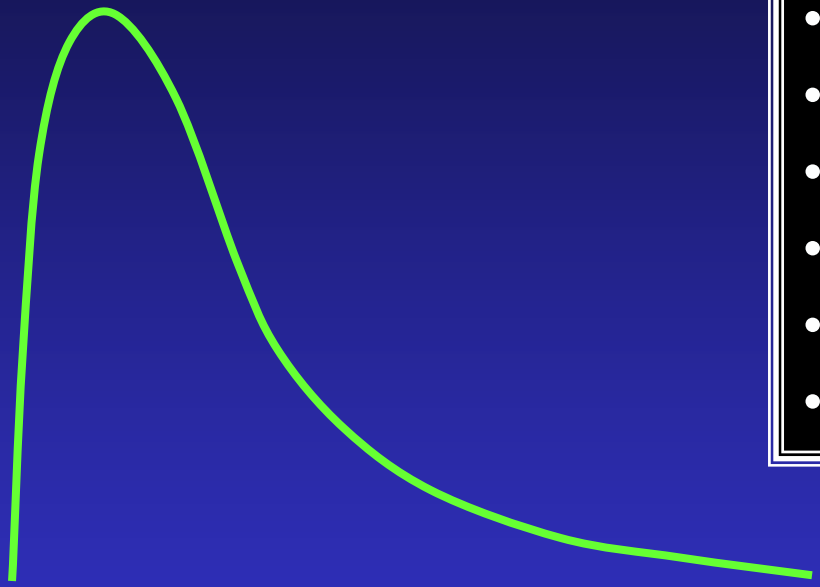
ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
PK/PD of Anti-Infectives Study Group

ISAP

The general Concepts of Pharmacokinetics



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

What is this jargon ?

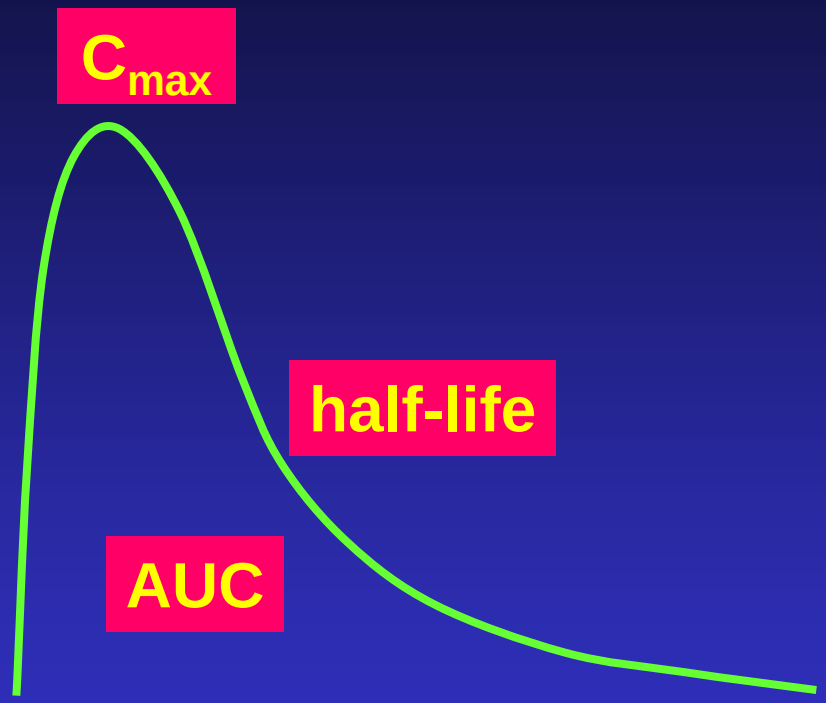
Is it useful ?

With the support of *Wallonie-Bruxelles-International*

WBI Wallonie-Bruxelles International

Pharmacokinetics is speed !

The general Concepts of Pharmacokinetics (PK)



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- Vd,
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- AUC,
- bioavailability,
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Let us travel together !!

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

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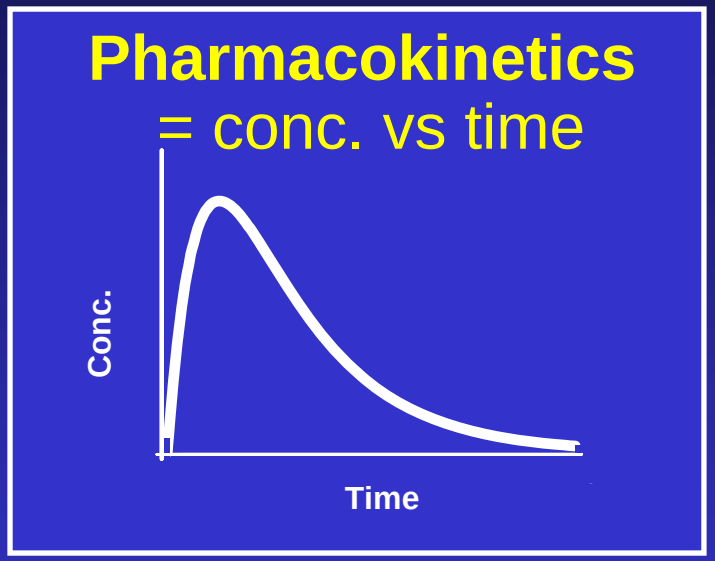


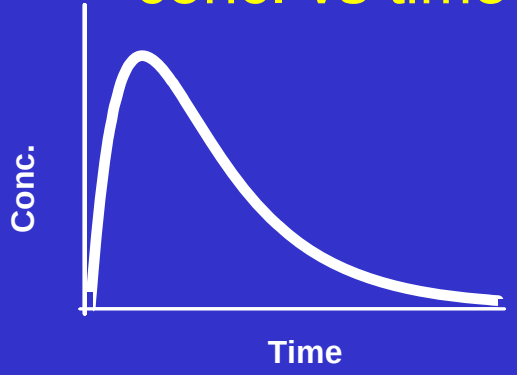
- the time course of drug and metabolite concentrations in the body

What is PK for ?

