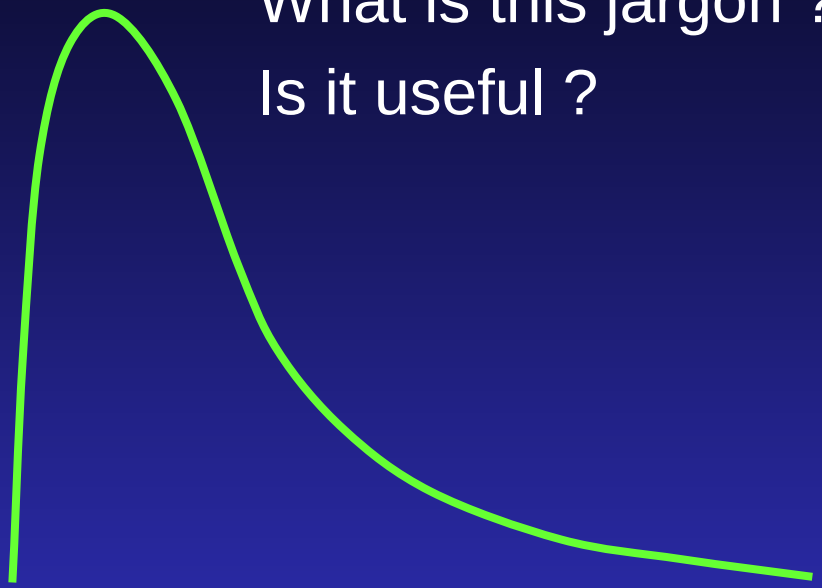
The general Concepts of Pharmacokinetics

What is this jargon ?

Is it useful ?



- C_{max},
- clearance,
- Vd,
- half-life,
- AUC,
- bioavailability,
- protein binding

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With some slides from H. Derendorf *(University of Florida)*

ISAP

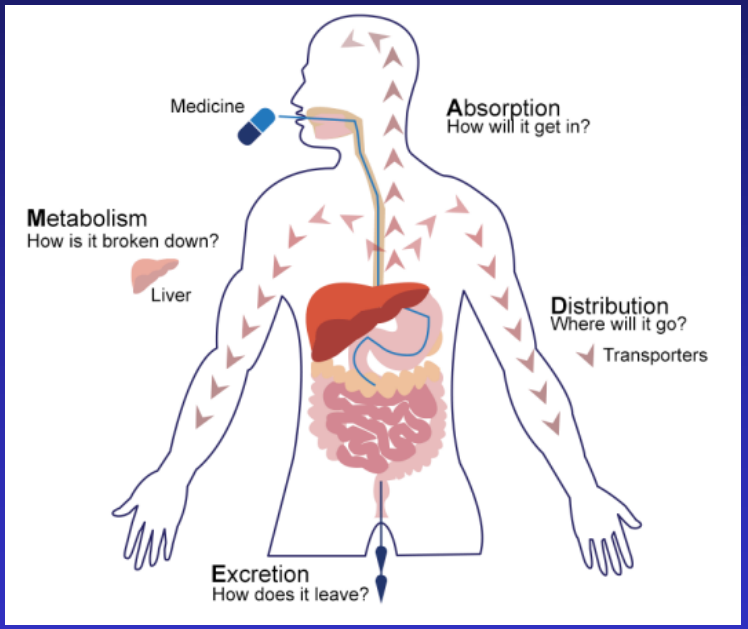
ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
PK/PD of Anti-Infectives Study Group

Pharmacokinetics (PK) is speed !

What is pharmacokinetics ?

- " **what the body does to the drug** "

- the fate of the drug in terms of
  - Absorption
  - Distribution
  - Metabolism
  - Excretion



- the time course of drug and metabolite concentrations in the body

What is pharmacokinetics ?

- " **what the body does to the drug** "

- the fate of the drug in terms of
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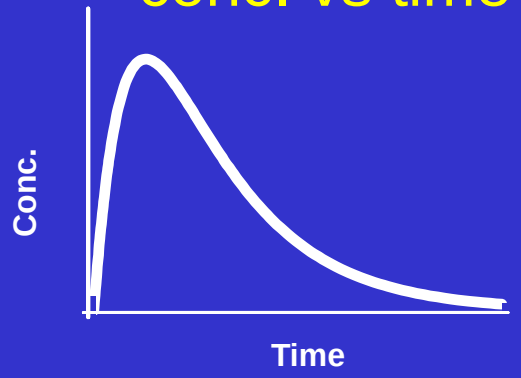
  - Metabolism
  - Excretion

Pharmacokinetics
= conc. vs time



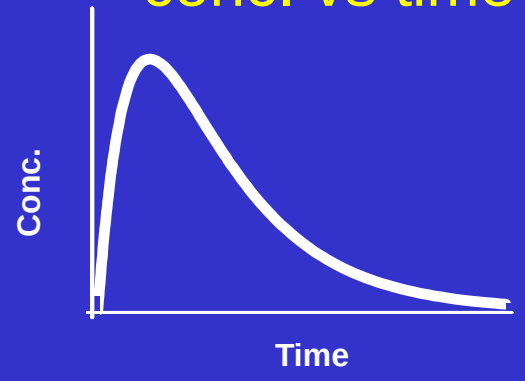
- the time course of drug and metabolite concentrations in the body

What is PK for ?

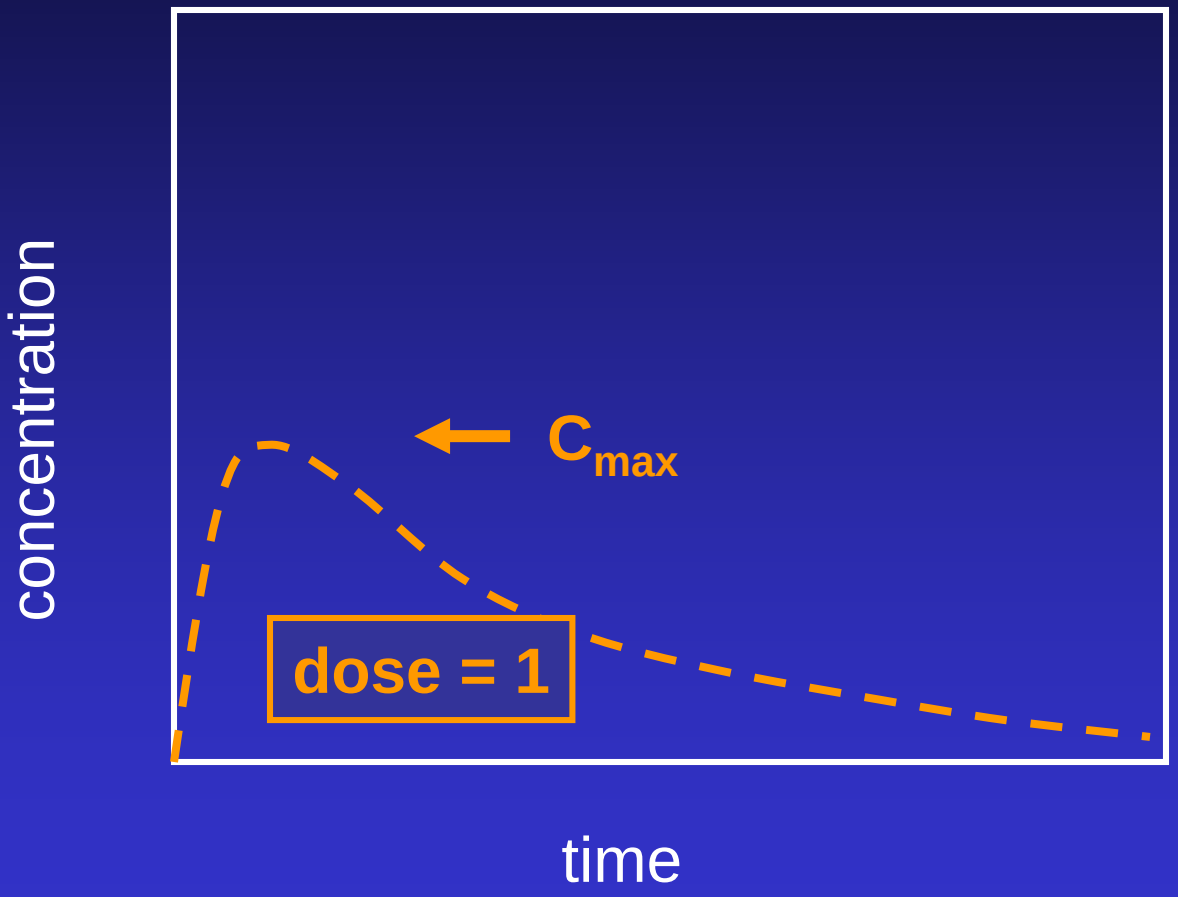
PK is the way to see if the drug can be made useful …

- **does it reach the target in sufficient amounts ?**
- **for long enough ?**
- **does it each non-desired targets ?**

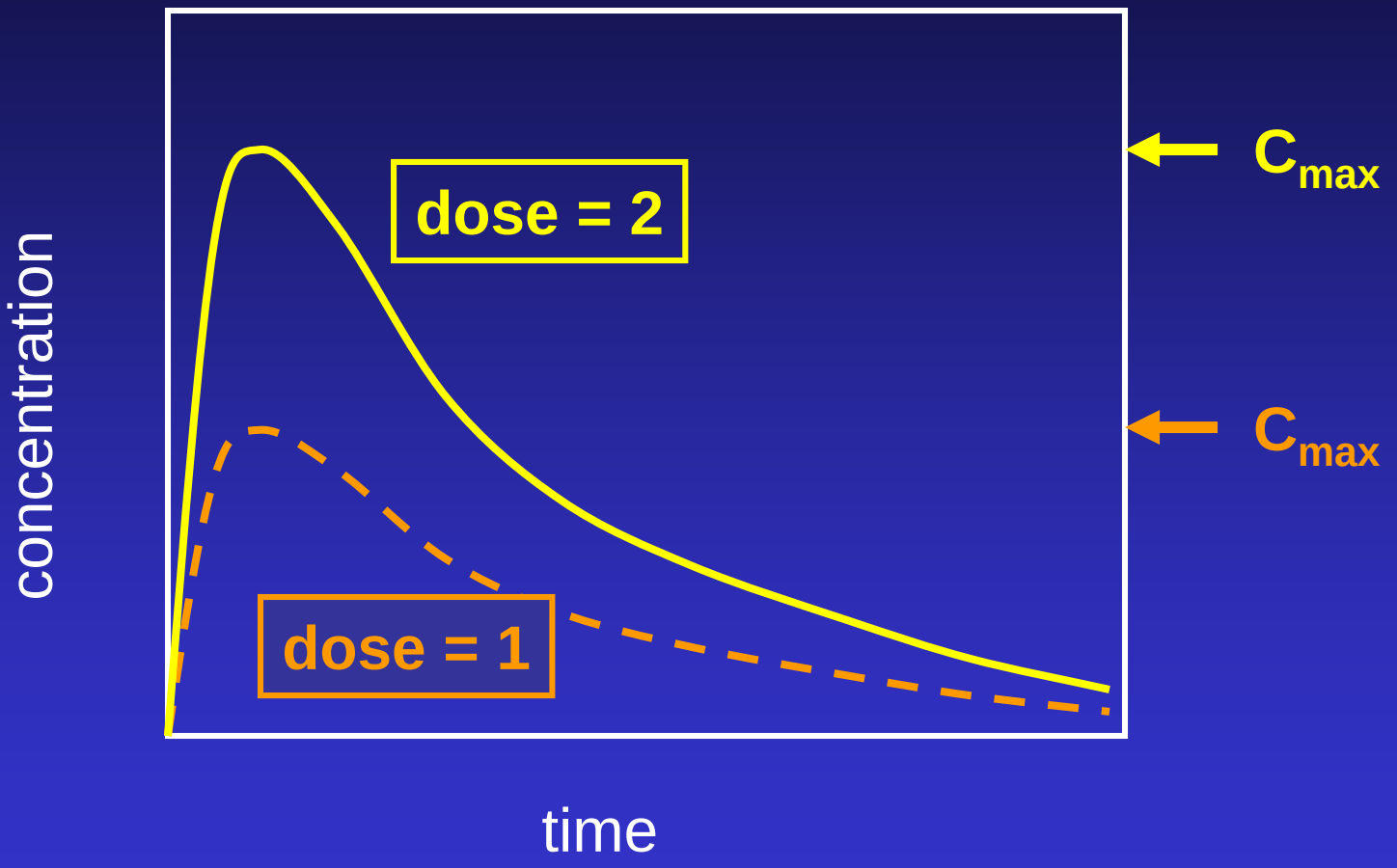
Pharmacokinetics
= conc. vs time



The C_{max} is the highest concentration in plasma after administration ...



