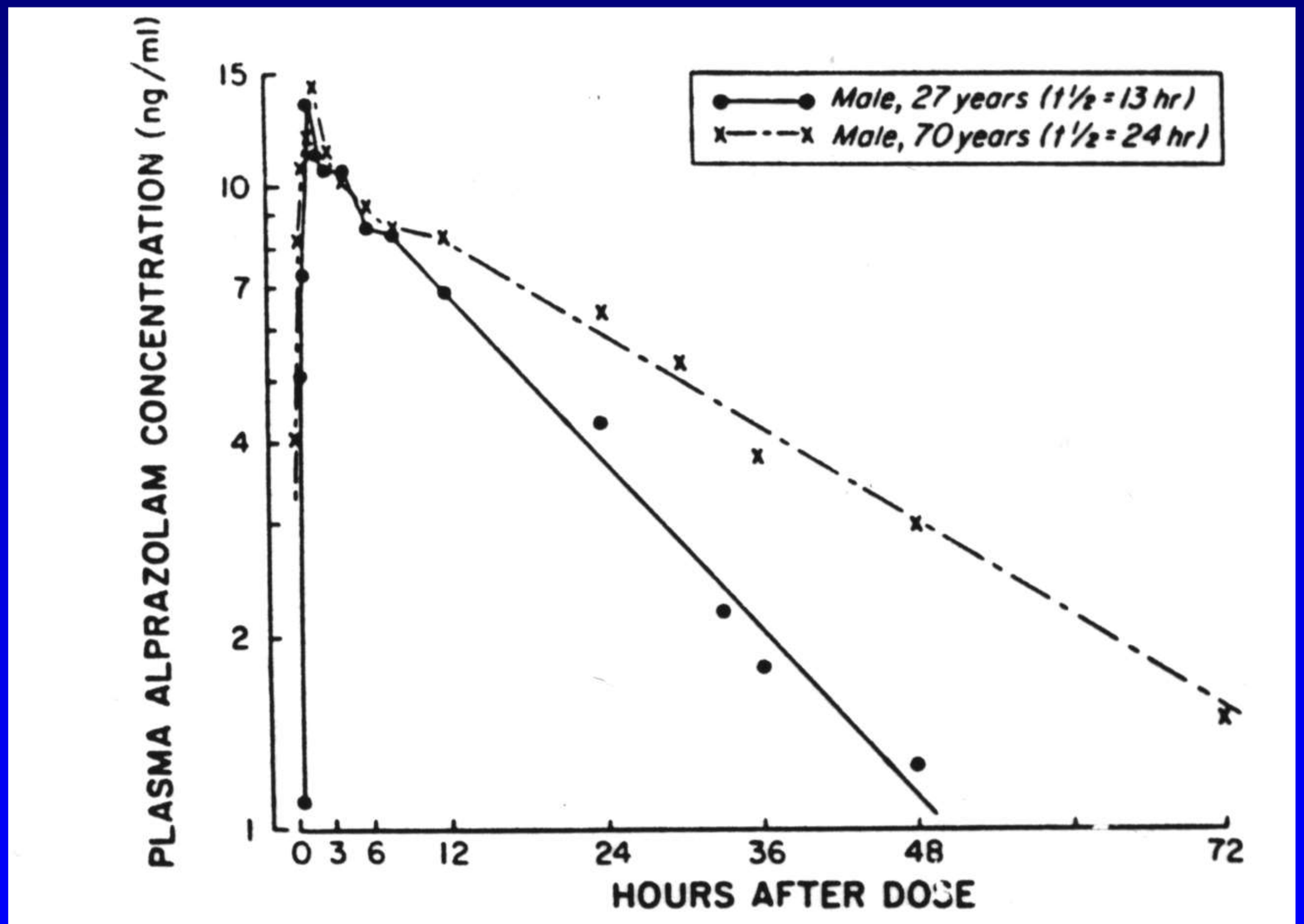
Influência da idade

Meia-vida do diazepam



Influência da idade

Meia-vida do alprazolam



Plasma alprazolam concentrations following single l
oral doses of alprazolam in representative young and eld
male volunteers.

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Função renal

influência da idade

idade	clearance da creatinina (mL/min)	
	homens	mulheres
20	120	102
55	85	72
90	50	43

Mühlberg, W., Platt D., gerontology, 1999, v.45 p.423-253

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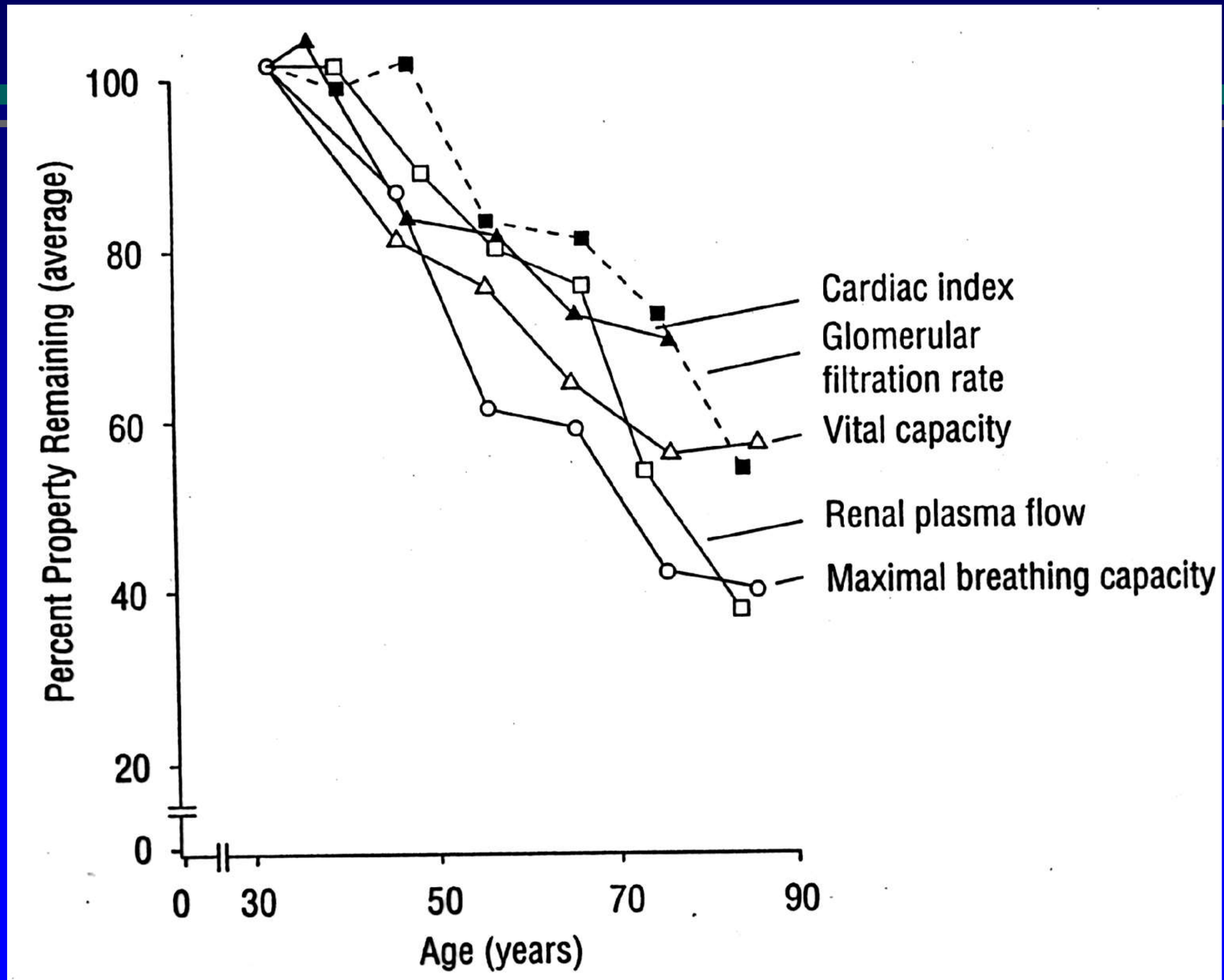
Funções fisiológicas vs idade



Drug Absorption

	Neonate	Infants	Children
Physiological alteration			
Gastric pH	> 5	4 to 2	Normal (2-3)
Gastric emptying time	irregular	increased	slightly increased
Intestinal motility	reduced	increased	slightly increased
Intestinal surface area	reduced	near adult	adult pattern
Muscular blood flow	reduced	increased	adult pattern
Skin permeability	increased	increased	near adult pattern
Pharmacokinetic consequences			
Oral absorption	reduced	increased	near adult pattern
Intra-muscular absorption	variable	increased	adult pattern
Percutaneous absorption	increased	increased	near adult pattern
Rectal absorption	very efficient	efficient	near adult pattern

Drug distribution

	Neonate	Infants	Children
Physiological alteration			
plasma albumin	reduced	near normal	near adult pattern
total proteins	reduced	decreased	near adult pattern
serum free fatty acids	increased	normal	normal adult pattern
total body water	increased	increased	near adult pattern
extracellular water	increased	increased	near adult pattern
muscular blood flow	reduced	increased	near adult pattern
Pharmacokinetic consequences			
free fraction	increased	increased	slightly increased
Vd	increased	increased	slightly increased

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Ligação às proteínas plasmáticas

neonatos *vs* adultos

	Fração livre		Vd (L/kg)	
	neonato	adulto	neonato	adulto
fenobarbital	0,68	0,53	1	0,55
sulfametoxipirazina	0,43	0,38	0,47	0,24
digoxina	0,8	0,7	10	7
fenitoina	0,2	0,1	1,3	0,63

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Fluido corporal *vs* idade

idade	fluido		
	total	extracelular	Intracelular
neonato	75	35 - 44	33
1 ano		26 - 30	
puberdade	60	20	40
adulto	50 - 60	20	40

Drug Metabolism

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	Neonate	Infants	Children
Physiological alteration			
liver/body weight ratio	increased	increased	slightly increased
CYP activity	reduced	increased	slightly increased
hepatic blood flow	reduced	increased	near adult pattern
Phase II enzyme activity	reduced	increased	near adult pattern
Pharmacokinetic consequences			
metabolism rate	reduced	increased	near adult pattern
presystemic clearance	reduced	increased	near adult pattern
total body clearance	reduced	increased	near adult pattern

HINES, R N., Pharmacology & Therapeutics, 2008, v.118, p.250-267
KEARNS, G L., et al., N Engl J Med, 2003, v.349, p.1157-67

Ontogeny of drug transporters in liver

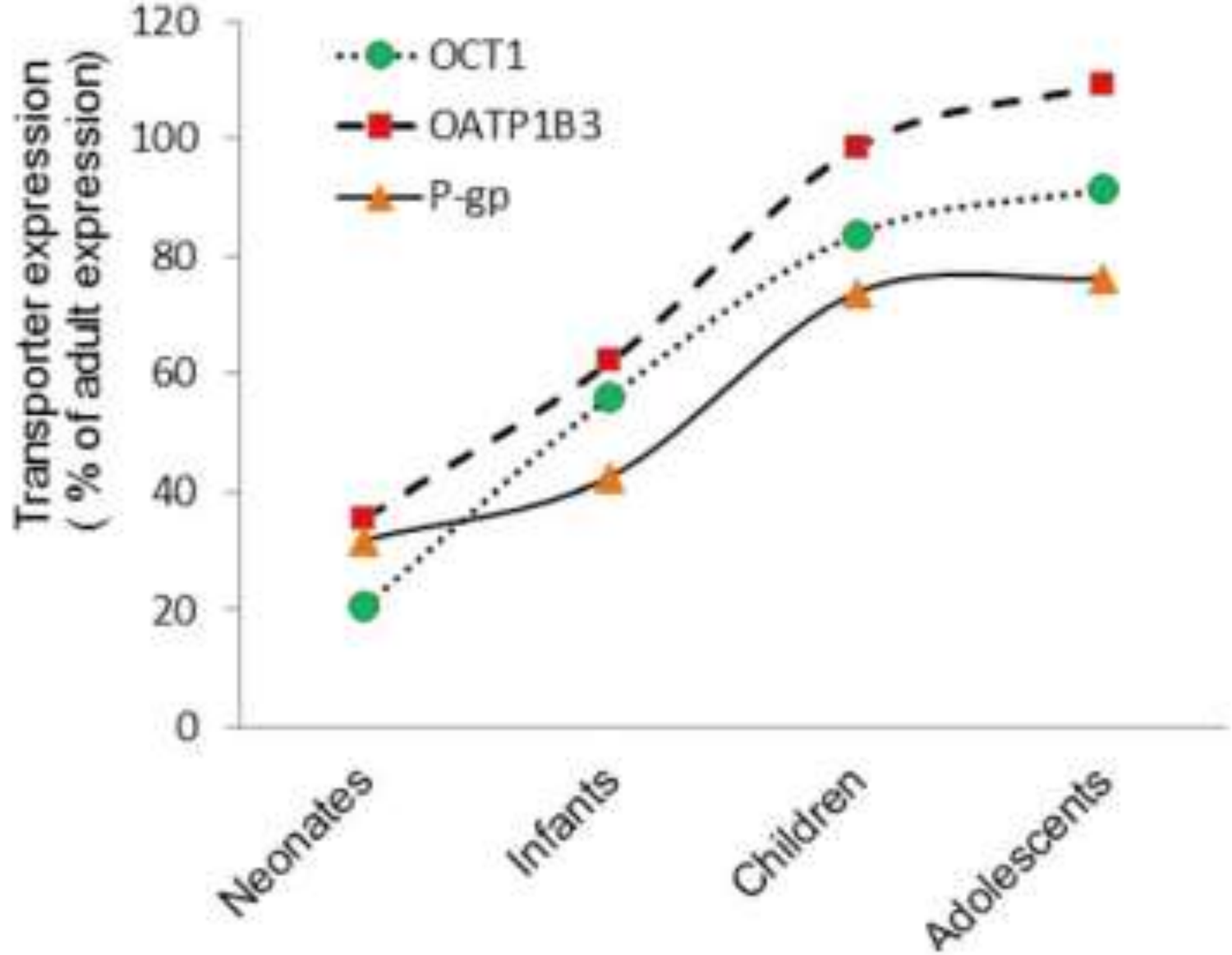

Figure 1 Ontogeny of protein expression of OCT1, OATP1B3, and P-gp in liver tissue from neonates to adults. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