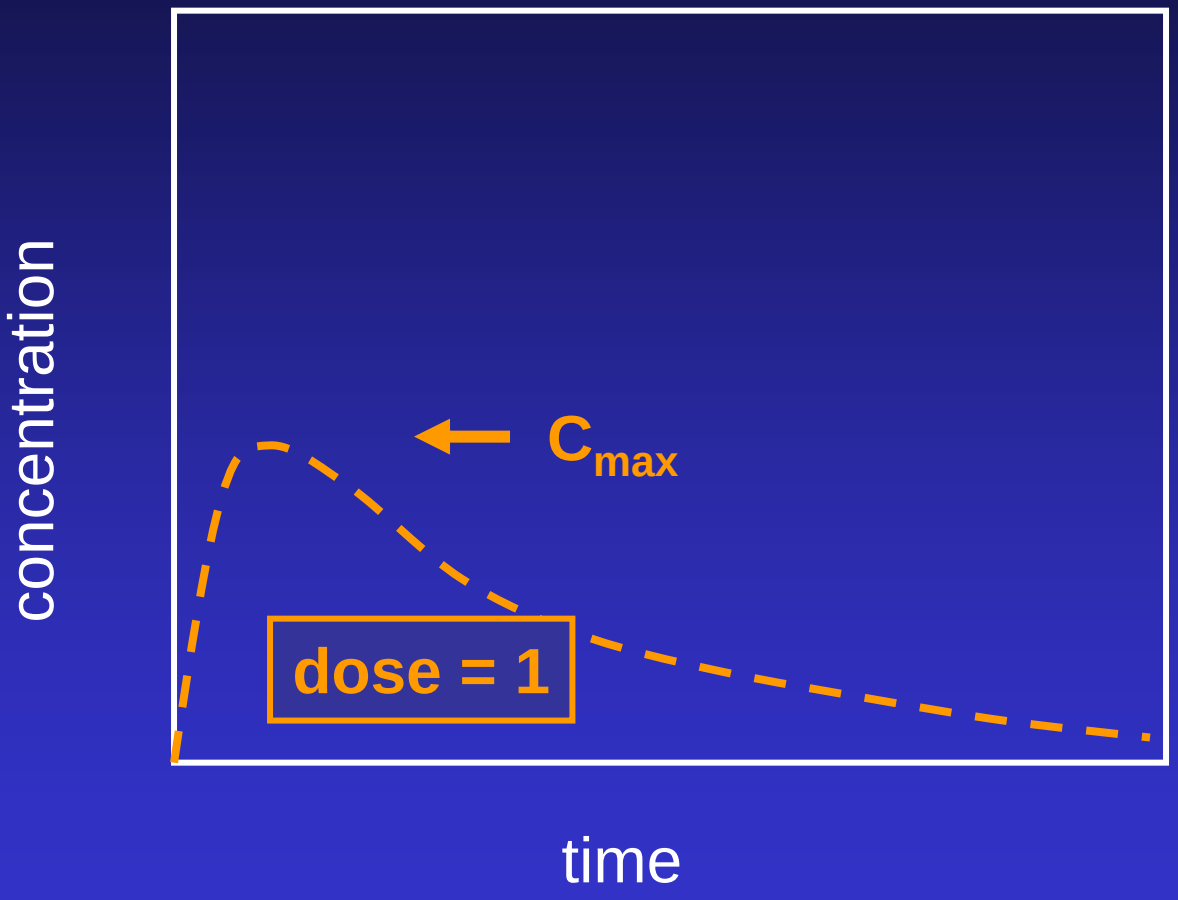
PK is the way to see if the drug can be made useful …