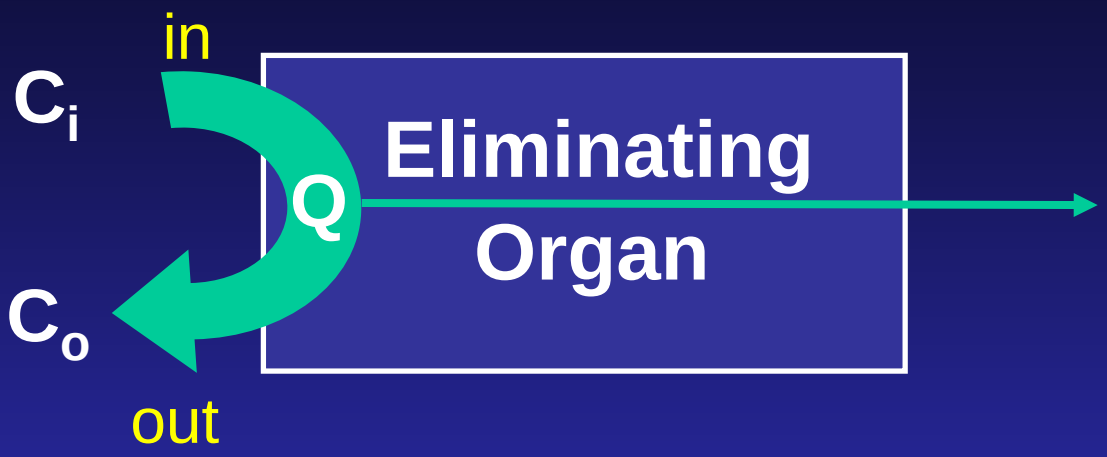
C_{max} ... is proportional to the dose ...



What is the significance of the C_{max} ?

- A drug with a (too) low C_{max} may be ineffective if its activity is concentration-dependent
- A drug with a (too) high C_{max} may become toxic if toxicity is related to C_{max} (this NOT always the case.... !)
- you have to adjust the dose to get the appropriate C_{max} !

Clearance (Cl)



Quantity eliminated per unit of time

➔ $C_o < C_i$

the rate at which the drug will be excreted is proportional to
- the blood flow in the eliminating organ (Q)
- the extraction the organ is capable of (E)

the clearance is thus Q x E (= L/h or ml/min)

Clearance

Clearance can be calculated from

- **Excretion rate / Concentration**

  e.g. (mg/h) / (mg/L) = L/h

- **Dose / Area under the curve (AUC)**

  e.g. mg / (mg·h/L) = L/h

Clearance

Total body clearance is the sum of the individual organ clearances

$$CL = CL_{renal} + CL_{hepatic} + CL_{other}$$

What is the significance of the clearance ?

- A drug with a fast clearance will not stay around for long … and may require readminstration...

- But a drug may show a slow clearance because it is bound to proteins and therefore largely unavailable (see later …)

- If clearance falls during treatment (or is abnormally low at the beginning of treatment), patient will be overdosed !!

Volume of distribution (V_d)

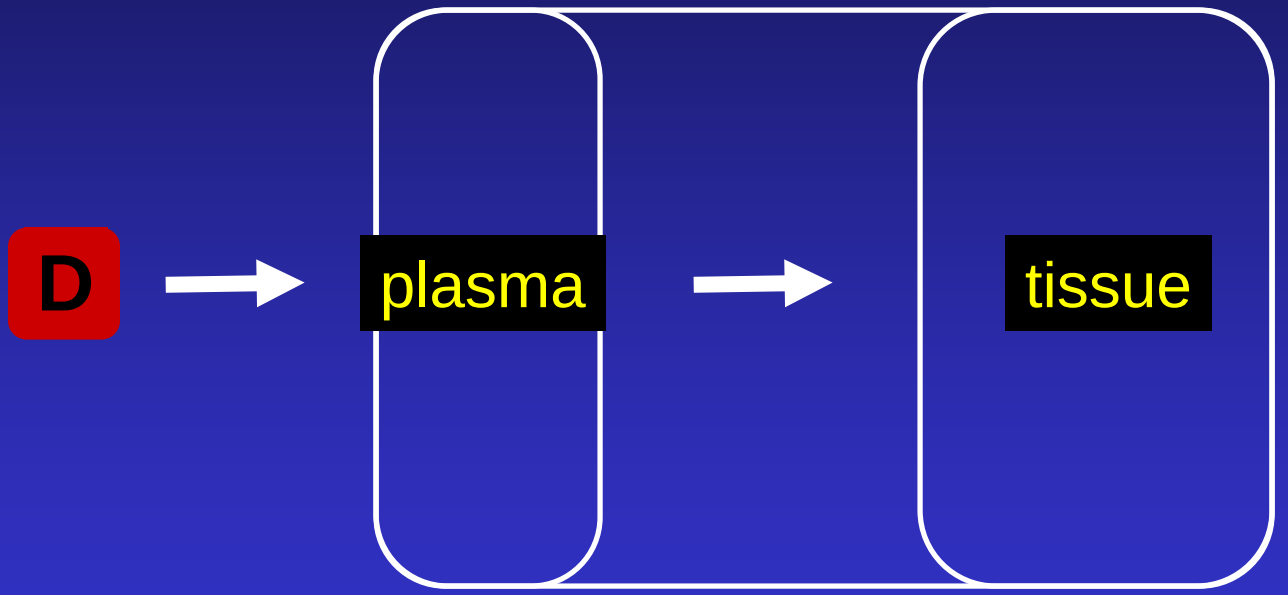
- Quantifies how the drug has access to the various compartments of the body

- relates drug concentration (C) in the blood to the amount of drug that has been introduced in the body (= Dose)

V_d = Dose / Concentration in blood

What is V_d ?

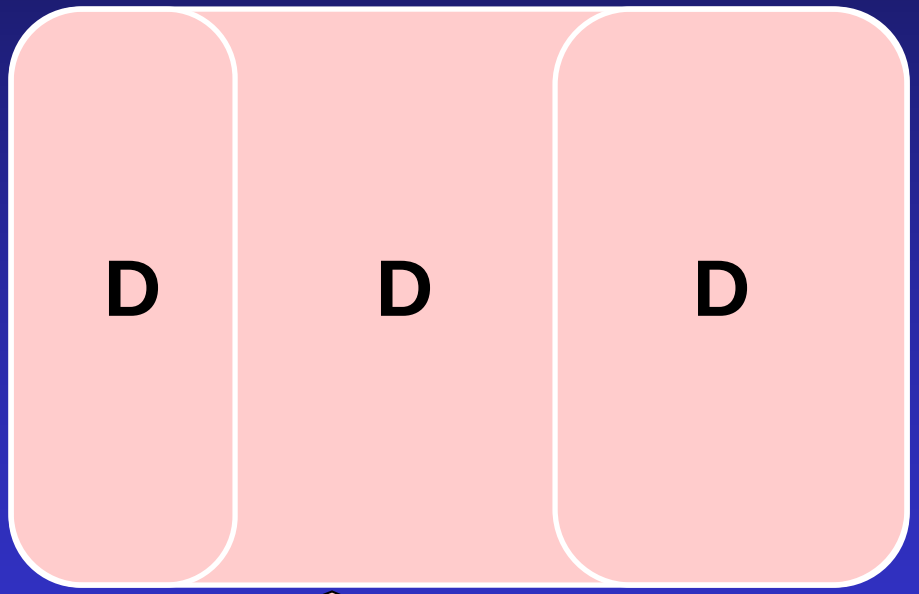
Think about the body as a large "bag" with compartments in which you drop a drug ...



What is V_d ?

If drug diffuses throughout the body ...

Vd = 1 L/kg



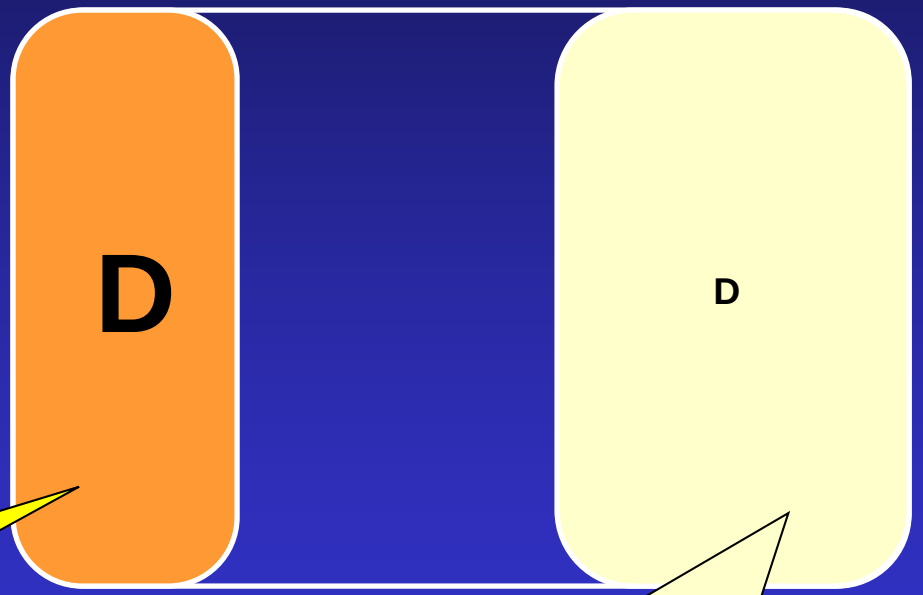
serum concentration = tissue concentration

What is V_d ?

If the drug reaches only the plasma and the extracelular fluids ...

Vd < 1 L/kg

C_{max} ↗



high serum concentration

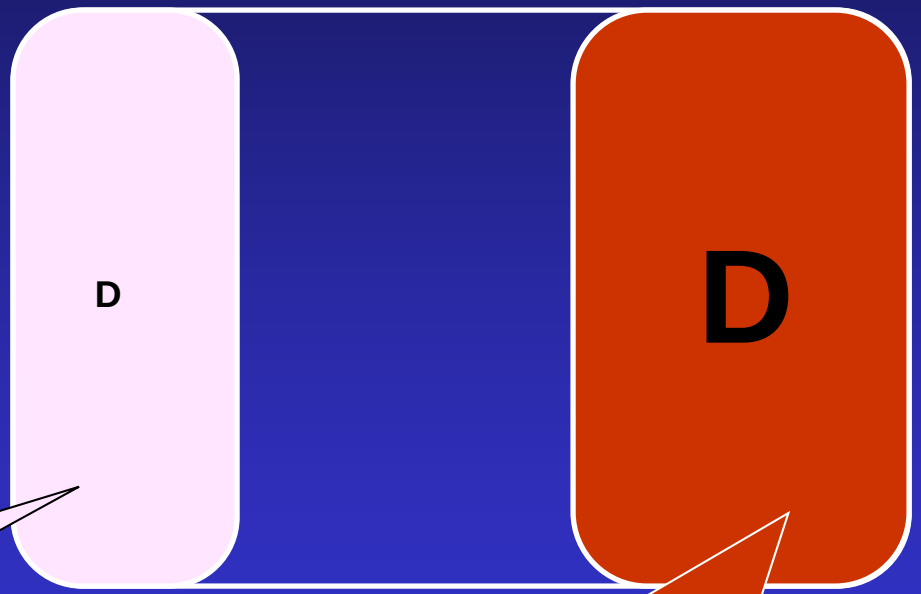
no or little tissue concentration

What is V_d ?