PRASAD, B, clin. pharmacol. & ther., 2016, v. 100:4. p.362-70

Renal excretion

	Neonate	Infants	Children
Physiological alteration			
Kidney/body weight ratio	increased	increased	near adult values
GFR	reduced	normal (by 12 mo)	normal adult values
Tubular secretion	reduced	near normal	normal adult values
Tubular reabsorption	reduced	near normal	normal adult values
Pharmacokinetic consequences			
Active drug excretion	reduced	near normal	normal adult pattern
Passive drug excretion	reduced	near normal	normal adult pattern

HINES, R N., Pharmacology & Therapeutics, 2008, v.118, p.250-267
KEARNS, G L., et al., N Engl J Med, 2003, v.349, p.1157-67

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Clearance renal
neonatos *vs* adultos

	neonato	adulto
peso (kg)	3,5	70
água (%)	77	58
água (L)	2,7	41
clearance $_{inulina}$ (mL/min)	3	130
clearance $_{PAH}$ (mL/min)	12	650

	meia-vida de eliminação (h)	
	neonato	adulto
penicilina G	3,2	0,5
ampicilina	4	1
gentamicina	5	2

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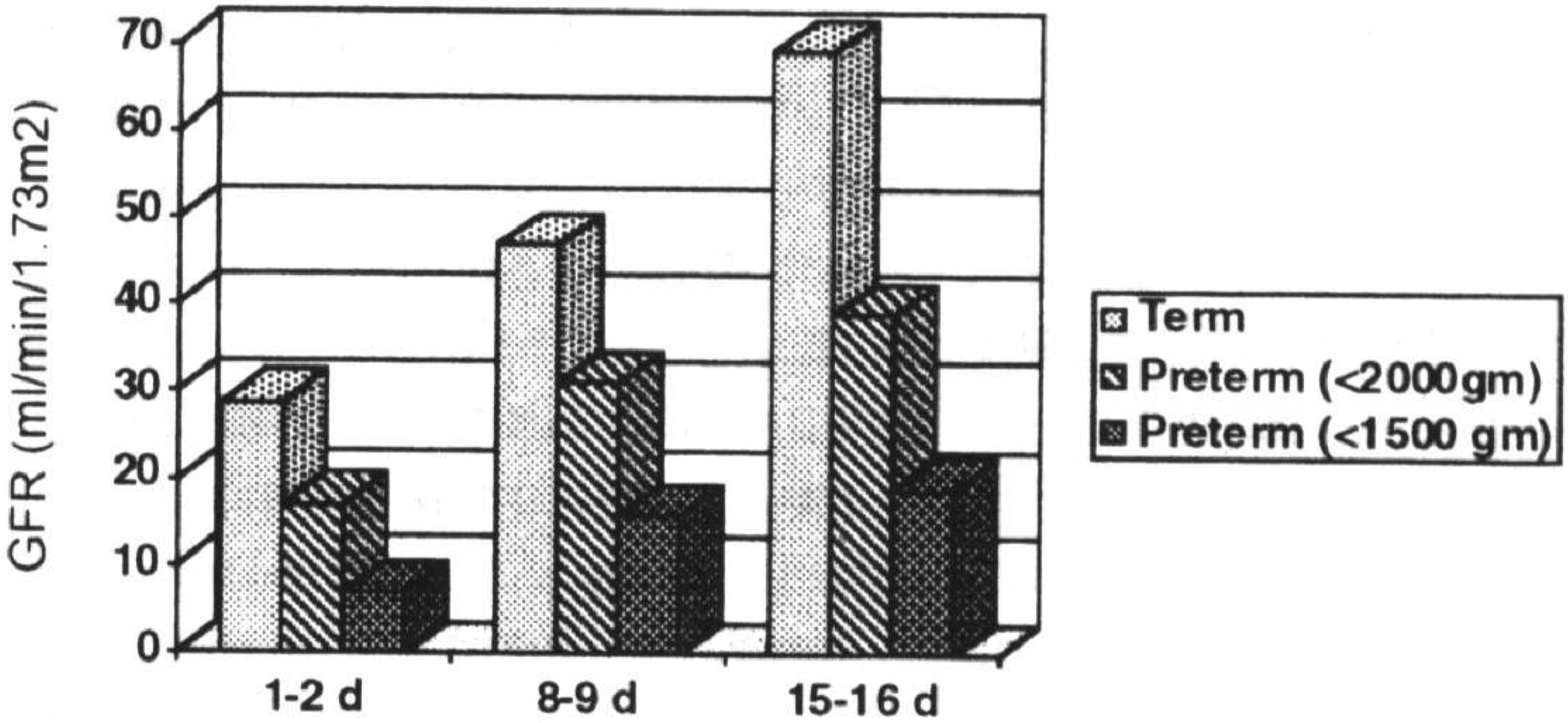
Ontogeny of glomerular filtration in the neonate



Efeito do peso, tamanho e maturação

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Crianças

$$\text{dose}_{\text{criança}} = \text{dose}_{\text{adulto}} \cdot \left(\frac{\text{peso}_{\text{criança}}}{70}\right)^{0.75}$$

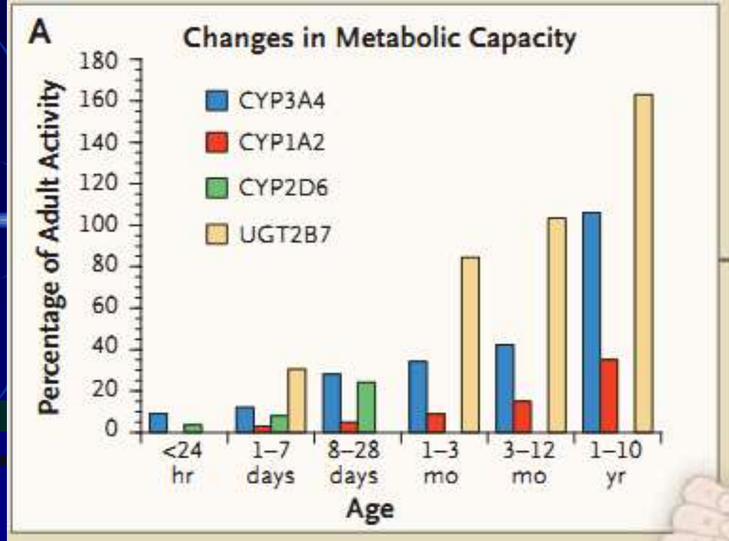
$$\text{CL}_{\text{criança}} = \text{CL}_{\text{adulto}} \cdot \left(\frac{\text{peso}_{\text{criança}}}{70}\right)^{0.75} \cdot \text{MF} \cdot \text{OF}$$

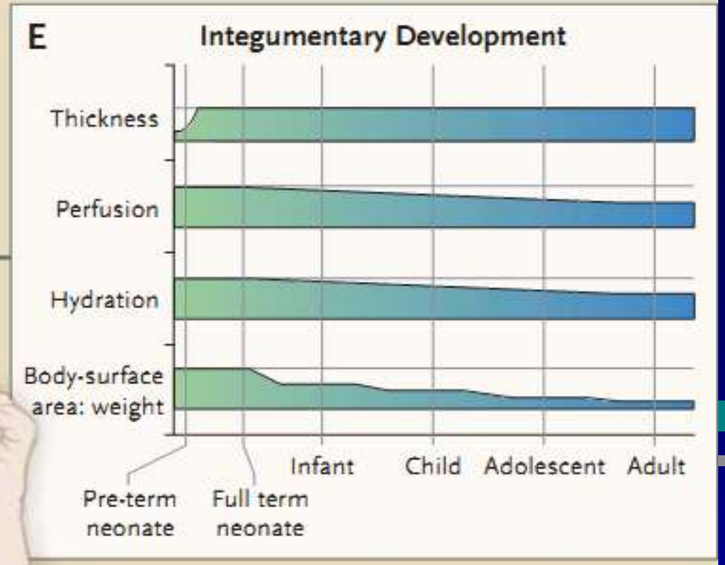
MF: maturation function
OF: organ function

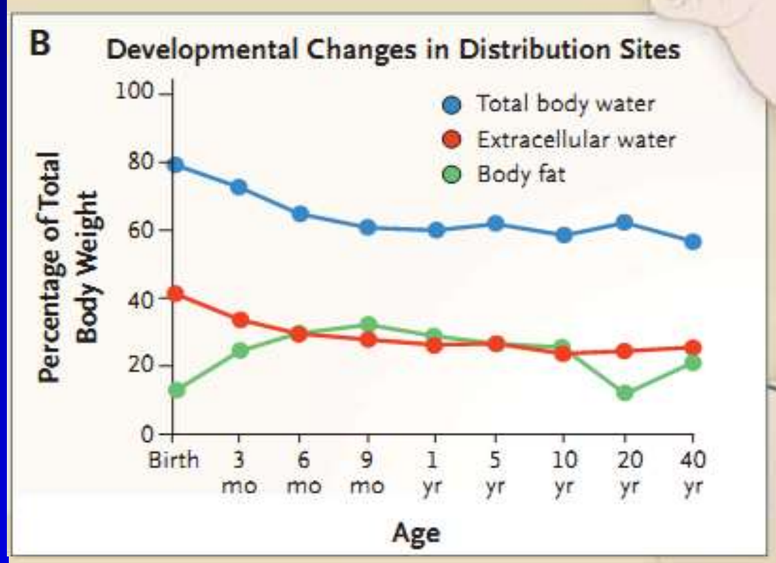
$$\text{Vd}_{\text{criança}} = \text{Vd}_{\text{adulto}} \cdot \left(\frac{\text{peso}_{\text{criança}}}{70}\right)^{1}$$

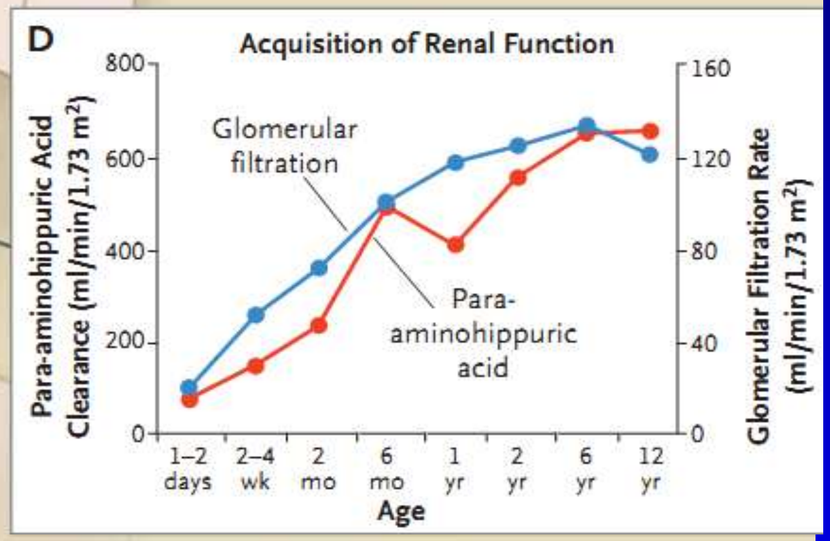
CELLA, M., et al., Br J Clin Pharmacol., 2010, v.70:4, p.597-603
ANDERSON, B J., HOLFORD, N.H.G., Annu. Rev. Pharmacol. Toxicol., 2008. v.48, p.303–32
MAHMOOD, I., Br J Clin Pharmacol., 2006, v.61:5, p.545-557
ZHENG, S., Pharmacometrics & Systems Pharmacology, 2014, v.3, e138
MAHARAJ, A R., EDGINTON, A N., Pharmacometrics & Systems Pharmacology, 2014, v.3, e.148

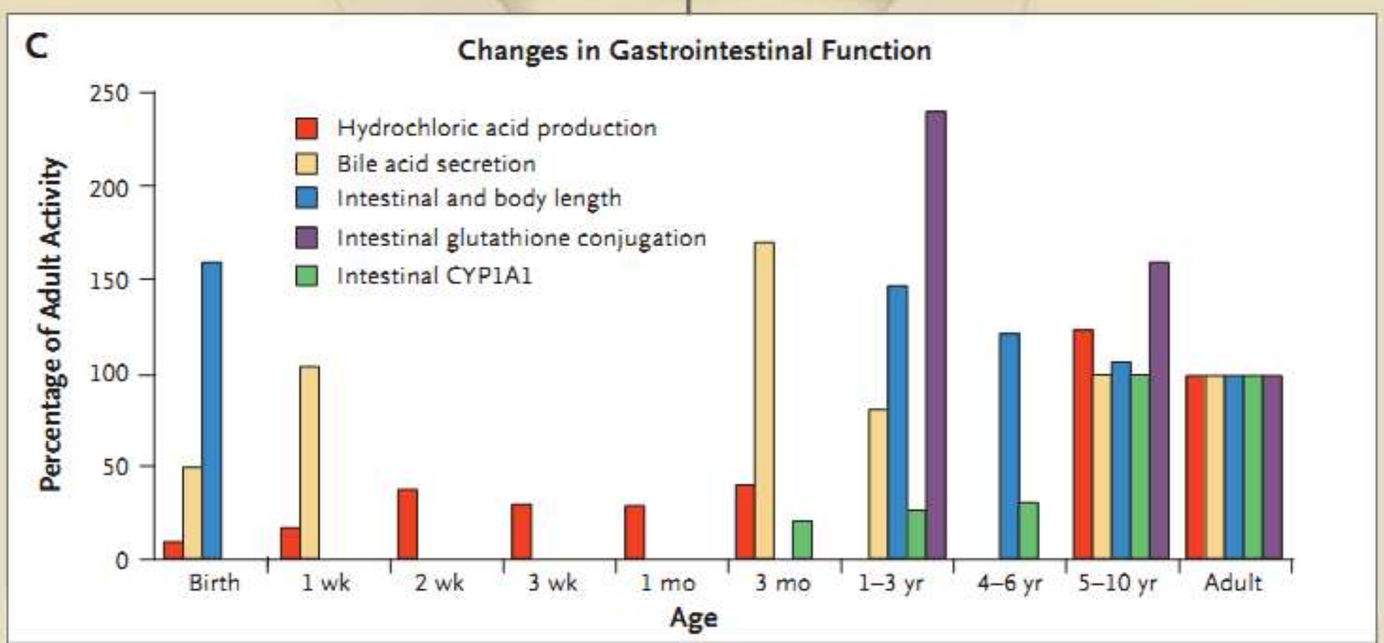
Developmental Changes in Physiologic Factors that Influence Drug Disposition