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

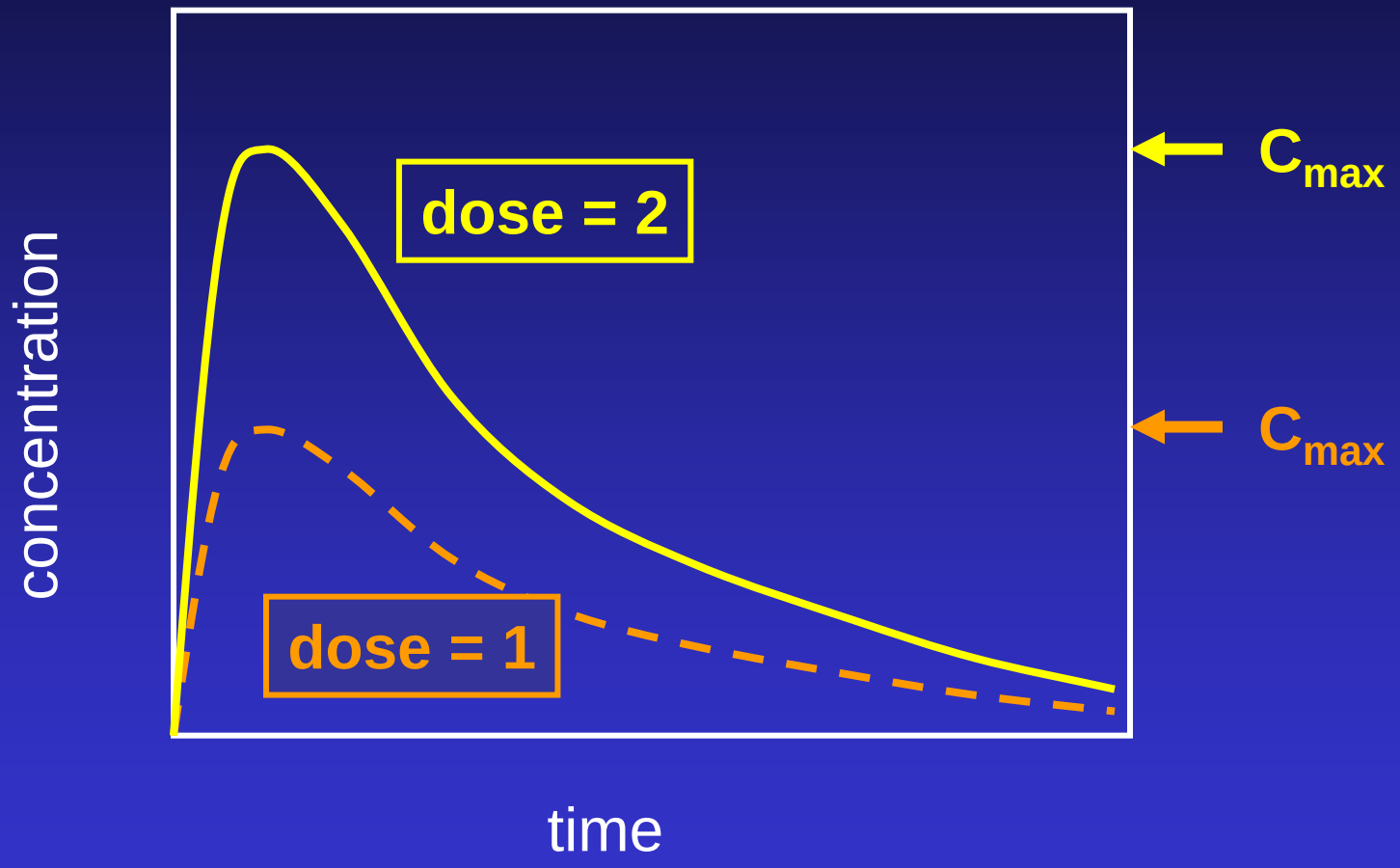
Pharmacokinetics
= conc. vs time



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



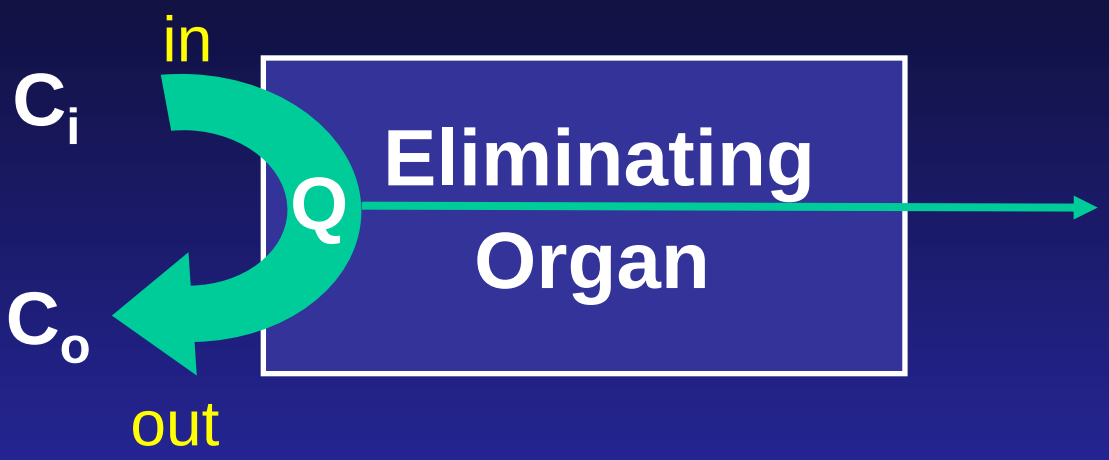
C_{max} ... is proportional to the dose ...



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 Cmax (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)

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)

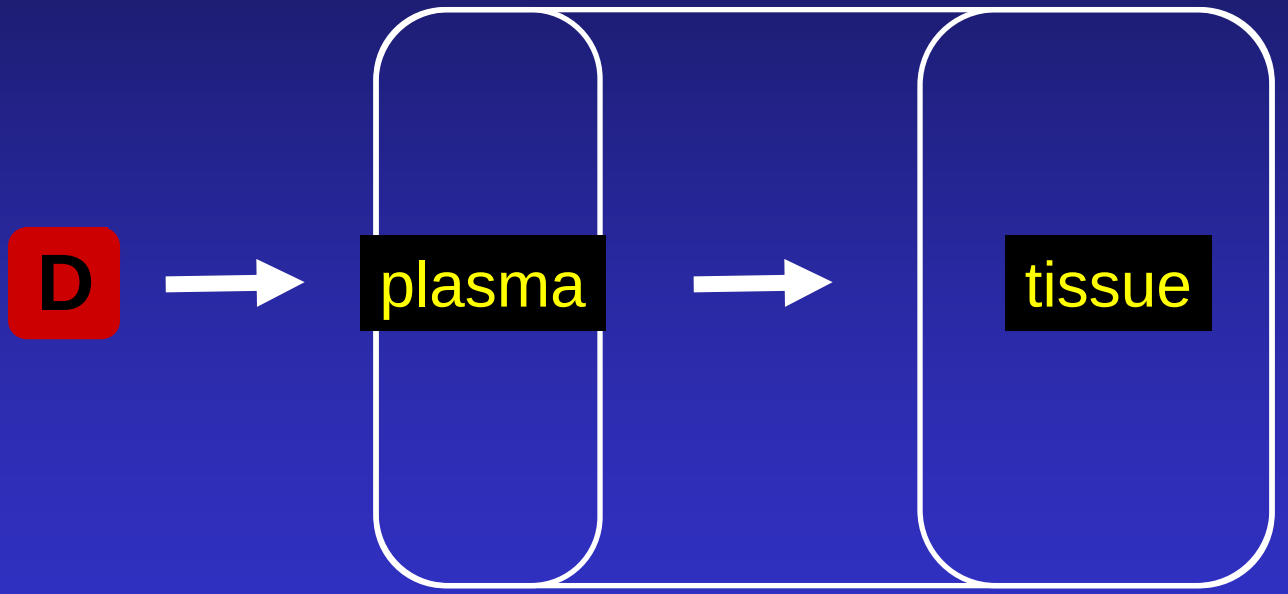
- Quantifies how the drug has access to the various compartments of the body

- 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 ...

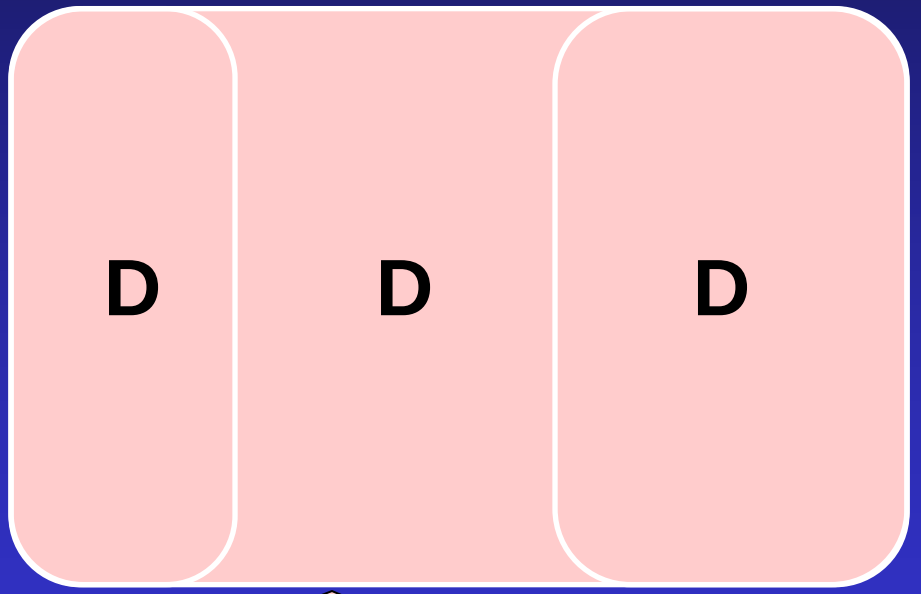


What is V_d ?

