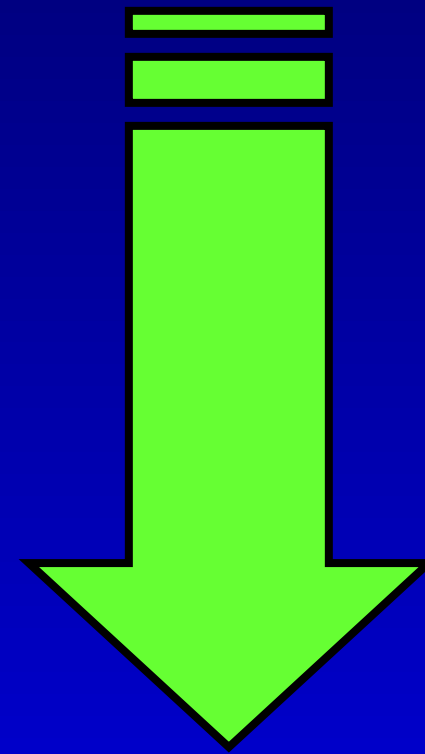


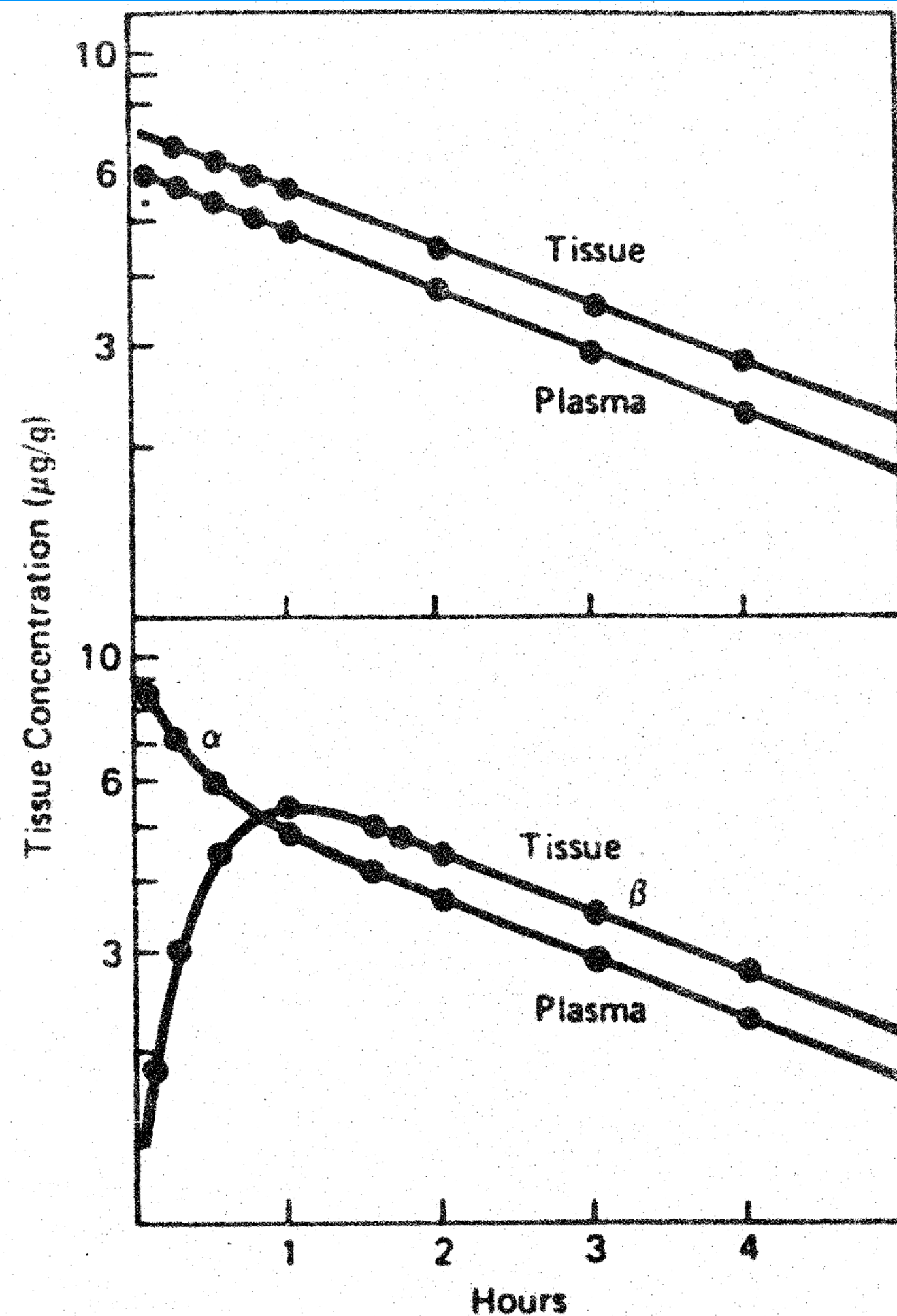
MONITORIZAÇÃO TERAPÊUTICA



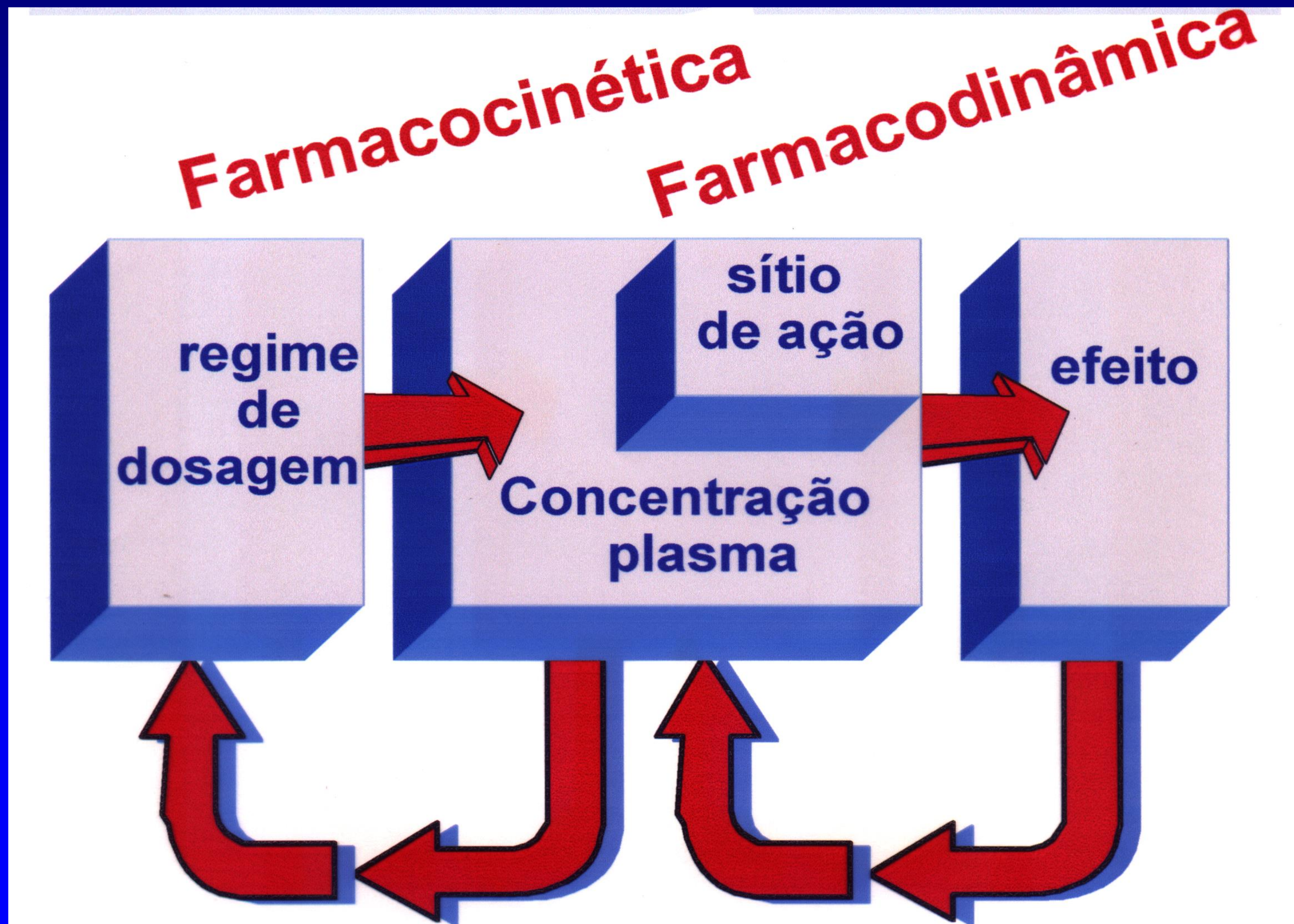
FARMACOCINÉTICA

individualização do regime de dosagem

MONITORIZAÇÃO TERAPÊUTICA



MONITORIZAÇÃO TERAPÊUTICA





eficácia não facilmente mensurável



baixo índice terapêutico

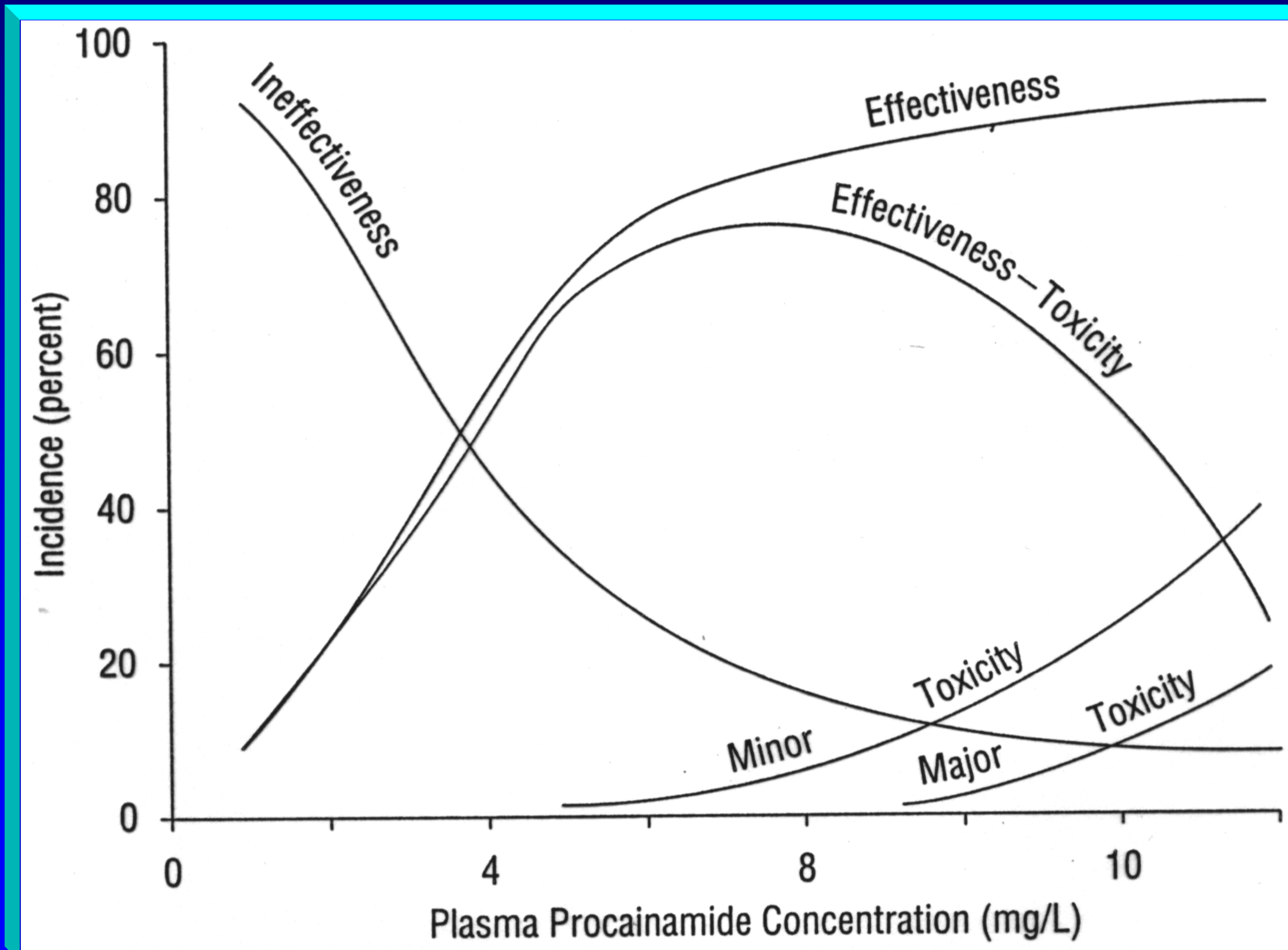


intervalo terapêutico estabelecido



alta variabilidade na farmacocinética

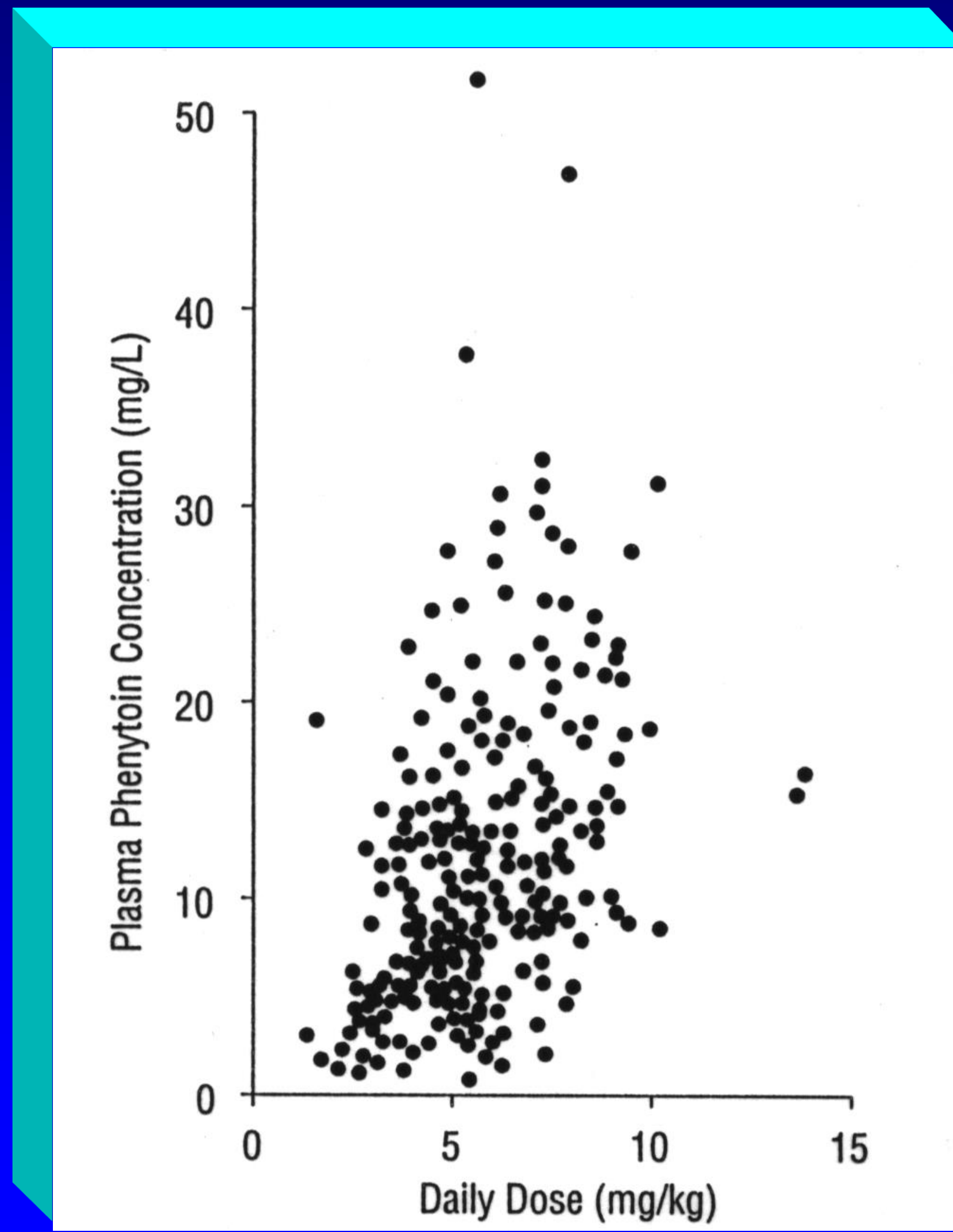
INTERVALO TERAPÊUTICO



Procainamida
4 - 8 mg/L

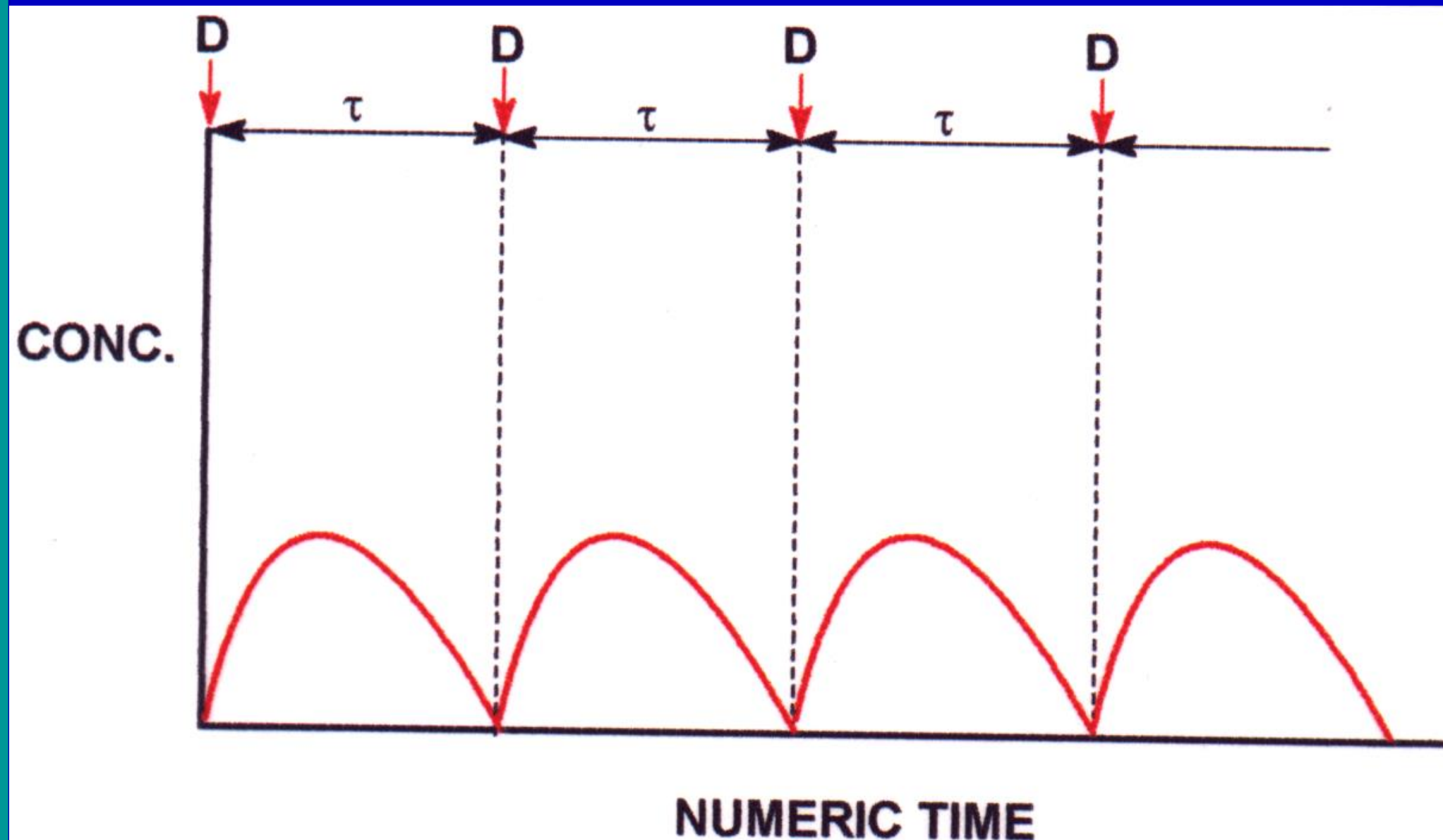
Dose vs concentração plasmática

FENITOÍNA

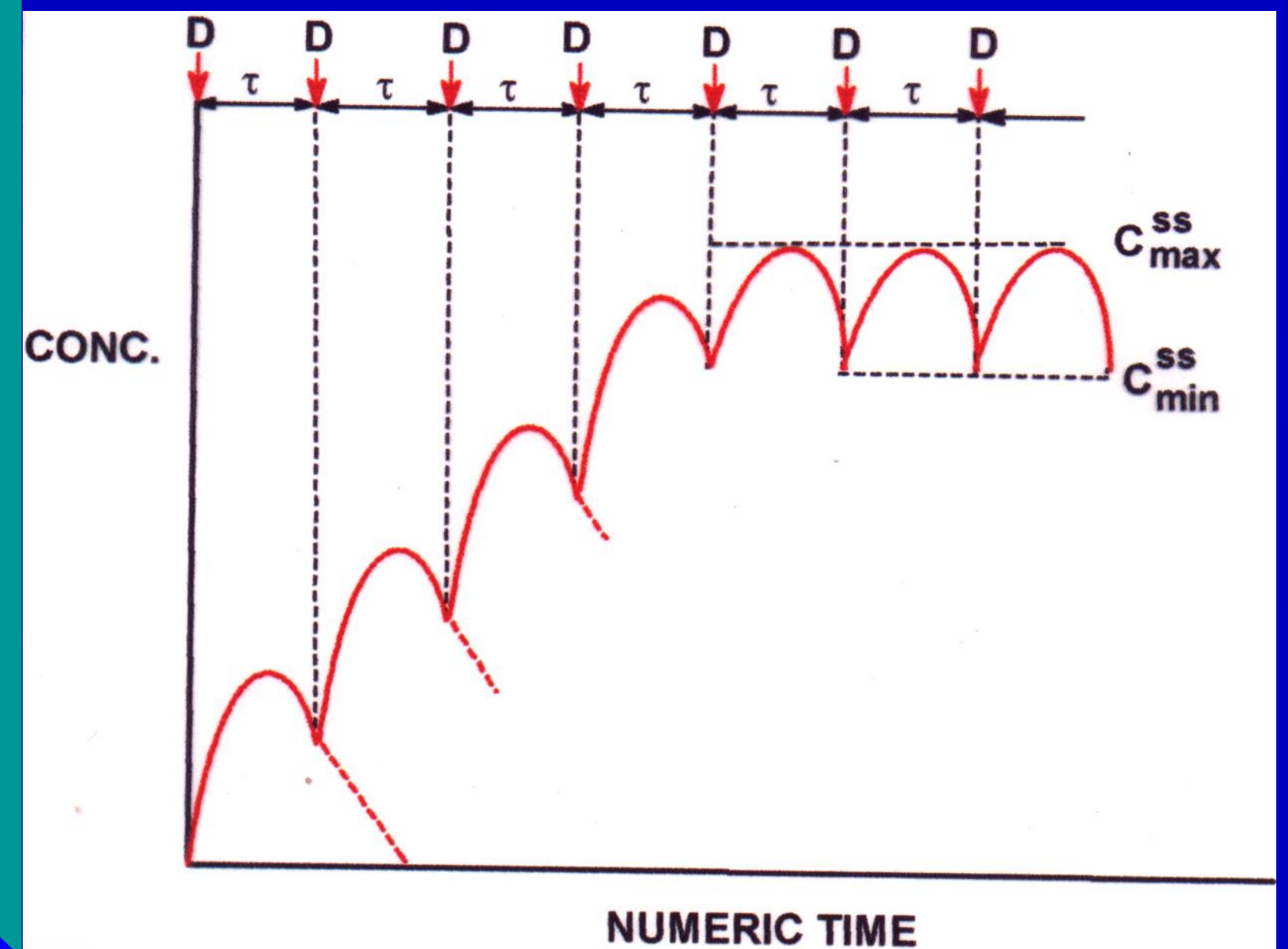


Blood level versus time curves

SINGLE DOSE



MULTIPLE DOSE



$e^{-k_{el} \cdot \tau}$ = fraction remaining at the end of a time interval

$1 - e^{-k_{el} \cdot \tau}$ = fraction lost during a dosing interval

TIME FOR DRUG ELIMINATION

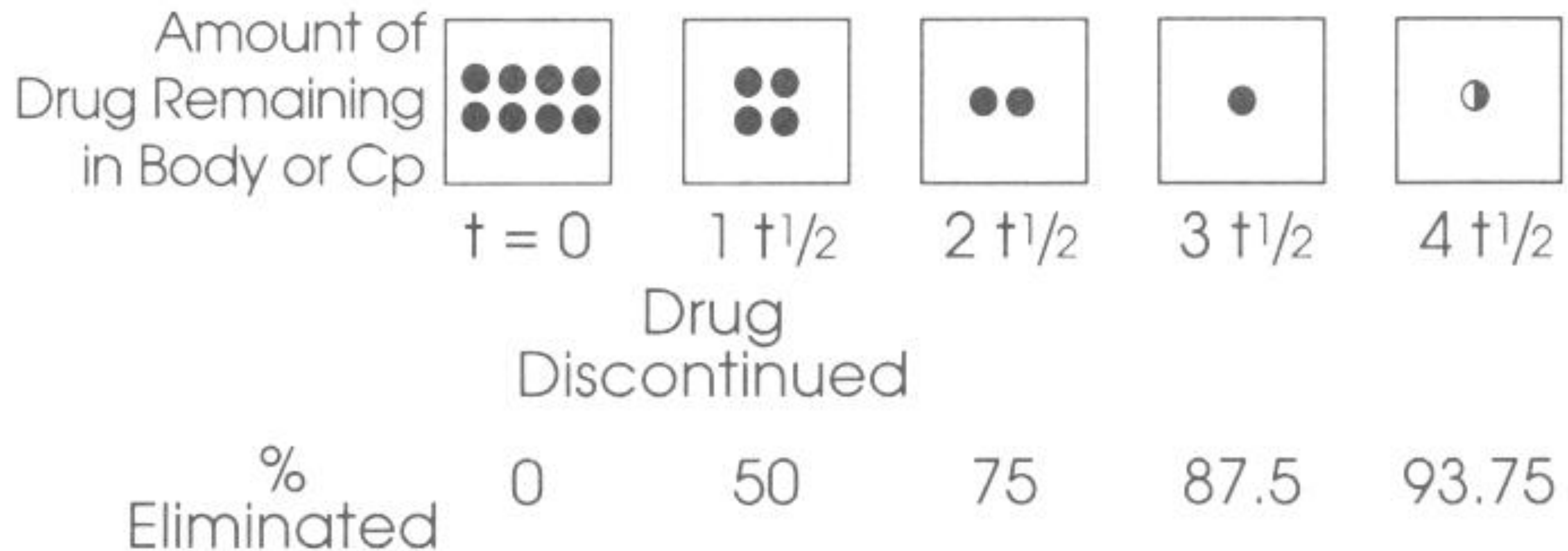
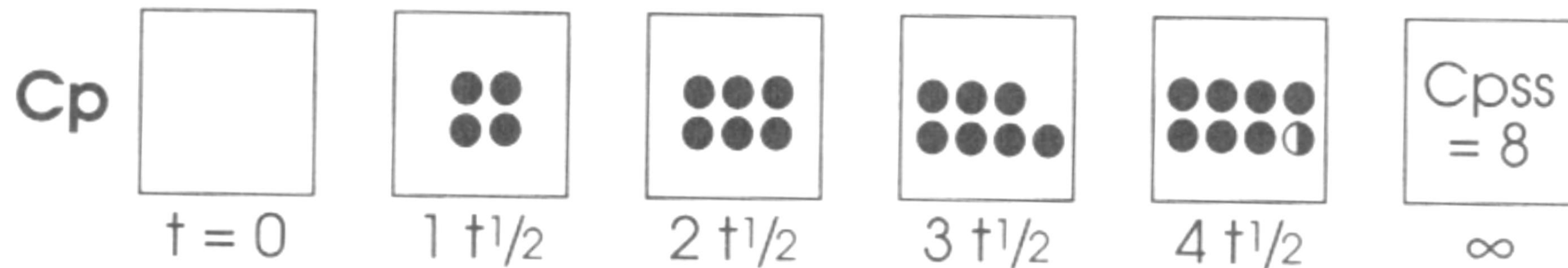


Figure 18. First-Order Elimination: Amount of Drug Remaining in the Body After One to Four Half-Lives Have Passed. The amount of drug eliminated per unit of time diminishes over time, but the fraction eliminated in each time interval (in this case, 0.5) remains the same.

- In 1 x t_{1/2} the concentration will reach 100/2=50%
- In 2 x t_{1/2} the concentration will reach 50 + 50/2=75%
- In 3 x t_{1/2} the concentration will reach 75 + 25/2=87.5%
- In 4 x t_{1/2} the concentration will reach 87.5 + 12.5/2=93.75%
- In 5 x t_{1/2} the concentration will reach 93.75 + 6.25/2=96.875%