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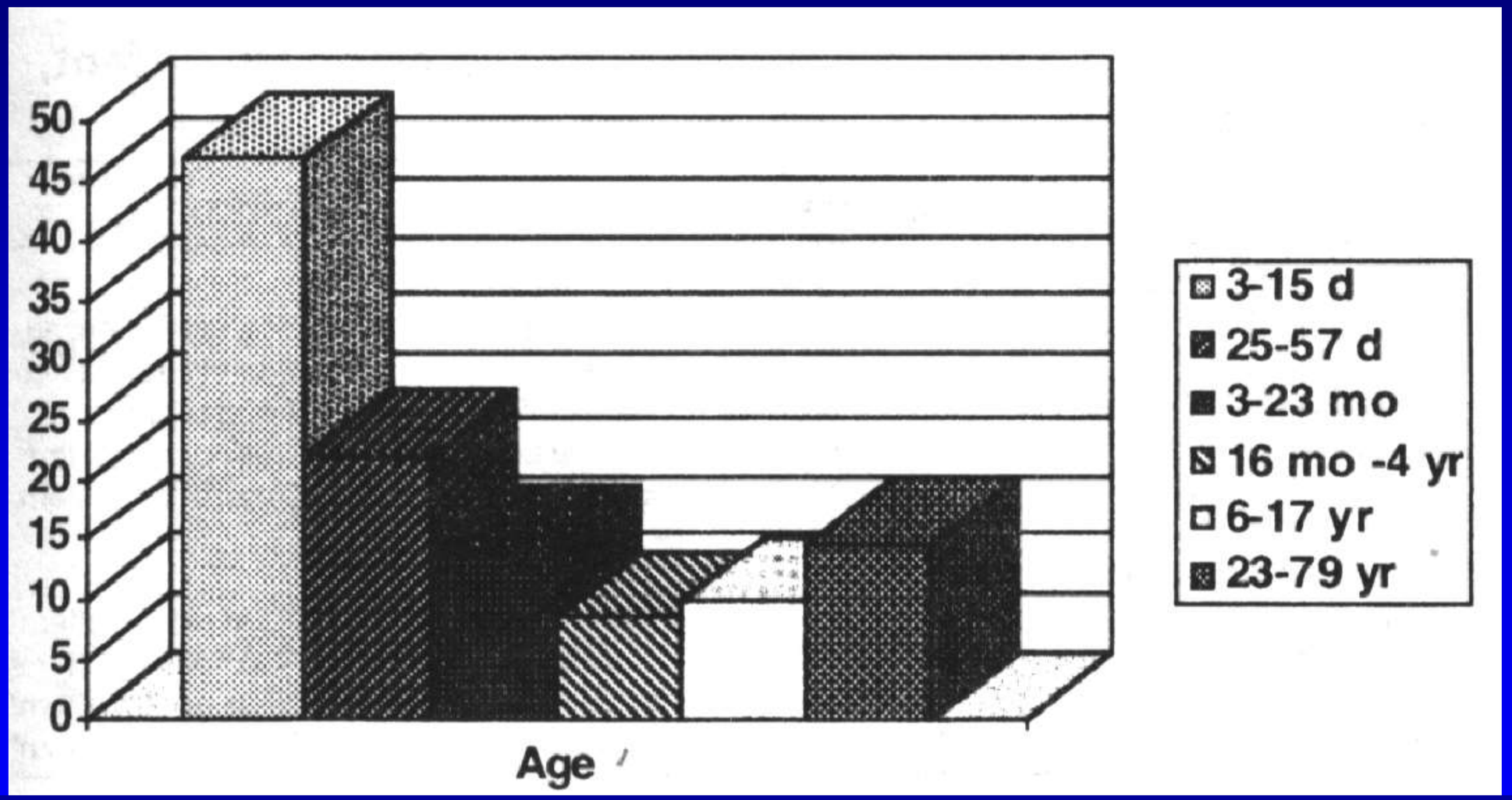
Impact of development on theophylline plasma concentrations



Steady state mean serum theophylline concentrations from a dose of 20mg/kg/day administered to patients of varying age

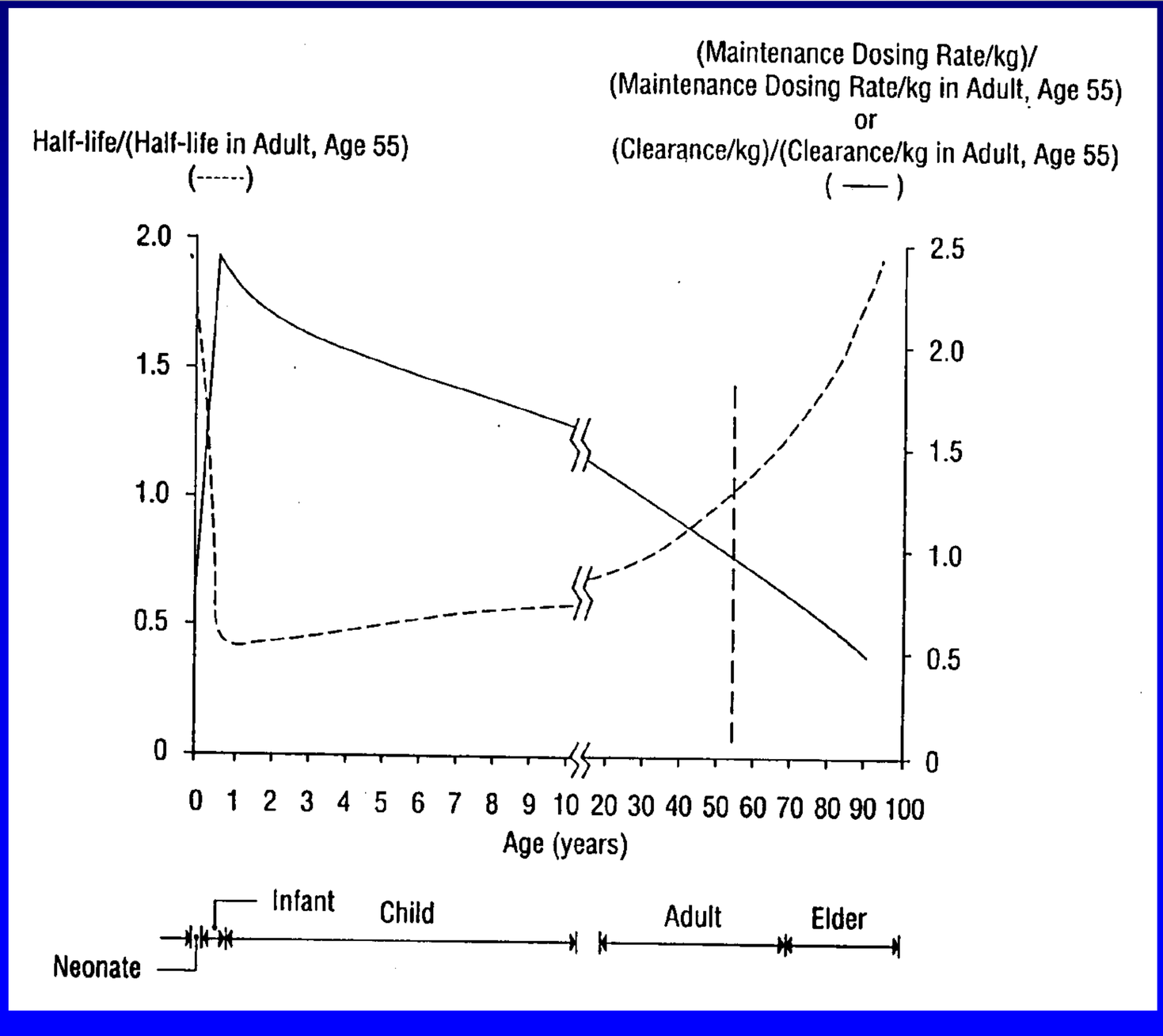
Farmacocinética

neonatos *vs* adultos

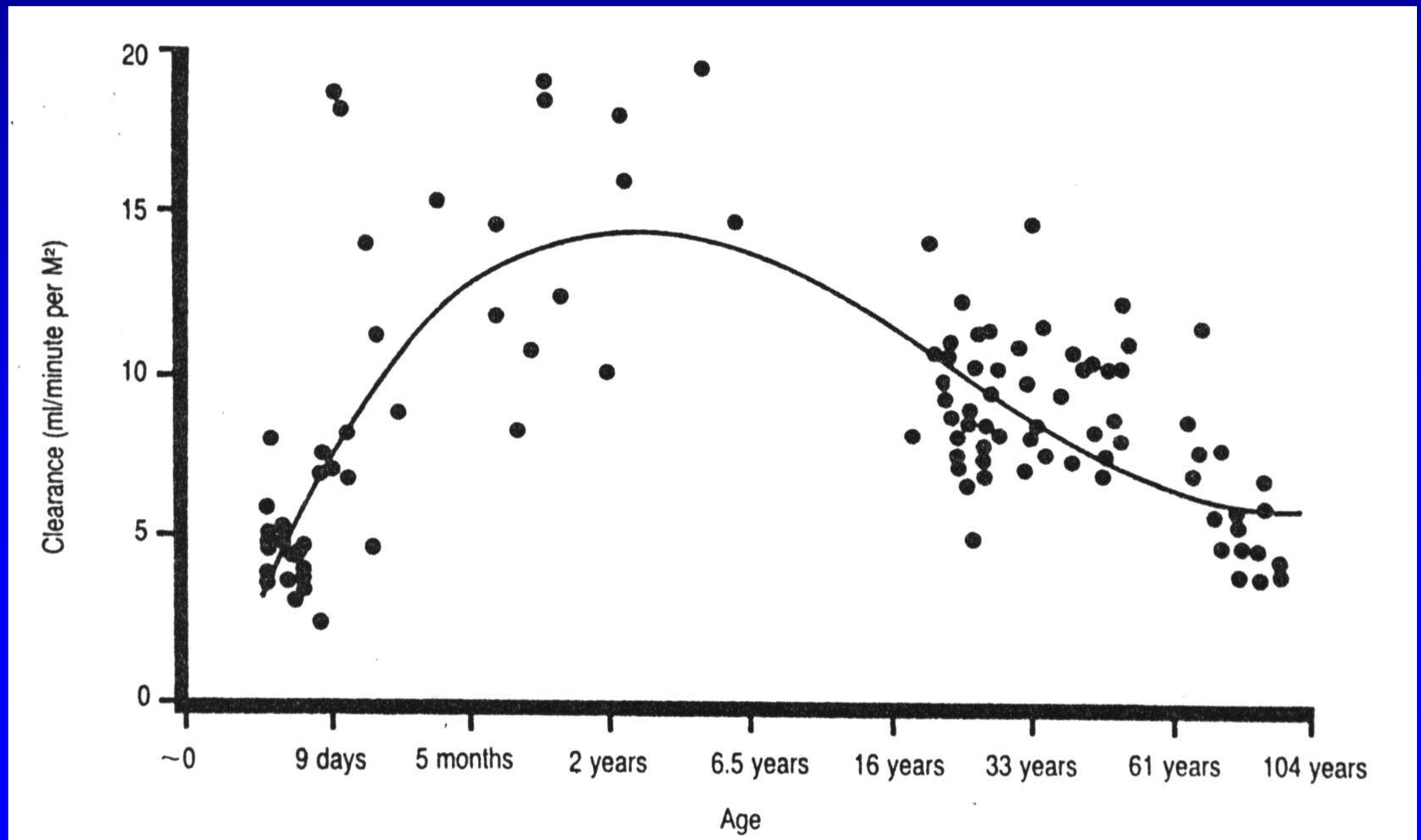
	neonato *vs* adulto	farmacocinética	exemplo
Vd	↑	↓ C_{max}	penicilinas sulfonamidas
%pp	↓	↑ fração livre	teofilina
metabolismo	↓	↓Cl	teofilina
excreção	↓	↑AUC ↑ t½	gentamicina