If drug diffuses throughout the body ...

Vd = 1 L/kg

C_{max} = dose /weight



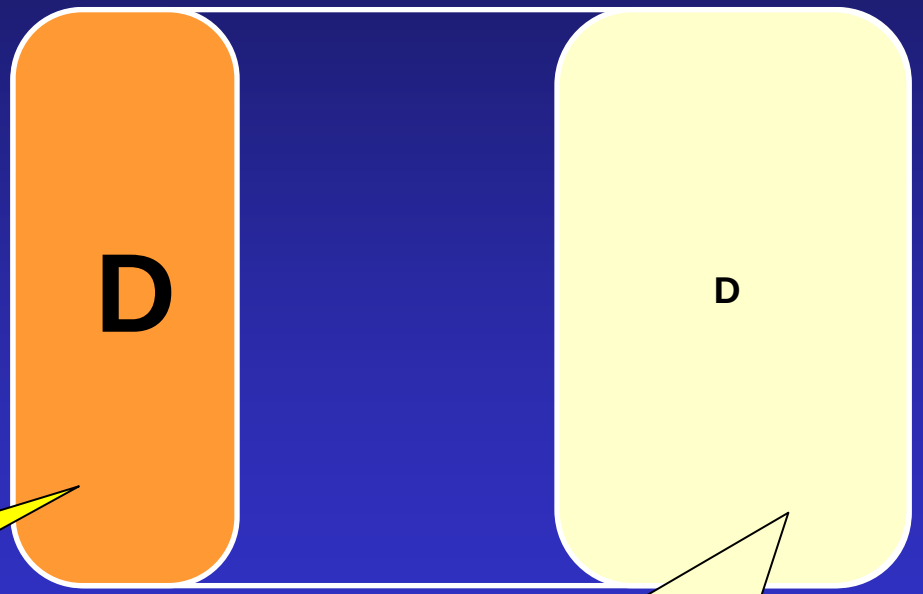
serum concentration = tissue concentration

What is V_d ?

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

Vd < 1 L/kg

C_{max} > dose /weight



high serum concentration

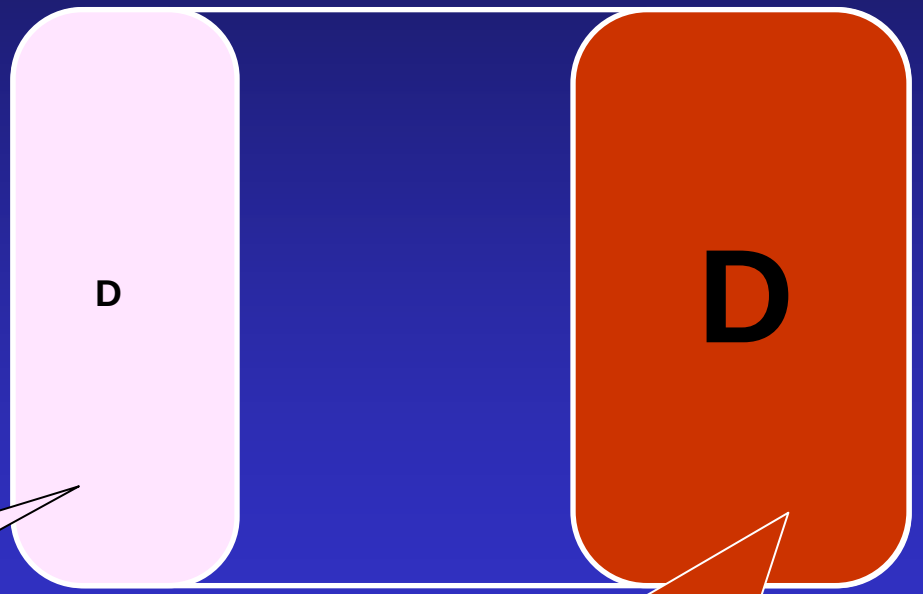
no or little tissue concentration

What is V_d ?

If drug accumulates in tissues...

Vd > 1 L/kg

C_{max} < dose /weight



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 moder. accumul. in tissues)	1.8
• azithromycin (marked accum. 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

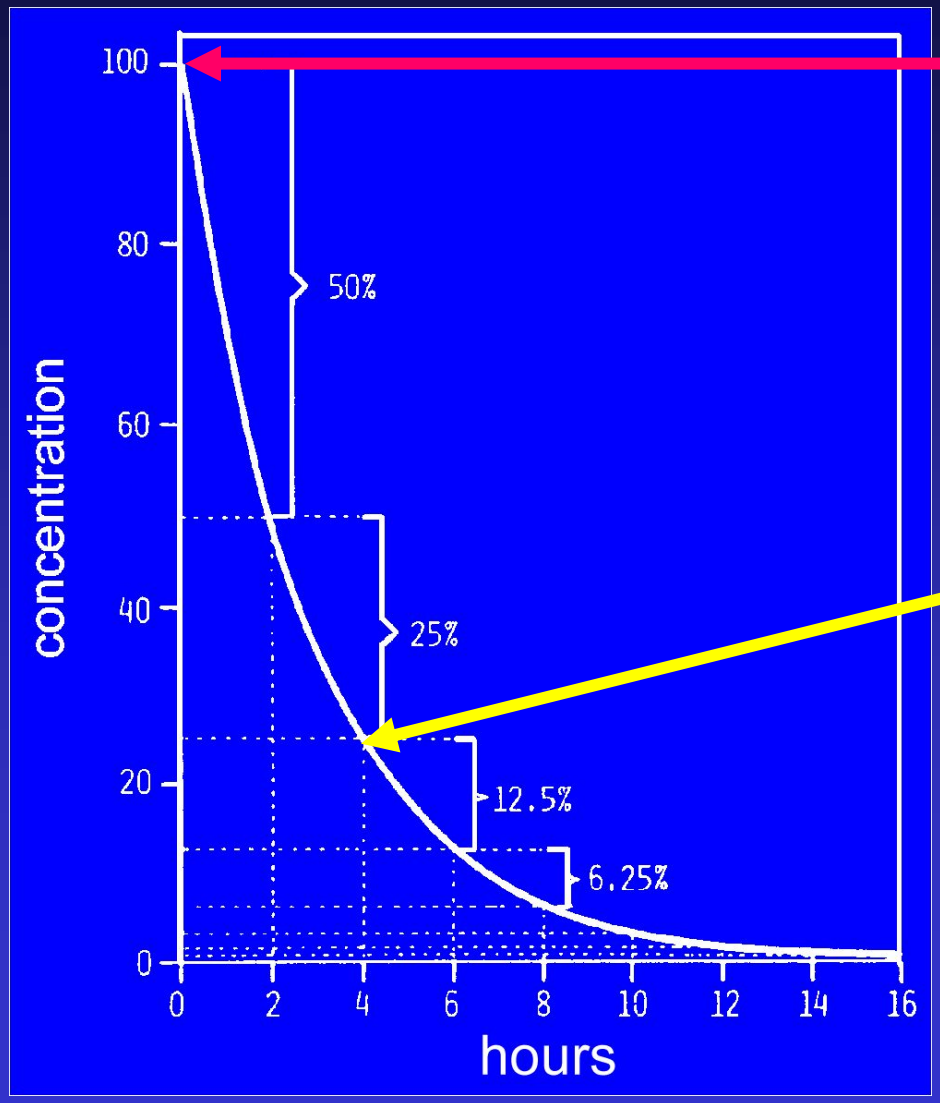
Half-life ($t_{1/2}$)