Maintenance Dose of Drug Initiated

% OF STEADY STATE ACHIVIED

| % Accumulation or % of Steady State Achieved | 50 | 75 | 87.5 | 93.75 | 100 |
|--|----|----|------|-------|-----|
|--|----|----|------|-------|-----|

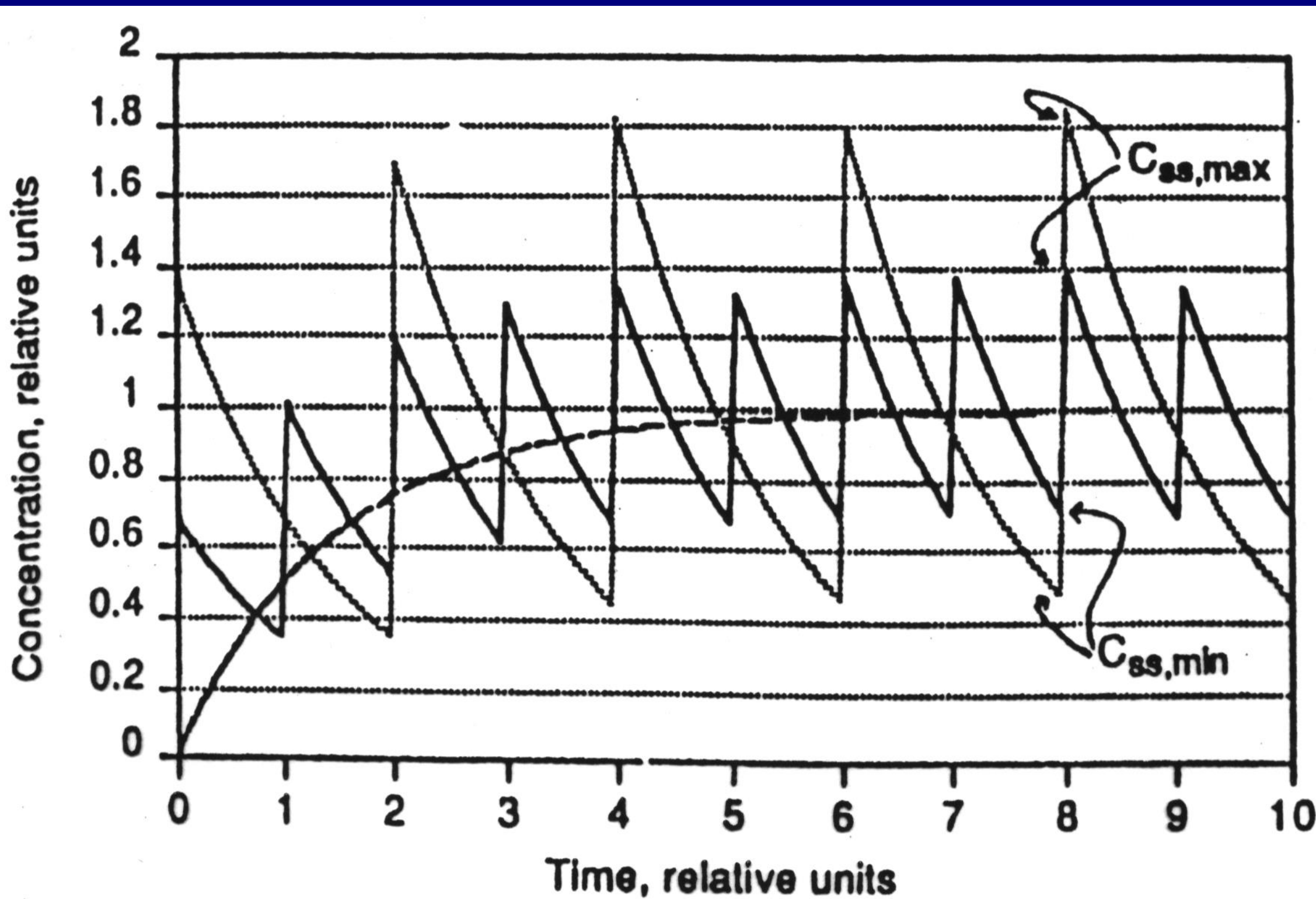
Figure 17. First-Order Accumulation. When a maintenance dose is initiated, it takes 4 or more half-lives to reach steady-state plasma levels. This example assumes that the maintenance dose administered will produce an average steady-state level (C_{pss} ave or C_{pss}) of 8.

Elimination half-life

It can be used to predict how long it will take to reach steady-state levels during multiple dosing or continuous i.v. infusion

| | | |
|----------------|---|---------------------------|
| 1 half-life | → | 50% of steady-state level |
| 2 half-lives | → | 75% of steady-state level |
| 3.3 half-lives | → | 90% of steady-state level |
| 4-5 half-lives | → | 95% of steady-state level |
| 6.6 half-lives | → | 99% of steady-state level |

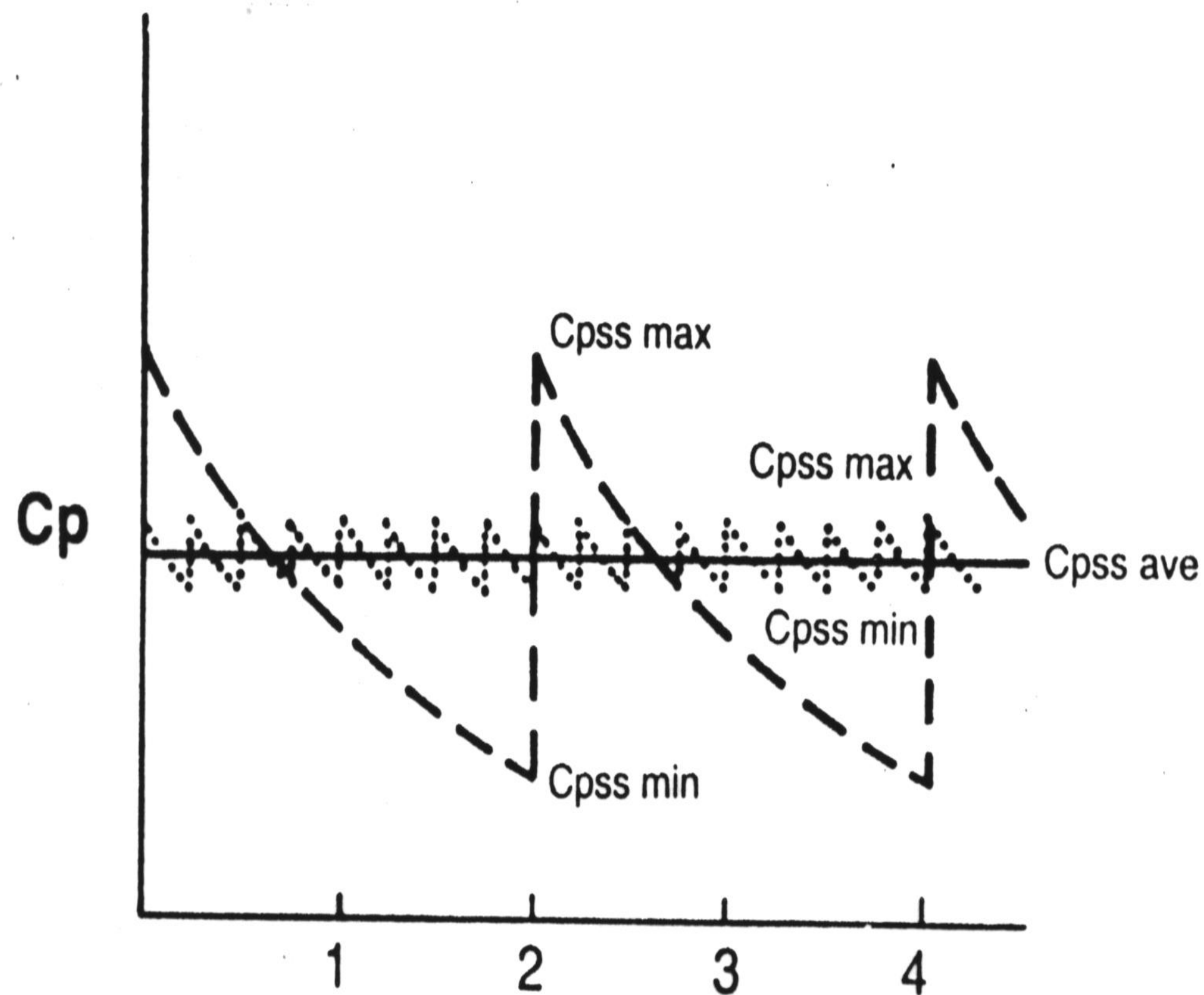
Tempo para atingir o estado de equilíbrio



| medicamento | $t_{1/2}$ (h) | t^{ss} |
|--------------|---------------|----------|
| tobramicina | 2-3 | > 8 h |
| lítio | 20-58 | > 4 dias |
| fenobarbital | 50-150 | >11 dias |

$t^{ss} = 4 - 5$ meias-vidas

Clearance Total



Concentração plasmática média no estado de equilíbrio

$$C_p^{ss} = \frac{\text{Dose} / \tau}{Cl}$$

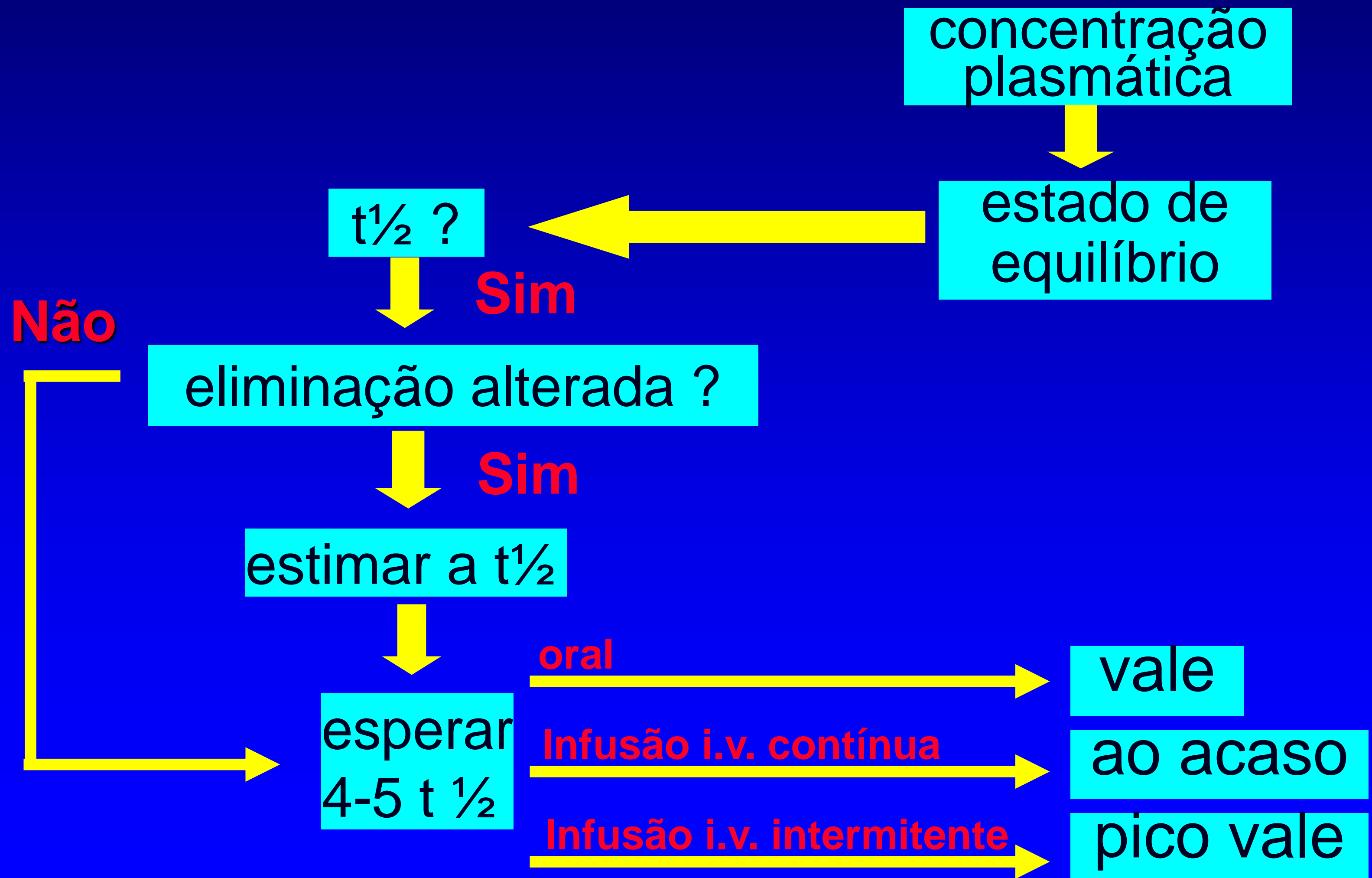
Dose de manutenção

$$\text{Dose} = (Cl) (C_p^{ss}) (\tau)$$



Estado de Equilíbrio (C_{ss})