Influência da idade

Meia-vida, clearance e dose de manutenção

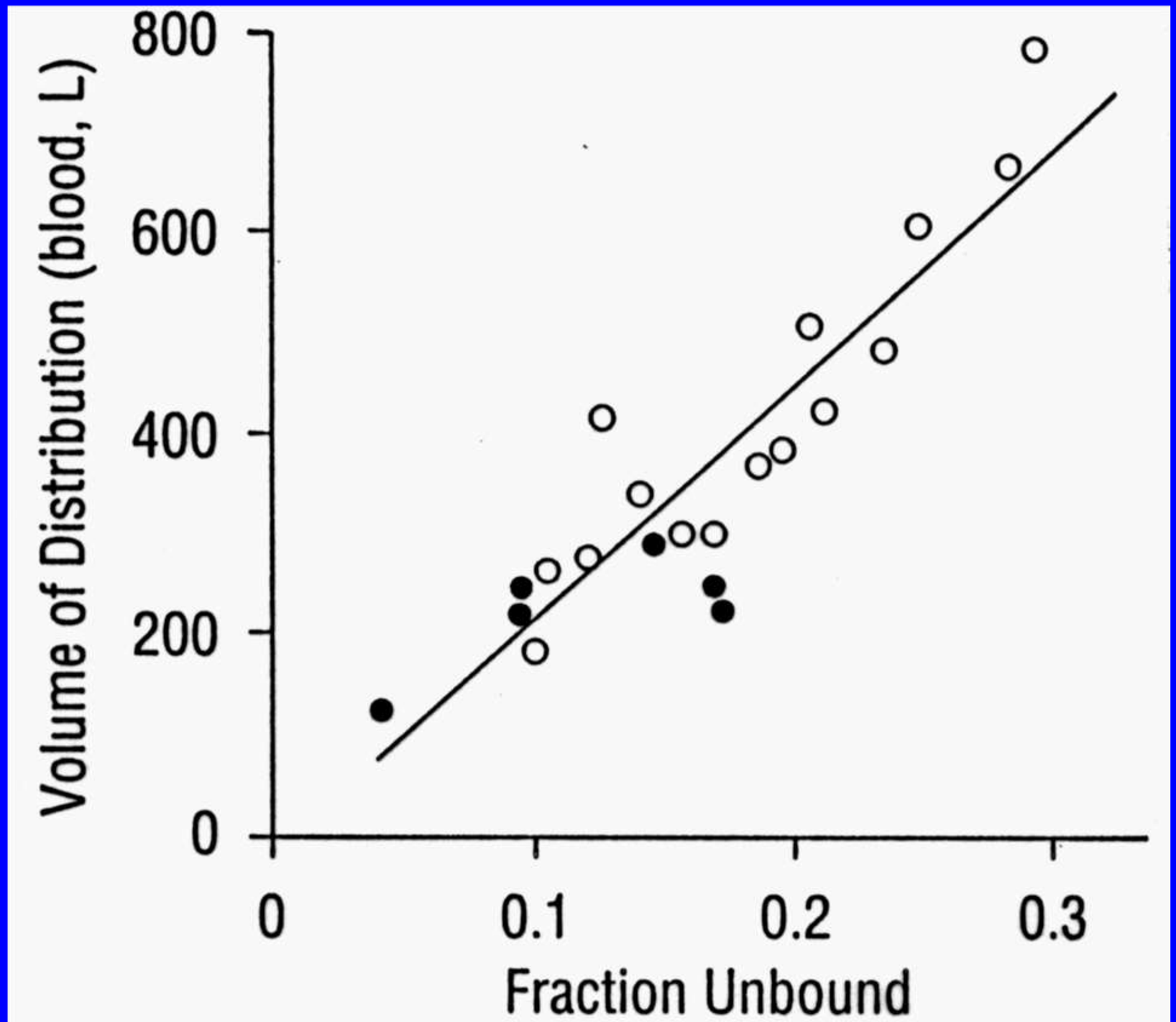


A figura abaixo representa a variação do clearance do antibiótico ceftriaxone em pacientes de 1 dia a 92 anos de idade. Em pacientes adultos jovens o antibiótico é eliminado por excreção renal (50%) e por excreção biliar (50%). Discutir as alterações observadas em neonatos (< 1 mês), crianças de 1 a 5 anos e pacientes idosos (> 65 anos) assim como as possíveis implicações no regime de dosagem.



HEPATOPATIAS

Aumento da fração livre



Effect on Clearance

Extraction Ratio (*E*)	Blood Flow (*Q*) (L/hour)	Clearance (Cl) (L/hour)
High (0.7-1.0)	Low	Low
Low (<0.3)	High	Low
High (0.7-1.0)	High	High
Low (<0.3)	Low	Low

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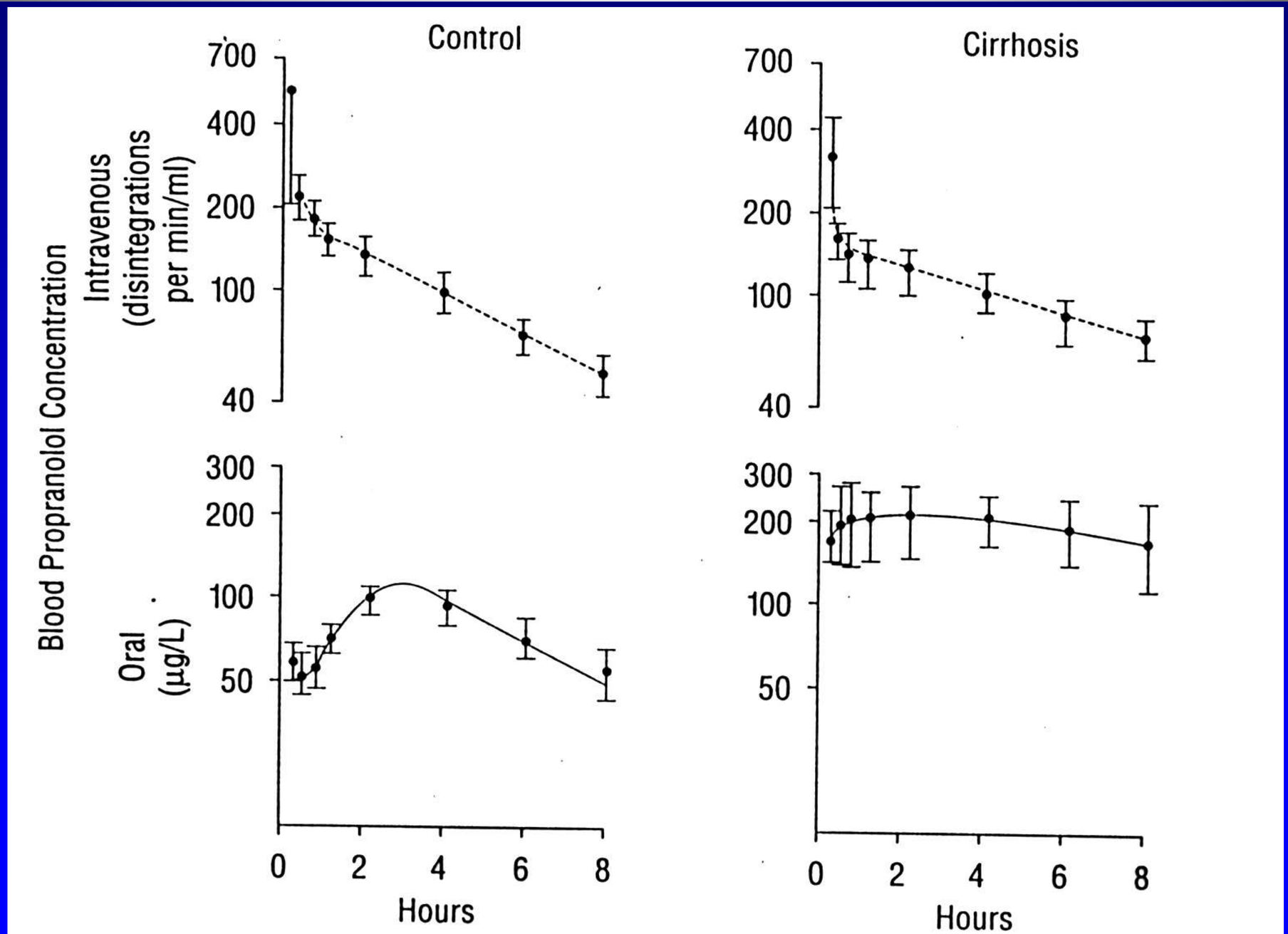
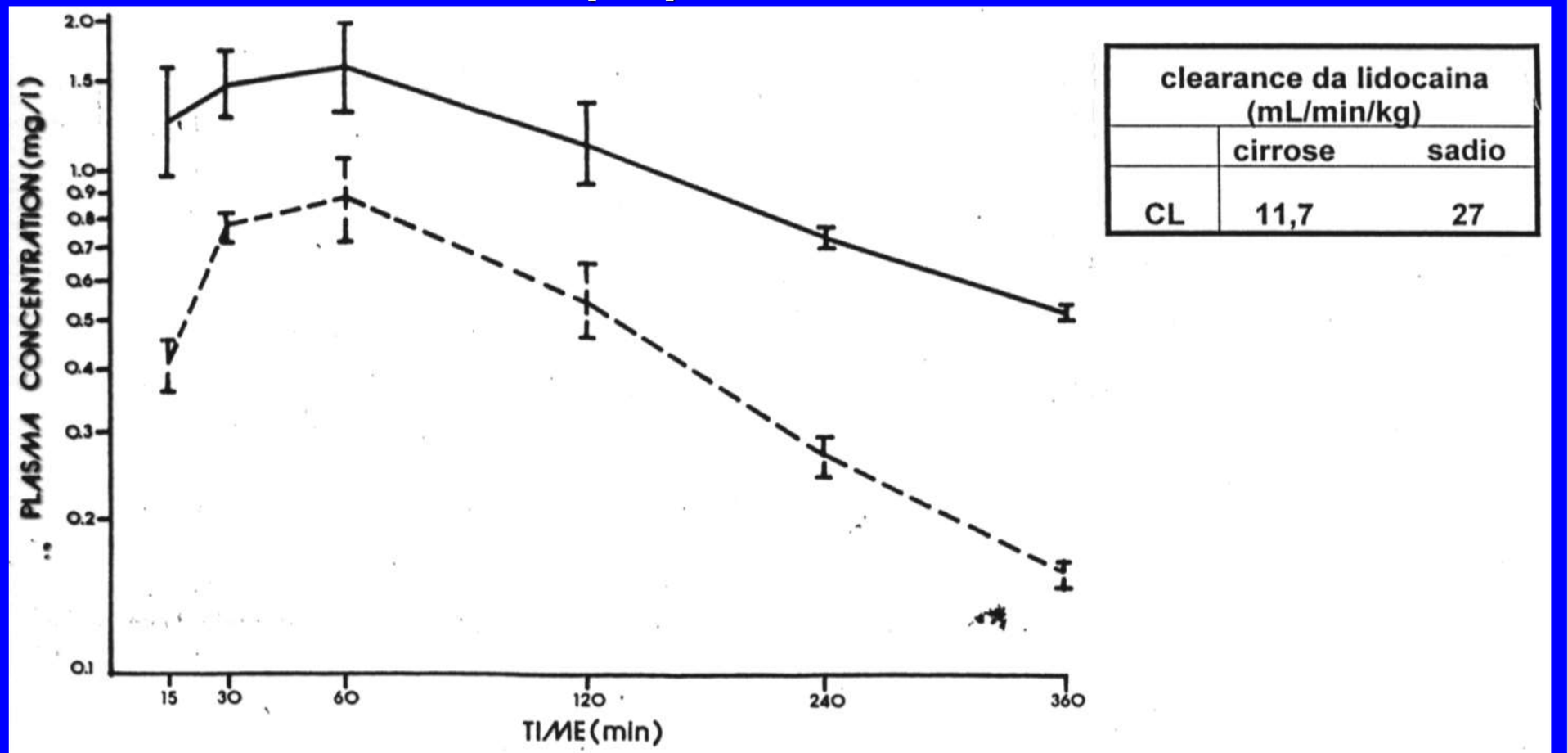
Biodisponibilidade oral do propranolol na cirrose



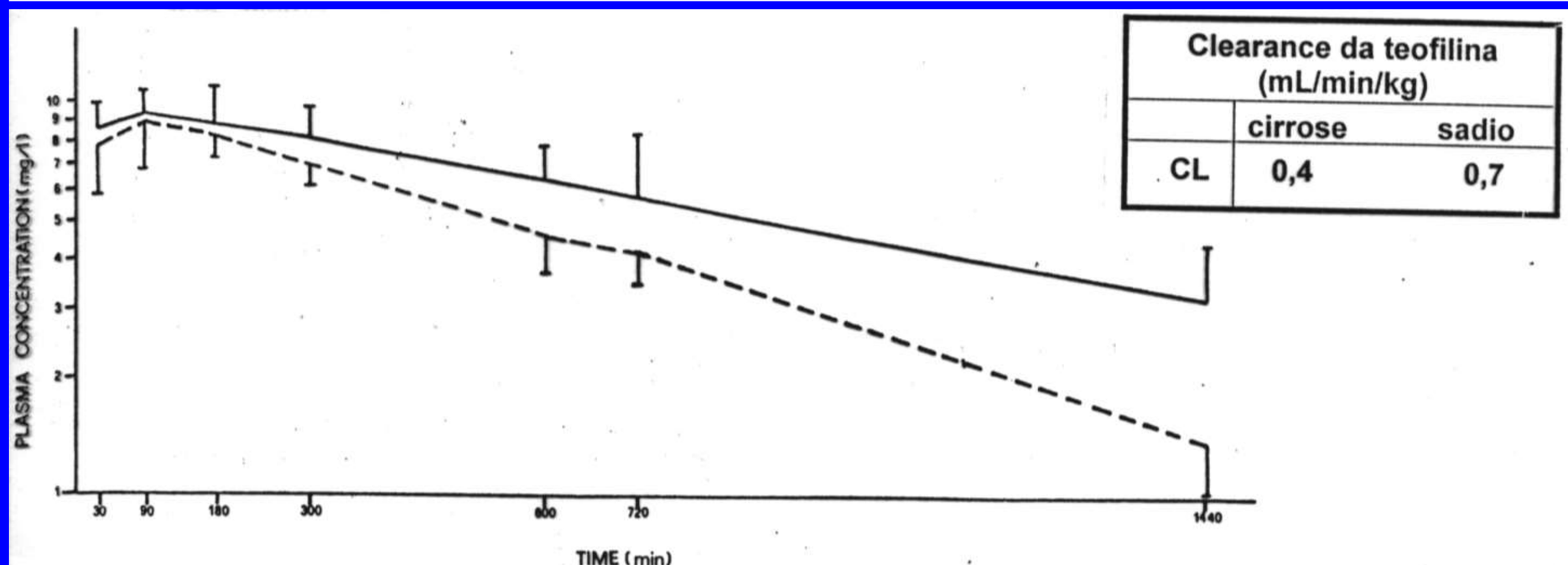
Cirrose Hepática

Clearance da lidocaina (dependente do fluxo)