- 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

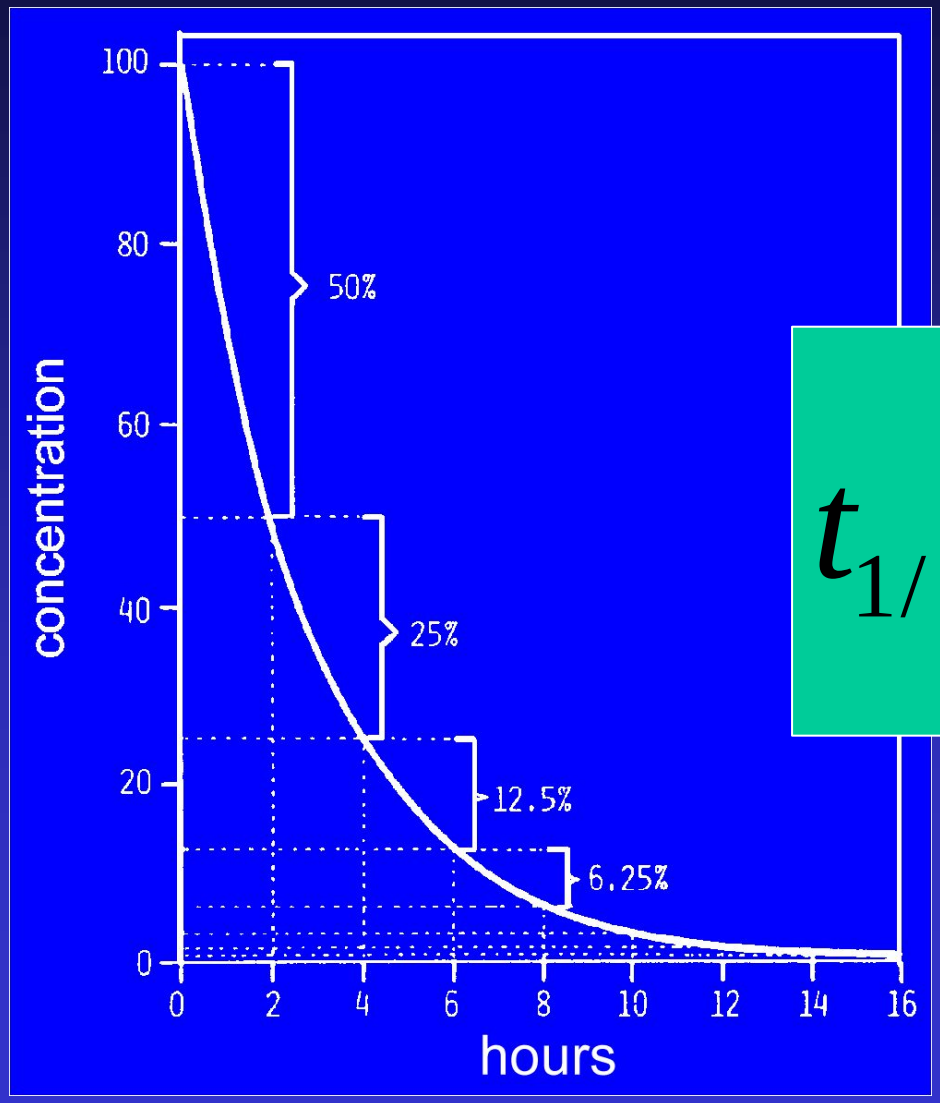
Why is half half-life a secondary parameter ?



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 ?