Colheita da amostra





Dose / Concentração Plasmática

especialidade farmacêutica

paciente

fármacos associados

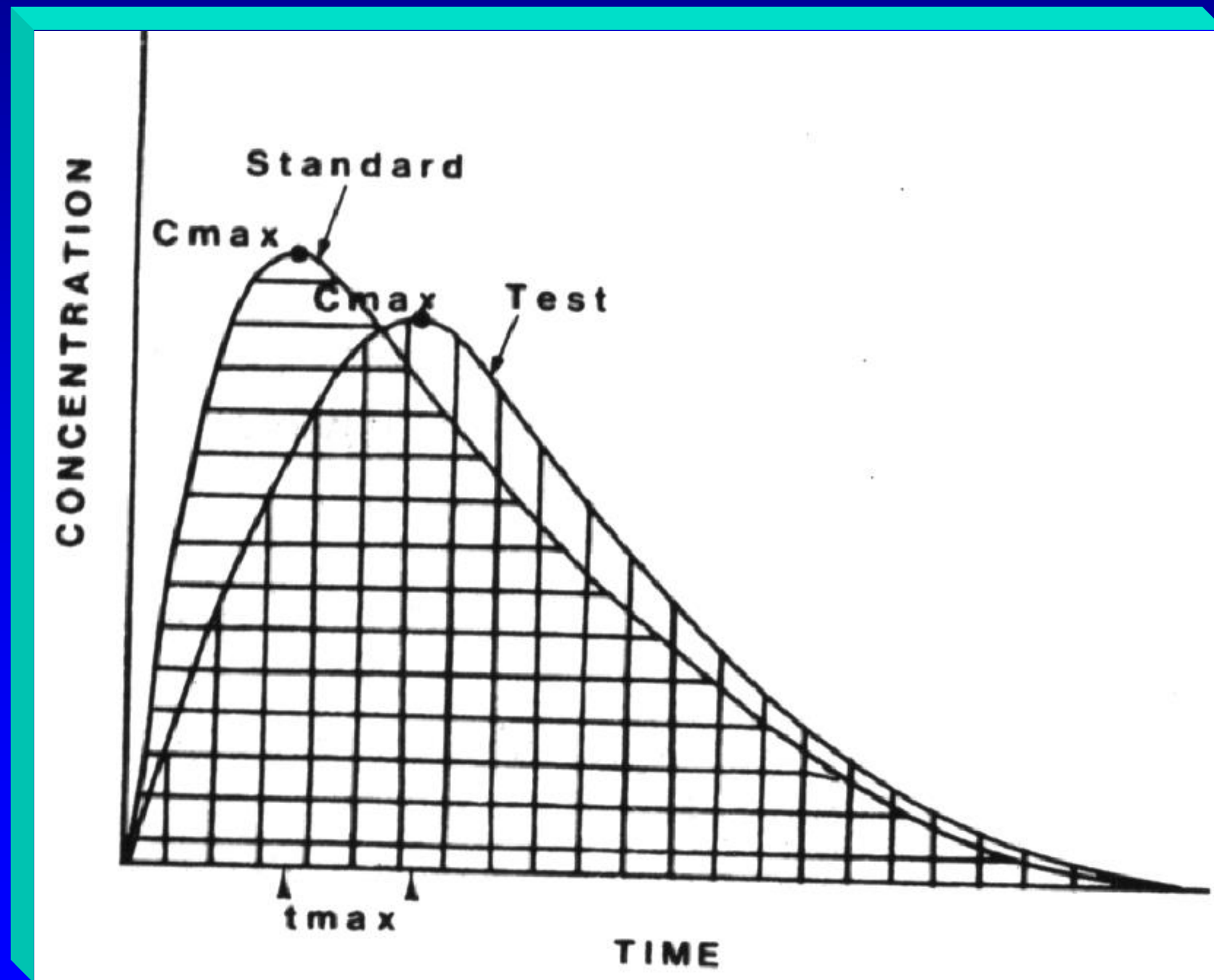
BIOEQUIVALÊNCIA

Dois medicamentos são considerados bioequivalentes se as suas quantidades e velocidades de absorção não apresentam diferenças estatisticamente significativas, quando administrados à mesma dose molar do princípio ativo, sob as mesmas condições experimentais



Biodisponibilidade relativa ou bioequivalência

formulação teste *versus* formulação referência



BIODISPONIBILIDADE RELATIVA BIOEQUIVALÊNCIA

Lei 9787 de 10 de fevereiro de 1999

Estabelece o medicamento genérico

Resolução RDC nº 136, de 29 de maio de 2003

Dispõe sobre o registro de medicamento novo

Resolução RDC nº 17, de 02 de março de 2007

Dispõe sobre o registro de medicamento similar

Centros certificados ANVISA

16 no Brasil

Ceará (1), Goiás (1), Minas Gerais (3), Paraná (1),
Pernambuco (1), Rio de Janeiro (1), São Paulo (8)

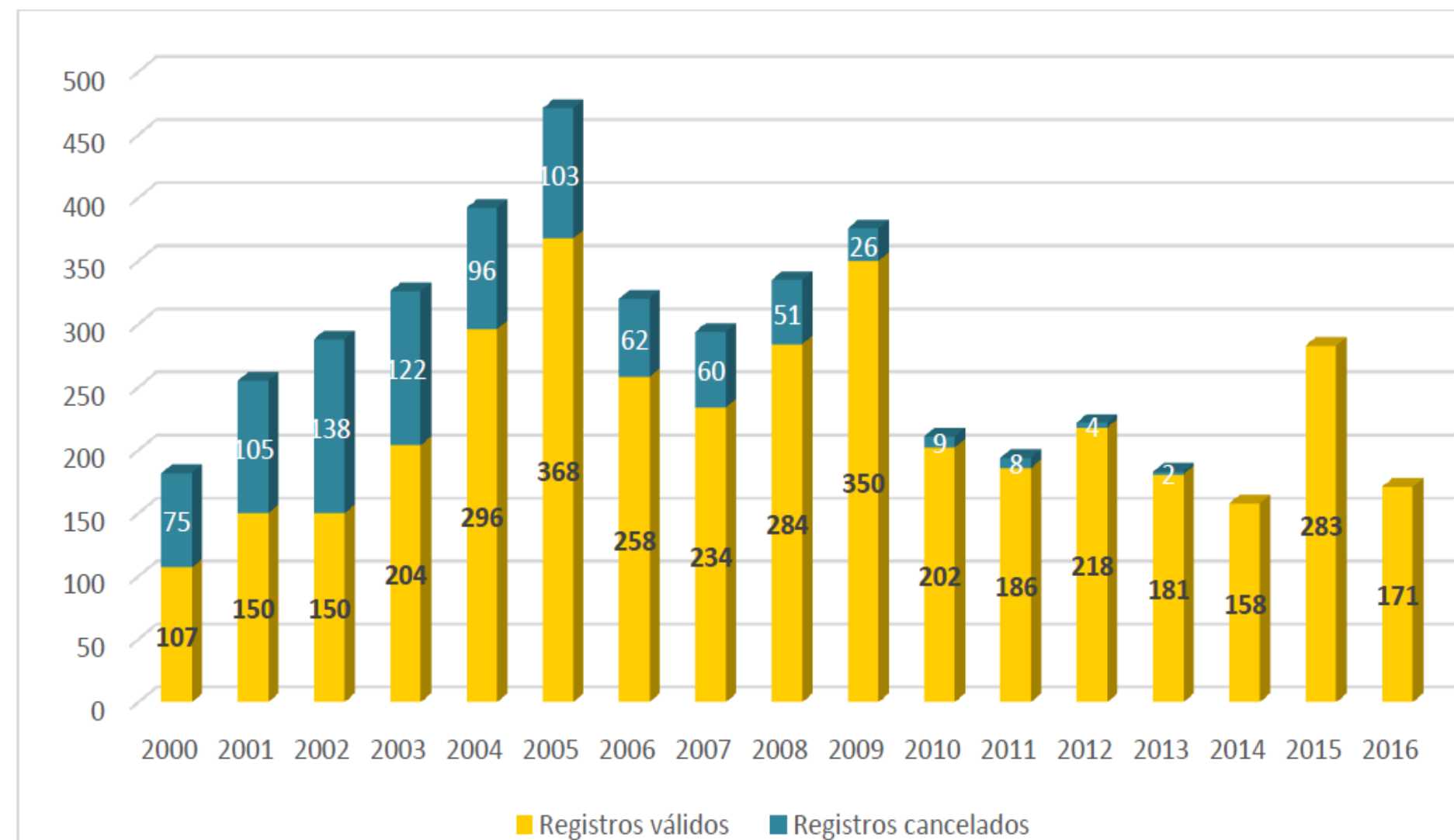
33 no exterior

Alemanha (2), Argentina (1), Canadá (4), Espanha (1),
Estados Unidos (3), Índia (18), Itália (1), México (1),
Portugal (1), Romênia (1).

Medicamentos Genéricos

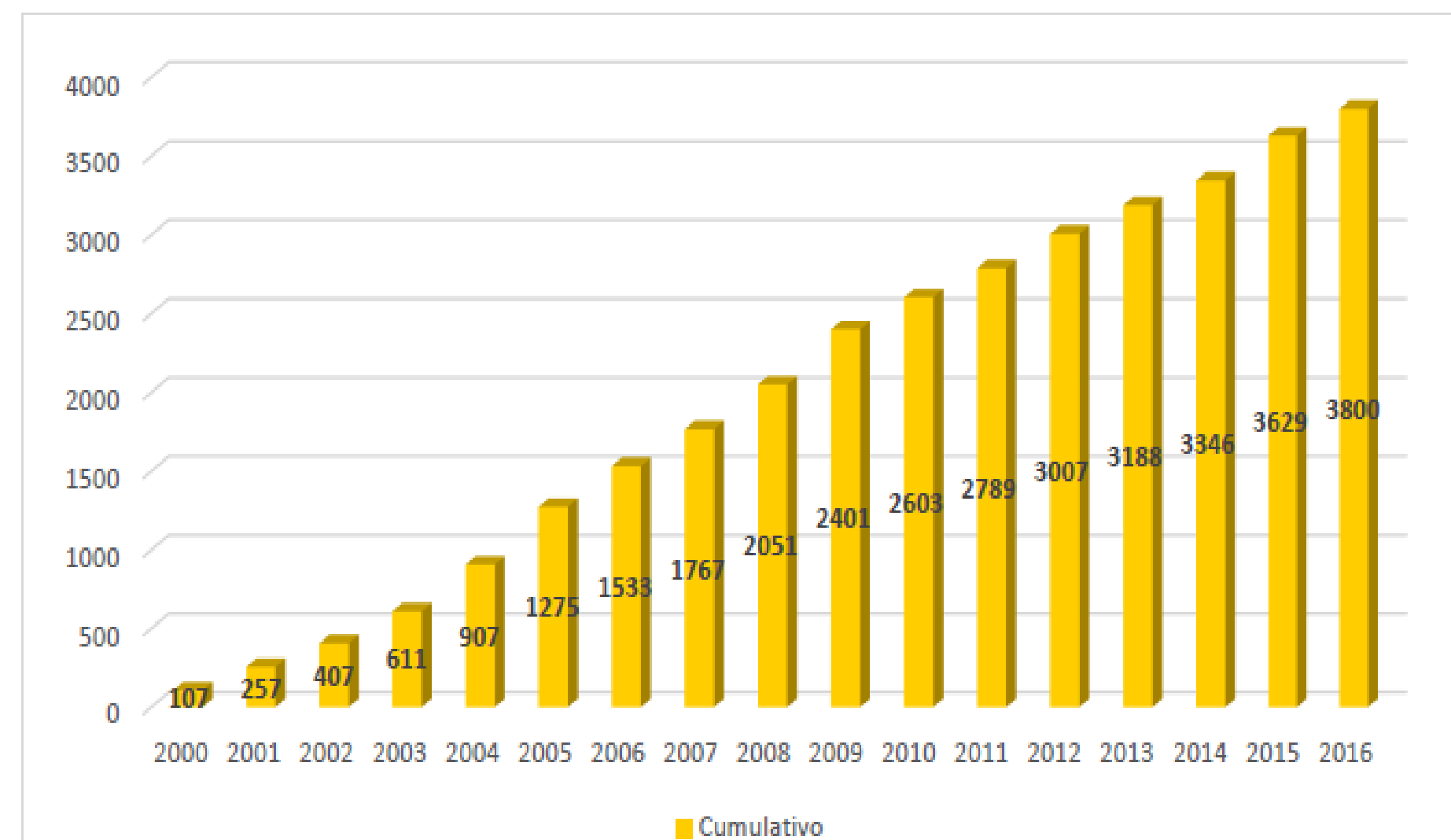
Registrados

Número de Medicamentos Genéricos Registrados



Valores acumulados

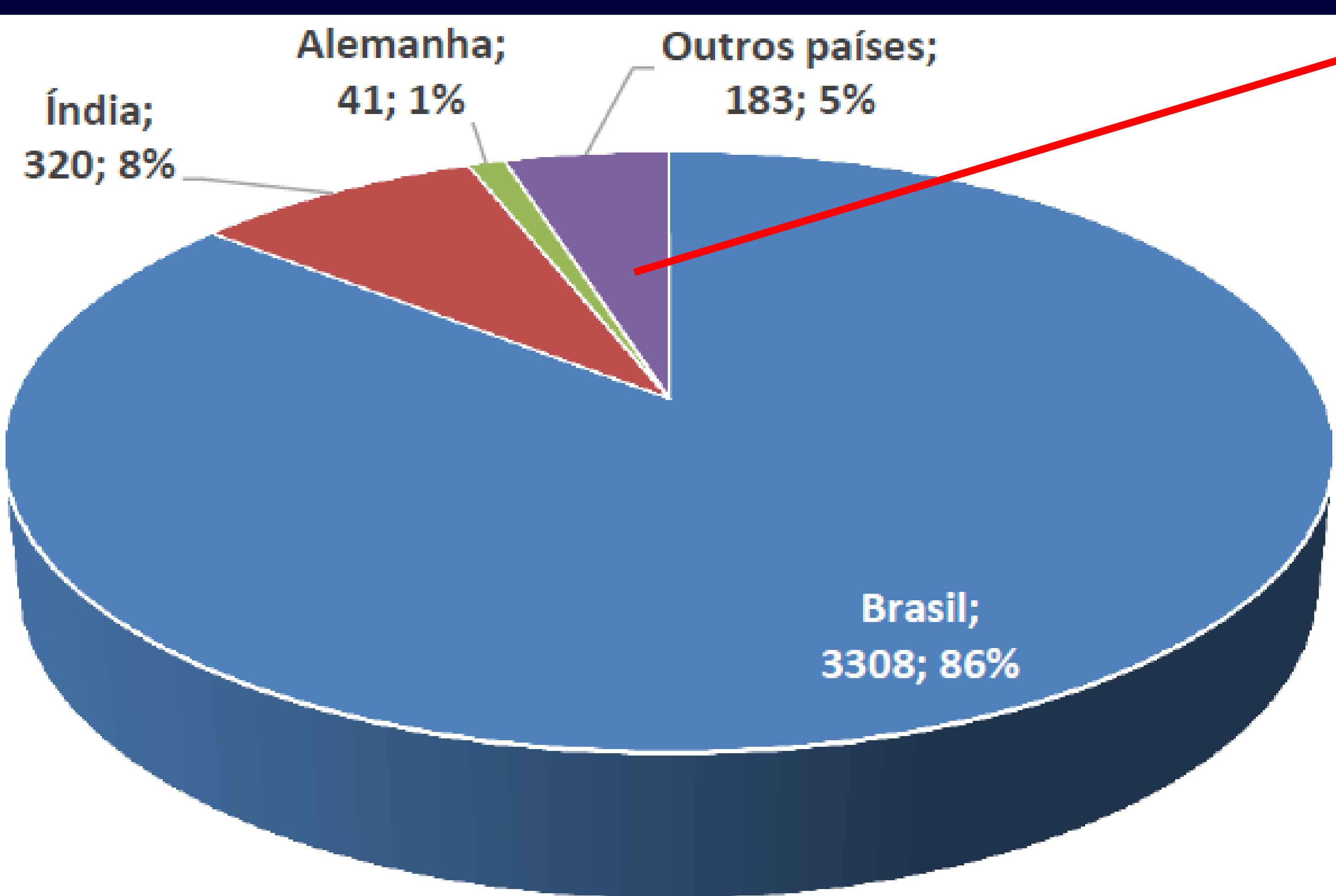
Número de Medicamentos Genéricos com registros válidos (valores acumulados)



Medicamentos Genérico

Países de fabricação

FCFRP-USP



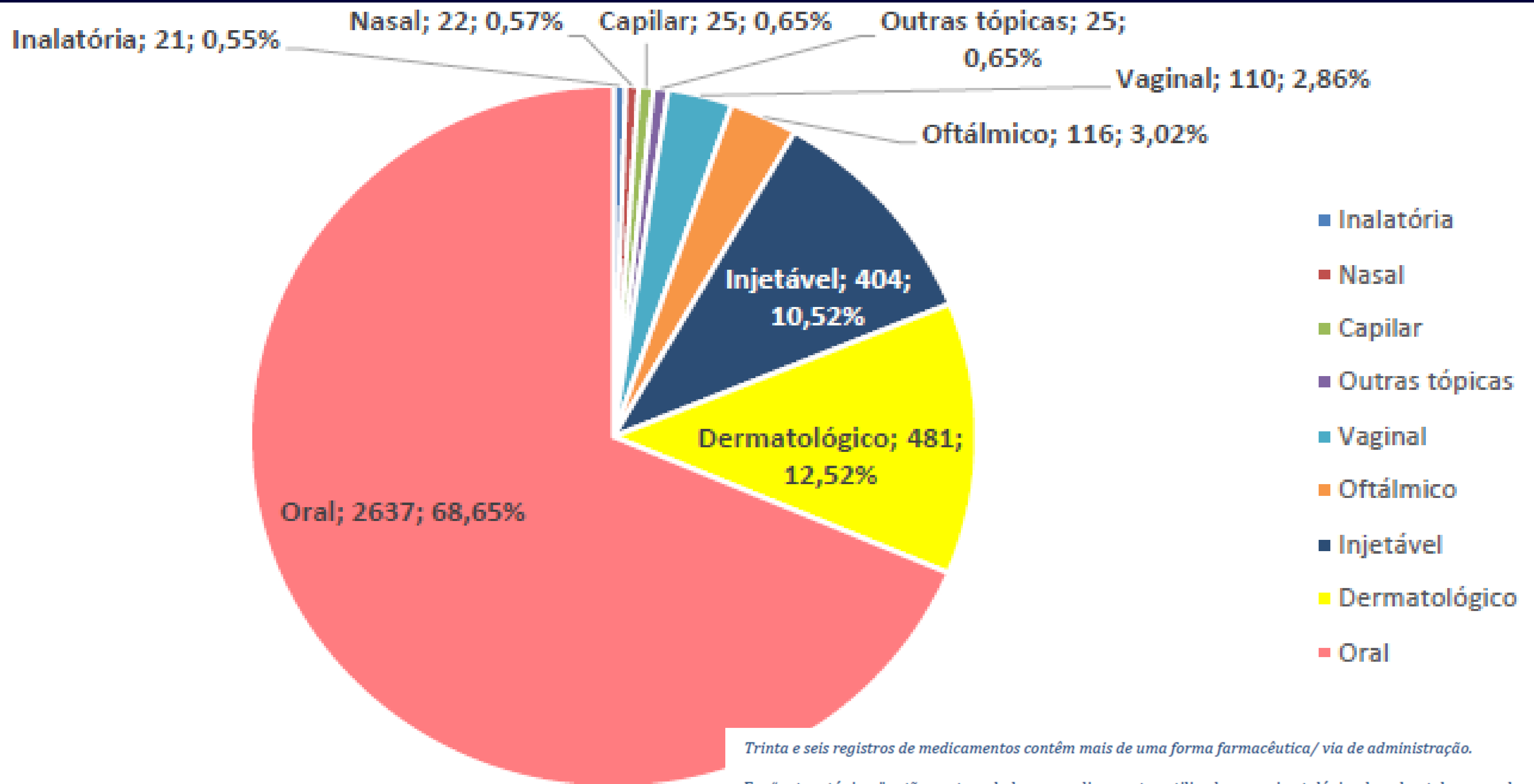
| | |
|-------------|----|
| Argentina | 22 |
| Canadá | 29 |
| França | 12 |
| Eslovênia | 11 |
| Espanha | 11 |
| EUA | 10 |
| Suíça | 9 |
| Áustria | 8 |
| Porto Rico | 11 |
| Grécia | 6 |
| Israel | 5 |
| Irlanda | 5 |
| Holanda | 3 |
| Turquia | 3 |
| Malta | 4 |
| Bangladesh | 6 |
| México | 3 |
| Dinamarca | 2 |
| Bélgica | 2 |
| Suécia | 2 |
| Uruguai | 6 |
| Finlândia | 2 |
| Polônia | 2 |
| Áustria | 2 |
| Reino Unido | 1 |
| Inglaterra | 1 |
| Romênia | 1 |
| Chile | 1 |
| Paraguai | 1 |

30 registros possuem dois países de fabricação, 8 registros possuem três países de fabricação e 2 registros possuem quatro países de fabricação.