Clearance da teofilina (dependente da atividade enzimática)



clearance da lidocaina (mL/min/kg)		
	cirrose	sadio
CL	11,7	27



Clearance da teofilina (mL/min/kg)		
	cirrose	sadio
CL	0,4	0,7

HEPATOPATIAS

Clearance hepático vs extração hepática

fármaco	extração hepática	%pp	cirrose CL_H
Dependente do fluxo			
lidocaina	0,8	45 - 80	↓
propranolol	0,8	93	↓
morfina	0,7	35	↓
Dependente da atividade enzimática e %pp			
tolbutamida	0,02	98	↑
diazepam	0,03	98	↓
Dependente da atividade enzimática			
teofilina	0,09	59	↓
antipirina	0,07	10	↓
amilobarbital	0,03	61	↓

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Child-Pugh Scores for Patients with Liver Disease

TEST/SYMPTON	SCORE 1 POINT	SCORE 2 POINT	SCORE 3 POINT
Total bilirubin (mg/dL)	< 2.0	2.0 – 3.0	> 3.0
Serum albumin (g/dL)	> 3.5	2.8 – 3.5	< 2.8
Prothrombin time (seconds prolonged over control)	< 4	4 – 6	> 6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

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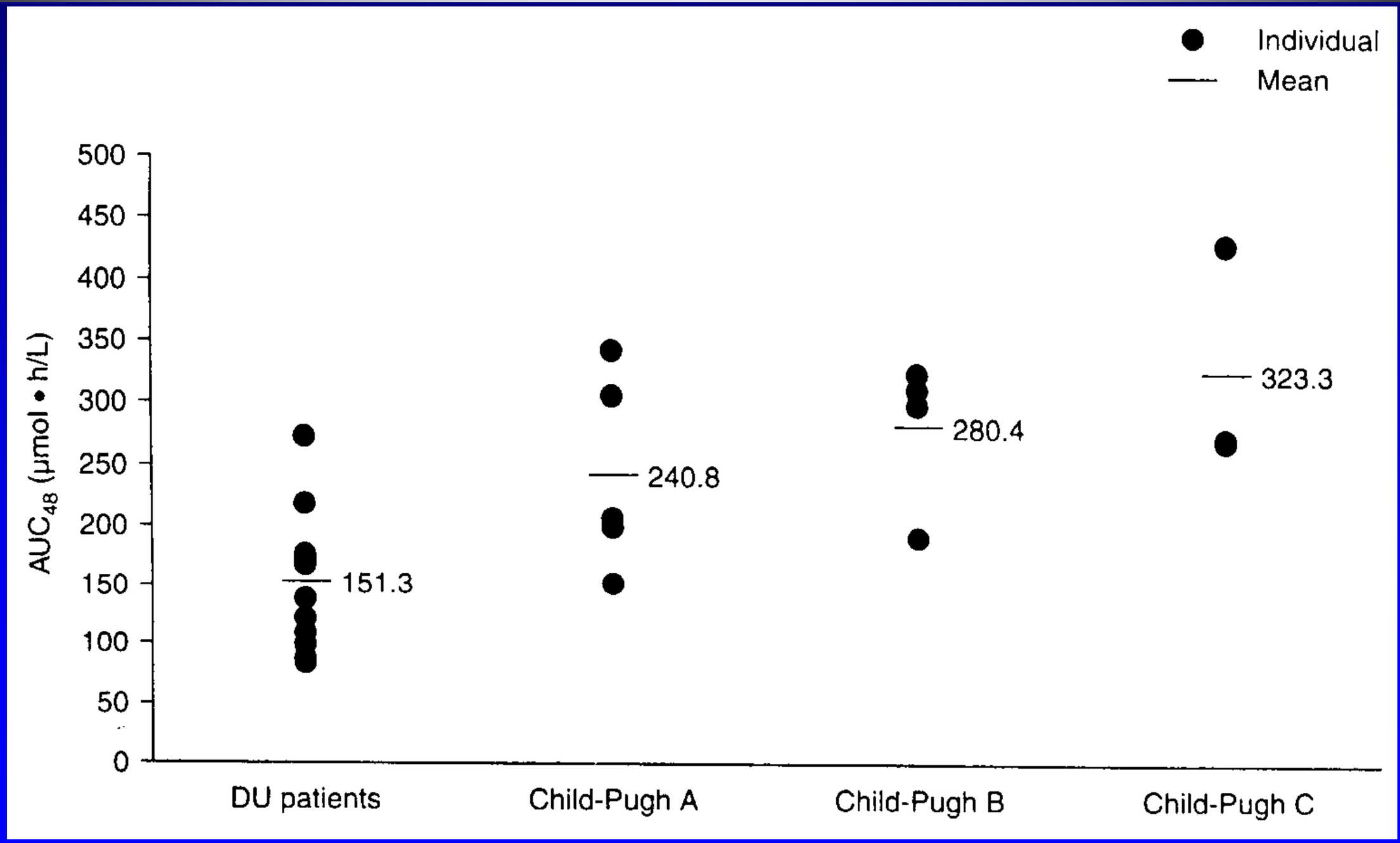
Pharmacokinetics of omeprazole

Patients with varying degrees of hepatic dysfunction



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?

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Clearance renal

fração eliminada pelos rins = **quantidade excretada na urina** / **dose**

Fel = Ae / dose

clearance renal = clearance total X Fel

clearance renal = Ae^{∞} / $AUC^{0-\infty}$

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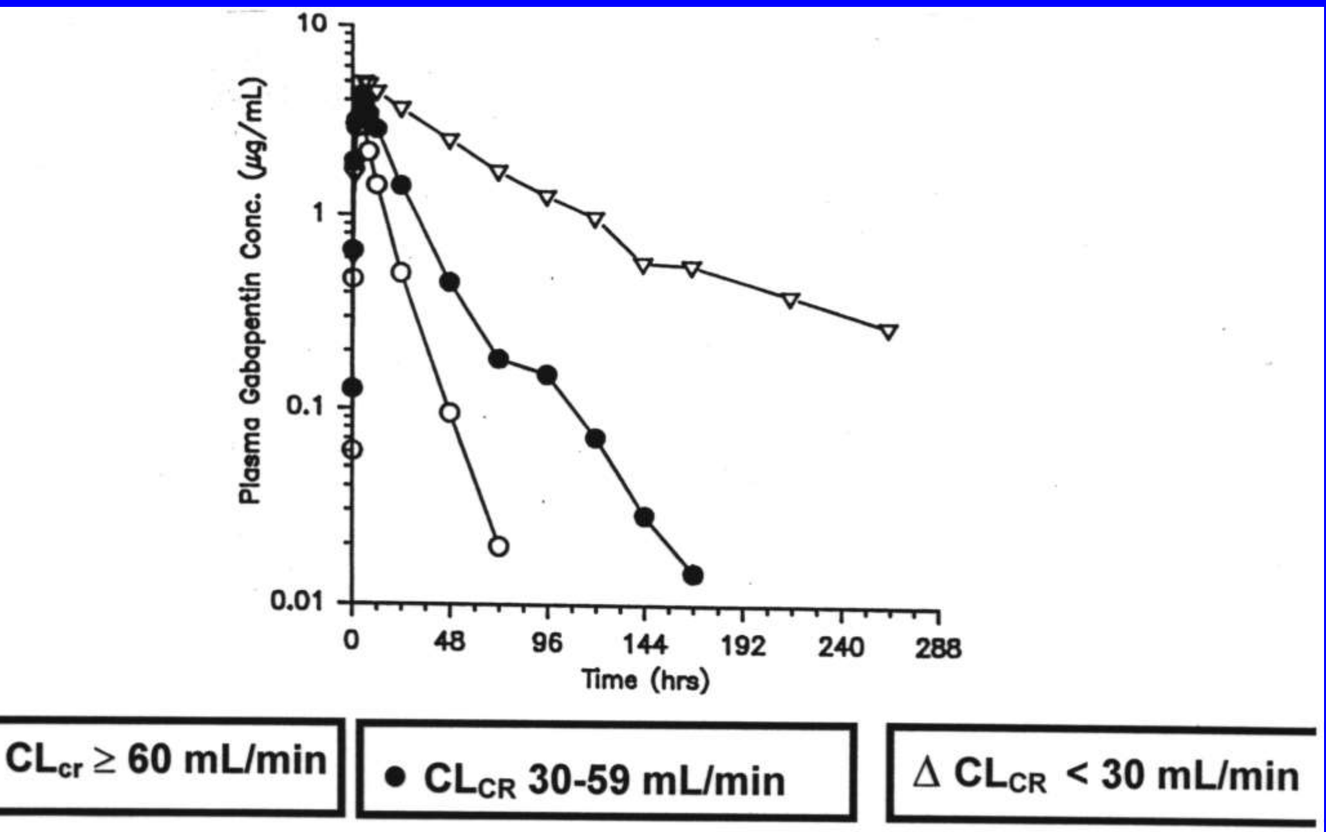
Fração eliminada inalterada pelos rins

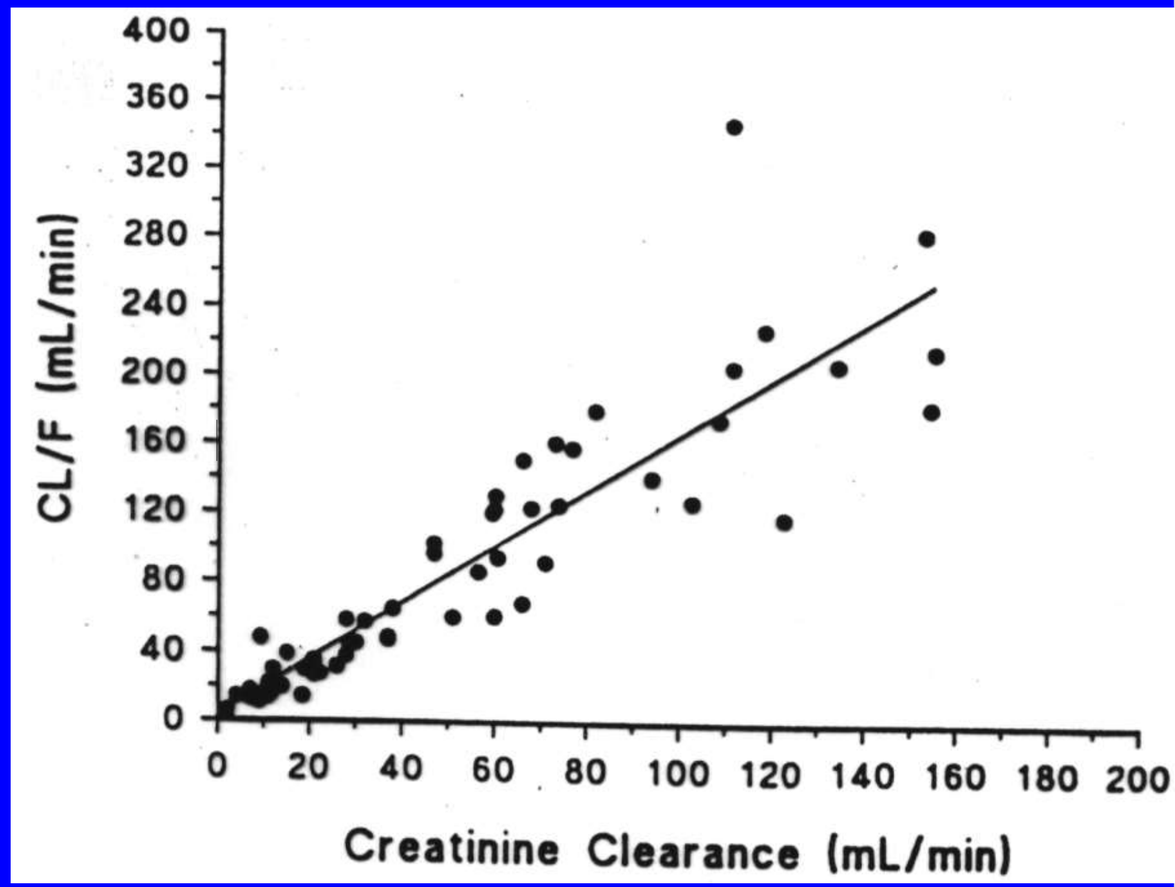
função renal normal

fármaco	Fel
vancomicina	> 0,95
tobramicina	> 0,95
tetraciclina	0,6
sulfadiazina	0,6
clindamicina	0,1
dapsona	0,1

INSUFICIÊNCIA RENAL

Farmacocinética do gabapentina





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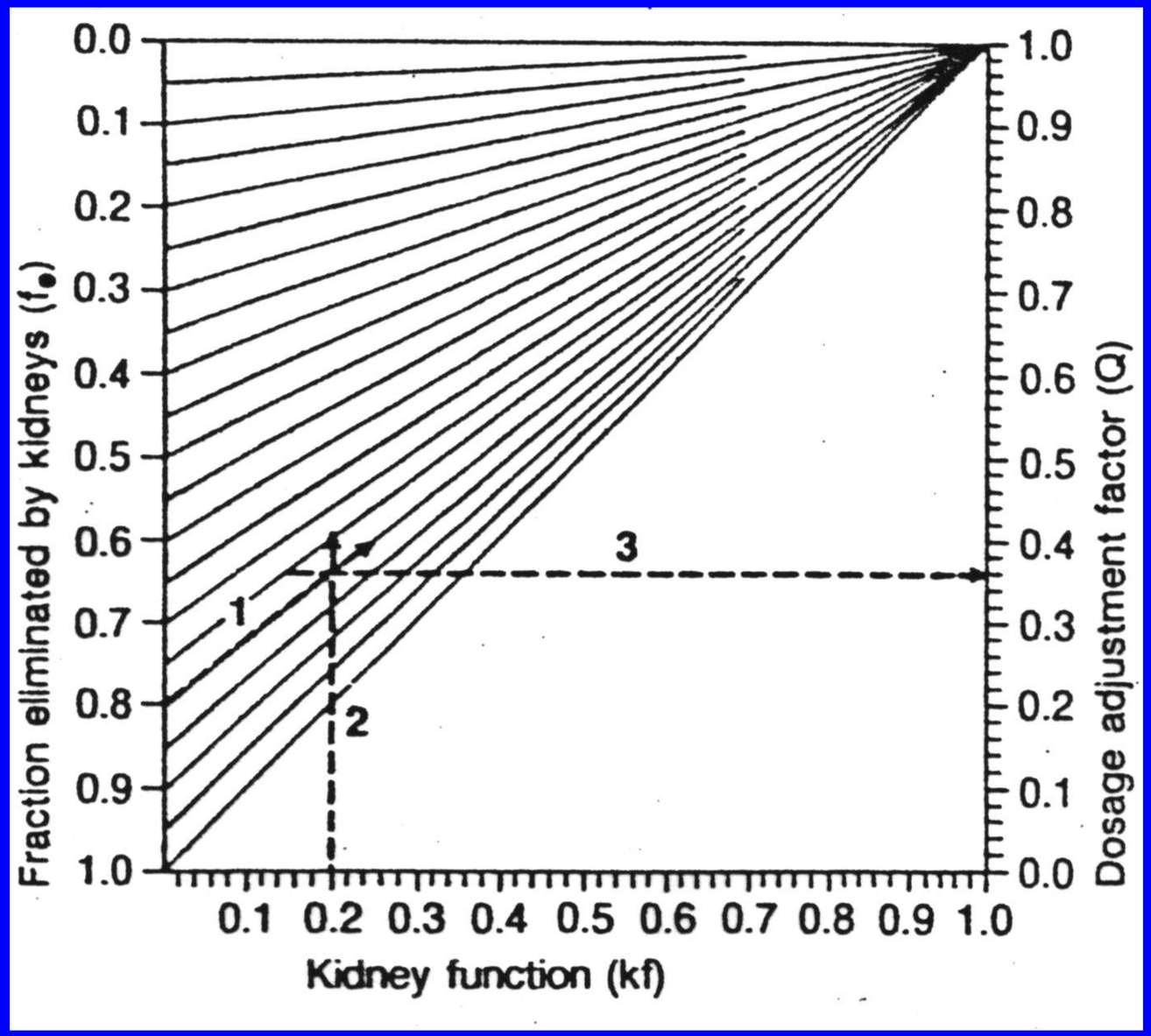
INSUFICIÊNCIA RENAL