If drug accumulates in tissues...

V_d > 1 L/kg

C_{max} ↘



low serum concentration

high tissue concentration

Typical volumes of distribution of antibiotics

	L/kg
• dicloxacillin (serum only)	0.1
• gentamicin (serum plus extracell. fluids)	0.25
• ciprofloxacin (fluids plus moderate accumulation in tissues)	1.8
• azithromycin (marked accumulation in tissues)	**31**

What is the clinical significance of the Vd ?

- A drug with a small V_d will have high initial blood levels but will not reach tissues...

- A large V_d will cause low initial blood levels …
  - if patient-related, you will need to give more of the drug (e.g., burn patients)
  - if drug-related, it may become ineffective in blood-related (invasive) infections

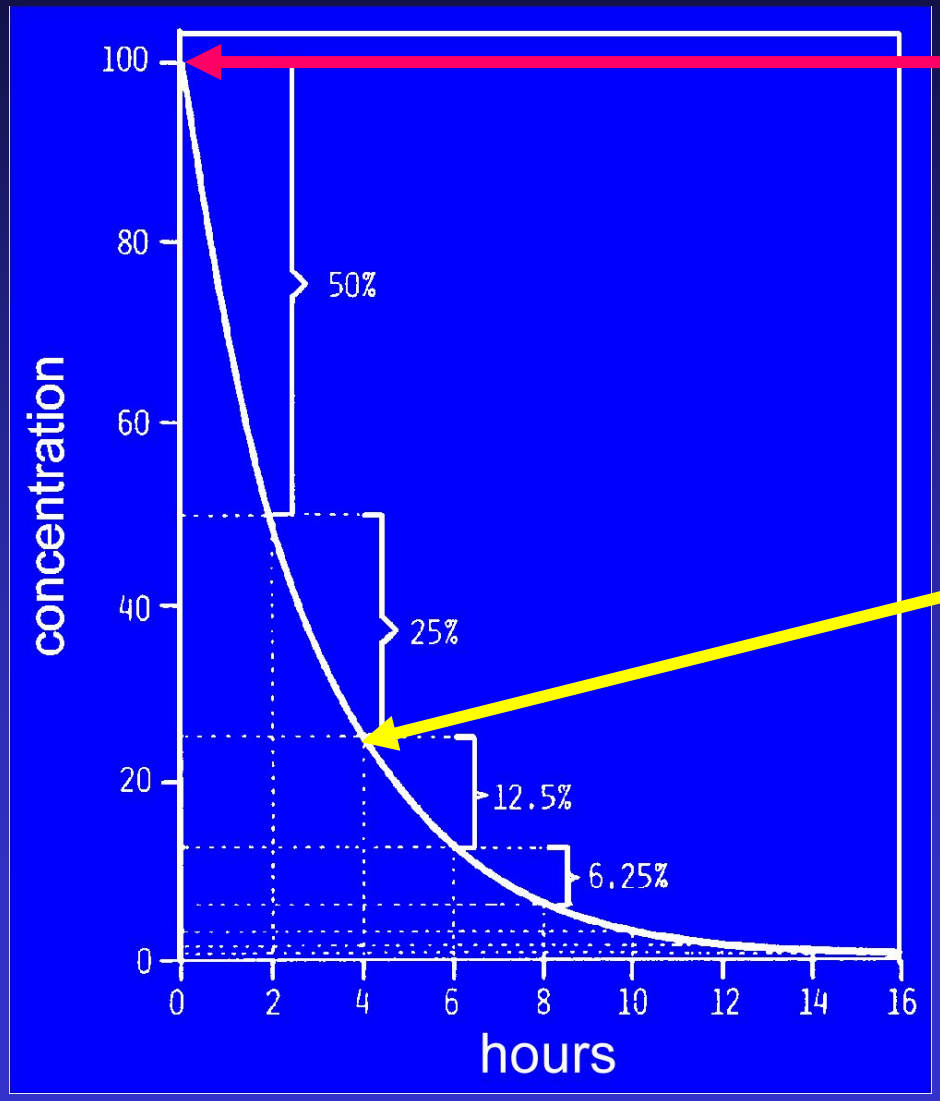
Half-life ($t_{1/2}$)

- Half-life is the time it takes for the concentration to fall to half of its previous value
- This is a parameter which is easy to measure, (just take a few blood samples…)

  BUT ...

- it is **secondary** pharmacokinetic parameter because it depends on both the clearance AND the volume of distribution

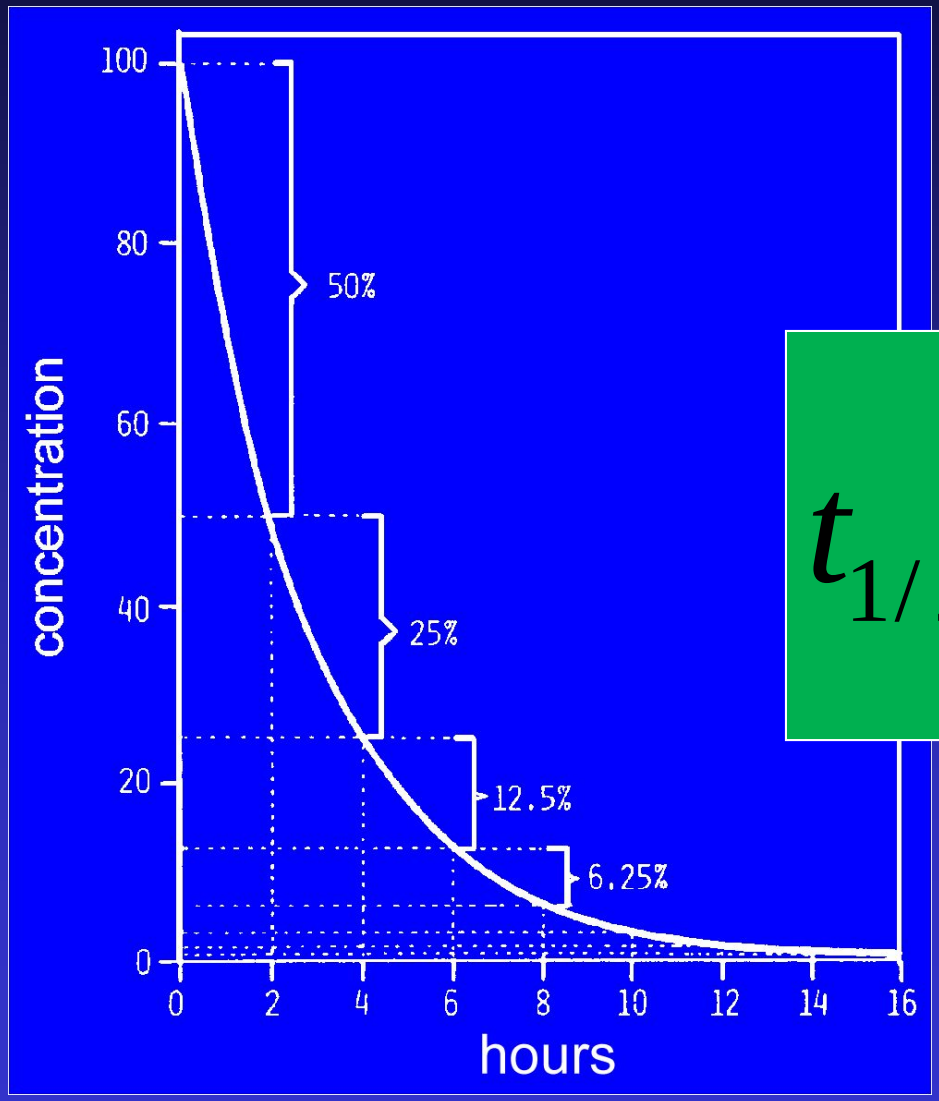
Why is half half-life a secondary parameter ?



You start from here, but …
this is C_{max},
i.e. Dose / Vd

And you follow a slope which is dictated by the drug elimination rate, i.e the total body clearance

Why is half half-life a secondary parameter ?



$$t_{1/2} = \frac{0.693 \cdot Vd}{CL}$$

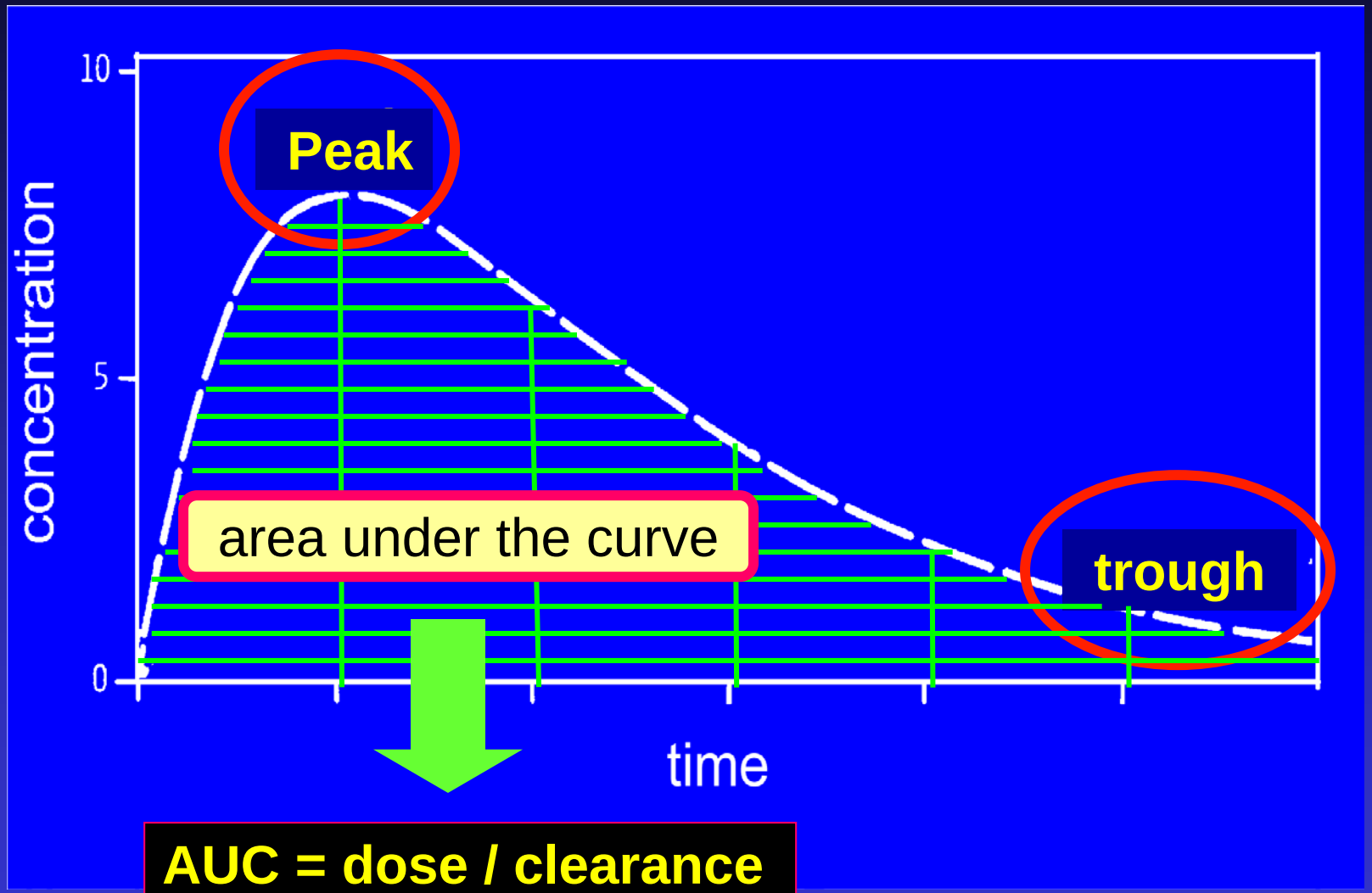
What is useful in half-life for the clinician ?