Dados atualizados em 03/08/2016

Medicamentos Genéricos

Vias de administração



Dados atualizados em 03/08/2016

GUIA PARA PROVAS DE BIODISPONIBILIDADE RELATIVA/ BIOEQUIVALÊNCIA

Resolução-RE no 1170, de 19 de abril de 2006

**Guia para provas de biodiponibilidade
relativa/bioequivalência**

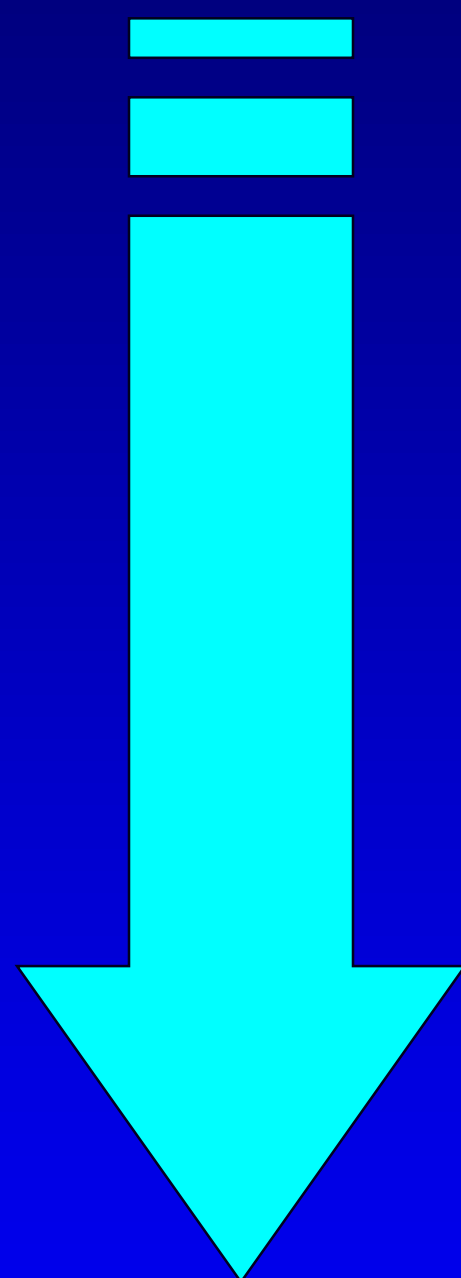
CLÍNICA

ETAPAS:

ANALÍTICA

ESTATÍSTICA

ELABORAÇÃO DO PROTOCOLO DE ESTUDO



OBJETIVO
DELINEAMENTO
POPULAÇÃO
REAÇÕES ADVERSAS
CONSIDERAÇÕES ÉTICAS
MÉTODO ANALÍTICO
TRATAMENTO ESTATÍSTICO
DESVIOS DE PROTOCOLO

APROVAÇÃO PELO COMITÊ DE
ÉTICA EM PESQUISA

PROJETO DE PESQUISA

**TERMO DE CONSENTIMENTO
LIVRE E ESCLARECIDO**

ETAPA CLÍNICA

Teste *versus* Referência

- ★ Equivalência farmacêutica e perfil de dissolução
- ★ T e R com o mesmo teor ($< 5\%$)
- ★ avaliação farmacocinética ou farmacodinâmica

ETAPA CLÍNICA

Teste *versus* Referência

- ★ **Fármaco inalterado**
- ★ **Metabólito ativo formado por metabolismo pré-sistêmico**

**BRASIL. Agência Nacional de Vigilância Sanitária. Resolução
RE nº-1170 de 29 de abril de 2006- Lista 2 (415 FÁRMACOS)
atualizada em 03 de junho de 2016**

FCFRP-USP

| INALTERADO | METABÓLITO | INALTERADO | METABÓLITO |
|------------------------|---|--------------------------|---------------------------------------|
| Ácido acetilsalicílico | Ac. Salicílico | Fenofibrato | Ácido Fenofíbrico |
| Aminofilina | Teofilina | Flutamida | 2-hidroxi-flutamida |
| Axetil cefuroxima | Cefuroxima | Fosamprenavir | Amprenavir |
| Azatioprina | 6-Mercaptopurina | Fosinopril | Fosinoprilato |
| Benazepril | Benazeprilato | Hesperidina | Hesperetin |
| Benzoilmetronidazol | Metronidazol | Leflunomida | Terflunomida [M1 (A771726)] |
| Betaistina | Ácido 2-piridil acético | Levodopa + Benserazida | Levodopa + 3-O-Metildopa |
| Candesartana | Candesartana CV11974 | Limeciclina | Tetraciclina |
| Ciclesonida | Desisobutyryl ciclesonide | Micofenolato de sódio | Ácido Micofenólico |
| Citicolina | Colina | Micofenolato de mofetila | Ácido Micofenólico |
| Clopidogrel | Ácido carboxílico clopidogrel (SR26334) | Nitazoxanida | Tizoxanida |
| Cloxazolam | Clordesmetildiazepam | Oxcarbazepina | 10,11-dihidro,10-hidroxicarbamazepina |
| Deflazacorte | 21-OH-Deflazacorte | Prednisona | Prednisolona |
| Desogestrel | 2-3-cetodesogestrel (Etonogestrel) | Sultamicilina | Ampicilina + Sulbactam |
| Diacereína | Reína | Tibolona | 3-alfa-hidroxitibolona |
| Diidroergotamina | 8-Hidroxi-diidroergotamina | Tiocolchicosídeo | M1 |
| Diosmina | Diosmetin | Valaciclocir | Aciclovir |
| Dipirona | 4-N-metilaminoantipirina (MAA) | Valganciclovir | Ganciclovir |
| Divalproato Sódico | Ácido valpróico livre | | |

DELINEAMENTO DO ESTUDO

CRUZADO 2x2 (*CROSSOVER*)

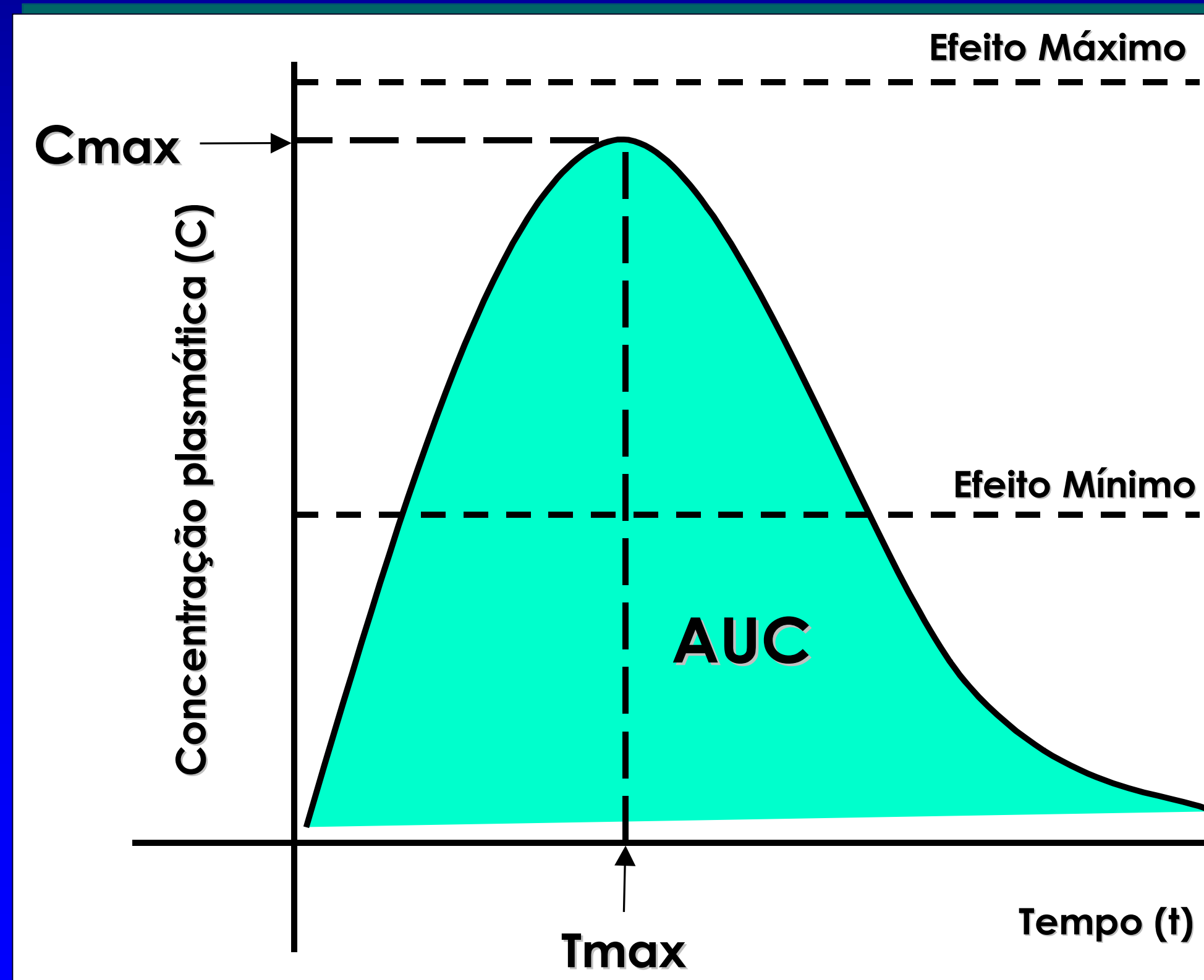
| Seqüência | Período | |
|-----------|---------|---|
| | 1 | 2 |
| 1 | R | T |
| 2 | T | R |

R= referência; T= teste

Dose simples ou múltipla administrada em jejum com volume de líquido padronizado (200ml)

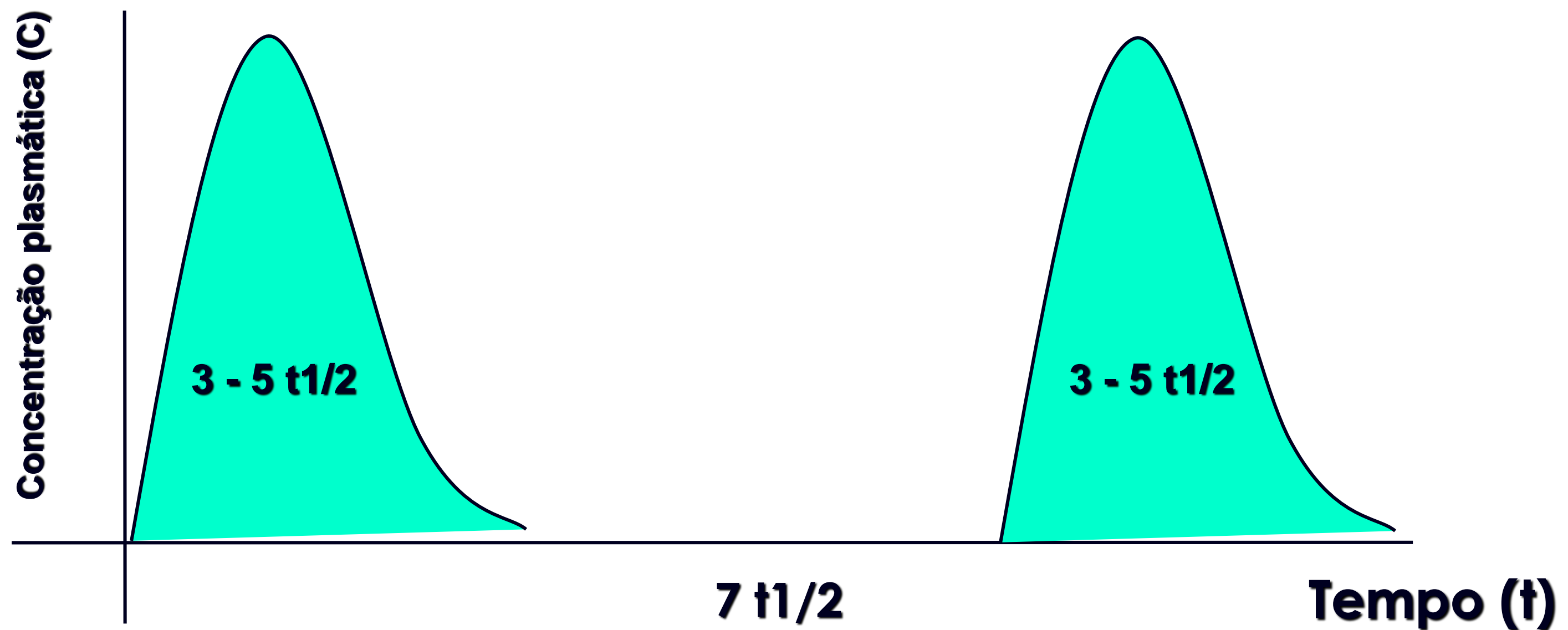
CRONOGRAMA DE COLETA DAS AMOSTRAS

Tempo igual ou superior a 3-5x $t_{1/2}$



PERÍODO DE “WASHOUT”

Intervalo de, no mínimo, 7 meias-vidas

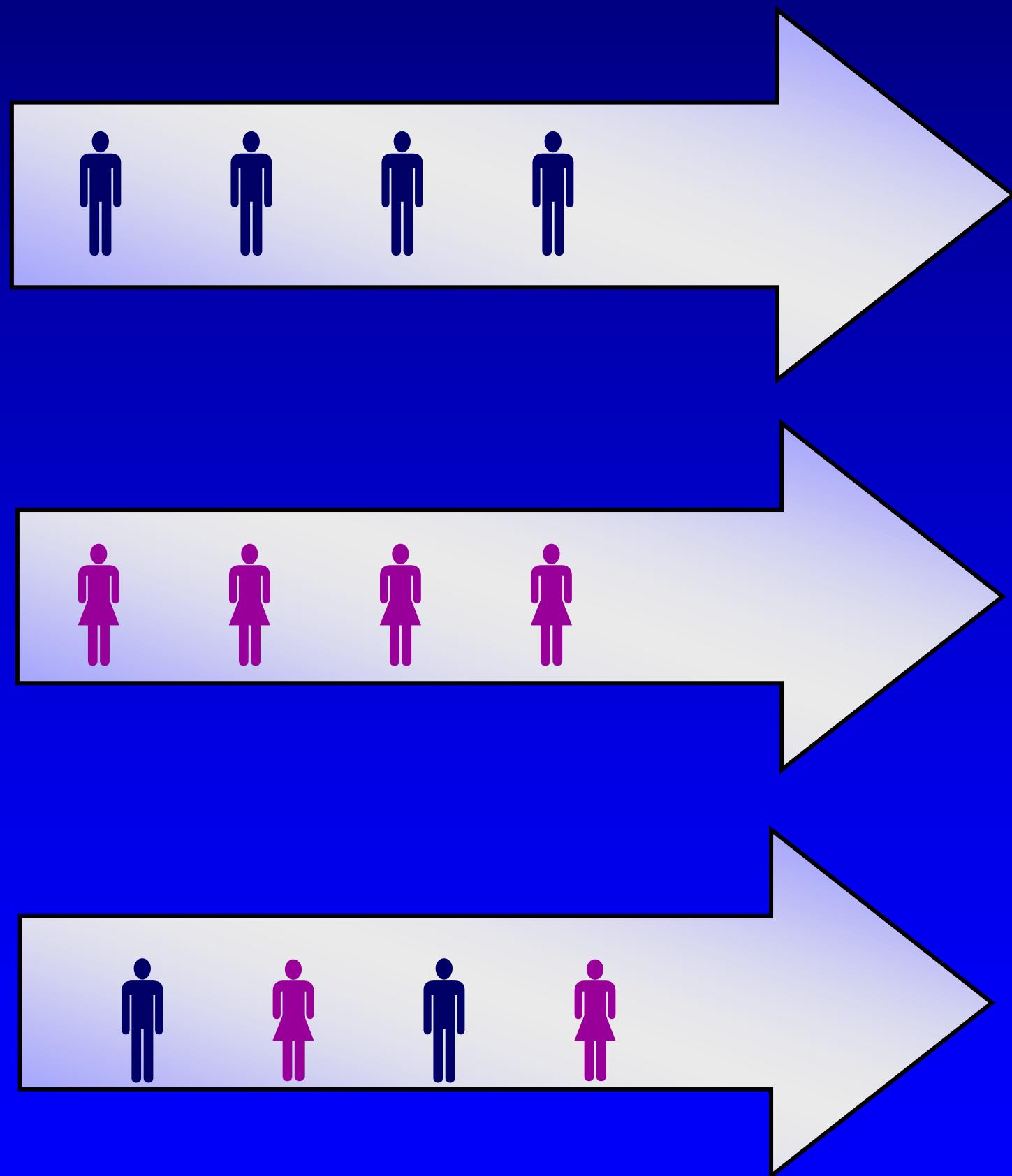


ETAPA CLÍNICA

Número de voluntários (≥ 12)

- ★ poder do teste
- ★ coeficiente de variação intra-individual
- ★ “dropouts”

POPULAÇÃO DO ESTUDO



>18 ANOS

+/- 15% PESO

CONSIDERADO NORMAL

EVITAR FUMANTES E

VOLUNTÁRIOS COM

HISTÓRICO DE ABUSO DE

DROGAS

ETAPA CLÍNICA

Inclusão de voluntários saudáveis

EXAMES CLÍNICOS

EXAME FÍSICO

ELETROCARDIOGRAMA

EXAMES LABORATORIAIS

EXAMES HEMATOLÓGICOS

BIOQUÍMICOS (FUNÇÃO HEPÁTICA E RENAL)

SOROLÓGICOS (HEPATITE B, HEPATITE C E HIV)

BETA HCG (PARA MULHERES)

URINA TIPO I

ESTUDOS COM ALIMENTAÇÃO

- ➡ Formas farmacêuticas orais de liberação prolongada ou controlada
- ➡ Formas farmacêuticas orais com revestimento gastro-resistente e formas farmacêuticas orais de liberação imediata → consultar lista 1 ANVISA – Forma de administração

Influência de alimentos na biodisponibilidade de fármacos

ANVISA, Resolução RE nº-1170 de 19 de abril de 2006
atualizada em 03 de junho de 2016

ALIMENTAÇÃO

| | | | |
|--------------------------|----------------------------|---------------------------|-----------------------------|
| Acarbose | Diacereína | Lercanidipino | Pinavério |
| Ácido Ursodesoxicólico | Etionamida | Linagliptina + Metformina | Propafenona |
| Acitretina | Exemestano | Lovastatina | Ritonavir |
| Albendazol | Fenofibrato | Mefloquina | Rivaroxabana 20 mg |
| Axetil cefuroxima susp | Ganciclovir | Metformina | Rivastigmina |
| Biperideno | Glicosamina | Metformina + Pioglitazona | Rosiglitazona + Glimepirida |
| Bromocriptina | Glibenclamida + Metformina | Nelfinavir | Saquinavir |
| Capecitabina | Glimepirida + Metformina | Nitazoxanida | Selegilina |
| Cetoconazol | Hidroxicloroquina | Nitrendipino | Ticlopidina |
| Cetoprofeno | Imatinib | Nitrofurantoína | Trazodona |
| Cinacalcete (cloridrato) | Isotretinoína | Omidazol | Valganciclovir |
| Darunavir | Itraconazol | Pentoxifilina | Ziprasidona |

ALIMENTAÇÃO e JEJUM

| | | | | |
|--------------|--------------------|---------------------|------------|---------------|
| Alfuzosina | Darifenacina | Medroxiprogesterona | Sirolimo | Tenofovir |
| Amiodarona | Divalproato sódico | Piridoxina | Sulpirida | Trimetazidina |
| Buspirona | Everolimo | Pitavastatina | Tacrolimo | |
| Ciclosporina | Fampridina | Propiltiouracil | Talidomida | |

ETAPA ANALÍTICA

Resolução-RE no 27, de 17 de maio de 2012

**Guia para validação de métodos analíticos e
bioanalíticos**

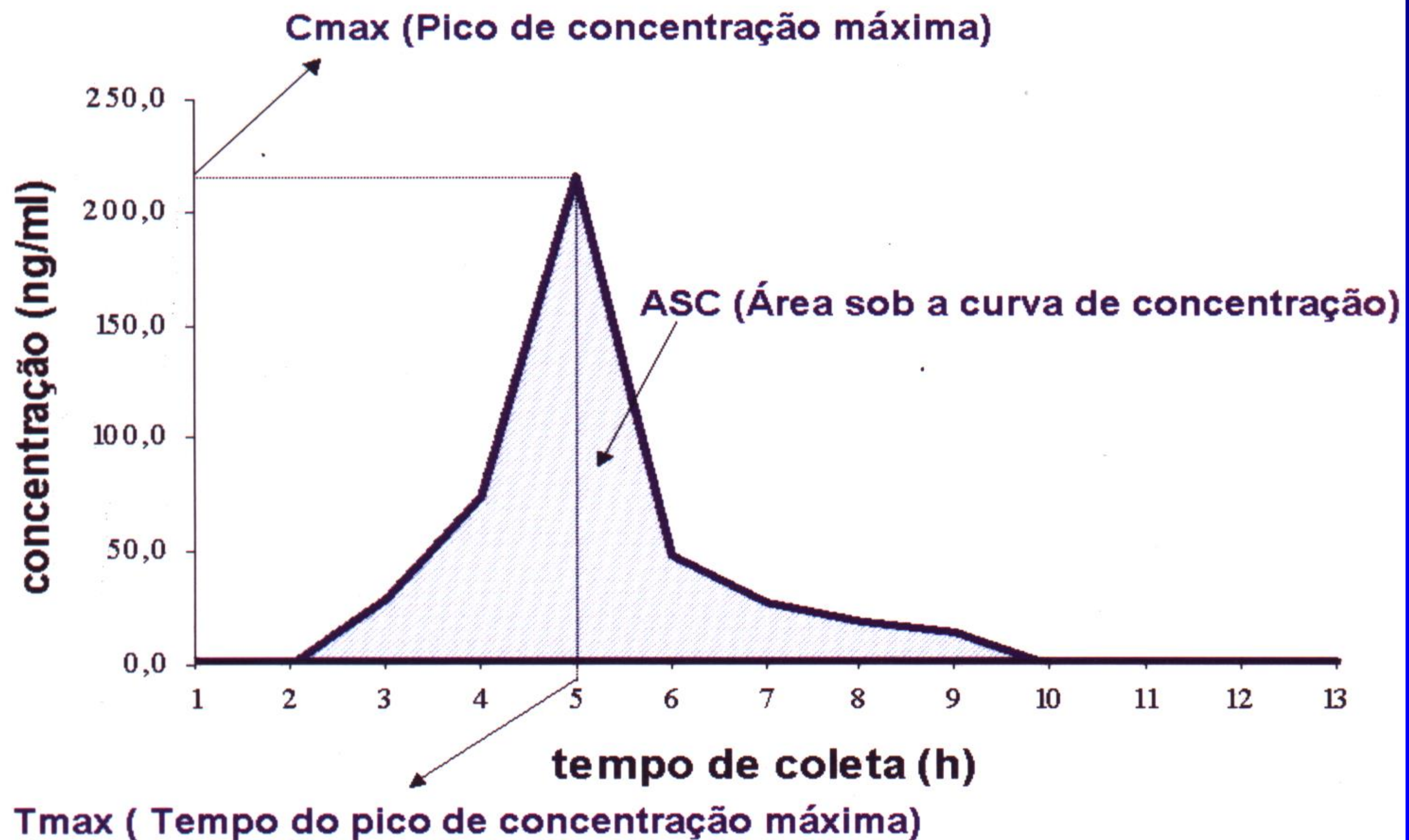
ETAPA ANALÍTICA

Normas internacionais de BPL

- ★ Método validado descrito na forma de POP
- ★ Reanálise de no máximo 20% das amostras
- ★ Análise sem réplica, em duplicata ou triplicata
- ★ Determinações com valores $< \text{LIQ}$ deverão ser consideradas iguais a zero