Farmacocinética do gabapentina

	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

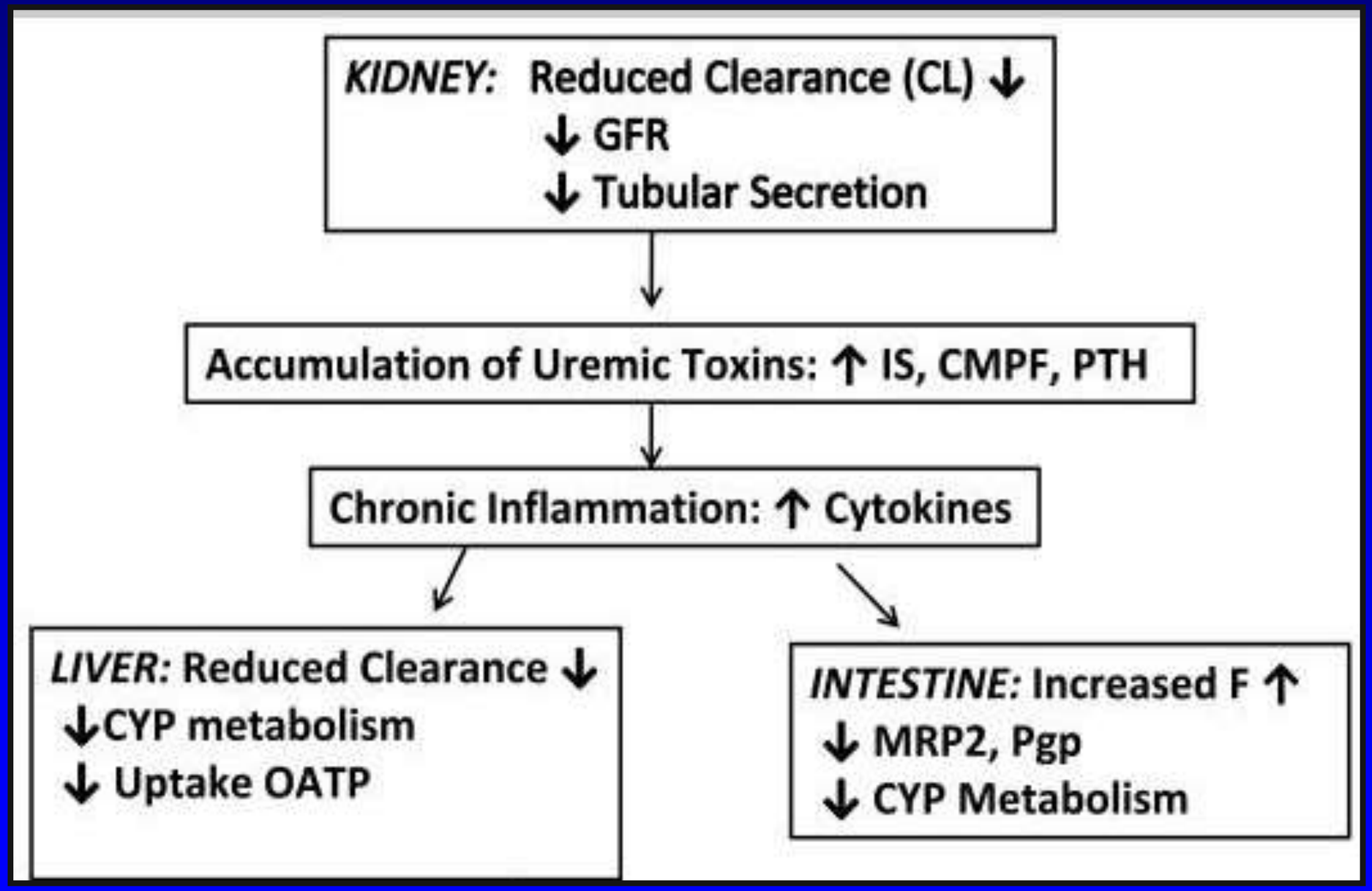
INSUFICIÊNCIA RENAL

Nomograma para ajuste de dose



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

Physiological and Pharmacologic Effect of CRF on Drug Metabolism and Transport



Dreisbach and Lertora, 2008

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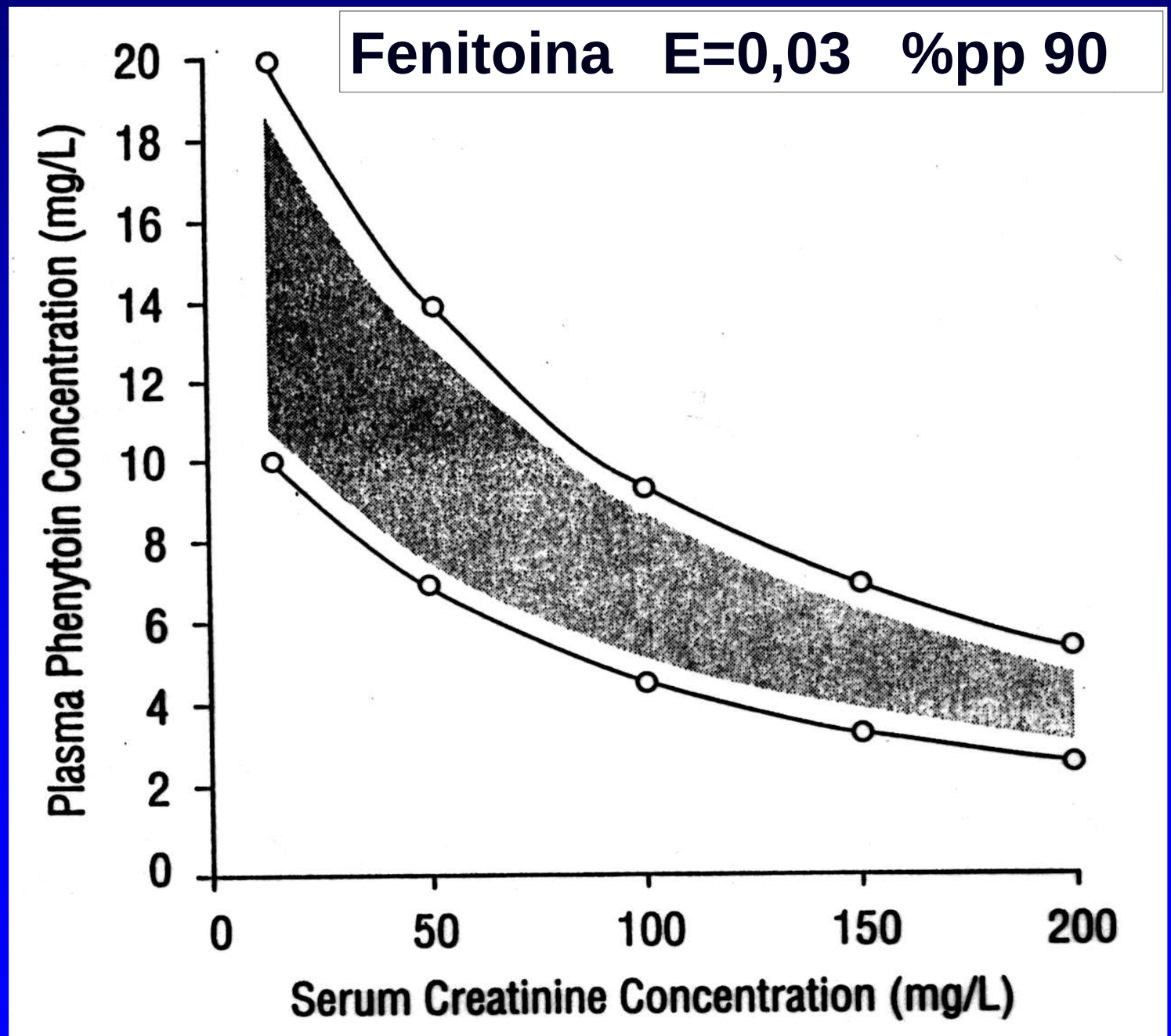
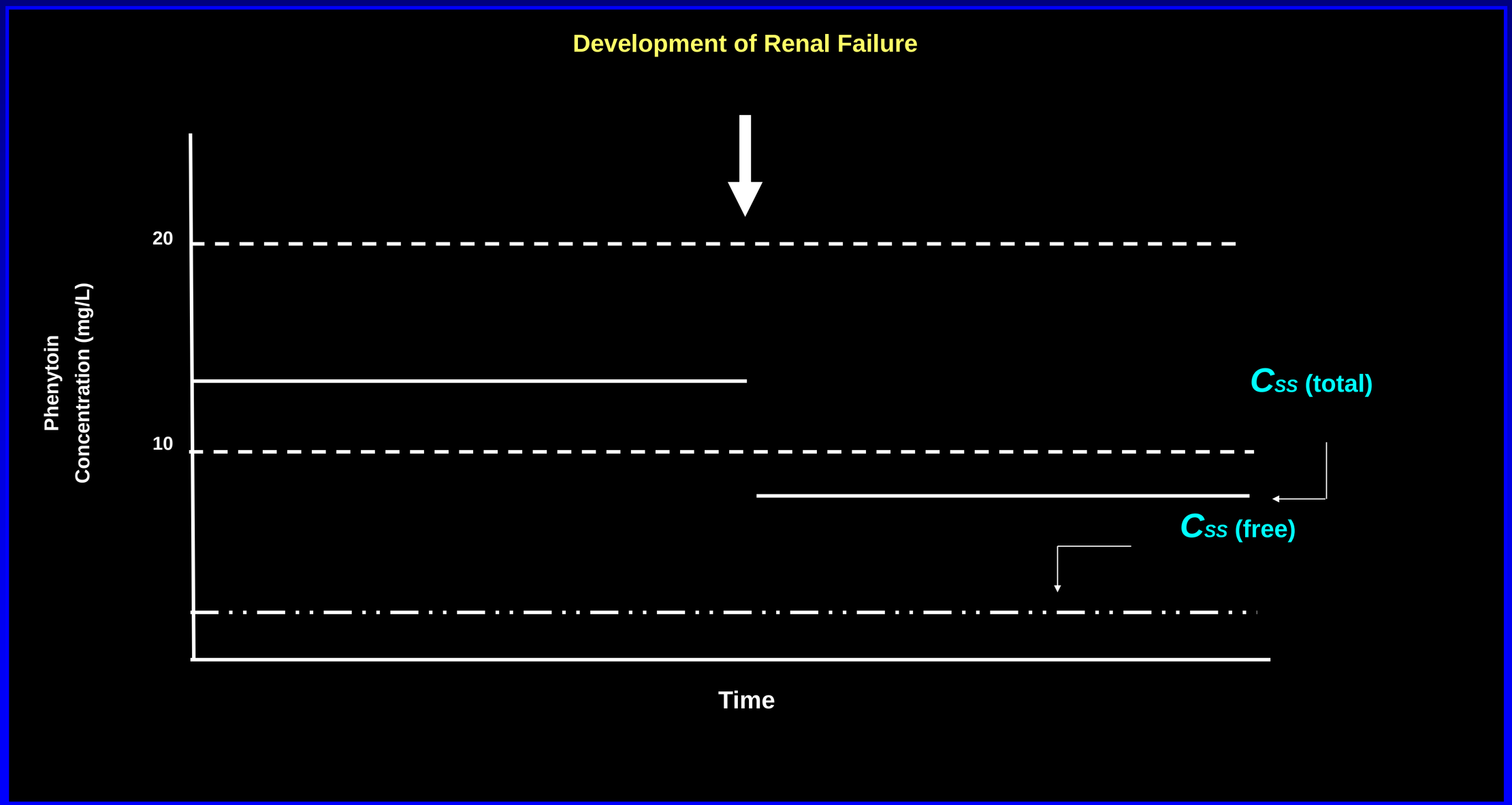
Concentrações plasmáticas de fenitoina na insuficiência renal



Phenytoin has a low E and possesses high protein binding



EFFECT OF END-STAGE RENAL DISEASE ON NONRENAL CLEARANCE

Drug	Change in nonrenal clearance (%)
Codeine	17
Aztreonam	33
Ciprofloxacin	33
Roxithromycin	42
Cefmenoxime	45
Minoxidil	46
Captopril	50
Cefotaxime	50
Cefsulodin	52
Nicardipine	37
Verapamil	54
Aciclovir	55
Ceftizoxime	55
Procainamide	60
Cefonicid	62
Cimetidine	62
Latamoxef (moxalactam)	63
Metoclopramide	66
Cefmetazole	80
Imipenem	85