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

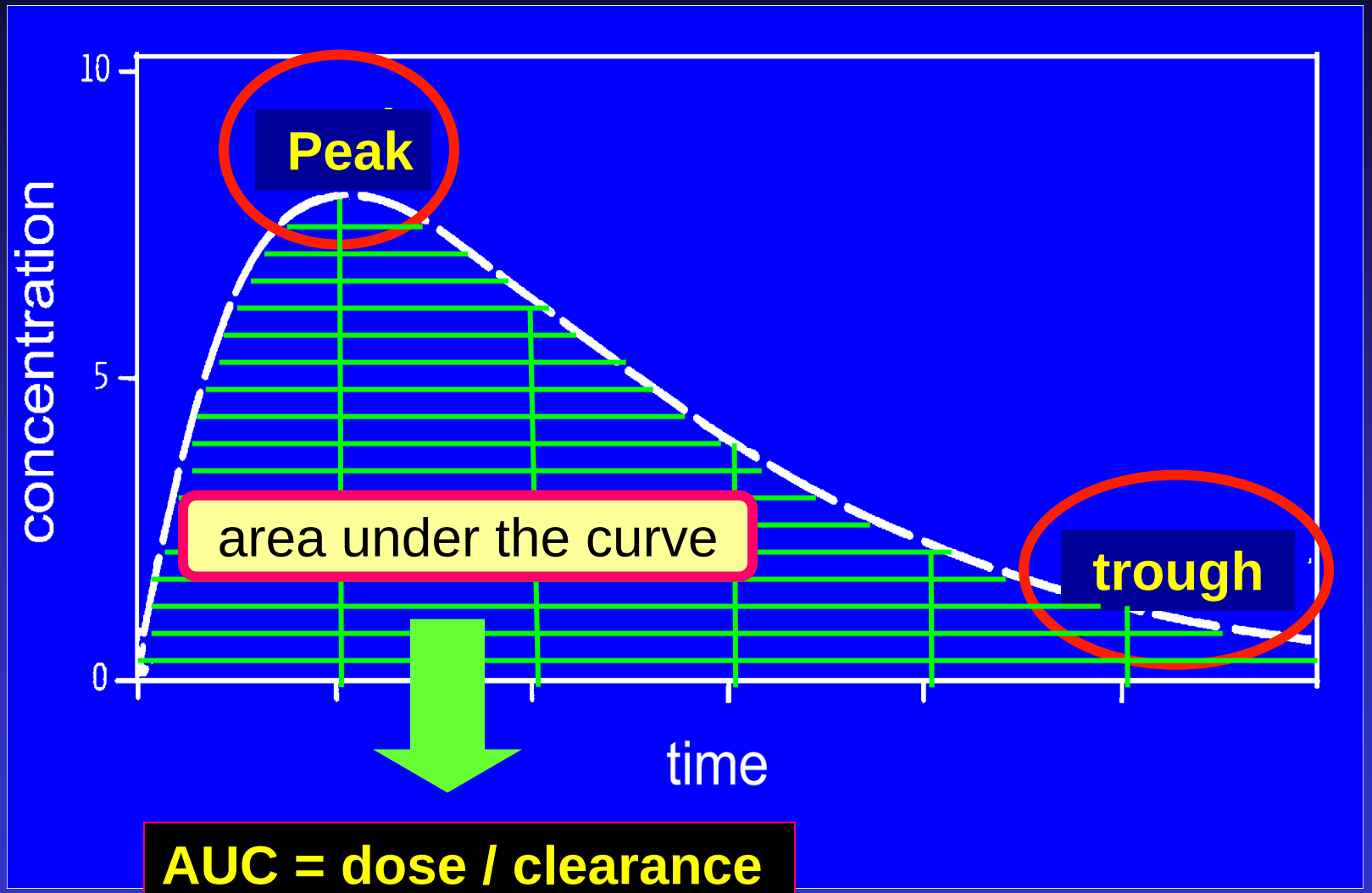
What is useful in half-life for the clinician ?

- 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 Vd) and azithromycin (high Vd), 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 llinked to the drug AND the patient: **the clearance ...**

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

- useful to assess the total drug exposure

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 !!

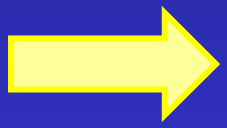
* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, and AVELOX®

\# litterature data

\+ first dose to equilibrium

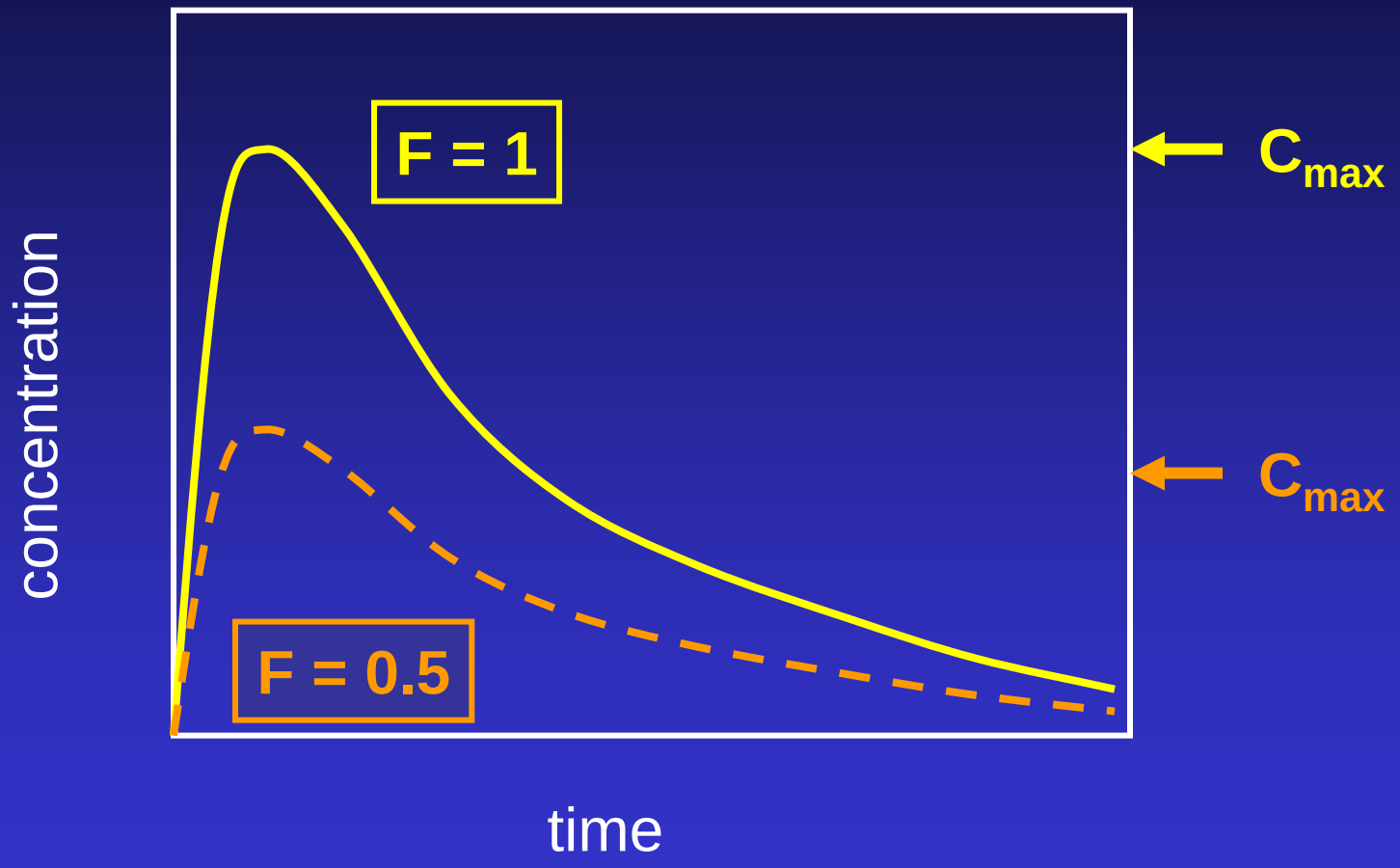
Bioavailability

- quantifies **ABSORPTION** from the site fo 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