ETAPA ESTADÍSTICA

CURVA DE CONCENTRAÇÃO PLASMÁTICA DE UM FÁRMACO



Análise descritiva das concentrações plasmáticas

concentração plasmática (ng/ml) *versus* tempo (h) (n=24)

Medicamento referência

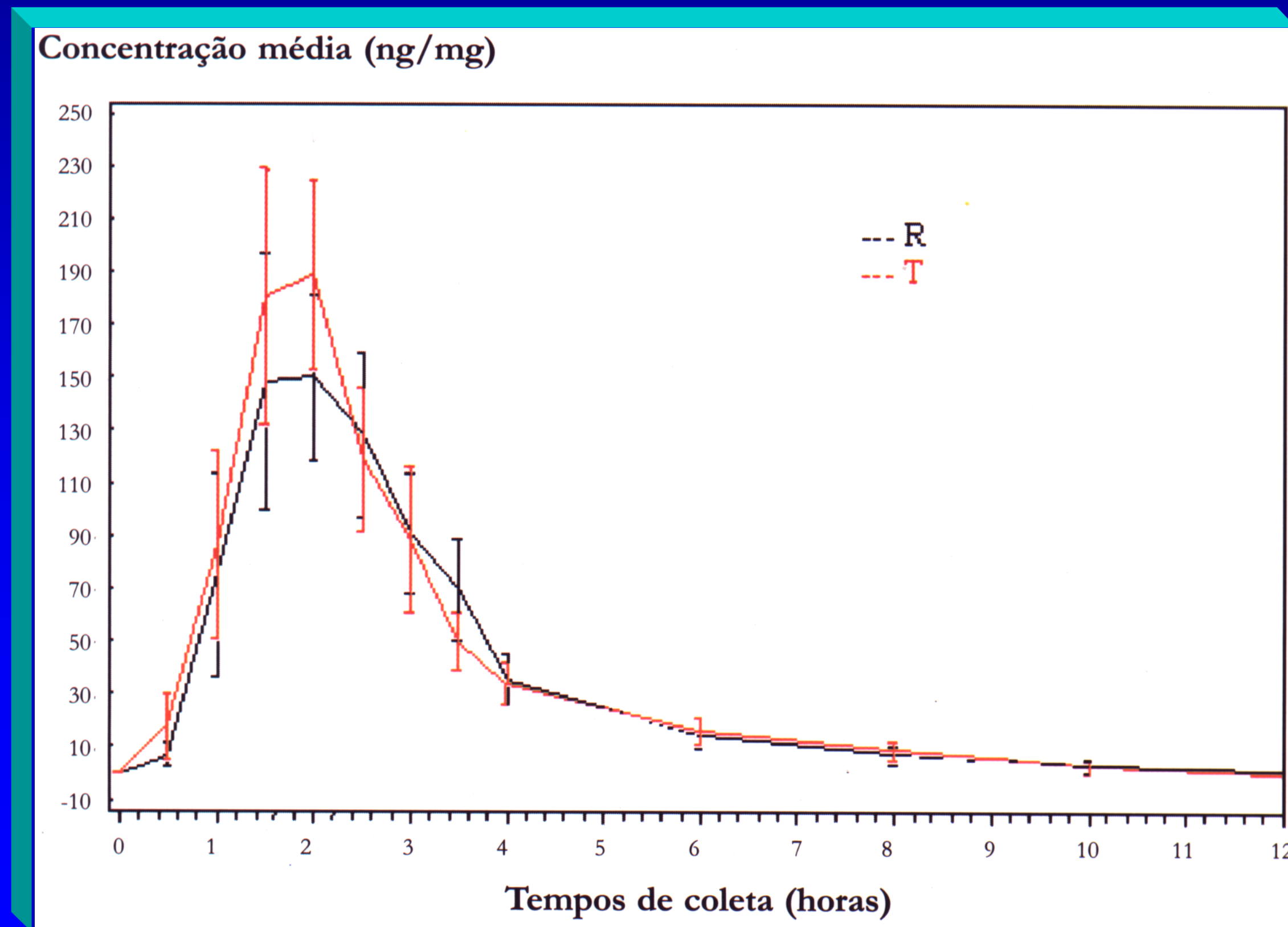
Medicamento teste

| Tempo | Média | Mediana | Desvio-Padrão | Erro-Padrão | CV(%) | Mínimo | Máximo |
|-------|--------|---------|---------------|-------------|--------|--------|--------|
| 0 | 0,00 | 0,00 | 0,00 | 0,00 | - | 0,00 | 0,00 |
| 0,5 | 6,99 | 0,00 | 10,85 | 2,22 | 155,33 | 0,00 | 32,50 |
| 1,0 | 75,45 | 43,25 | 95,16 | 19,42 | 126,12 | 0,00 | 357,10 |
| 1,5 | 148,15 | 115,20 | 116,04 | 24,20 | 78,32 | 0,00 | 515,50 |
| 2 | 149,86 | 146,30 | 75,61 | 15,43 | 50,45 | 23,50 | 317,20 |
| 2,5 | 128,12 | 117,95 | 75,42 | 15,39 | 58,86 | 25,10 | 297,40 |
| 3 | 91,08 | 65,90 | 56,46 | 11,52 | 61,99 | 14,20 | 217,90 |
| 3,5 | 69,93 | 56,90 | 47,28 | 9,65 | 67,60 | 11,50 | 177,90 |
| 4 | 35,24 | 29,30 | 24,62 | 5,03 | 69,88 | 0,00 | 81,30 |
| 6 | 15,04 | 13,70 | 13,26 | 2,71 | 88,14 | 0,00 | 37,20 |
| 8 | 7,34 | 0,00 | 8,79 | 1,79 | 119,70 | 0,00 | 22,80 |
| 10 | 2,87 | 0,00 | 5,86 | 1,20 | 204,56 | 0,00 | 17,50 |
| 12 | 0,69 | 0,00 | 3,37 | 0,69 | 489,90 | 0,00 | 16,50 |

| Tempo | Média | Mediana | Desvio-Padrão | Erro-Padrão | CV(%) | Mínimo | Máximo |
|-------|--------|---------|---------------|-------------|--------|--------|--------|
| 0 | 0,00 | 0,00 | 0,00 | 0,00 | - | 0,00 | 0,00 |
| 0,5 | 17,24 | 0,00 | 29,76 | 6,07 | 172,59 | 0,00 | 129,70 |
| 1,0 | 85,81 | 56,30 | 87,92 | 17,95 | 102,46 | 0,00 | 291,40 |
| 1,5 | 180,17 | 188,40 | 118,08 | 24,10 | 65,54 | 12,40 | 586,20 |
| 2 | 187,76 | 200,25 | 87,47 | 17,85 | 46,59 | 38,90 | 335,50 |
| 2,5 | 118,49 | 93,40 | 67,03 | 13,68 | 56,57 | 22,50 | 297,70 |
| 3 | 87,66 | 63,90 | 68,87 | 14,06 | 78,57 | 23,70 | 324,50 |
| 3,5 | 49,29 | 43,40 | 27,46 | 5,61 | 55,71 | 11,30 | 116,90 |
| 4 | 33,42 | 27,80 | 19,61 | 4,00 | 58,67 | 10,70 | 88,20 |
| 6 | 15,26 | 15,35 | 11,58 | 2,36 | 75,87 | 0,00 | 39,20 |
| 8 | 8,39 | 8,95 | 8,70 | 1,77 | 103,67 | 0,00 | 23,20 |
| 10 | 2,36 | 0,00 | 5,47 | 1,12 | 231,37 | 0,00 | 17,10 |
| 12 | 0,00 | 0,00 | 0,00 | 0,00 | - | 0,00 | 0,00 |

Análise descritiva das concentrações plasmáticas

Curvas de concentração plasmática média \pm 2 erros padrão



AUC e C_{max}

Análise de variância (ANOVA)

seqüência

voluntário dentro da seqüência

período

tratamento

Análise de variância (ANOVA)

log natural (Cmax)

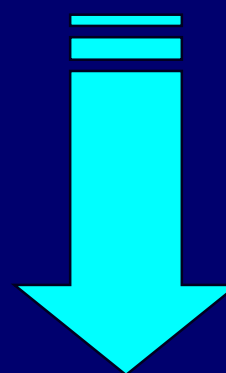
| FONTE | g.l. | SQ | QM | F | Valor-p | |
|---------------------|------|----------|----------|----------|-----------|-----|
| Período | 1 | 0,01752 | 0,01752 | 0,605045 | 0,4443 | NS |
| Voluntário (Seq) | 24 | 2,95699 | 0,123208 | 4,25485 | 0,0003702 | *** |
| Formulação | 1 | 0,066798 | 0,066798 | 2,3068 | 0,1419 | NS |
| Seqüência | 1 | 0,001325 | 0,001325 | 0,010754 | 0,9183 | NS |
| Erro | 24 | 0,69497 | 0,028957 | | | |
| Total | 51 | 3,7376 | | | | |

ANÁLISE ESTATÍSTICA

Bioequivalência média

- ★ Log natural de AUC e C_{max}
- ★ IC90% para a diferença das médias

★ Antilogarítmos dos IC90%



IC90% para a razão das médias geométricas entre os produtos teste e referência



ANÁLISE ESTATÍSTICA

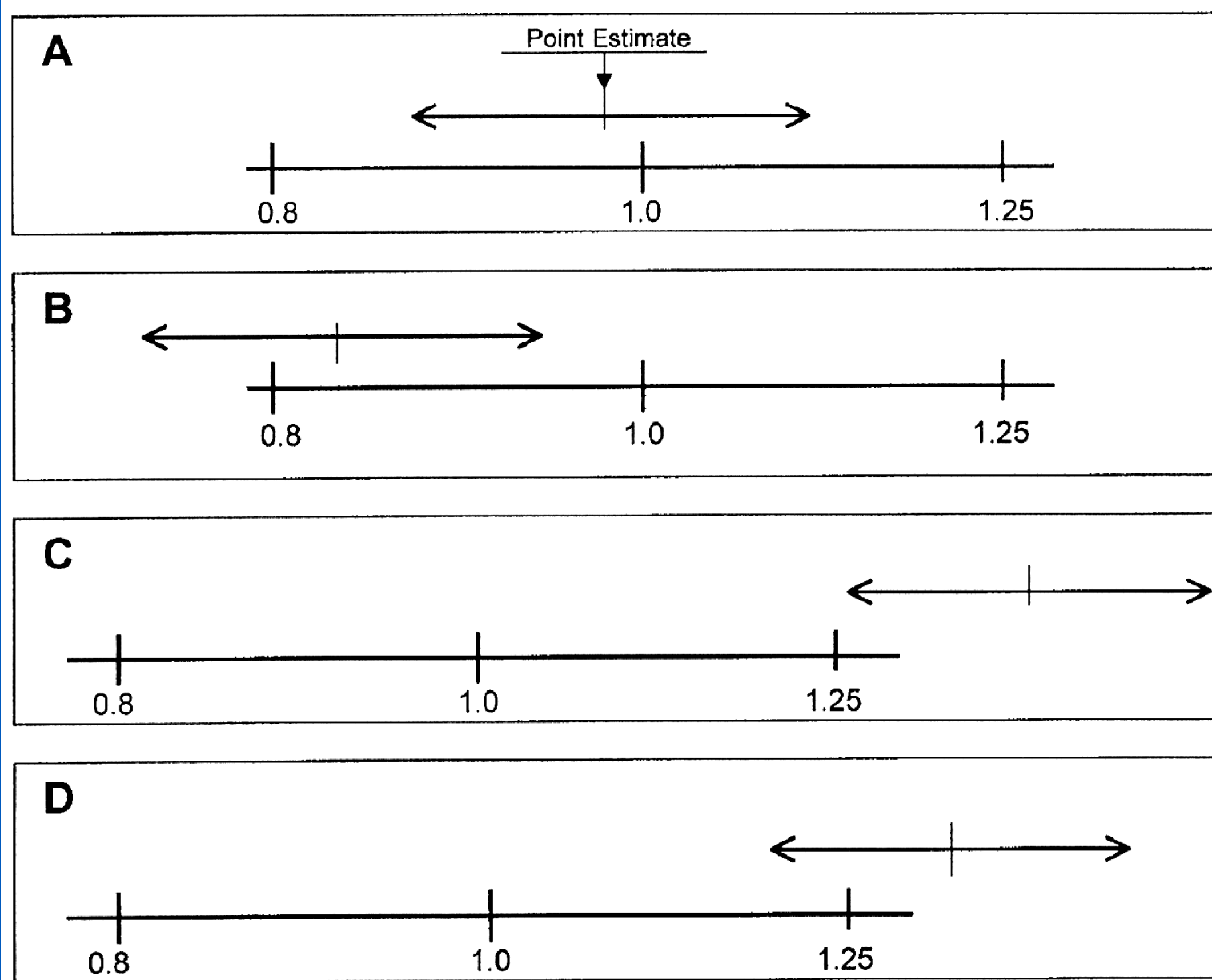
Bioequivalência média

**Tmax é analisado como
diferença individual,
construindo-se IC90%,
utilizando-se teste não paramétrico**

ANÁLISE ESTATÍSTICA

Conclusão de bioequivalência

IC 90% compreendido entre 80 e 125%

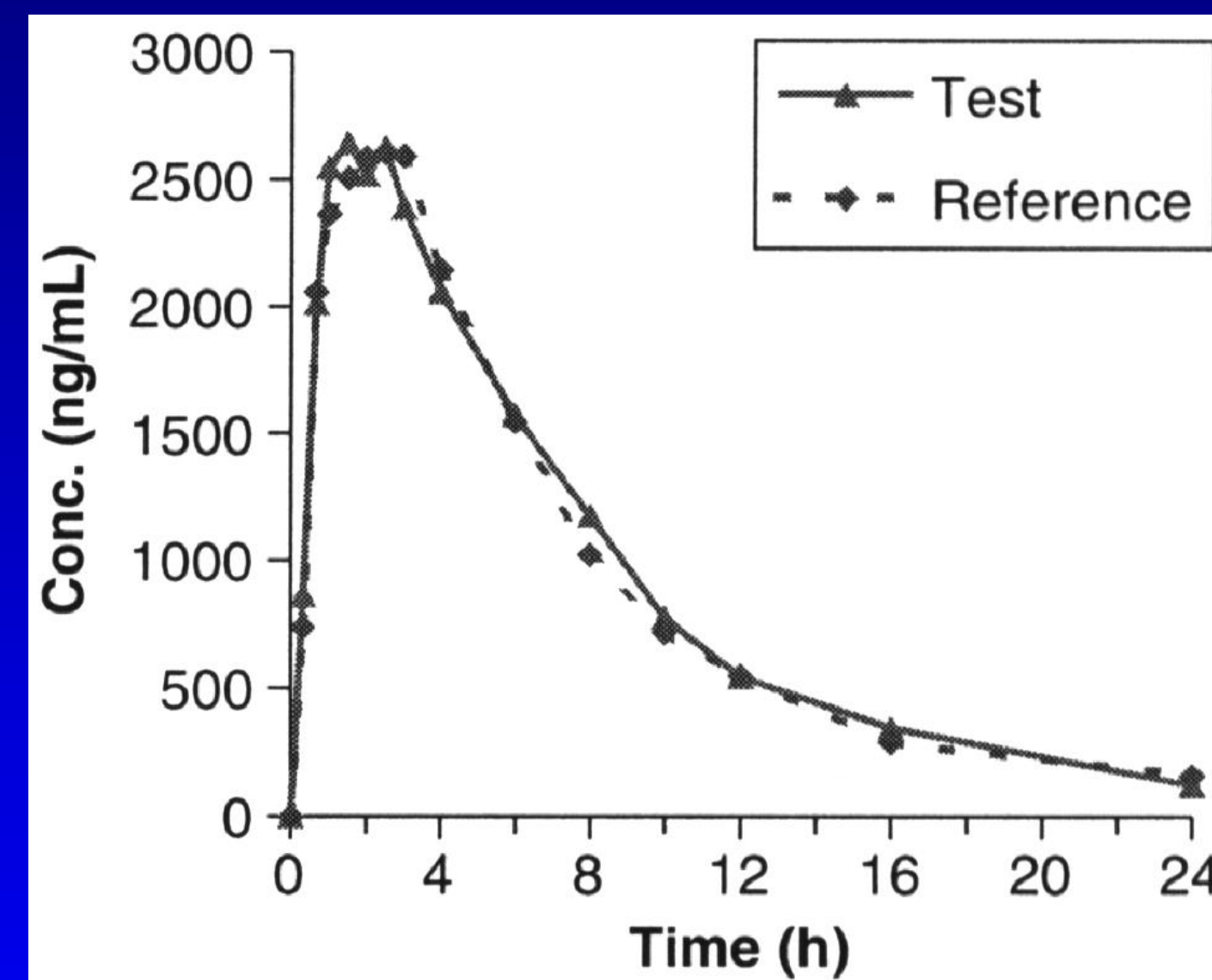


Bioequivalência de duas formulações de claritromicina 500mg

IC90%

$AUC^{0-\infty}$ (razão teste/referência) 0,90 - 1,11

C_{max} (razão teste/referência) 0,91 - 1,10



$n = 24$

IC 90% compreendido entre 80 e 125%

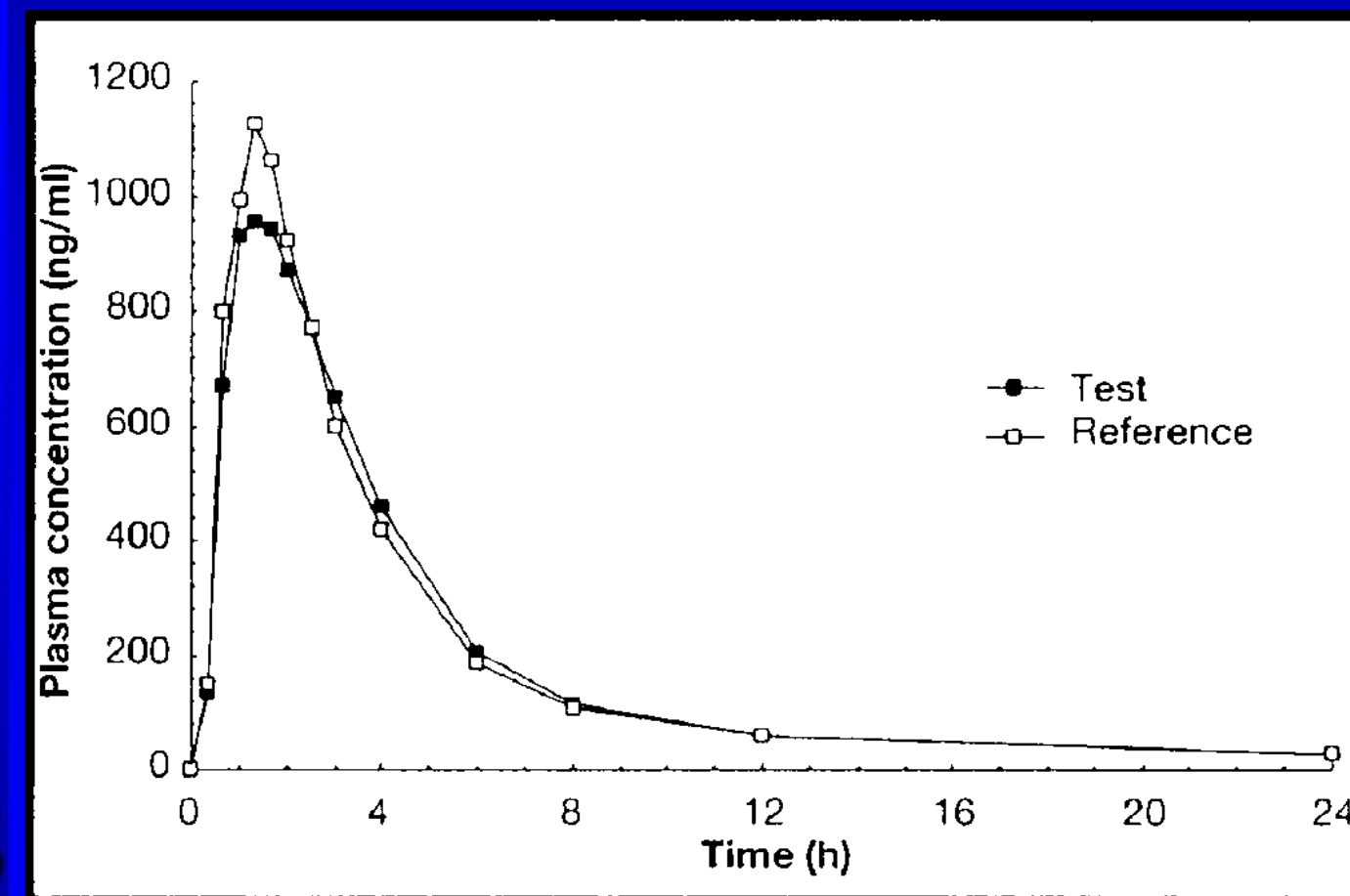
Critérios de aceitação do IC de 90% para C_{max}