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INSUFICIÊNCIA RENAL

acúmulo de metabólitos ativos

fármaco	metabólito
procainamida	N-acetilprocainamida
petidina	norperidina
adriamicina	adriamicinol
azatioprina	6-mercaptopurina
ciclofosfamida	4-cetociclofosfamida

Cardiac Failure

Absorption

- ♥ Reduced gut mobility
- ♥ Mucosal oedema
- ♥ Reduced blood flow to gut

↓

Reduced GI absorption of hydrochlorothiazide, frusemide, procainamide

Distribution

- ♥ Reduced tissue blood levels

↓

Reduced Vd for quinidine, lignocaine, procainamide

Metabolism

- ♥ Blood flow to liver falls in proportion to cardiac output
- ♥ Hepatic metabolic capacity reduced by hepatocellular damage

↓

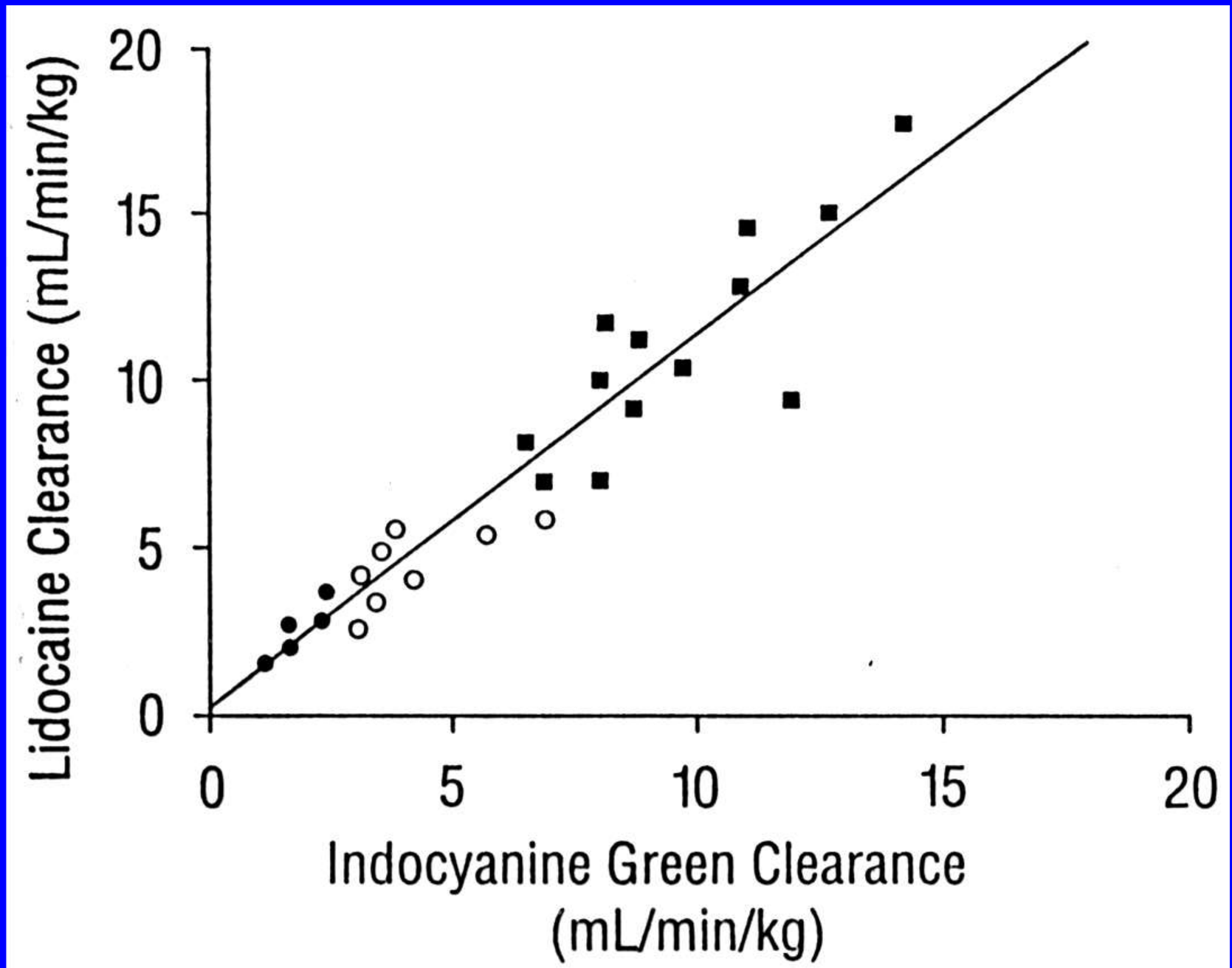
Higher levels of drugs with high extraction ratio, e.g. lignocaine

Excretion

- ♥ Decresead GFR resulting from hypoperfusion
- ♥ Increased reabsorption due to altered intrarenal blood flow

↓

Reduced renal clearance of procainamide, digoxin



■ voluntários sadios

○ leve ICC

● graveICC

Insuficiência cardíaca congestiva

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farmacocinética da digoxina

	Vd (L)	CL_R (L/h)	CL_H (L/h)
voluntários sadios	760	8,52	3,48
pacientes ICC	476	3,50	1,37

Insuficiência cardíaca

Vd ↓	↓ dose ataque
CL ↓	↓ dose manutenção
t½ ↑	↑ t^{ss}

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OBESIDADE

ajuste de dose de ataque

Dose = Cp . Vd

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

OBESIDADE

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ajuste de dose de manutenção

$$Dose / \tau = Cp^{ss} . CL$$

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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Mean 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

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Dose / Concentração Plasmática

paciente

fármacos associados

especialidade farmacêutica

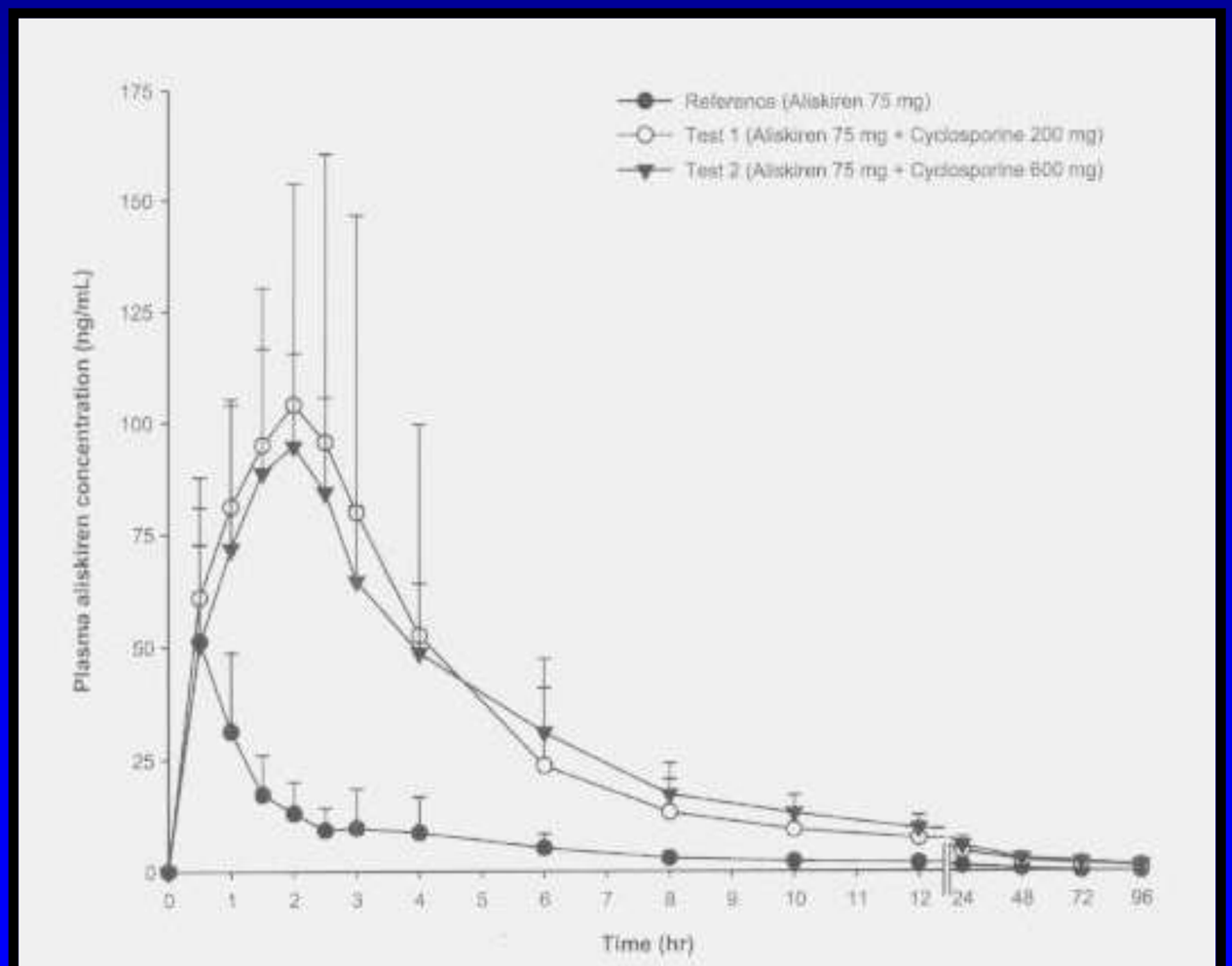
Examples of In Vivo Substrates for Selected Transporters

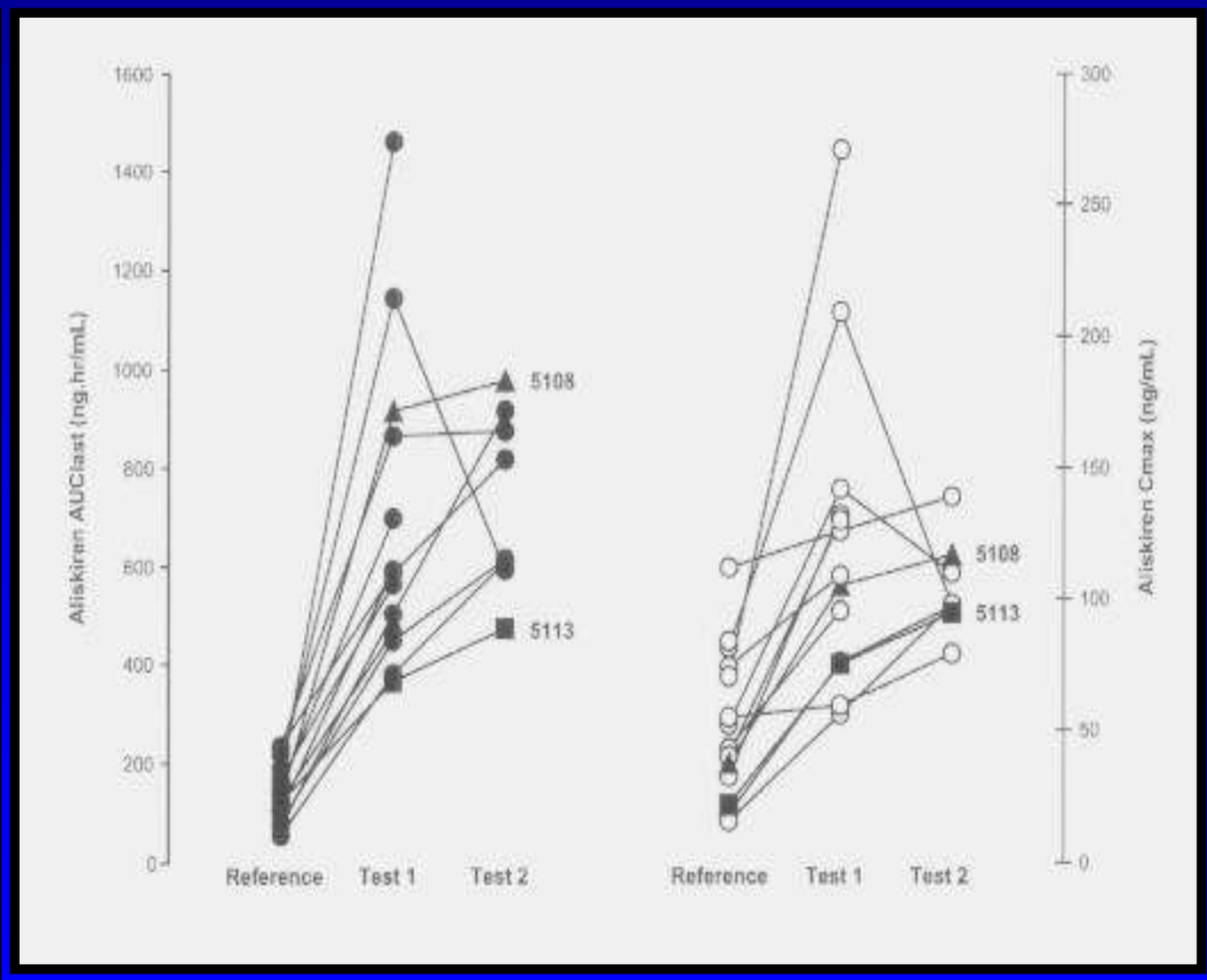
Transporter	Gene	Substrate
P-gp	*ABCB1*	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
BCRP	*ABCG2*	Methotrexate, mitoxantrone, imatinib, irrinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan
OATP1B1	*SLCO1B1*	Atrasentan, atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, SN-38 (active metabolite of irinotecan), rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, rifampin, valsartan, olmesartan
OATP1B3	*SLCO1B3*	Atorvastatin, rosuvastatin, pitavastatin, telmisartan, valsartan, olmesartan
OCT2	*SLC22A2*	Amantadine, amiloride, cimetidine, dopamine, famotidine, memantine, metformin, pindolol, procainamide, ranitidine, varenicline, oxaliplatin
OAT1	*SLC22A6*	Adefovir, captopril, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, zalcitabine, zidovudine
OAT3	*SLC22A8*	Acyclovir, bumetanide, ciprofloxacin, famotidine, furosemide, methotrexate, zidovudine, oseltamivir acid, (the active metabolite of oseltamivir), penicillin G, pravastatin, rosuvastatin, sitagliptin