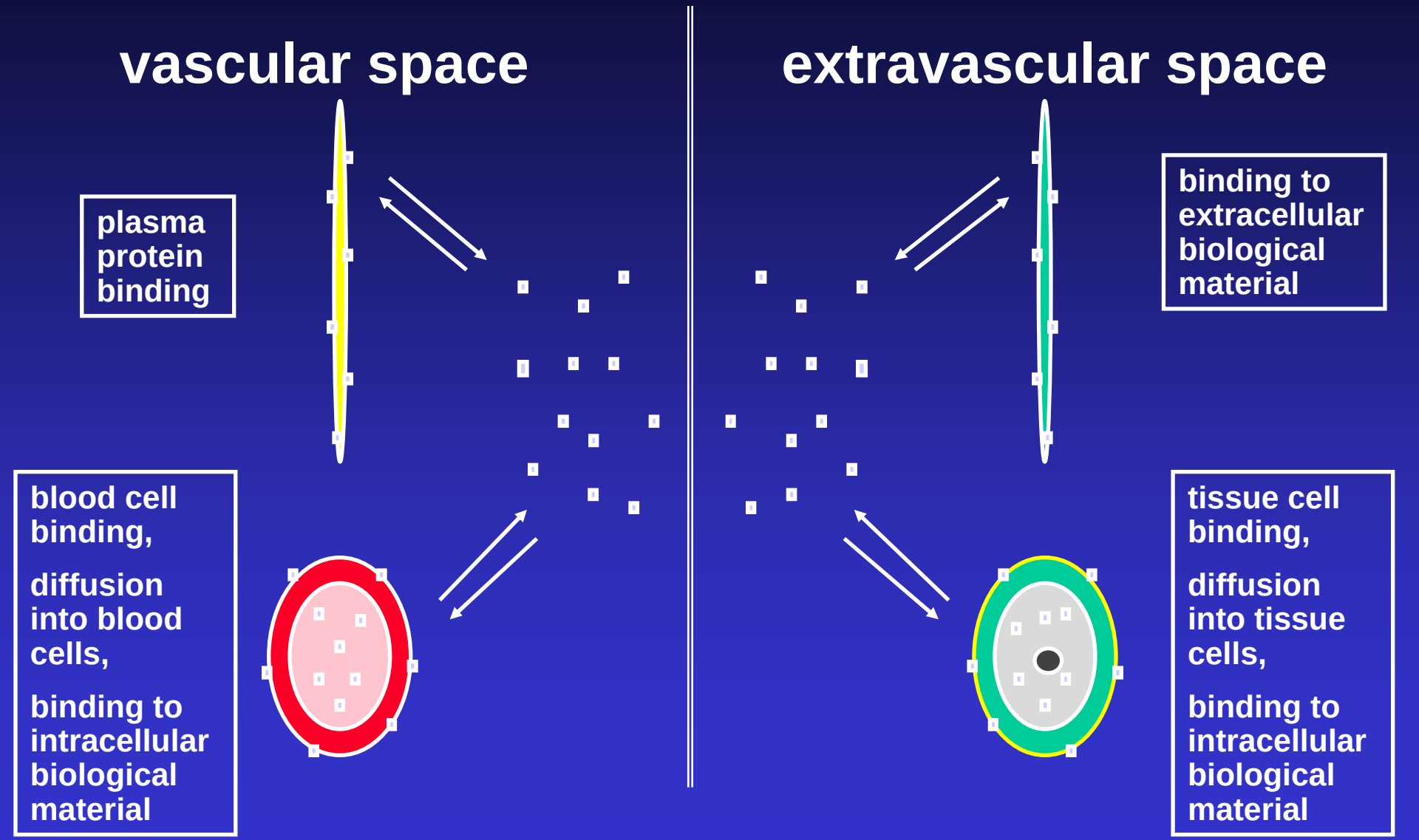
Fluoroquinolones : bioavailability (p.o.) and C_{max}