Terbinafina

IC 90% para C_{max} 0,70 - 1,43

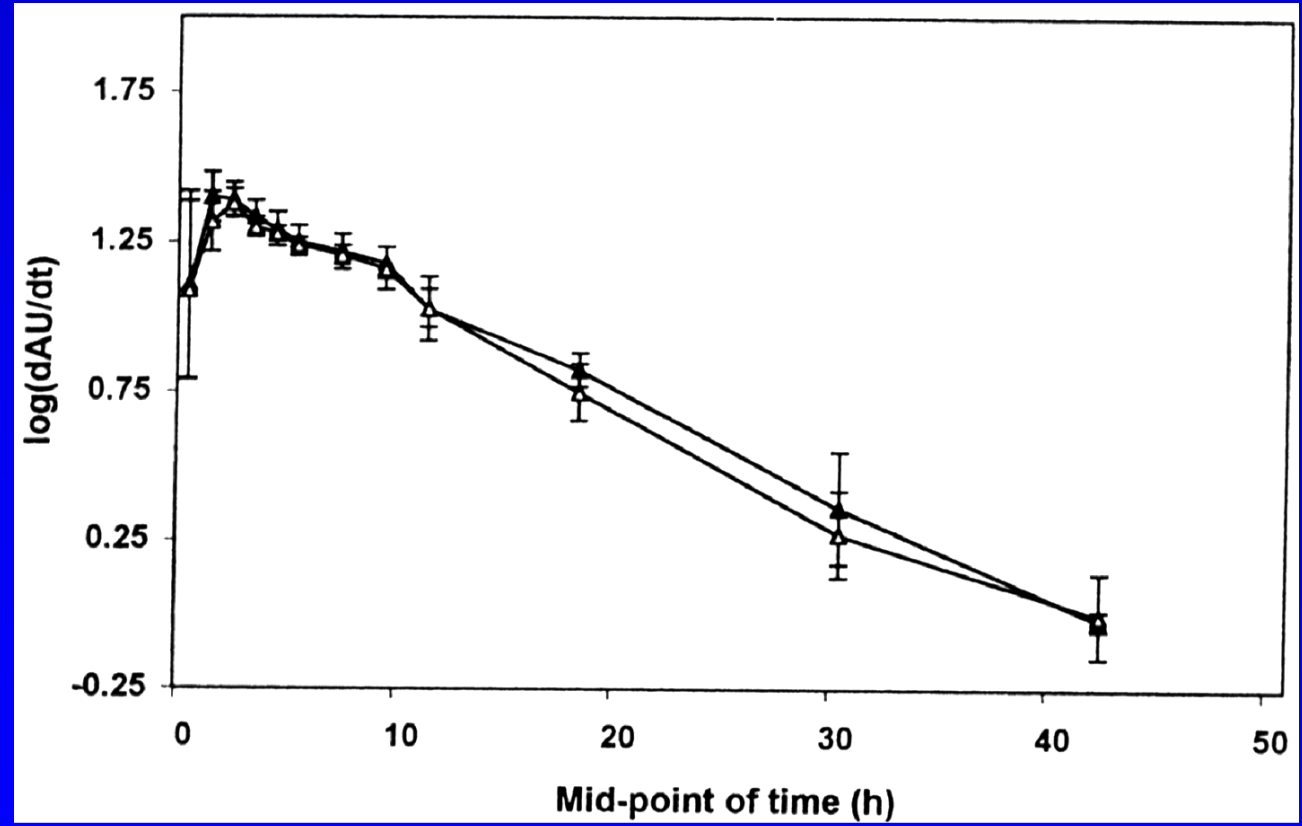
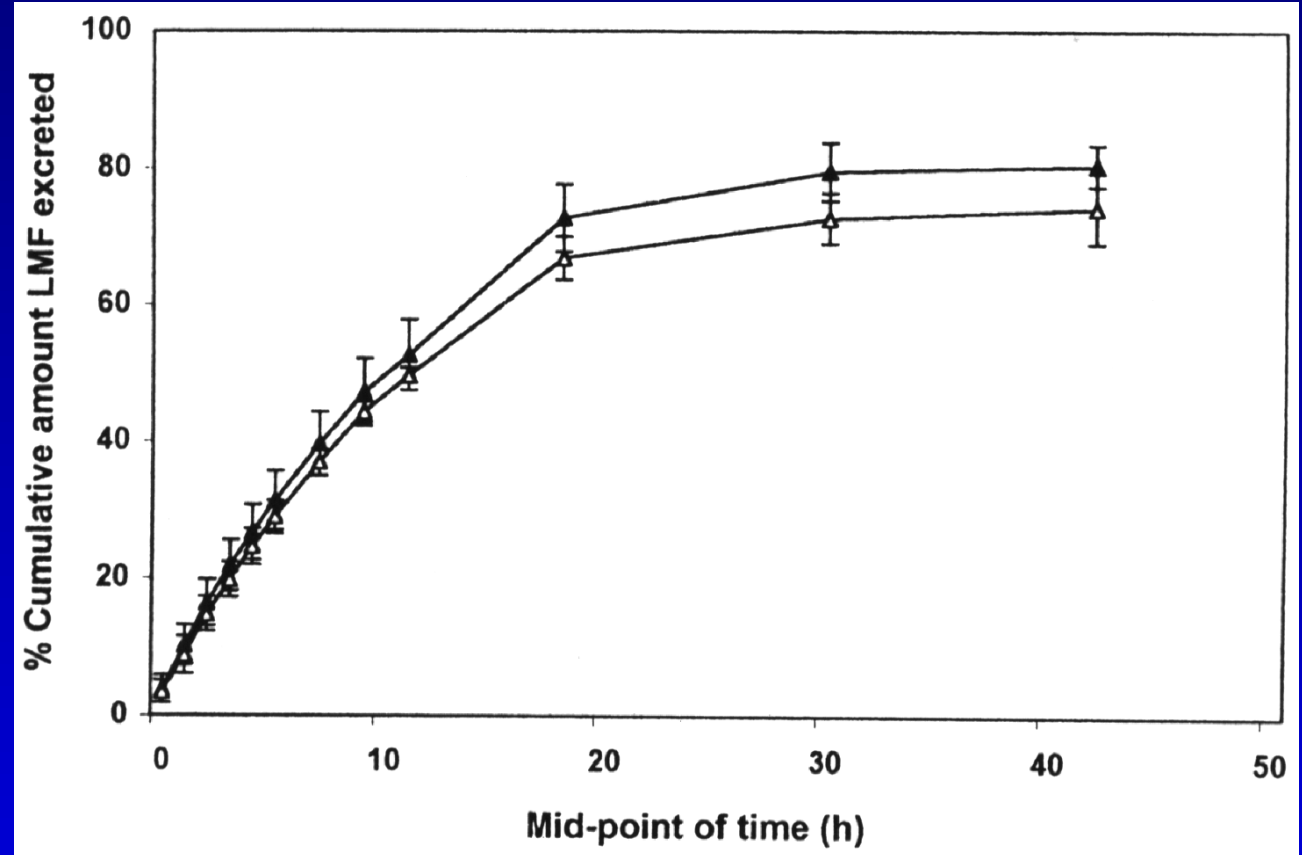
| | IC90% |
|---|-------------|
| AUC^{0-t} (razão teste/referência) | 0,89 - 1,09 |
| $AUC^{0-\infty}$ (razão teste/referência) | 0,91 - 1,11 |
| C_{max} (razão teste/referência) | 0,71 - 0,95 |
| t_{max} (h)(diferença teste - referência) | 0,00 - 0,40 |

$n = 18$





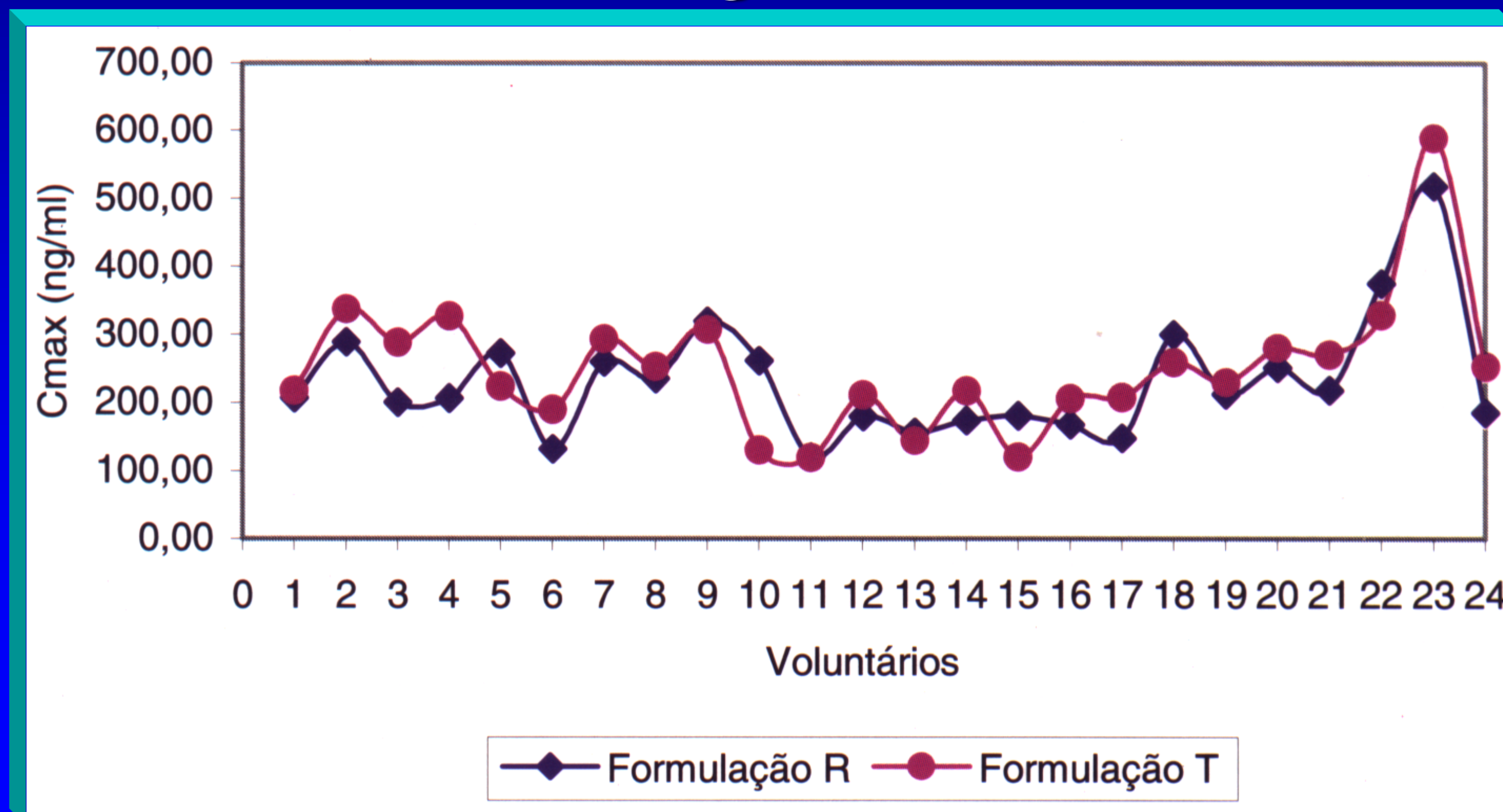
Bioequivalência de duas formulações de lomefloxacinina: dados de excreção urinária



| IC90% | |
|--|----------------------|
| AUC⁰⁻⁴⁸ (razão teste/referência) | 100,2 - 102,4 |
| AUC^{0-∞} (razão teste/referência) | 100,5 - 103,9 |
| (dAU/dt)_{max} | 97,90 - 105,0 |

Detecção de outliers (observações atípicas)

C_{max} por voluntário nas
formulações R e T





Dose / Concentração Plasmática

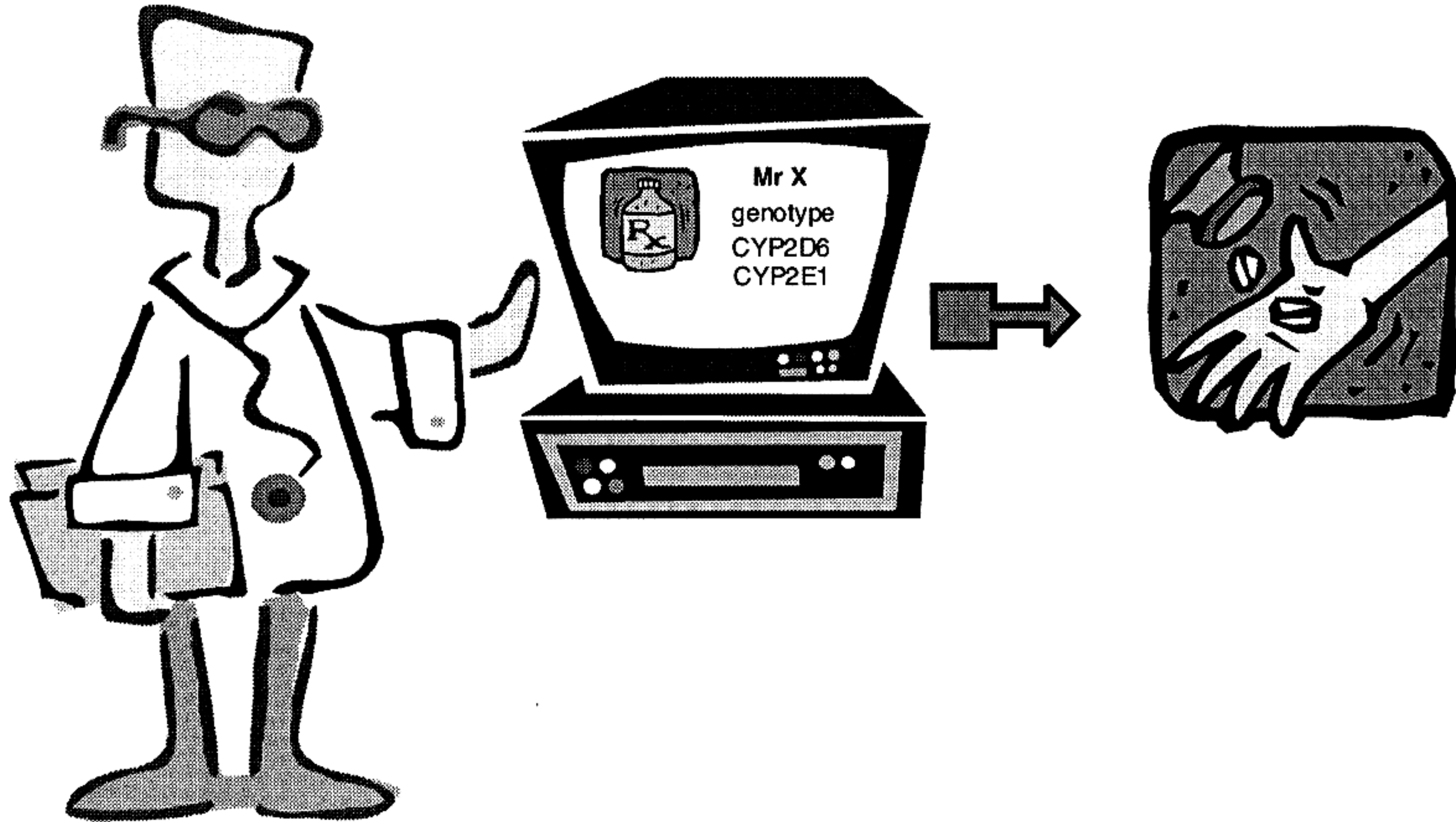
especialidade farmacêutica

paciente

fármacos associados

POLIMORFISMO

Figure 2. The future of prescribing.



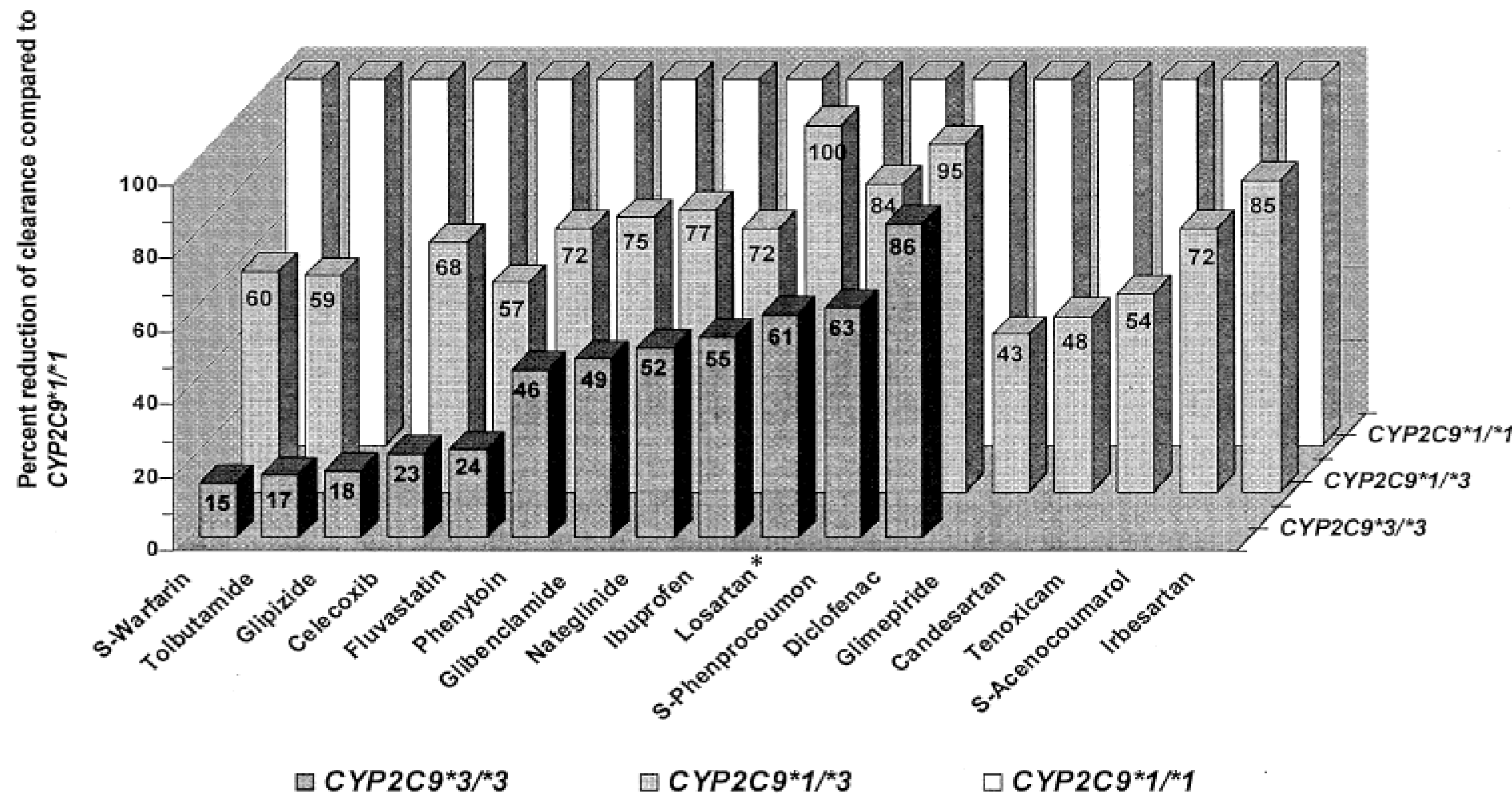
Projected future scenario where the patient has been screened for important polymorphisms that are involved in the regulation of a number of drugs. This information will be recorded electronically, (say by a 'smart card') and the information fed into a computer, which has software that advises the doctor about appropriate prescribing.

CYP: Cytochrome P450.