- Direct information as how serum concentrations will fall over time …and reach a pre-set threshold ... if you know the C_{max} (i.e. your starting point)

- Direct, practical comparisons between drugs … if sharing the same V_d ...

You can compare β-lactams between themselves for half-life, ...
BUT you CANNOT compare β-lactams (low V_d) and azithromycin (high V_d), e.g.

Area under the Curve (AUC)



Area under the Curve (AUC)

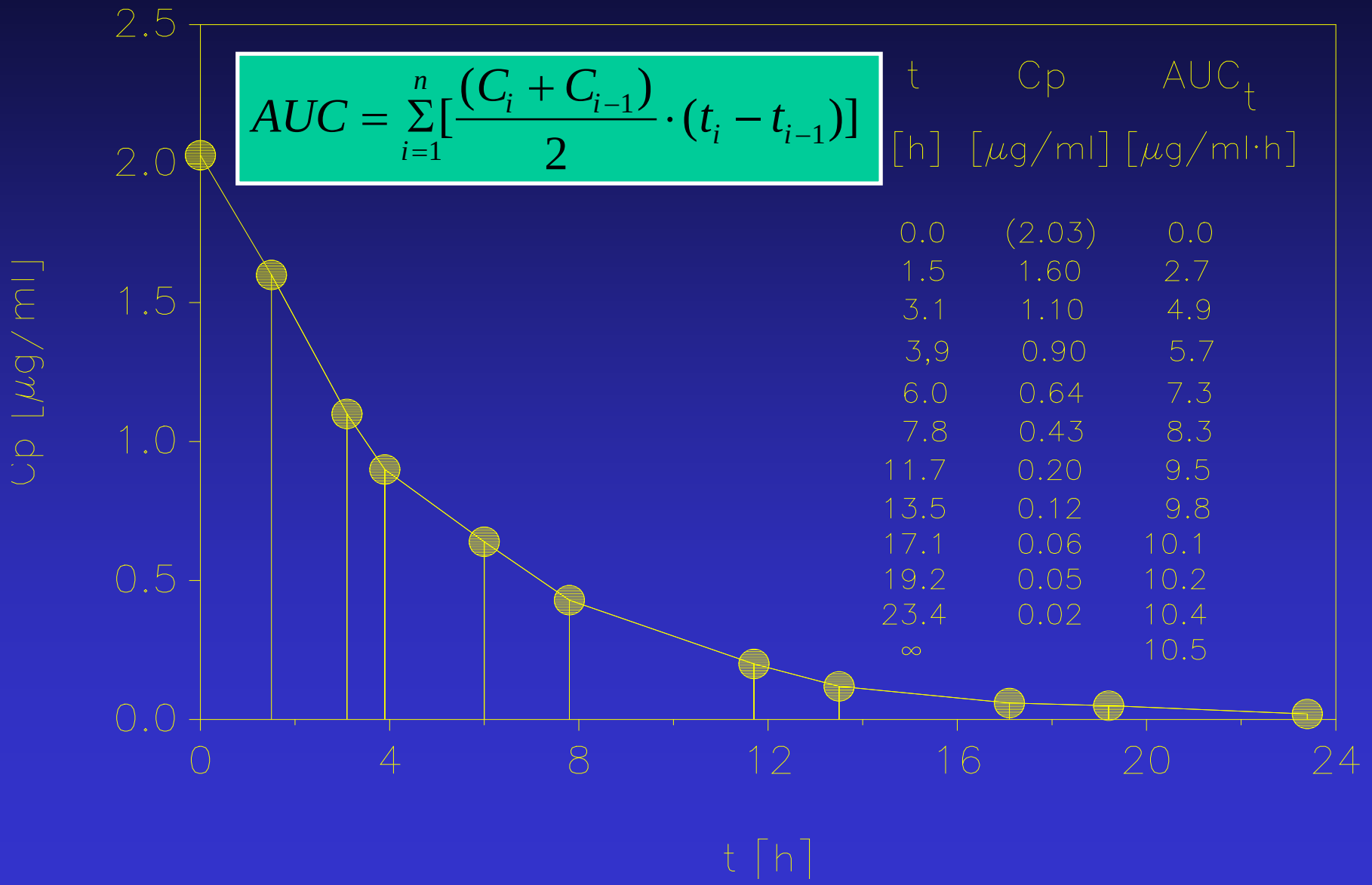
- combines
  - one parameter directly linked to the medical decision: **the dose of the drug** !
  - one parameter linked to the drug AND the patient: **the clearance** ...

- its value is independent of the scheme of administration ...

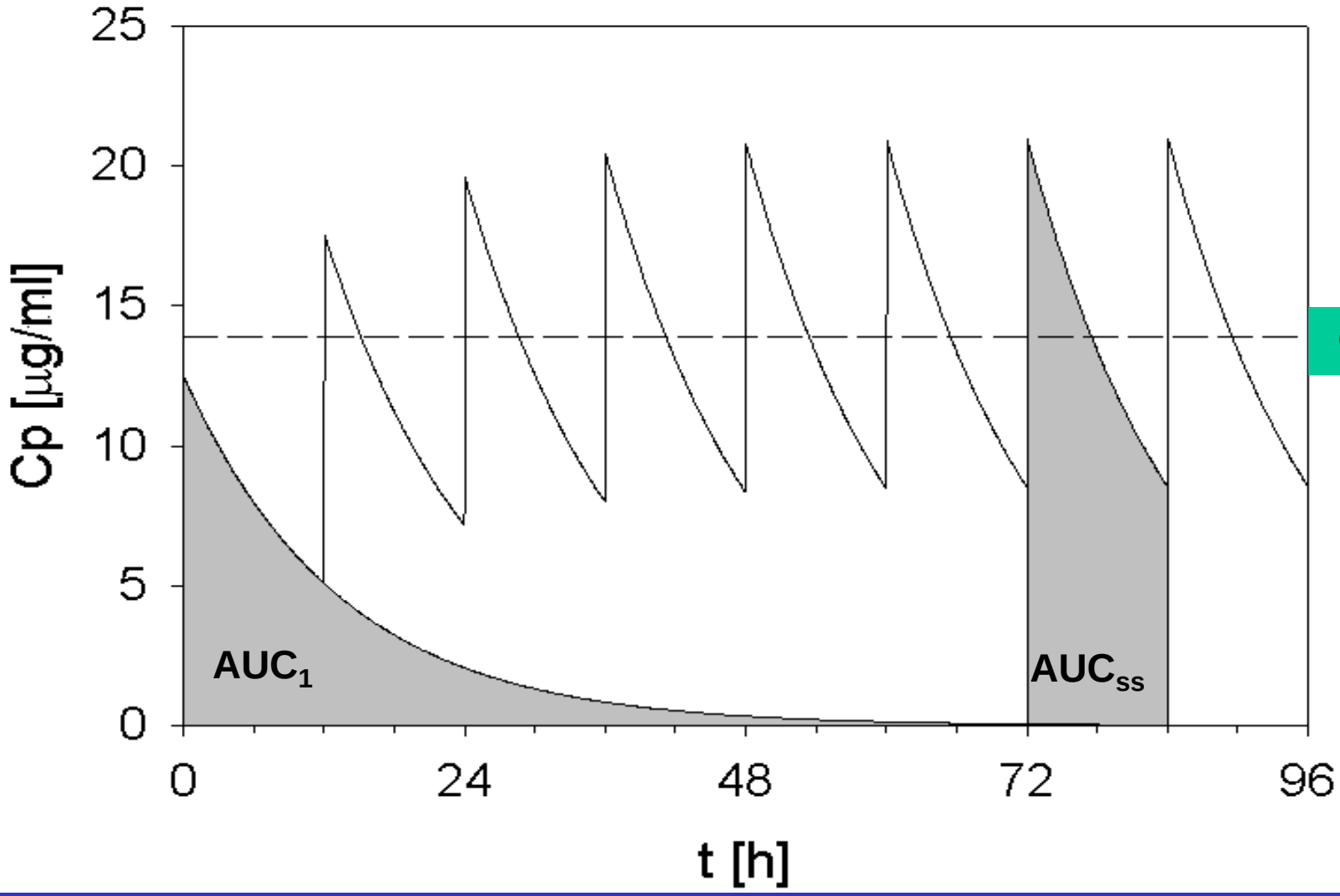
- useful to assess the total drug exposure

Determination of the AUC

$$AUC = \sum_{i=1}^{n}\left[\frac{(C_i + C_{i-1})}{2} \cdot (t_i - t_{i-1})\right]$$



t [h]	Cp [µg/ml]	AUC_t [µg/ml·h]
0.0	(2.03)	0.0
1.5	1.60	2.7
3.1	1.10	4.9
3,9	0.90	5.7
6.0	0.64	7.3
7.8	0.43	8.3
11.7	0.20	9.5
13.5	0.12	9.8
17.1	0.06	10.1
19.2	0.05	10.2
23.4	0.02	10.4
∞		10.5


25
20
15
10
5
0
Cp [µg/ml]
0
24
48
72
96
t [h]
AUC1
AUCss
Cpave(ss)

24h-AUC / MIC of fluoroquinolones (p.o.)

Drug	Dosage (mg/24h)	24h-AUC (mg/L x h)
norfloxacin	800	14 *, #
ciprofloxacin	500	12 *
ofloxacin	400	31 to 66 *, +
levofloxacin	500	47 *
moxifloxacin	400	48 *

poor if MIC is ↑

Much better !!

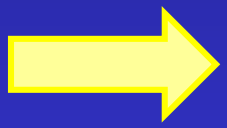
* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, and AVELOX®

\# litterature data

\+ first dose to equilibrium

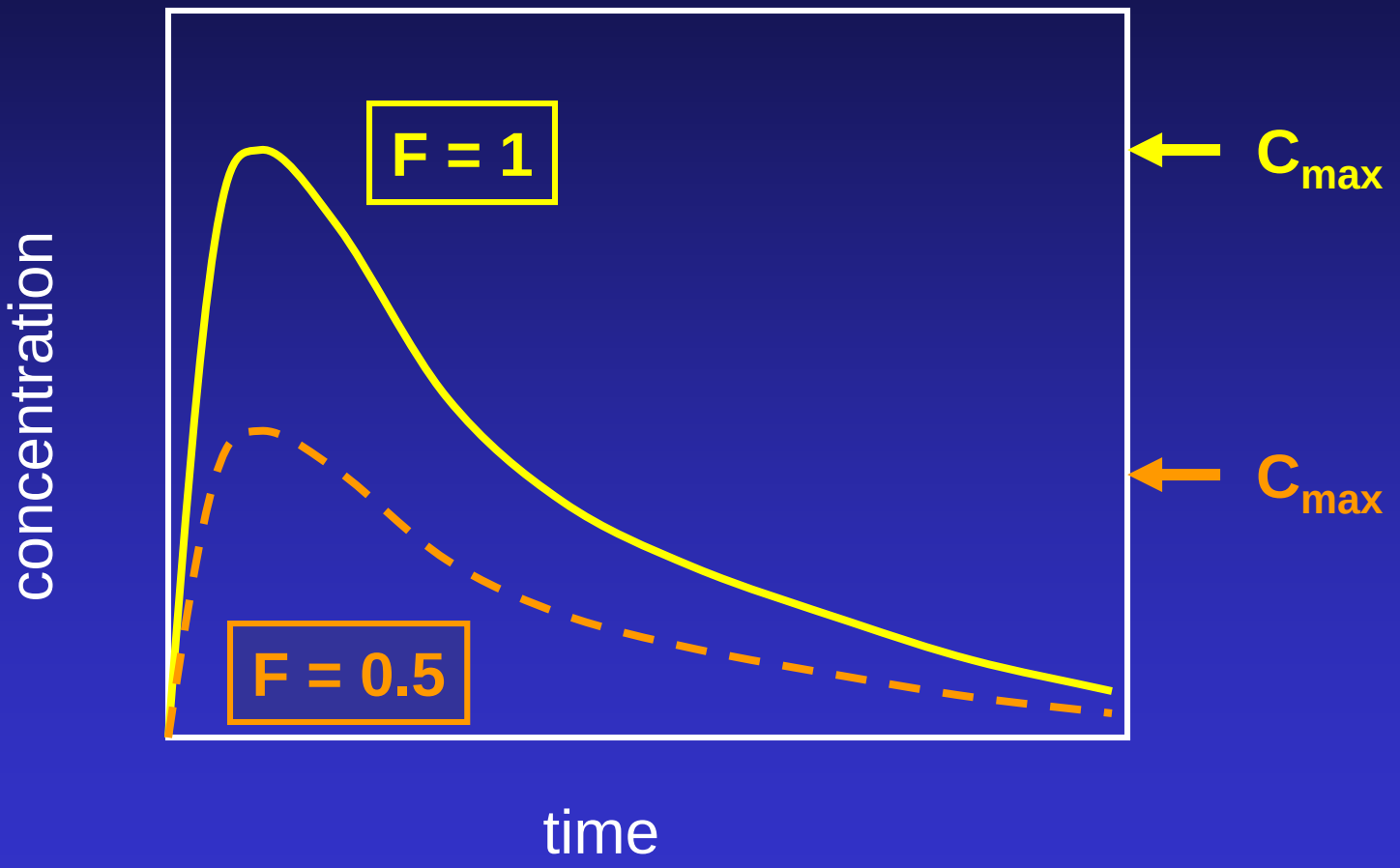
Bioavailability

- quantifies **ABSORPTION** from the site of administration **to the blood**
- is measured by comparing oral (or another mode of administration) to intravenous administration