Examples of In Vivo Inhibitors and Inducers of Selected Transporter

Transporter	Gene	Inhibitor	Inducer
P-gp	*ABCB1*	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil	Avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, tipranavir/ritonavir
BCRP	*ABCG2*	Cyclosporine, elacridar (GF120918), eltrombopag, gefitinib	Not known
OATP1B1	*SLCO1B1*	Atazanavir, cyclosporine, eltrombopag, gemfibrozil, lopinavir, rifampin, ritonavir, saquinavir, tipranavir	Not known
OATP1B3	*SLCO1B3*	Atazanavir, cyclosporine, lopinavir, rifampin, ritonavir, saquinavir	Not known
OCT2	*SLC22A2*	Cimetidine, quinidine	Not known
OAT1	*SLC22A6*	Probenecid	Not known
OAT3	*SLC22A8*	Probenecid cimetidine, diclofenac	Not known

Effect of cyclosporine on the pharmacokinetics of aliskiren in healthy subjects





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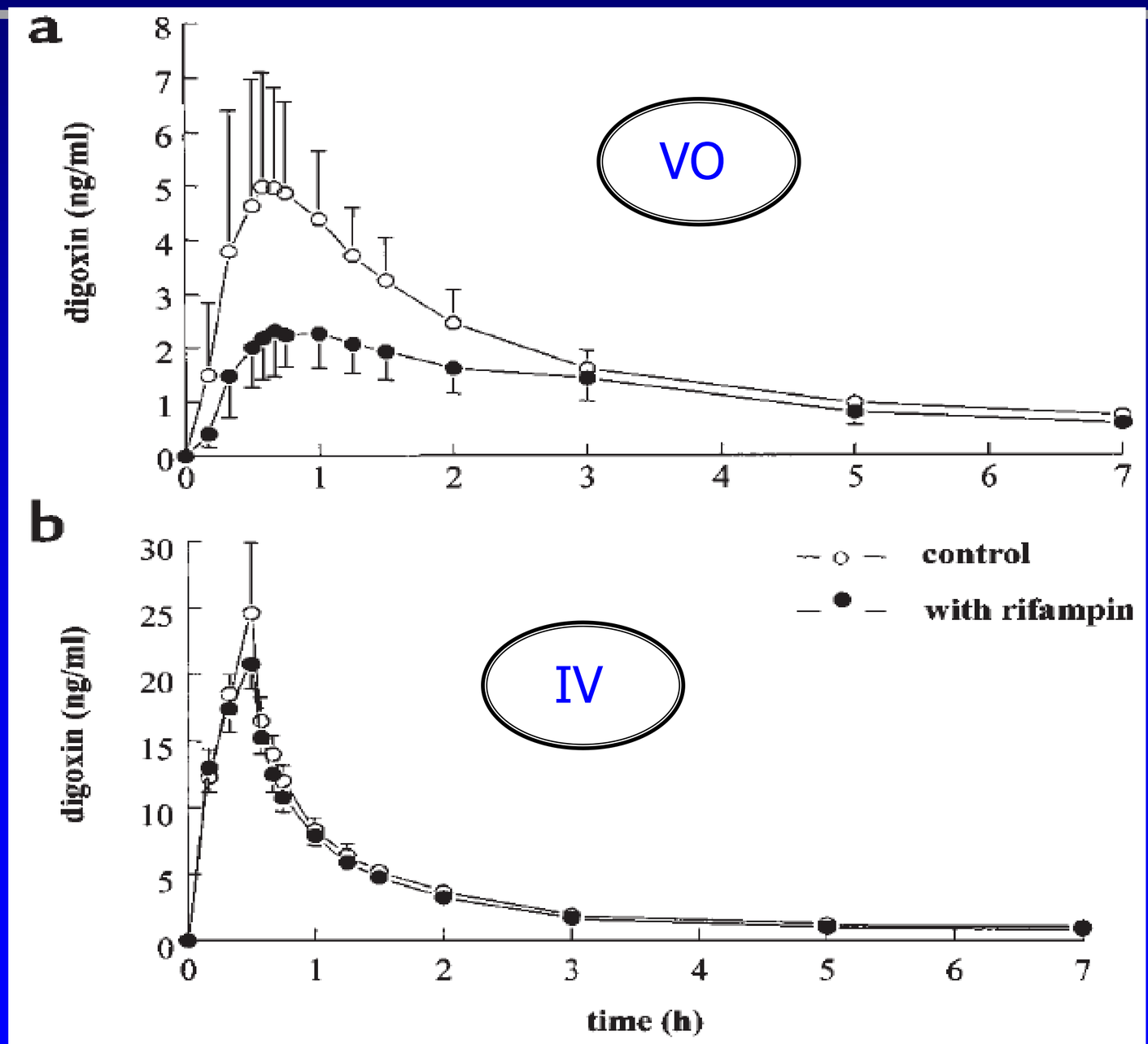
The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin



Transporter Mediated Clinical Significant Drug-Drug Interactions

Gene	Aliases	Tissue	Function	Interacting Drug	Substrate (Affected Drug)	Changes in Substrate Plasma AUC (AUC ratios)
ABC Transporters of clinical importance in the absorption, disposition, and excretion of drugs						
ABCB1	P-gp, MDR1	Intestinal enterocyte, kidney proximal tubule, hepatocyte (canalicular), brain endothelia	Efflux	Dronedarone	Digoxin	2.6-fold
				Quinidine	Digoxin	1.7-fold
				Ranolazine	Digoxin	1.6-fold
				Tipranavir/Ritonavir	Loperamide	0.5-fold
				Tipranavir/Ritonavir	Saquinavir/Ritonavir	0.2-fold
ABCG2	BCRP	Intestinal enterocyte, hepatocyte (canalicular), kidney proximal tubule, brain endothelia, placenta, stem cells, mammary gland (lactating)	Efflux	GF120918	Topotecan	2.4-fold
SLC Transporters of clinical importance in the disposition and excretion of drugs						
SLCO1B1	OATP1B1 OATP-C OATP2 LST-1	Hepatocyte (sinusoidal)	Uptake	Lopinavir/ritonavir	Bosentan	5-48 fold
				Cyclosporine	Pravastatin	9.9-fold
				Rifampin (single dose)	Glyburide	2.3-fold
SLCO1B3	OATP1B3, OATP-8	Hepatocyte (sinusoidal)	Uptake	Cyclosporine	Rosuvastatin	7.1- fold
				Cyclosporine	Pitavastatin	4.6-fold
				Lopinavir/ritonavir	Rosuvastatin	2.1-fold
SLC22A2	OCT2	Kidney proximal tubule	Uptake	Cimetidine	Dofetilide	1.5-fold
				Cimetidine	Pindolol	1.5-fold
				Cimetidine	Metformin	1.4-fold
SLC22A6	OAT1	Kidney proximal tubule, placenta	Uptake	Probenecid	Cephradine	3.6-fold
				Probenecid	Cidofovir	1.5-fold
				Probenecid	Acyclovir	1.4-fold
SLC22A8	OAT3	Kidney proximal tubule, choroid plexus, brain endothelia	Uptake	Probenecid	Furosemide	2.9-fold

Recent Labeling on Drug-Drug Interactions (Rosuvastatin

Coadministered Drug	Rosuvastatin AUC Fold-Change (Mean)	Rosuvastatin Cmax Fold-Change (Mean)	Rosuvastatin Labeling
			Approved dosing: 5-40 mg once daily; usual recommended starting dose: 10 mg once daily
Cyclosporine	7	11	"Patients taking cyclosporine... limited to 5 mg once daily"
Gemfibrozil	2	2	"Combination with gemfibrozil... limited to 10 mg once daily"

Huang et al., 2004

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REAÇÕES DE DESLOCAMENTO DE RELEVÂNCIA CLÍNICA

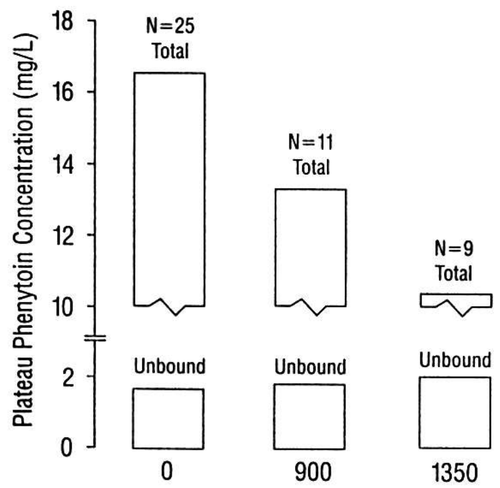
↑E, via i.v. lidocaina ⇨ Interação de relevância clínica

↓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



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%

Classification of In Vivo Inducers of CYP Enzymes

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

Classification of In Vivo Inhibitors of CYP

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 In Vivo Inhibitors of CYP

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 In Vivo Inhibitors of CYP

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,

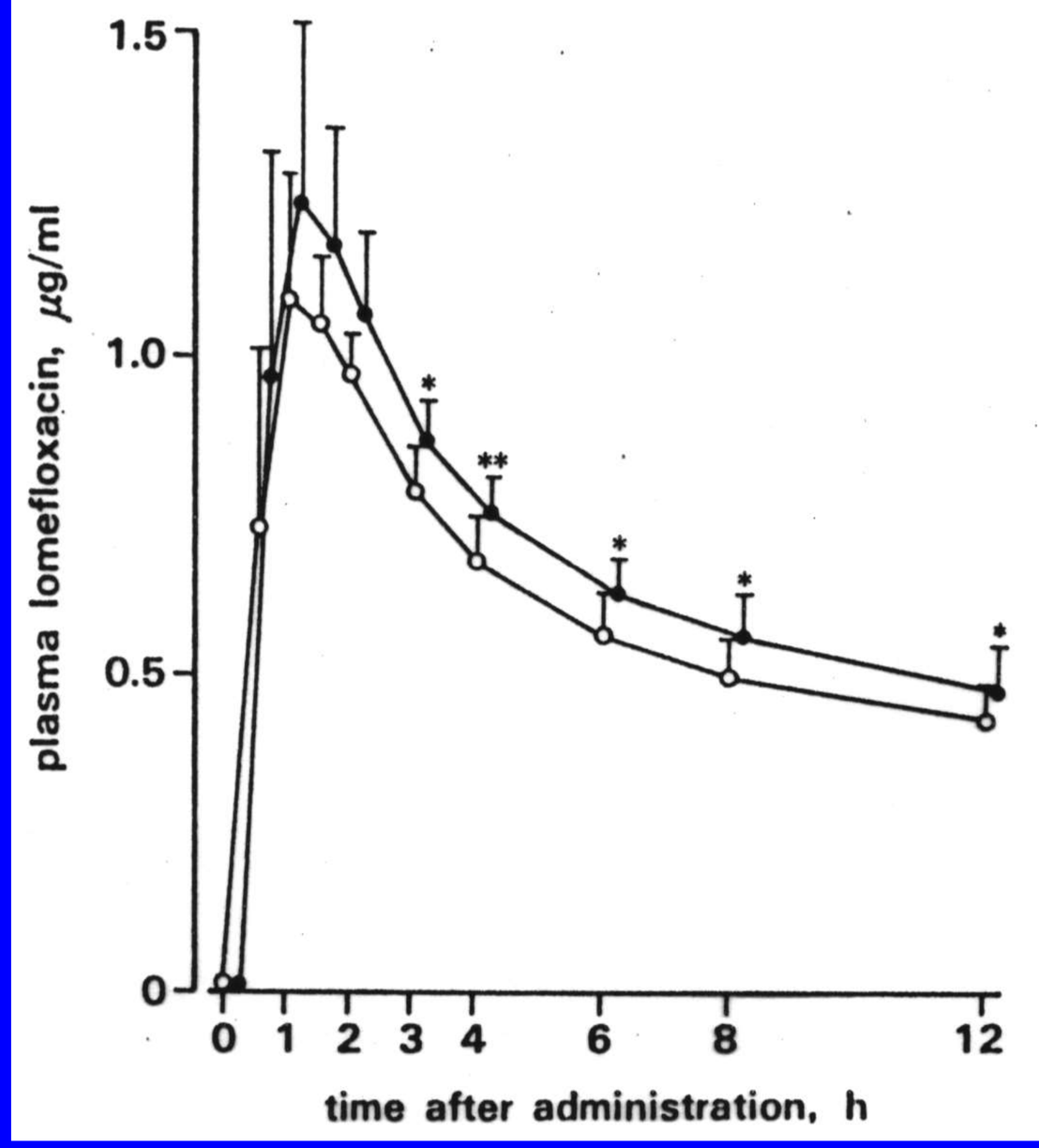
Recent Labeling on Drug-Drug Interactions (Vardenafil)

Coadministered Drug	Vardenafil AUC Fold-Change (Mean)	Vardenafil Cmax Fold-Change (Mean)	Vardenafil Labeling
			Approved dosing: 5-20 mg daily; recommended starting dose: 10 mg once per day
Ritonavir (600bid)	49	13	"<2.5 mg... not exceeded in 72 hr... taking ritonavir"
Indinavir (800tid)	167	7	"<2.5 mg daily... taking indinavir, ketoconazole 400 mg daily, itraconazole 400 mg daily"
Ketoconazole (200qd)	410	4	"<5 mg daily... taking ketoconazole/itraconazole 200 mg daily, or erythromycin"
Erytromycin (500tid)	4	3	

Huang et al., 2004

EXCREÇÃO RENAL

Lomefloxacina + furosemida



	lomefloxacina	lomefloxacina + furosemida
CL_T (mL/min/kg)	6,70	6,01
CL_R (mL/min/kg)	2,36	1,57