REFARGEN

REDE NACIONAL
DE
FARMACOGENÉTICA

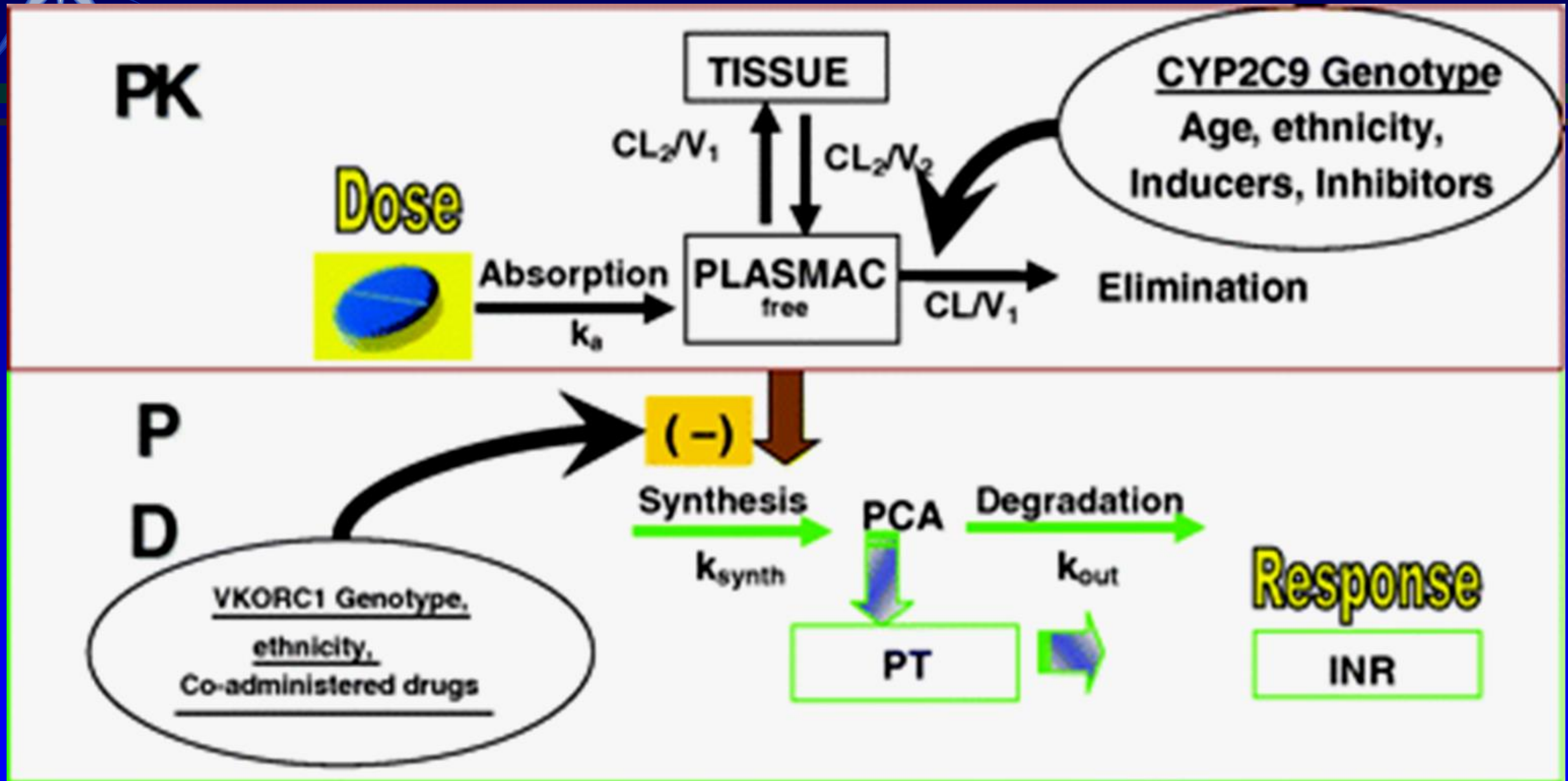
Genotype Frequencies of CYP2C9 Polymorphisms in Asian, African, and White Subjects



| Genotype | Activity | Population frequency (%) | | |
|-------------|----------------------|--------------------------|----------------|----------------|
| | | African subjects | Asian subjects | White subjects |
| CYP2C9*1/*1 | Normal | 87.0 | 96.5 | 65.3 |
| CYP2C9*1/*2 | Minor reduction | 8.7 | 0.0 | 20.4 |
| CYP2C9*2/*2 | Moderately reduction | 0.0 | 0.0 | 0.9 |
| CYP2C9*1/*3 | Moderately reduction | 4.3 | 3.5 | 11.6 |
| CYP2C9*2/*3 | Moderately reduction | 0.0 | 0.0 | 1.4 |
| CYP2C9*3/*3 | Very low | 0.0 | 0.0 | 0.4 |

Warfarin Therapy

FCFRP-USP



Schematic views of how various genetic and nongenetic factors affect warfarin pharmacokinetics (PK) and pharmacodynamics (PD) resulting in its anticoagulation effect (INR)³³ (adapted from reference³³). k_a , absorption rate constant; V , volume of distribution; CL , clearance; PCA, prothrombin complex activity; PT, prothrombin time; INR, international normalized ratio.

Warfarin Therapy

FCFRP-USP

Prediction of Warfarin Dose in a Typical Patient

CYP2C9 Genotype

VKORC1 Genotype

***1/*1**

***1/*2**

***1/*3**

***2/*2**

***2/*3**

***3/*3**

GG

6

5

4

4

3.5

3

GA

5

4

3

3

2.5

2

AA

3

2.5

2

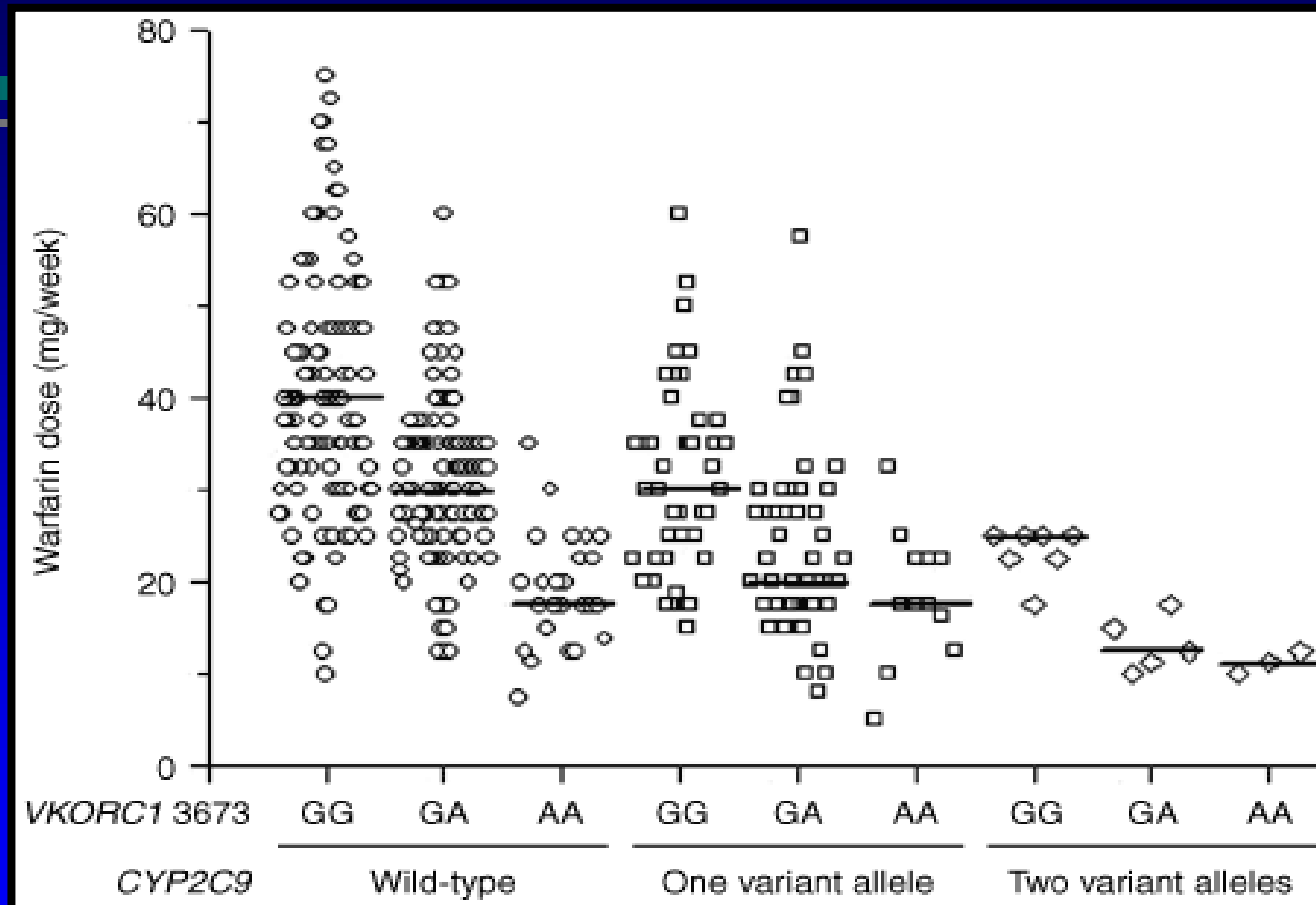
2

2

1.5

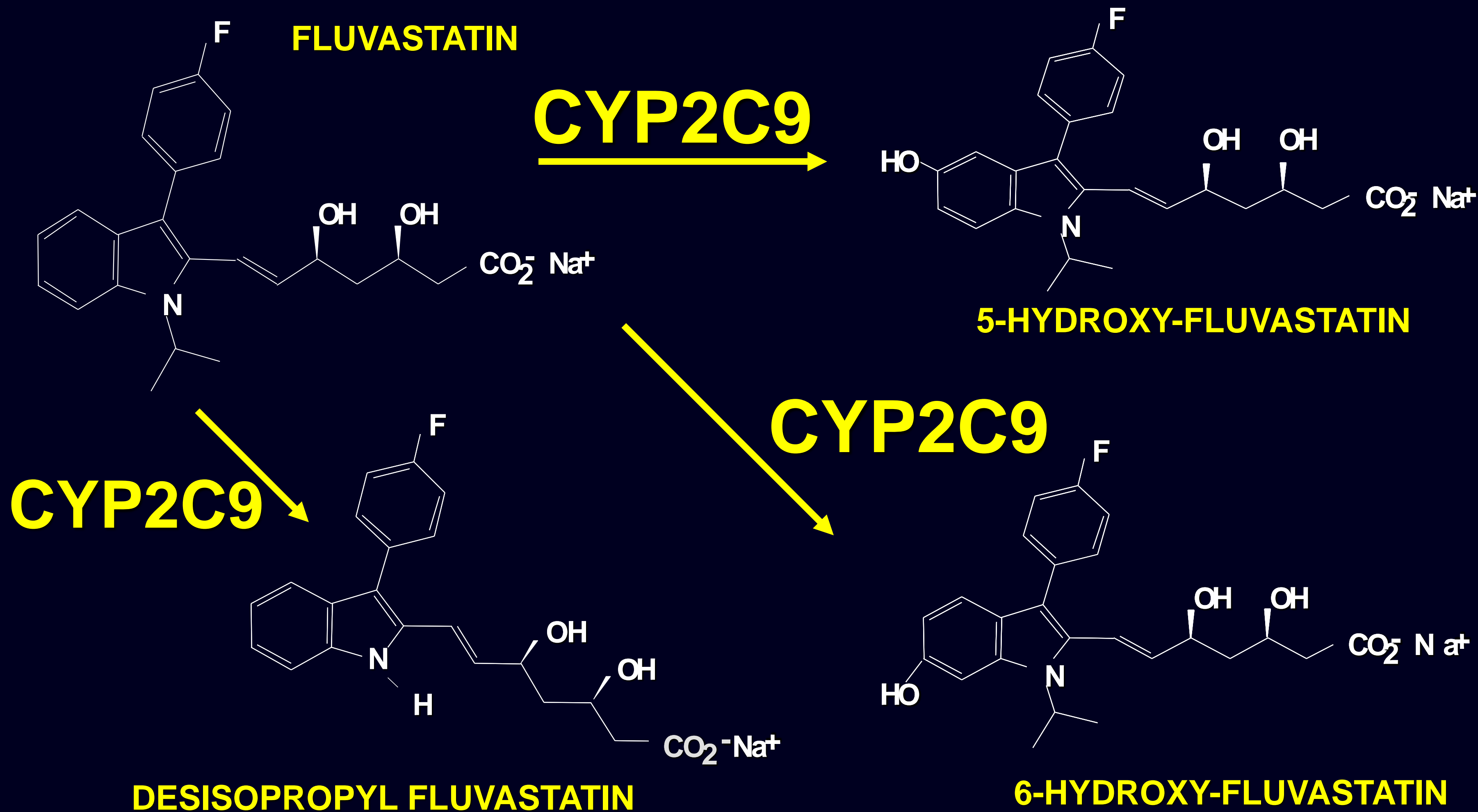
The estimated dose of warfarin (mg/d) according to genotype for a typical patient (65 years old, male, Caucasian, body surface area 2.0, nonsmoker, no other concomitant medications, with atrial fibrillation, target international normalized ratio of 2.5). Warfarin dose was predicted according to <http://www.warfarindosing.org> and adjusted to the next 0.5 mg.

Warfarin Therapy

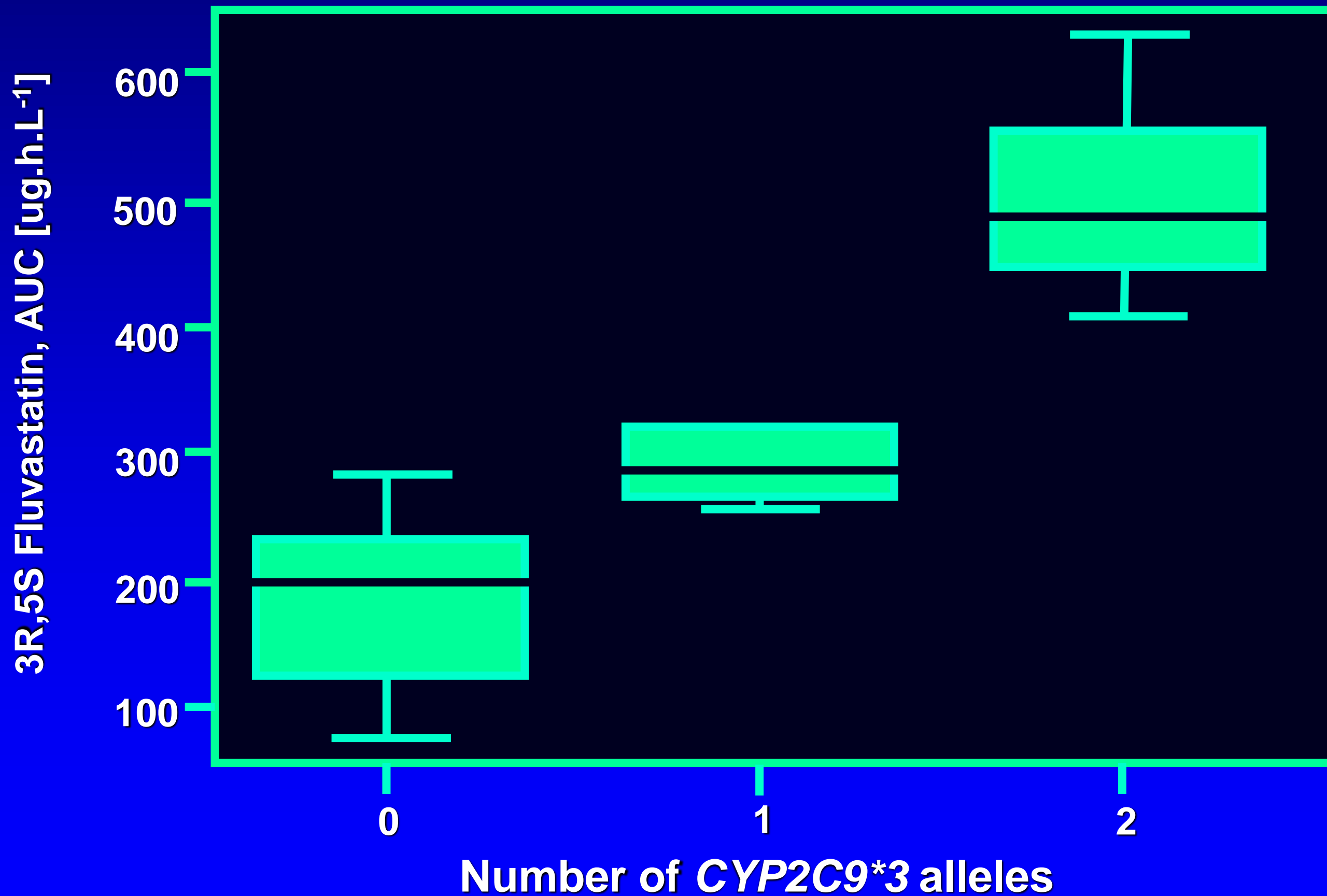


Association of *CYP2C9* and *VKORC1* 3673G>A polymorphisms (abscissa) with weekly warfarin dose requirements (ordinate). *CYP2C9* genotype is labeled as wild-type (*1/*1), one variant allele (*1/*2, *1/*3, or *1/*5), or two variant alleles (*2/*2, *2/*3, *2/*11, or *3/*3). Within each *CYP2C9* genotype, the *VKORC1* genotype at 3673G>A is shown as GG, GA, or AA.

FLUVASTATIN METABOLISM



DIFFERENCES IN AUC OF 3R,5S-FLUVASTATIN IN CARRIERS OF 0, 1 AND 2 CYP2C9*3 ALLELES



CYP2D6 PHENOTYPES

| LIKELY PHENOTYPE | ACTIVITY SCORE | GENOTYPES | EXAMPLE OF DILOTYPES |
|---|----------------|---|---|
| ASSIGNMENT OF CYP2D6 PHENOTYPE | | | |
| Ultrarapid metabolizer (~1-2% of patients) | > 2.0 | An individual carrying duplications of functional alleles | (*1/*1)xN (*1/*2)xN (*2/*2)xN |
| Extensive metabolizer (~77-92% of patients) | 1.0 – 2.0 | An individual carrying two functional alleles or two reduced function alleles or one functional and non functional allele or one functional and reduced function allele | *1/*1, *1/*2, *2,*2, *1/*9, *1/*41, *41/*41, *1/*5, *1/*4 |
| Intermediate metabolizer (~2-11% of patients) | 0.5 | An individual carrying one reduced function and one nonfunctional allele | *4/*41, *5/*9, *4/*10 |
| Poor metabolizer (~5-10% of patients) | 0 | An individual carrying only nonfunctional alleles | *4/*4, *3/*4, *5/*5, *5/*6 |

Codeine therapy recommendations based on CYP2D6 phenotype

| Phenotype | Codeine metabolism | Recommendations codeine therapy | Recommendation | Considerations for alternative opioids |
|-----------|---|---|-----------------|---|
| UM | ↑ morphine risk toxicity | Avoid codeine use due to potential for toxicity | Strong | <p>✓ Morphine, nonopioid analgesics (Not metabolized by CYP2D6)</p> <p>✗ Tramadol, hydrocodone, oxycodone (Metabolized by CYP2D6)</p> |
| EM | ↔ morphine | Use label recommended age or weight-specific dosing | Strong | ----- |
| IM | ↓ morphine | Use label recommended If no response: morphine or a nonopioid | Moderate | Monitor tramadol use for response |
| PM | ↓↓ morphine insufficient pain relief | Avoid codeine use due to lack of efficacy | Strong | <p>✓ Morphine, nonopioid analgesics (Not metabolized by CYP2D6)</p> <p>✗ Tramadol, hydrocodone, oxycodone (Metabolized by CYP2D6)</p> |

CYP2D6 e Tramadol

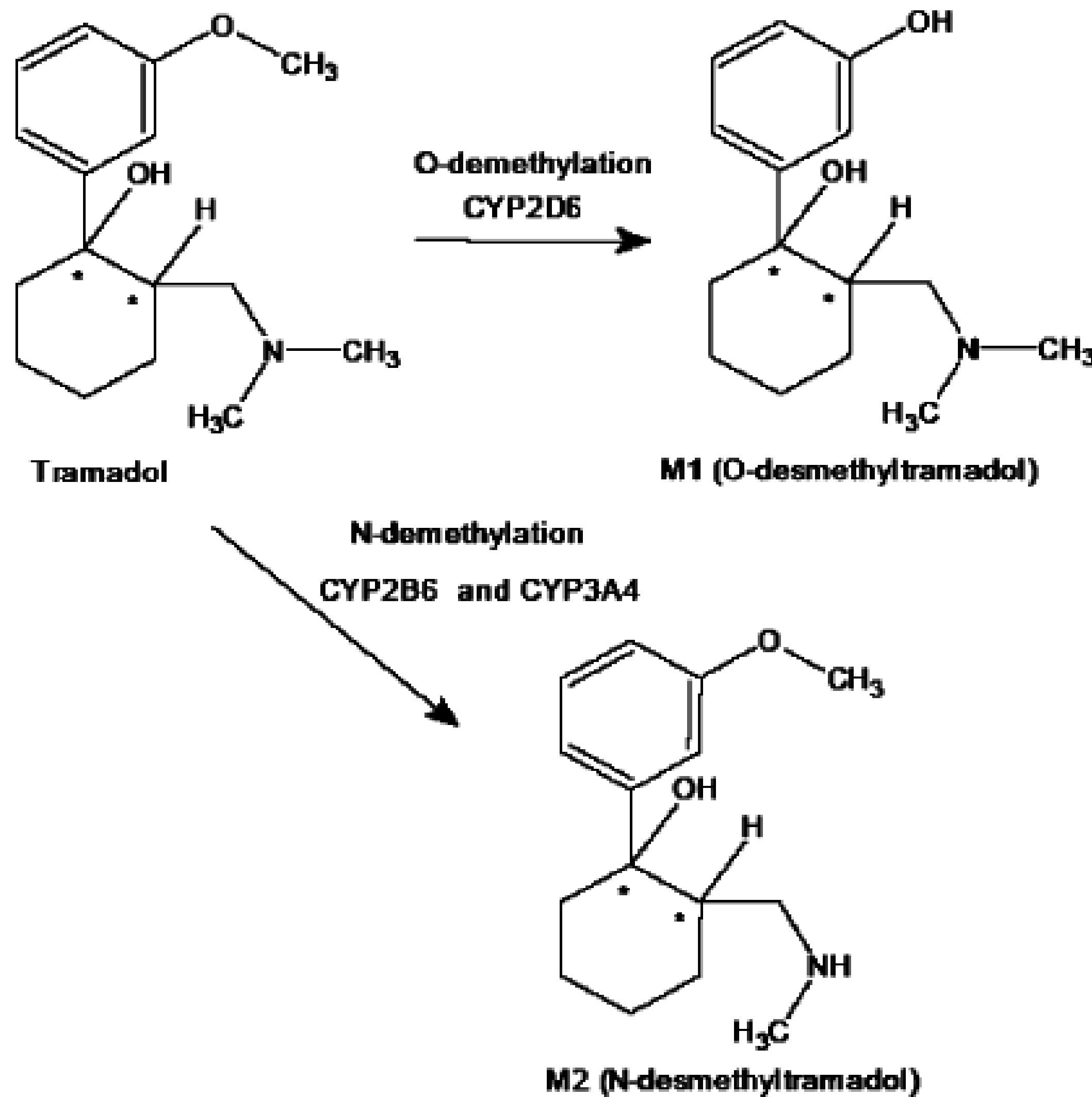


Fig. 1 Major in vivo metabolic pathways for tramadol

Polimorfismo do CYP2D6

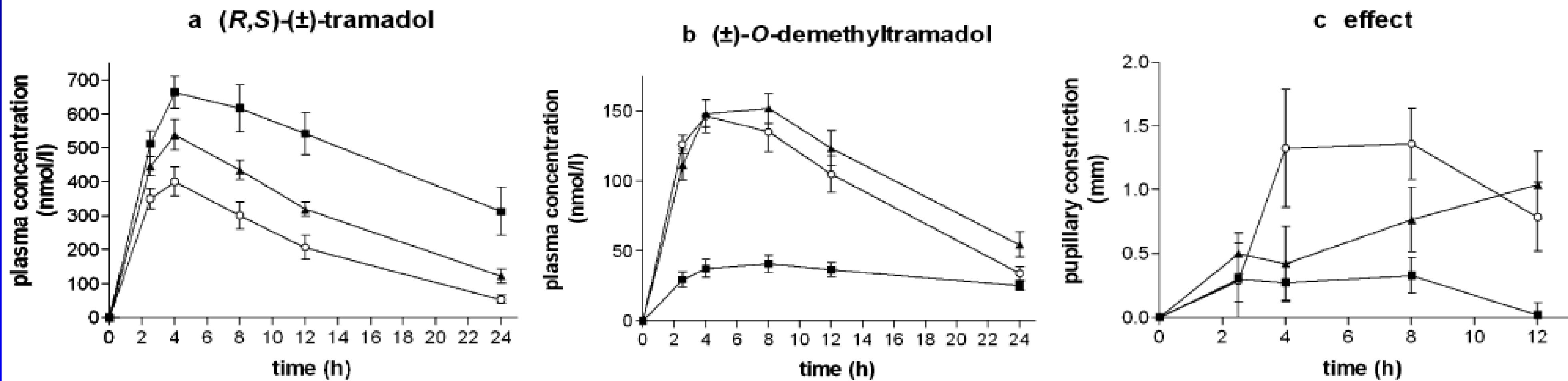


Fig. 1 Mean \pm SEM plasma concentration–time profiles of a (R,S)-(\pm)-tramadol, b (\pm)-O-demethyltramadol and c mean \pm SEM pupillary constriction (basal diameter–diameter at time t) after a single dose of 100 mg oral slow-release racemic tramadol for homozygous

extensive metabolizers (*open circles*), heterozygous extensive metabolizers (*solid triangles*), and poor metabolizers (*solid squares*) of CYP2D6