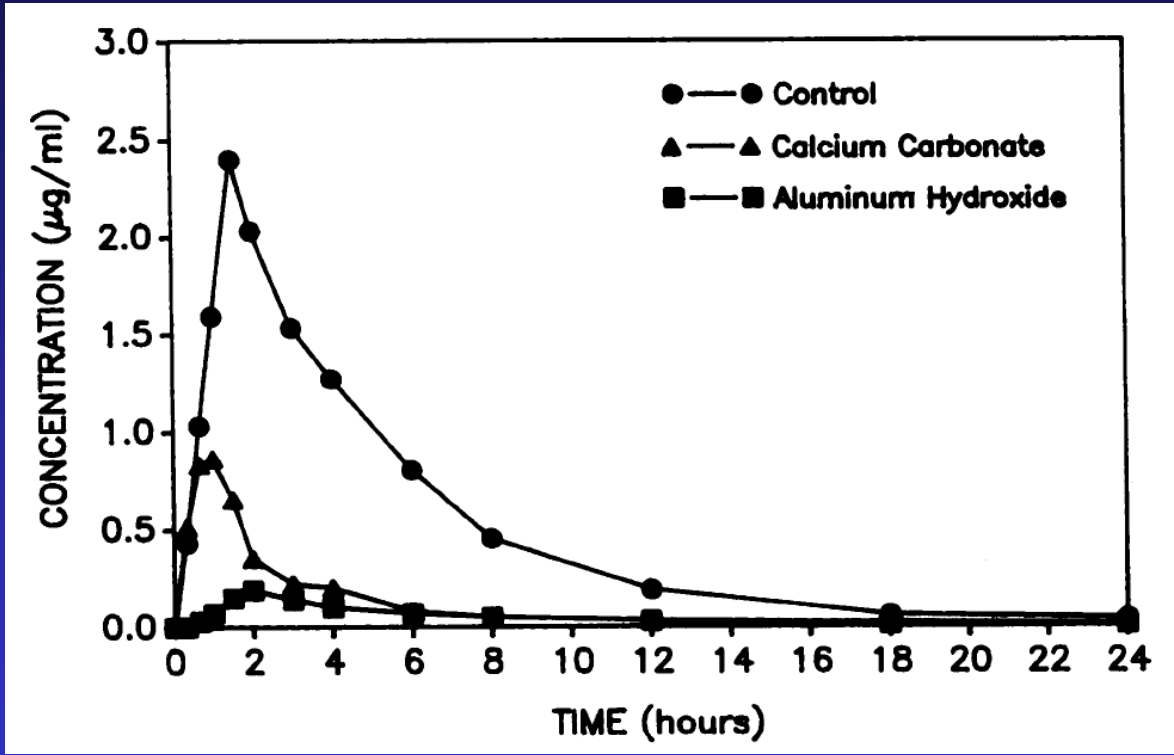


A poor bioavailability reduces both C_{max} and AUC ... and thereby decreases the potential for efficacy !!!

A low bioavailability (F) reduces both C_{max} and AUC



Fluoroquinolones : influence of cations on bioavailability



A. Cipro 750 mg

B. + 850 mg $CaCO_3$

C. + 600 mg $Al(OH)_3$

Treatment[a]	C_{max} (μg/ml)	AUC_{0-t} (μg/h/ml)
A	3.18 ± 1.29	13.50 ± 4.61
B	1.69 ± 0.48	7.82 ± 3.09
C	0.60 ± 0.58	2.08 ± 1.20

Frost et al AAC (1992) 36:830-2

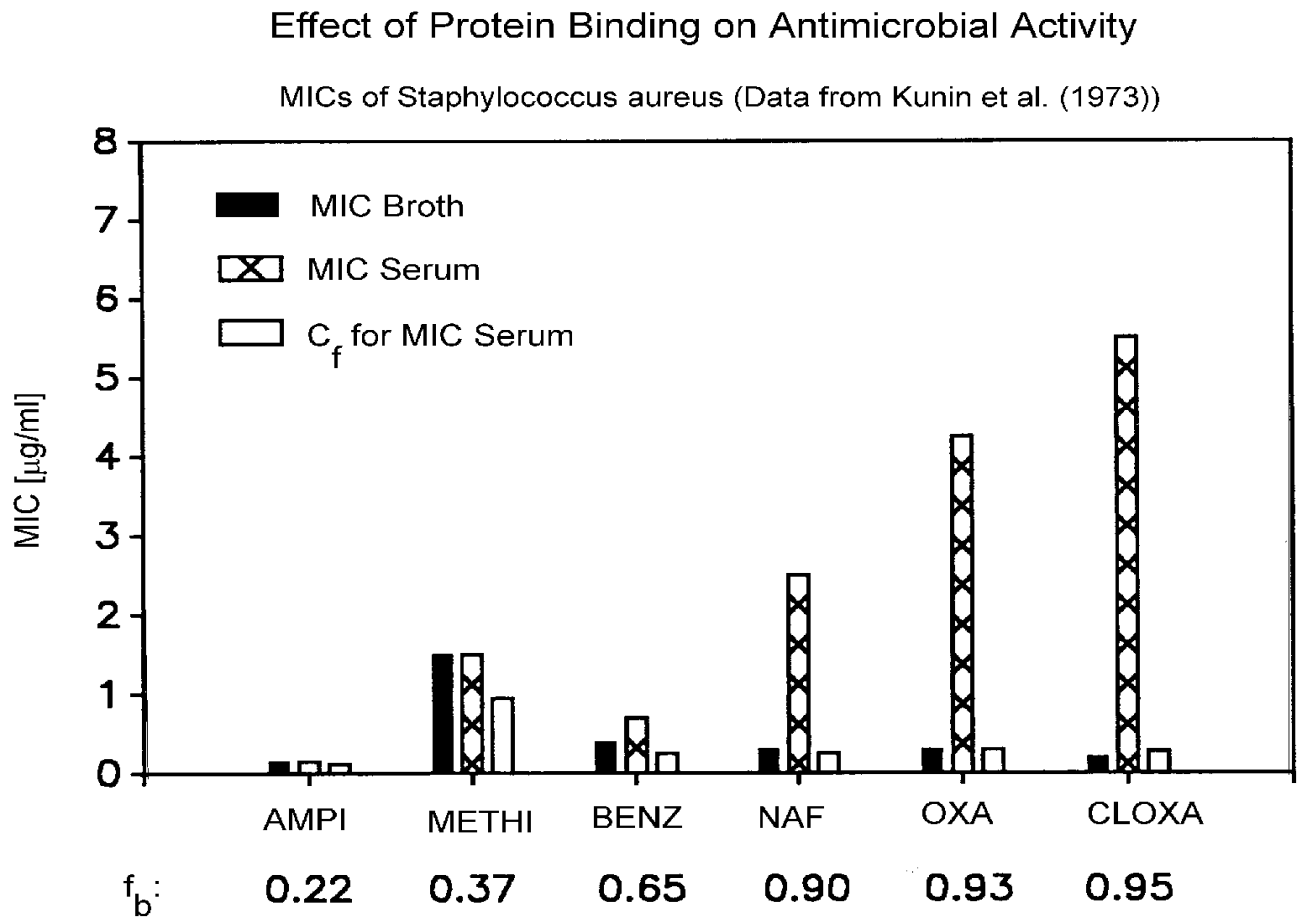
Fluoroquinolones : bioavailability (p.o.) and C_{max}

Drug	Dosage (mg/24h)	Bioav. (%)	C_{max} (mg/L)
norfloxacin	800	~ 35	2.4 *
ciprofloxacin	500	~ 70	2.4 *
ofloxacin	400	~ 95	3-4.5 *, +
levofloxacin	500	~ 99	5-6 *, +
moxifloxacin	400	~ 90	4.5 *

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, and AVELOX®

\+ first dose to equilibrium

Protein binding: it is (almost always) the free drug that acts ...