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®

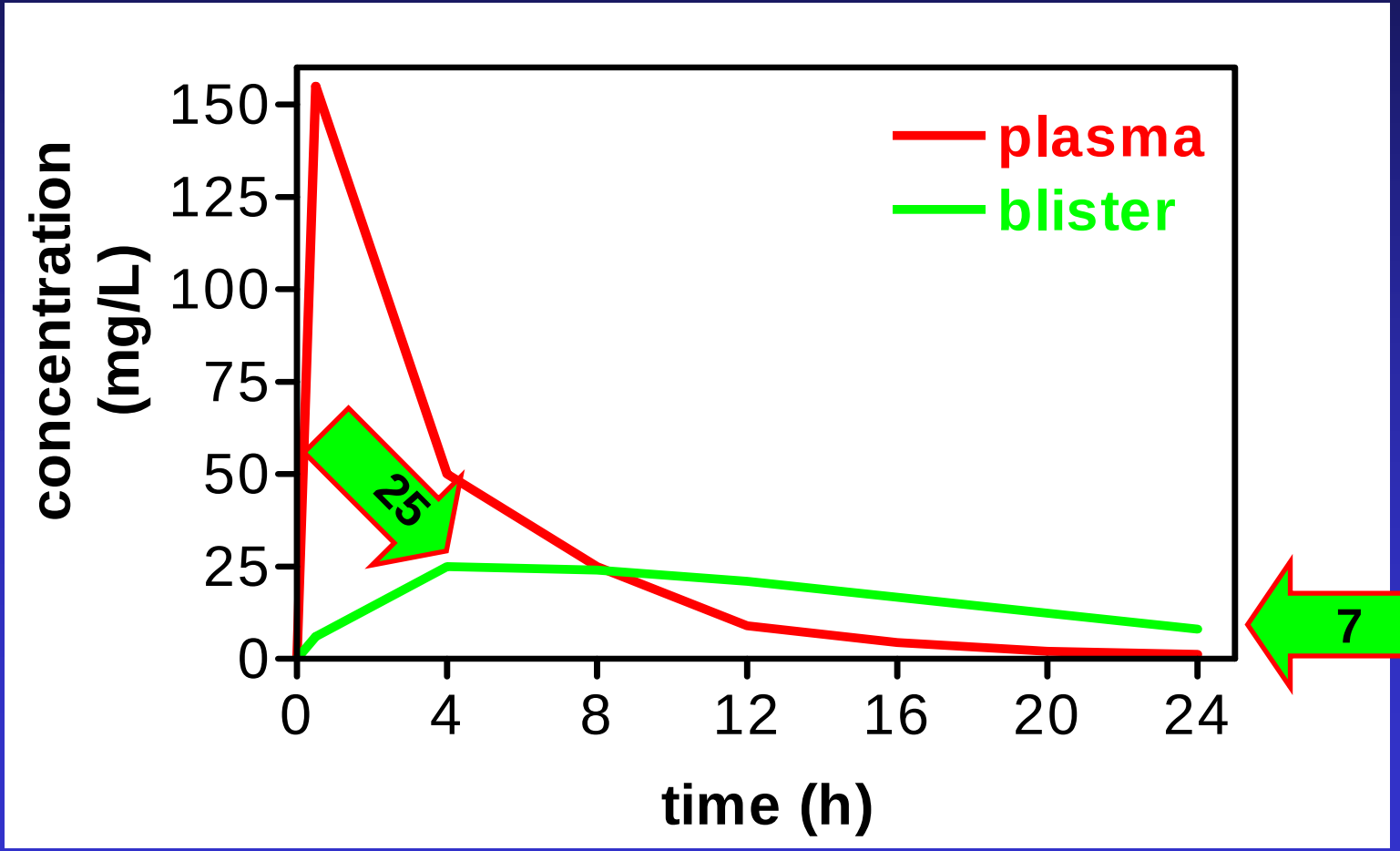
\+ first dose to equilibrium

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

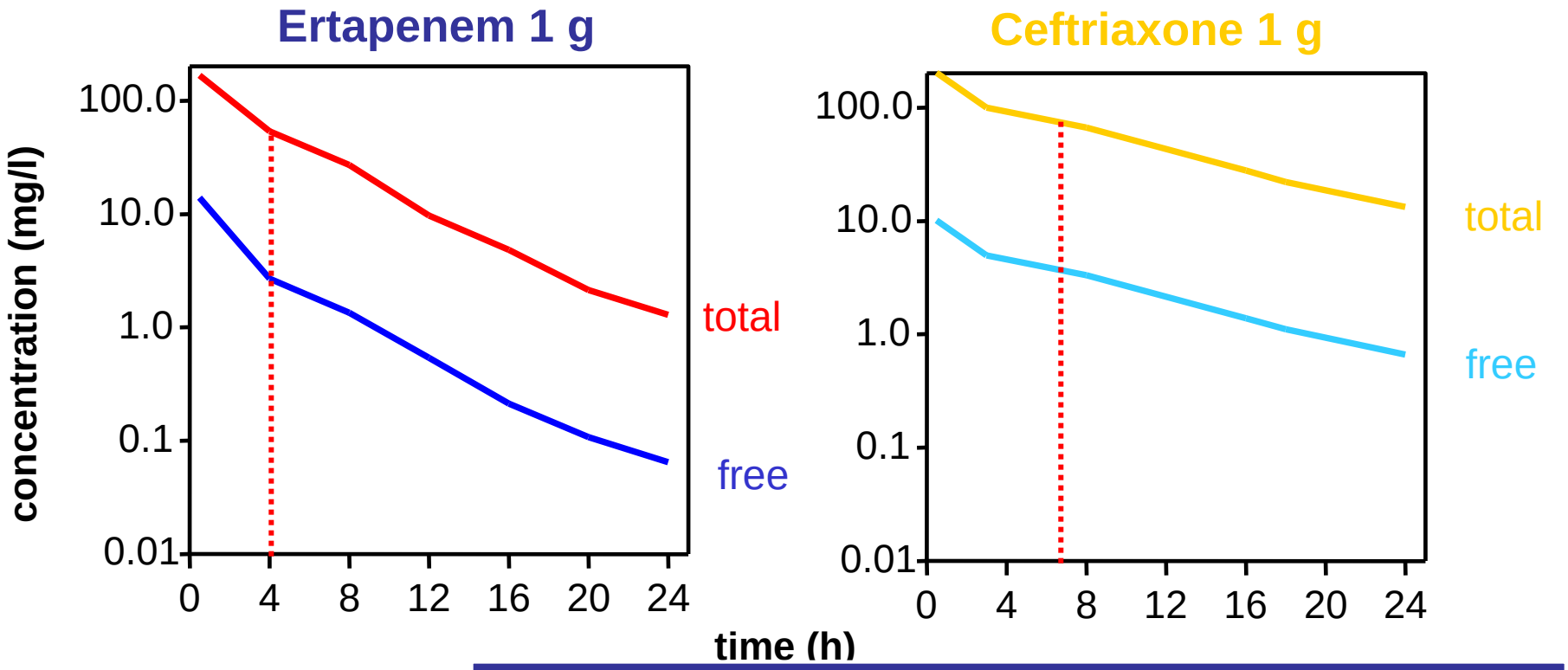


Protein binding impairs and slows down drug distribution...

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



But protein binding prolongs half-lilfe ...



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

This where we are ...

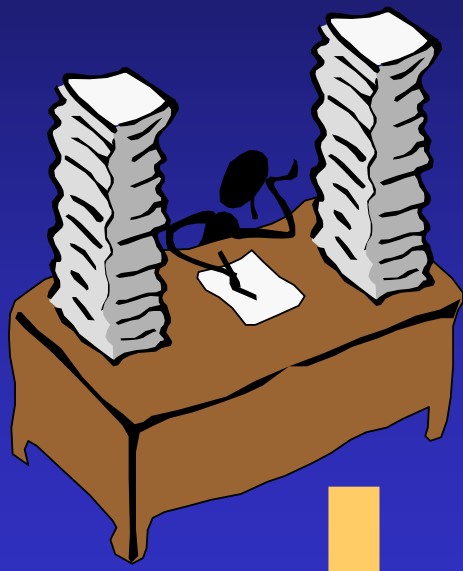
Pharmacokinetics

Concentration at site of infection

Dosing → **Concentration in blood**

Concentration in non-target tissues

Got it ?



Section 3A