CYP2C19 PHENOTYPES

| LIKELY PHENOTYPE | GENOTYPES | EXAMPLE OF DILOTYPES |
|---|--|---------------------------------|
| PHENOTYPE | | |
| Ultrarapid metabolizer : normal or increased activity (~5-30% of patients) | An individual carrying two increased activity alleles (*17) or one functional allele (*1) plus one increased-activity allele (*17) | *1/*17, *17/*17 |
| Extensive metabolizer : homozygous wild-type or normal activity (~35-50% of patients) | An individual carrying two functional (*1) alleles | *1/*1 |
| Intermediate metabolizer : heterozygote or intermediate activity (~18-45% of patients) | An individual carrying one functional allele (*1) plus one loss-of-function allele (*2-*8) or one loss-of-function allele (*2-*8) plus one increased-activity allele (*17) | *1/*2, *1/*3, *2/*17 |
| Poor metabolizer: homozygous variant, mutant, low, or deficient activity (~2-15% of patients) | An individual carrying two loss-of-function alleles | *2/*2, *2/*3, *3/*3 |

Antiplatelet therapy recommendations clopidogrel

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| PHENOTYPE (GENOTYPE) | IMPLICATIONS FOR CLOPIDOGREL | THERAPEUTIC RECOMMENDATIONS | CLASSIFICATION OF RECOMMENDATIONS |
|--|--|---|-----------------------------------|
| Ultrarapid metabolizer (UM) (*1/*17, *17/*17,) and extensive metabolizer (EM) (*1/*1) | Normal (EM) or increased (UM) platelet inhibition; normal (EM) or decreased (UM) residual platelet aggregation | Clopidogrel: label-recommended dosage and administration | Strong |
| Intermediate metabolizer (*1/*2, *1/*3, *2/*17) | Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events | Alternative antiplatelet therapy (if no contraindication), e.g, prasugrel, ticagrelor | Moderate |
| Poor metabolizer (*2/*2, *2/*3, *3/*3) | Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events | Alternative antiplatelet therapy (if no contraindication), e.g, prasugrel, ticagrelor | Strong |

MATERNAL-FETAL DRUG TRANSFER



More than 50% of pregnant women receive some form of drug during pregnancy

~ 40% of drugs used has no evidence of safety in pregnant women

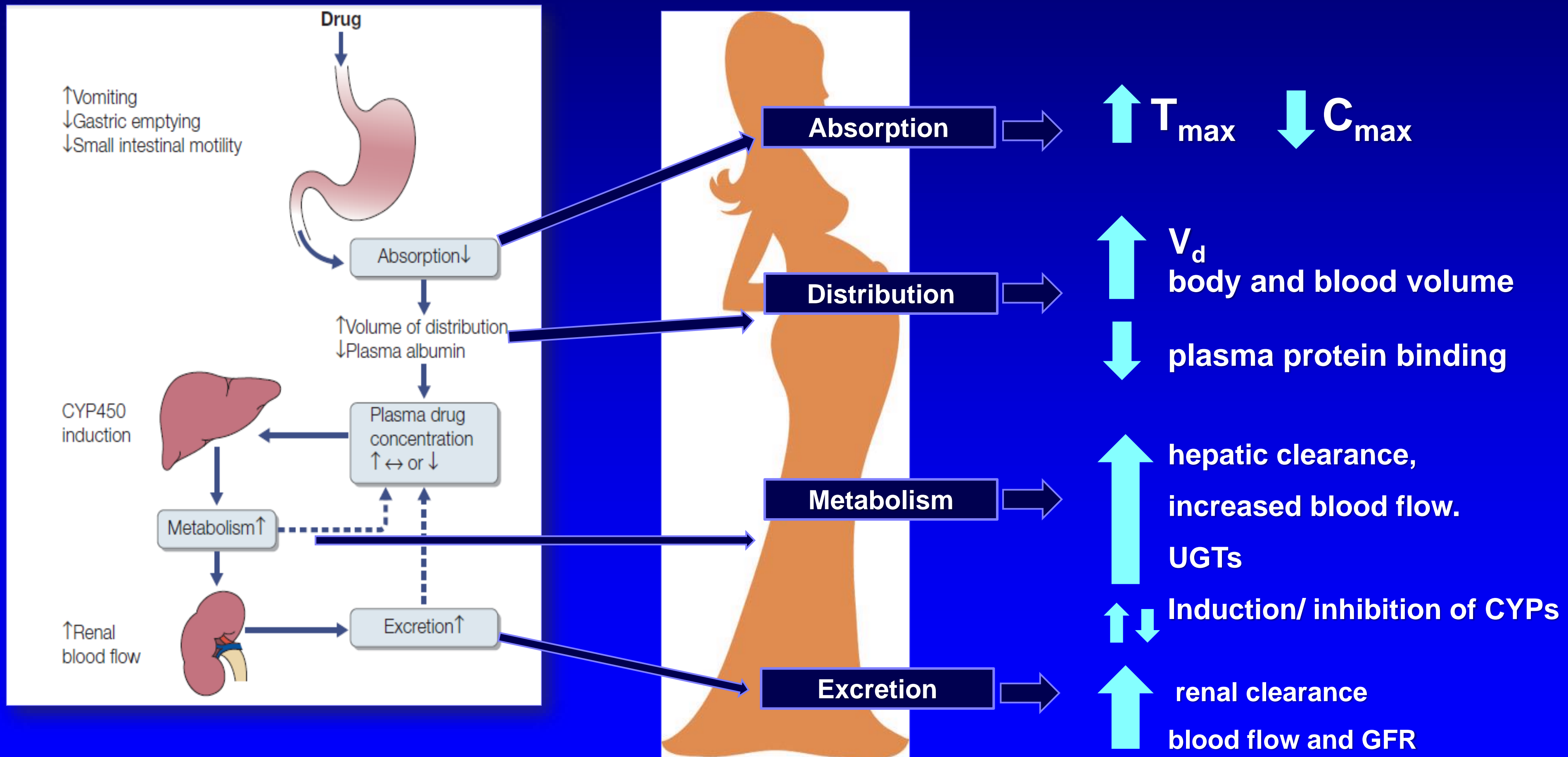


FACTORS AFFECTING PLACENTAL DRUG TRANSFER AND FETAL TISSUE

- **Physicochemical properties of drug**
- **Duration of exposure to drug**
- **Distribution characteristics in different fetal tissues**
- **Stage of placental and fetal development at time of exposure to the drug**
- **Effects of drug used in combination**
- **Transporters protein (drug efflux pumps) expressed in placenta**

PHARMACOKINETICS CHANGES IN PREGNANCY

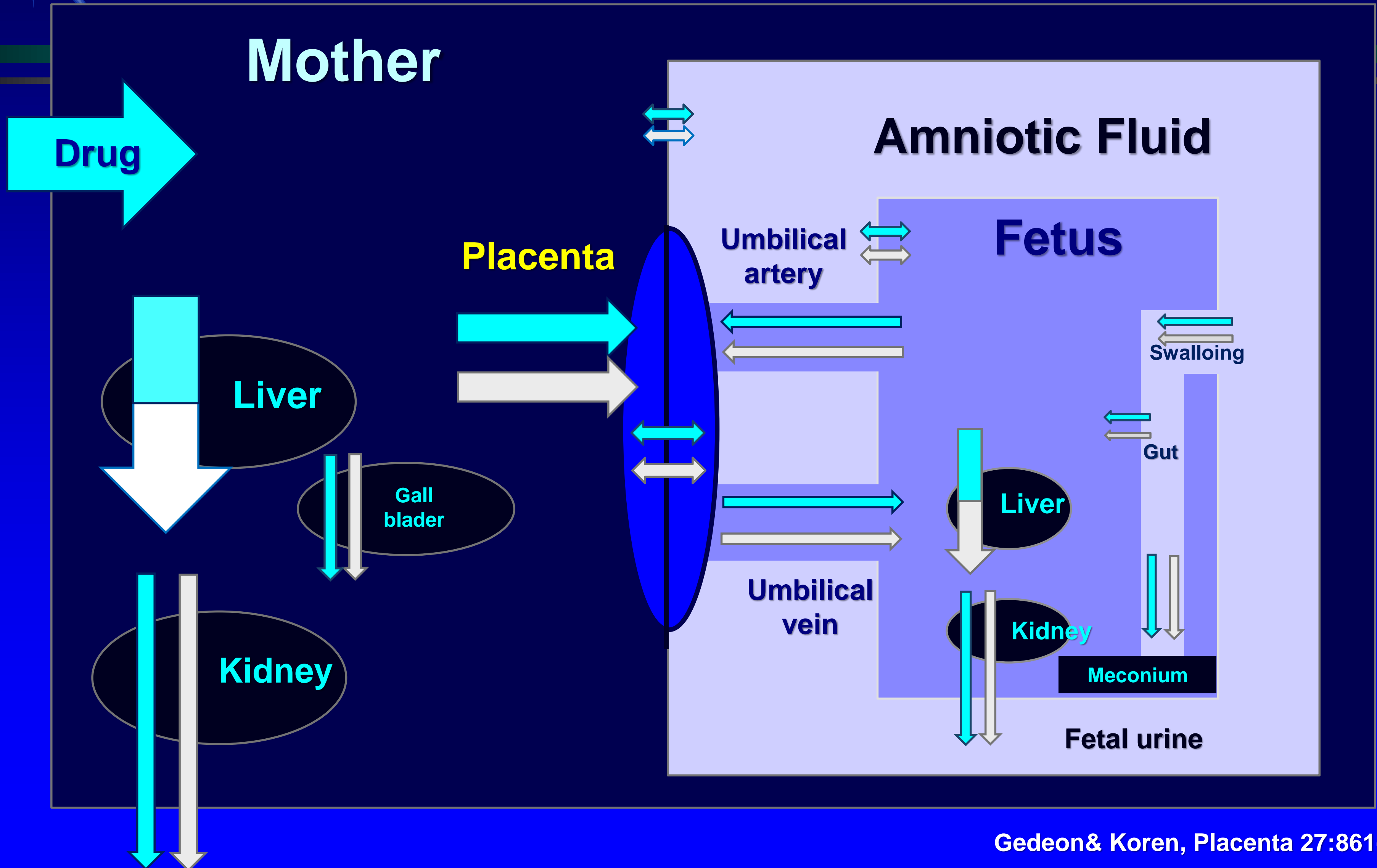
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PHARMACOKINETICS CHANGES DURING PREGNANCY

| Enzyme | Pregnancy-induced change | Potential substrates in obstetrics | Possible clinical consequences |
|--------|--------------------------|--|---|
| CYP3A4 | Increased | Nifedipine, methadone, indinavir | Significantly lower trough levels of methadone during pregnancy associated with symptoms of withdrawal. Increase daily dose by 5–10 mg or administer in more frequent doses to avoid withdrawal |
| CYP2D6 | Increased | Metoprolol, dextromethorphan, paroxetine, duloxetine, fluoxetine, citalopram | Increased metabolism of fluoxetine, desmethylcitalopram, lower plasma levels of the drug are associated with recurring symptoms of depression |
| CYP1A2 | Decreased | Theophylline, clozapine, olanzapine, ondansetron, cyclobenzaprine | Increase in theophylline half-life during pregnancy requiring dose reductions to avoid toxicity |
| UGT1A4 | Increased | Lamotrigine | Significant decrease in lamotrigine concentration resulting in loss of seizure control, recommended to measure plasma lamotrigine concentrations during each trimester and adjusting dose as needed |
| UGT1A1 | Increased | Acetaminophen | Increased acetaminophen glucuronidation resulting in decreased half-life, clinical consequences are unknown |
| NAT2 | Decreased | Caffeine | Decreased metabolism of caffeine Clinical consequences are unknown |

MATERNAL-FETAL DRUG TRANSFER



Farmacocinética em gestantes

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$$t_{1/2} = \frac{0,693 \times Vd}{CL}$$

CL ↑, ↔
Vd ↑
t_{1/2} ↑

↑ %pp
anticonvulsivantes
antidepressivos
benzodiazepínicos
xantinas

cefalosporinas
ácido salicílico

CL ↑,
Vd ↑
t_{1/2} ↑, ↔, ↓

↑ lipossolubilidade

↓ lipossolubilidade

CL ↔, ↓
Vd ↑, ↔
t_{1/2} ↑, ↔

antipirina

aminoglicosídicos
penicilinas
lítio

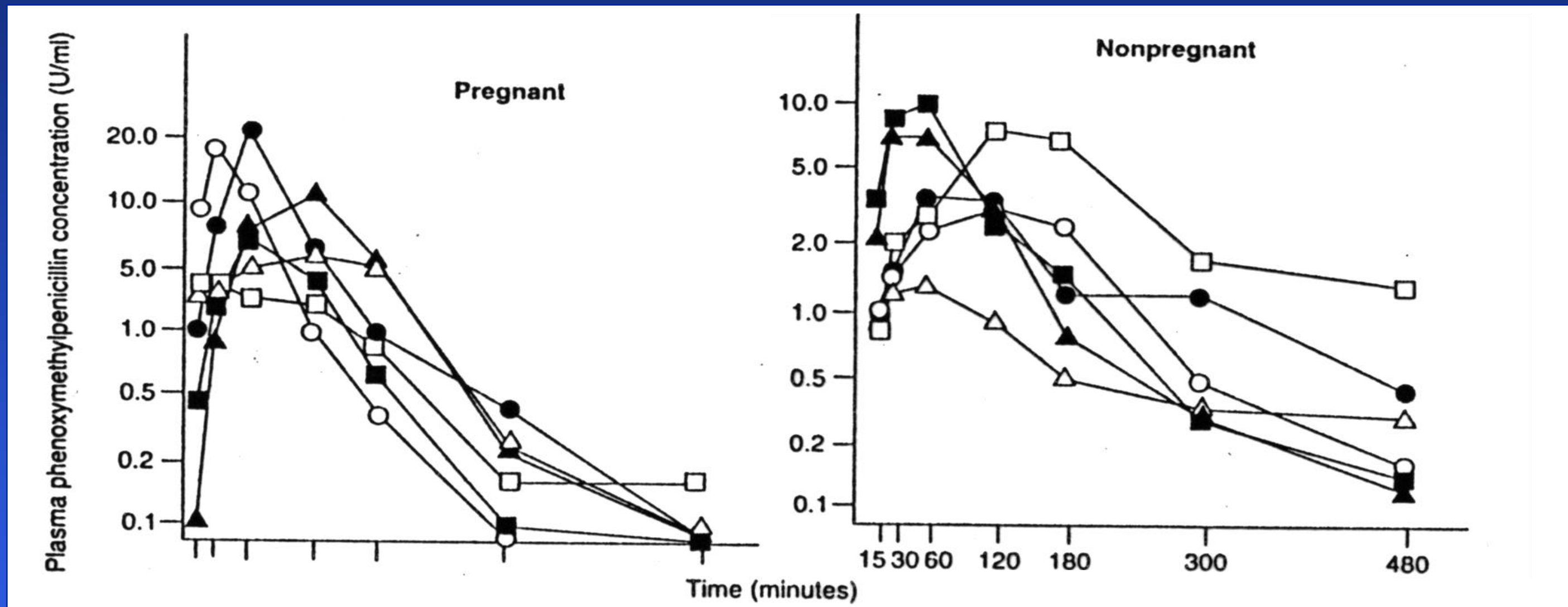
CL ↑
Vd ↑, ↔
t_{1/2} ↓

↓ %pp

GESTANTES

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Farmacocinética da fenoximetilpenicilina



| | C_{max} U/mL | AUC U/mL.min | $t_{1/2}$ min | CL mL/min/kg | CL_R mL/min/kg |
|---------------------|-------------------|-----------------|------------------|-----------------|---------------------|
| gestante* | 3,7 | 441 | 38 | 34,6 | 3,7 |
| não gestante | 5,6 | 887 | 38 | 15,6 | 3,6 |

* 19 semanas, dose única p.o . 660mg

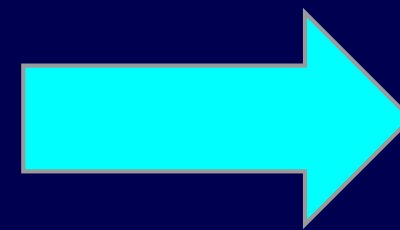
GESTANTES

Farmacocinética de antibióticos β -lactâmicos

| | semanas de gestação | C | $t_{1/2\beta}$ | Vd | CL |
|------------------|---------------------------|---|----------------|----|----|
| ampicilina | 9 - 36 | ↓ | ↓ | | ↑ |
| benzilpenicilina | 12 - 37 | ↓ | ↓ | ↑ | ↑ |
| cefalexina | | ↓ | | | |
| cefuroxina | | ↓ | ↓ | | ↑ |

FENTANYL

Placental transfer of fentanyl indicates the need of caution regarding the doses of drug administration



To prevent deteriorious effects on the fetus and/or newborn infant

Table 3 Fentanyl concentrations (in nanograms per milliliter) in maternal and fetal plasma determined by GC-MS, and fetal/maternal ratio

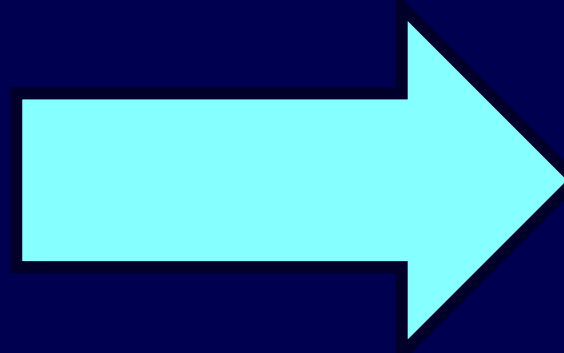
| Parameter ^a | Parturients (<i>n</i> = 8) [Median (P25–P75)] ^b |
|--------------------------------|--|
| Latency (min) | 28.50 (25.75–32.25) |
| Maternal concentration (ng/ml) | 0.31 (0.28–0.32) |
| Fetal concentration (ng/ml) | 0.25 (0.19–0.51) |
| Fetal/maternal ratio | 0.89 (0.75–1.62) |

^aLatency, Time between drug administration and birth; fetal/maternal ratio, ratio between fetal and maternal fentanyl concentration in plasma at the time of birth

^bP25, 25th percentile; P75, 75th percentile

METFORMIN

**CAUTION IS
RECOMMENDED**



**70% transplacental
transfer**

Table 3 Maternal and umbilical cord plasma metformin concentrations in eight parturients with PCOS

| Parameter | Median (minimum and maximum) |
|------------------------------|------------------------------|
| Maternal plasma (mg/L) | 0.4 (0.1–2.4) |
| Umbilical cord plasma (mg/L) | 0.3 (0.1–1.4) |
| Umbilical/maternal | 0.7 (0.4–1.3) |

Data are expressed as the median, with the minimum and maximum values given in parenthesis