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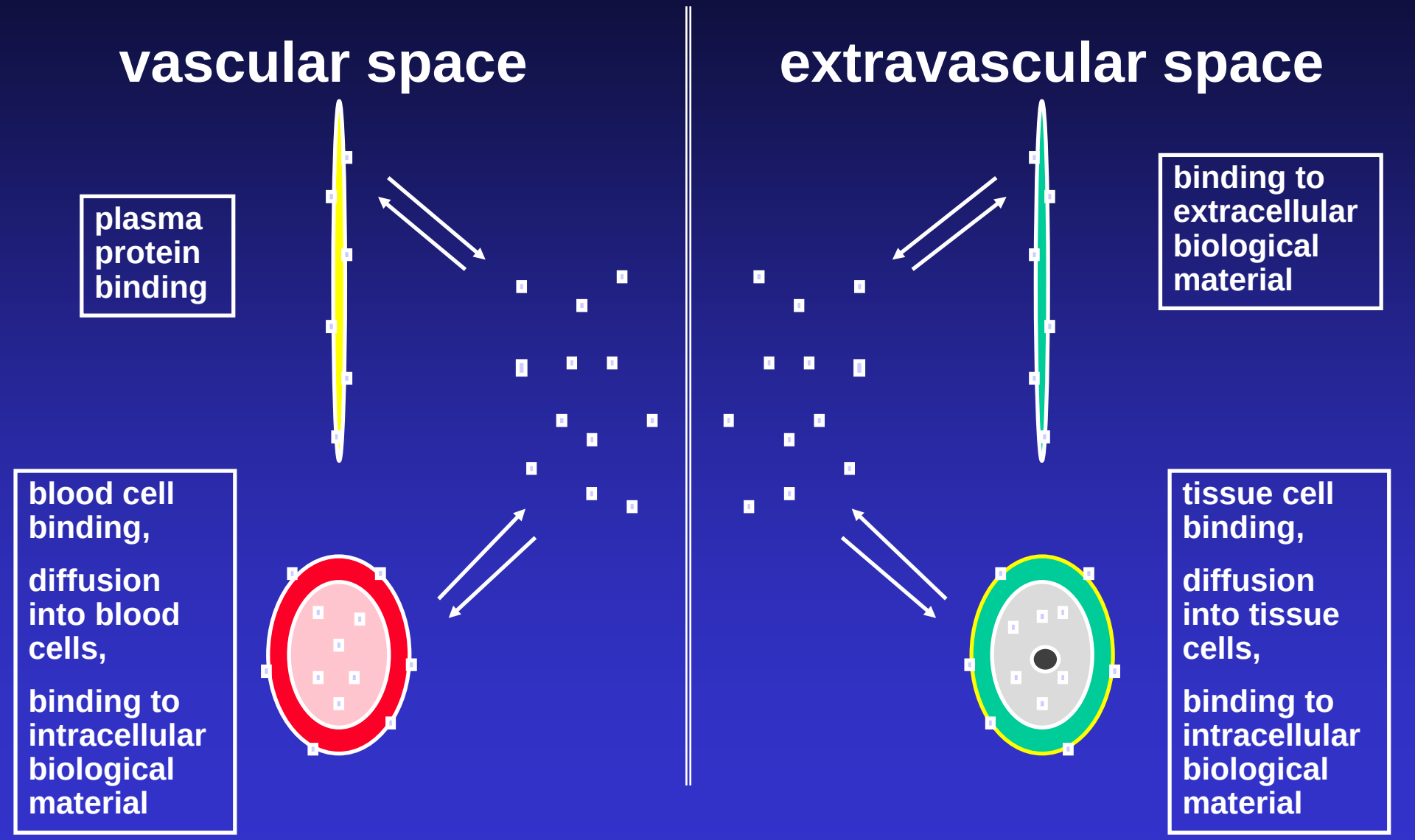
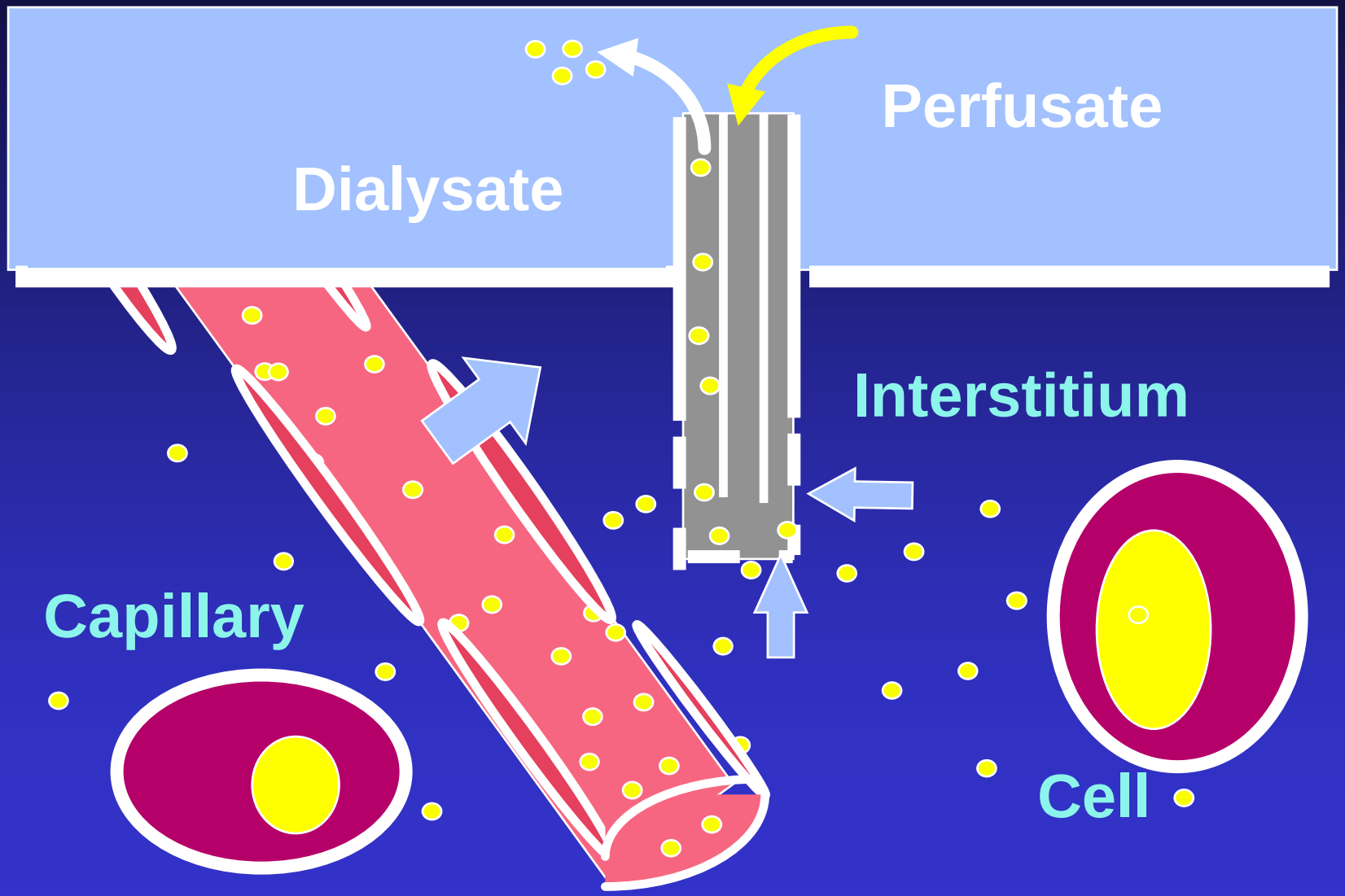
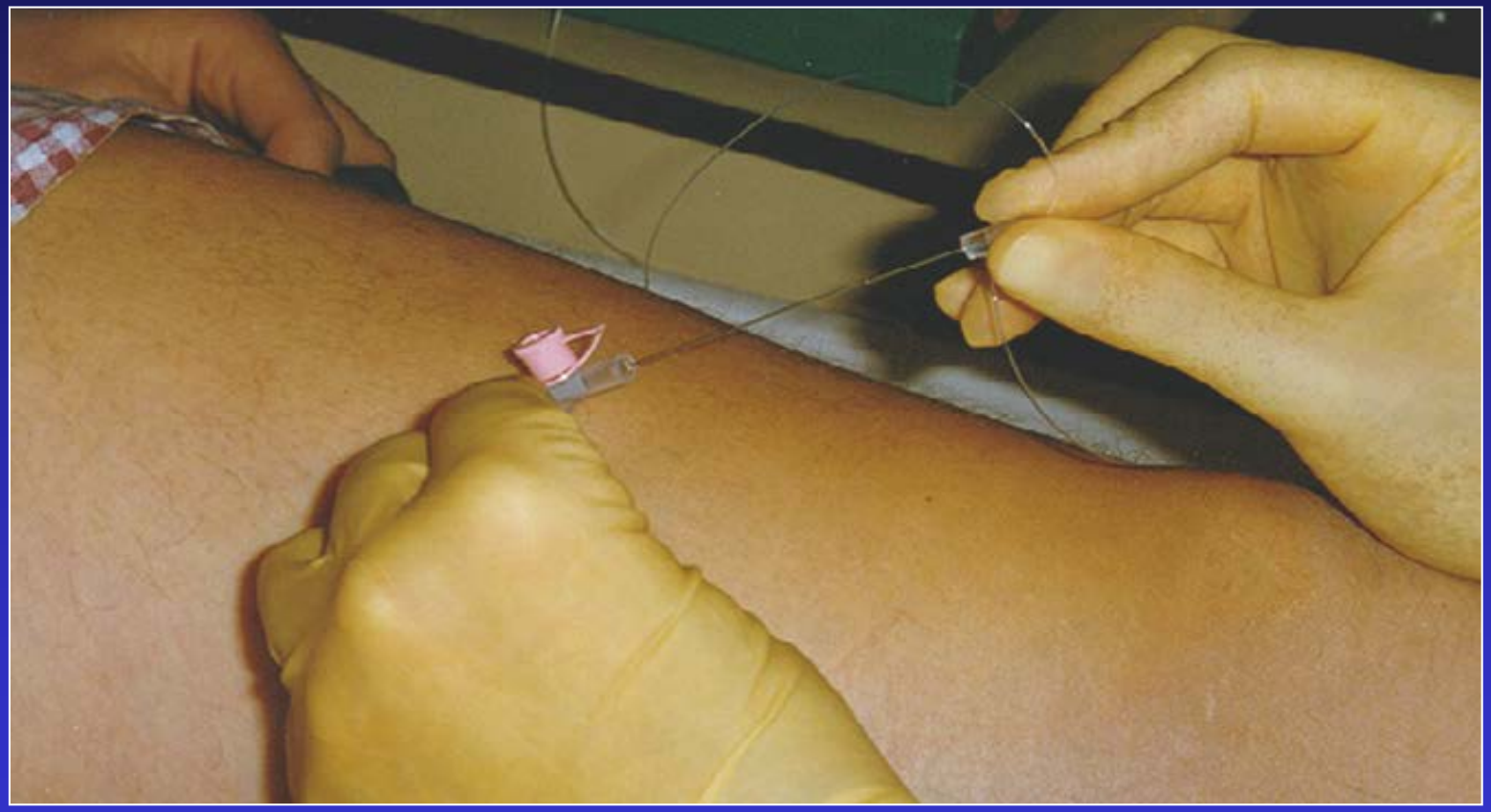


Microdialysis

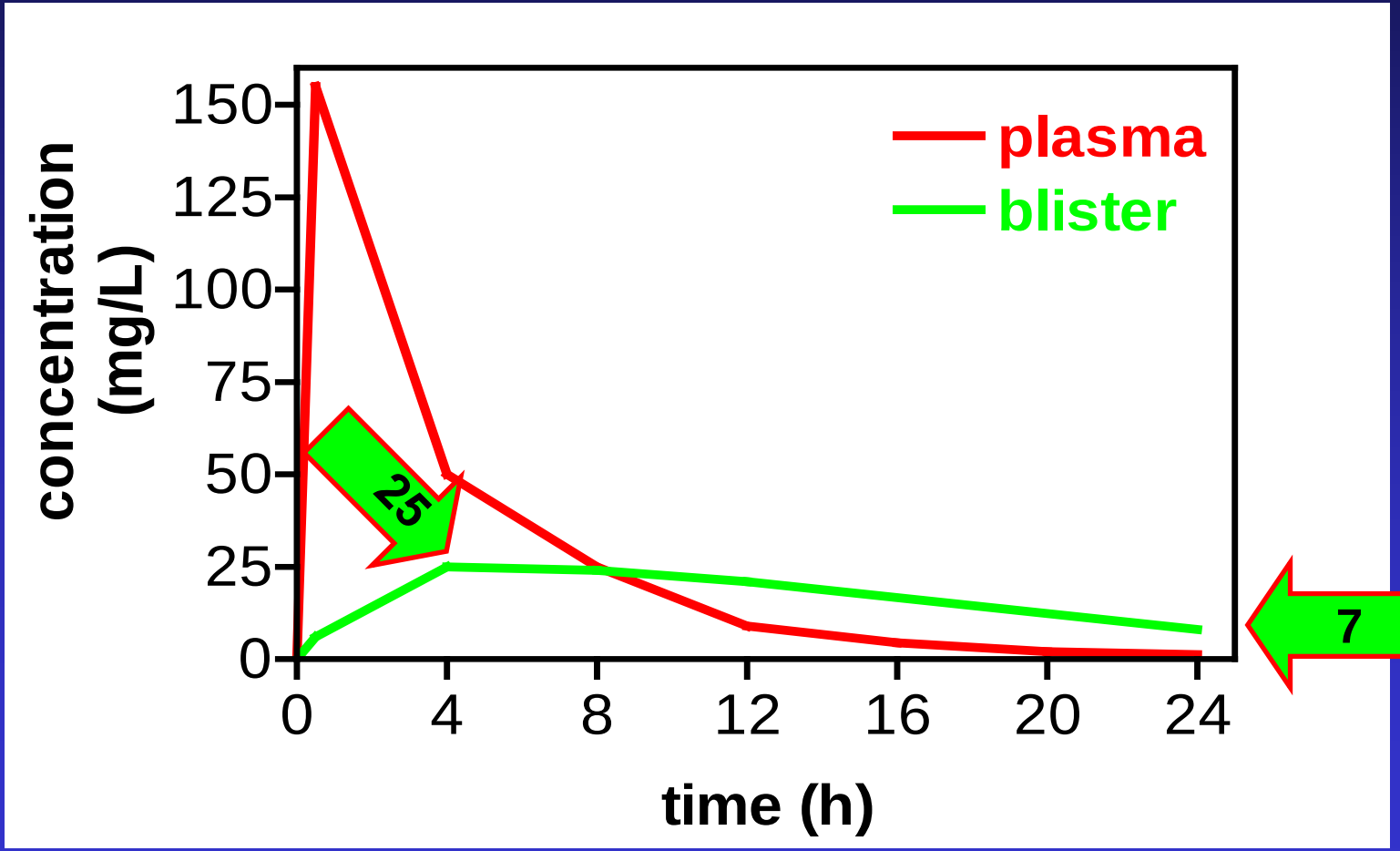


Microdialysis

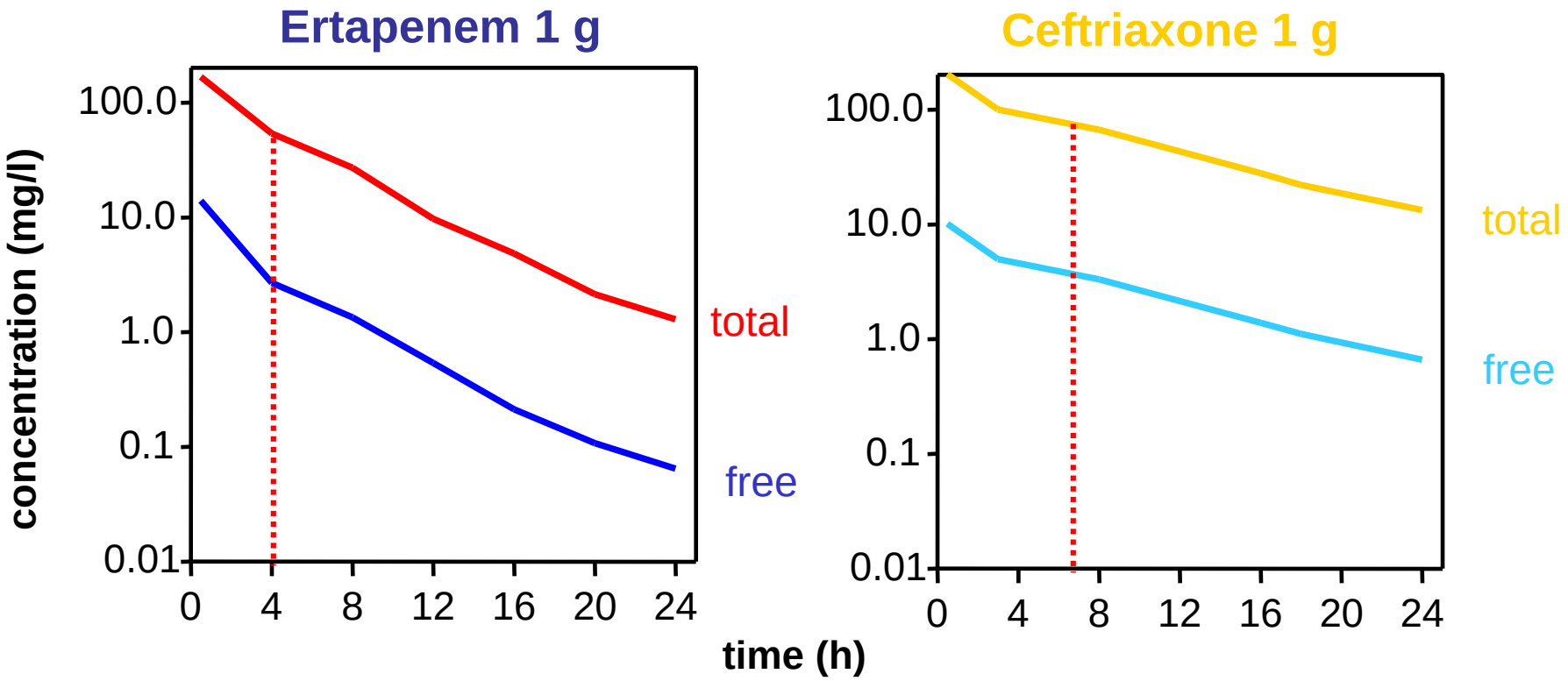


Protein binding impairs and slows down drug distribution...

TOTAL drug concentration of ertapenem (a high protein bound β-lactam) in plasma and blister fluid after 3 days of treatment

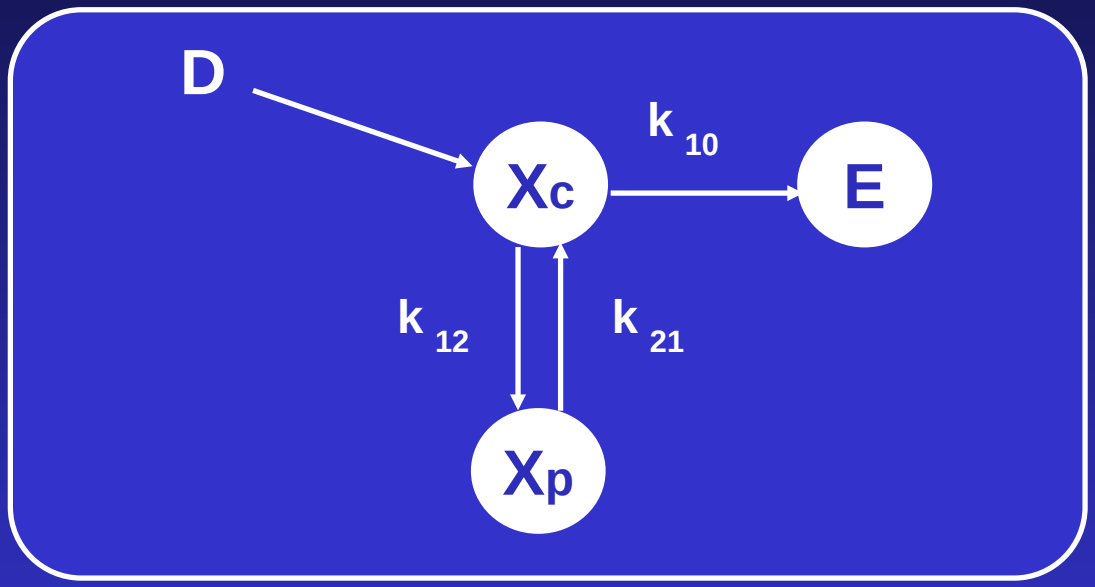


But protein binding prolongs half-lilfe ...



ceftriaxone data: Paradis *et al*, AAC 1992, 36: 2085-2092
Perry & Schentag, Clin Pharmacokinet. 2001, 40: 685-694

Two-compartment model



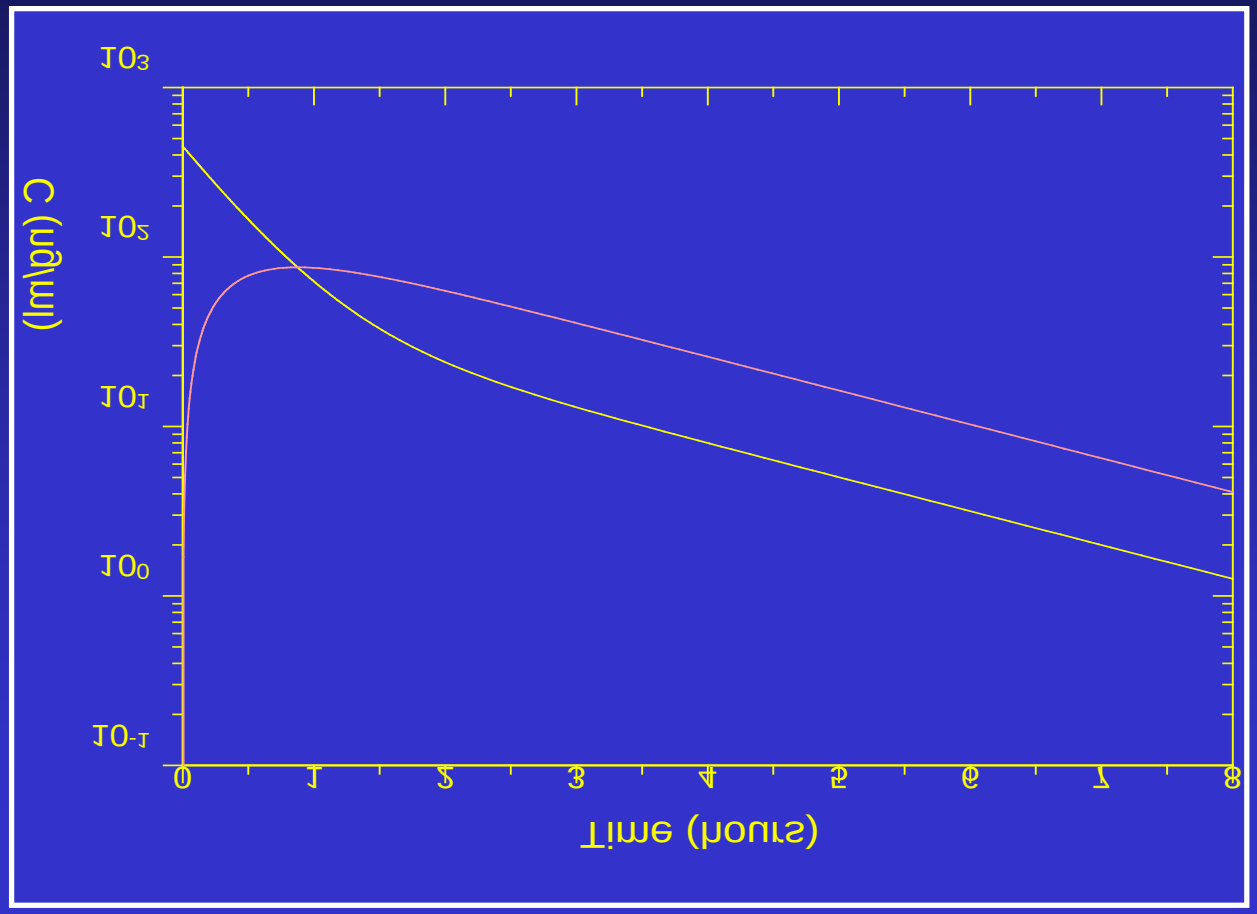
Dose

X_c Drug in the central compartment

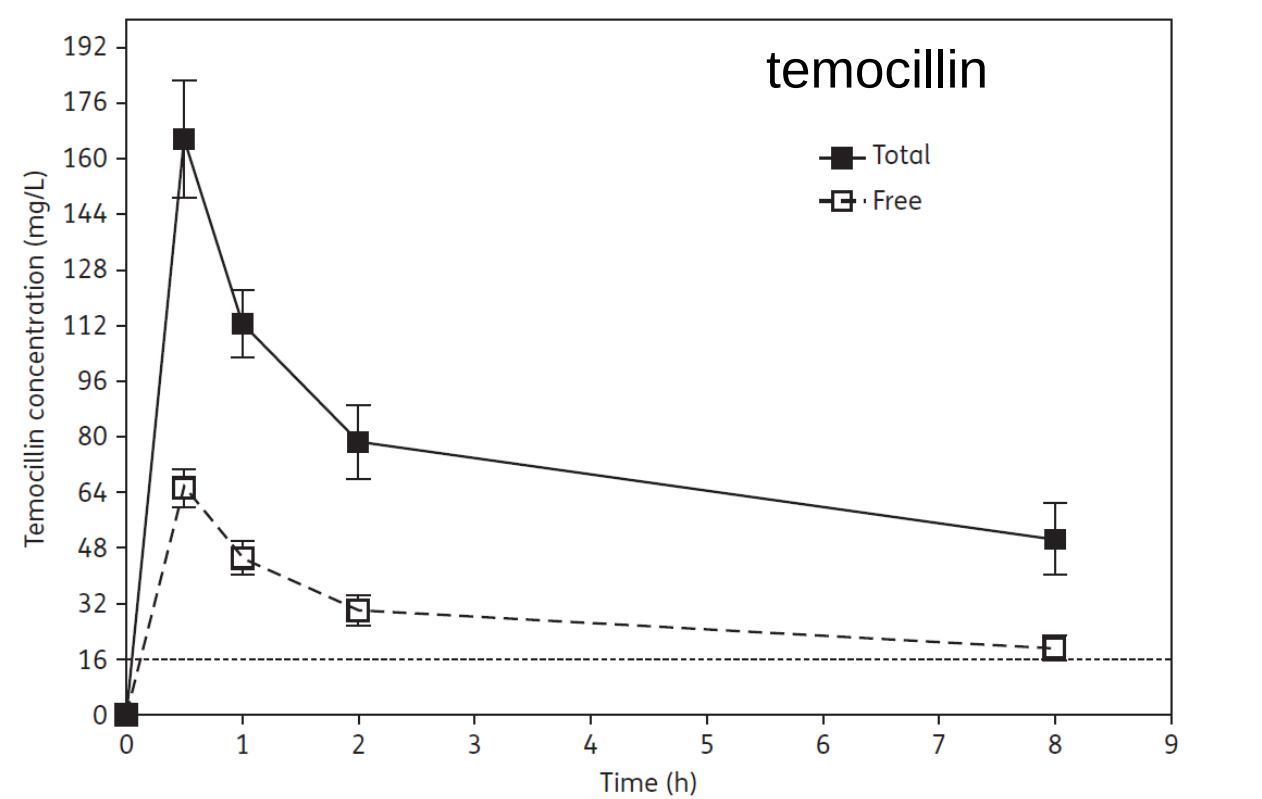
X_p Drug in the peripheral compartment

E Drug eliminated

Two-compartment model

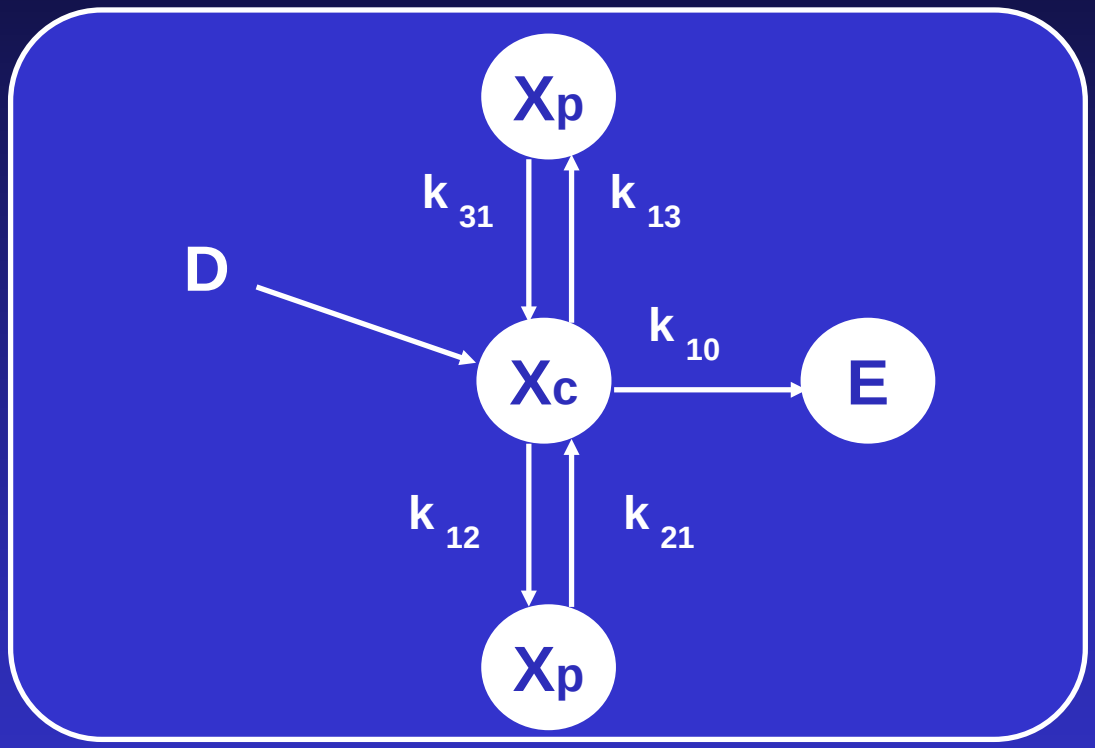


A typical example for a β-lactam



Laterre et al, JAC 2015, 70:891–898

Three-compartment model



D Dose

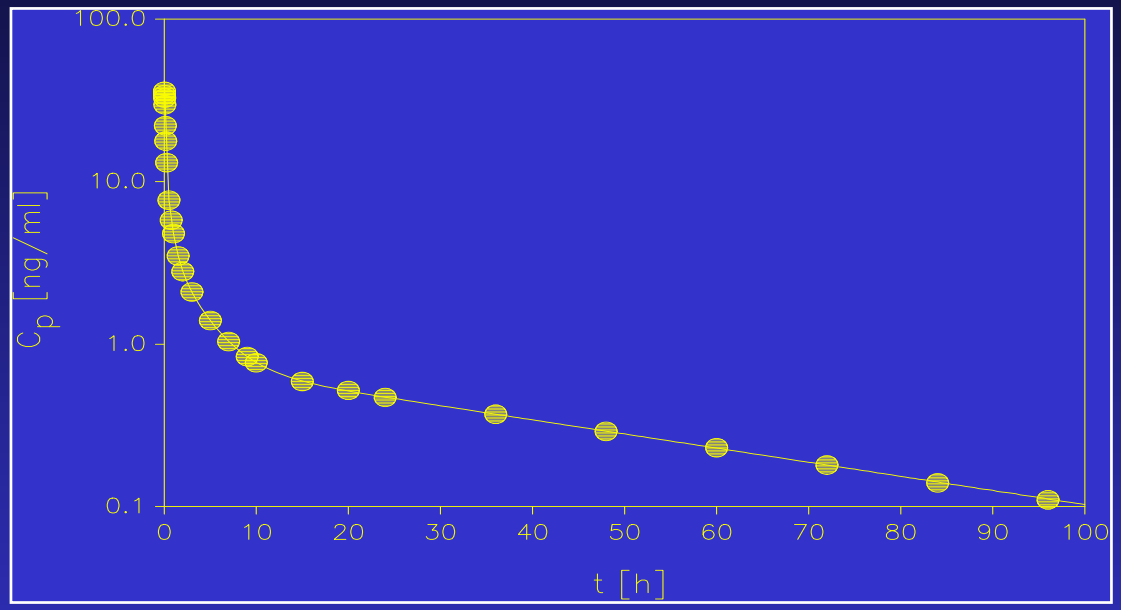
E Drug eliminated

X_c Drug in the central compartment

X_{ps} Drug in the shallow peripheral compartment

X_{pd} Drug in the deep peripheral compartment

Three-compartment model



α-phase: **distribution phase**

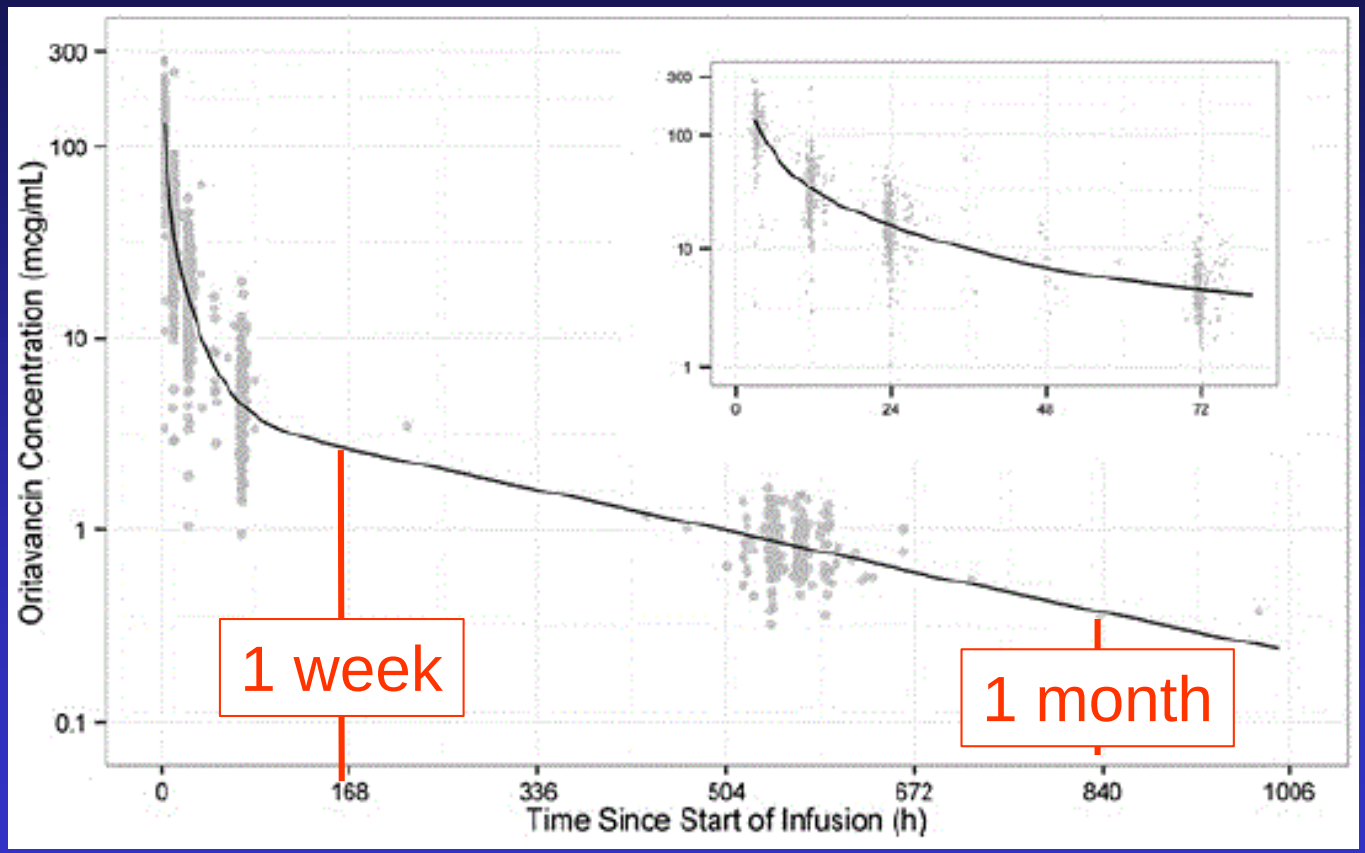
β-phase: **rapid elimination phase**

γ-phase: **slow elimination phase**

$$C = a \cdot e^{-\alpha \cdot t} + b \cdot e^{-\beta \cdot t} + c \cdot e^{-\gamma \cdot t}$$

Three-compartment model

The example of oritavancin … single dose treatment !



PHARMACOKINETICS

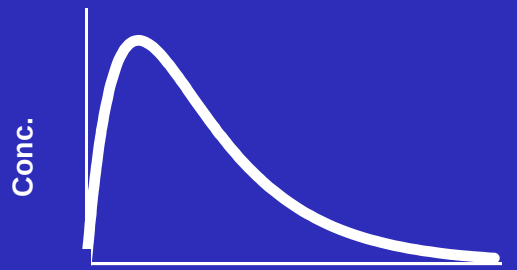
what the body does to the drug

PHARMACODYNAMICS

what the drug does to the body

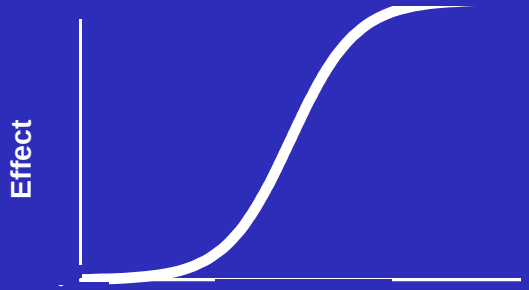
Pharmacokinetics

conc. vs time



Pharmacodynamics

conc. vs effect



PK/PD

effect vs time