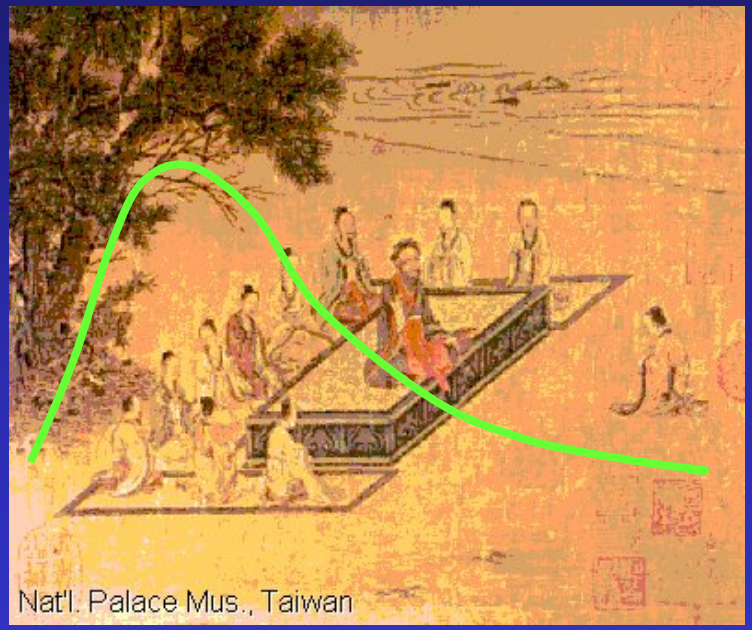
Asian PK/PD Educational Workshop

The general Concepts of Pharmacokinetics

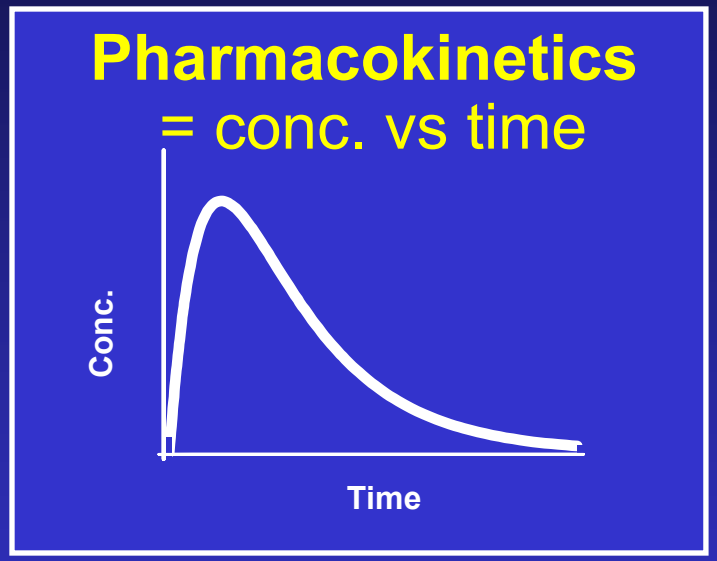


- C_{max}, AUC, clearance, half-life, etc…
- interrelations among PK parameters
- protein binding and tissue accumulation
- examples with β-lactams (including ertapenem), fluoroquinolones (moxifloxacin), and macrolides (telithromycin)

This part uses material from presentations by H. Derendorf (Gainesville, Fla.) made at the 2001 and 2001 ISAP Educational Workshops

What is pharmacokinetics ?

- "what the body does to the drug"
- the fate of the drug in terms of
  - Liberation
  - Absorption
  - Distribution
  - Metabolism
  - Excretion



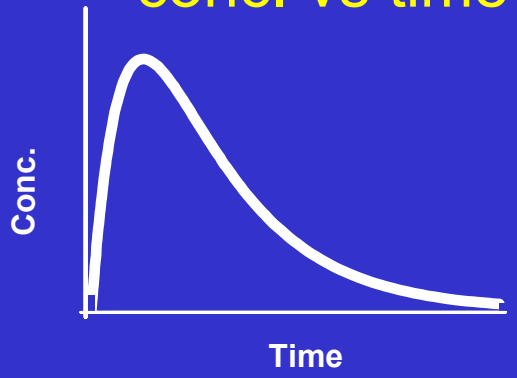
- the time course of drug and metabolite concentrations in the body

What is pharmacokinetics (PK) for ?

In its first inception, PK has been developed to help optimizing drug therapy with respect to:

- **dose**
- **dosage regimen**
- **dosage form**

Pharmacokinetics
= conc. vs time

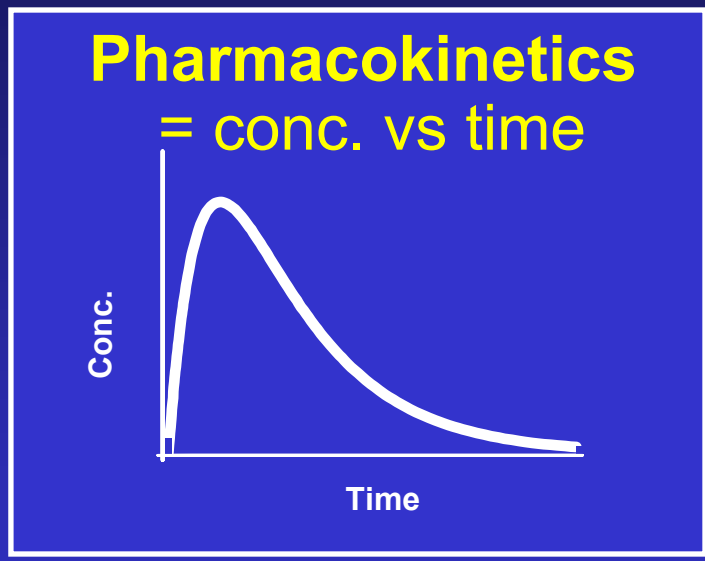


But in a second inception, PK can be considered as the way by which the drug can be made useful …

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

Key pharmacokinetic parameters ...

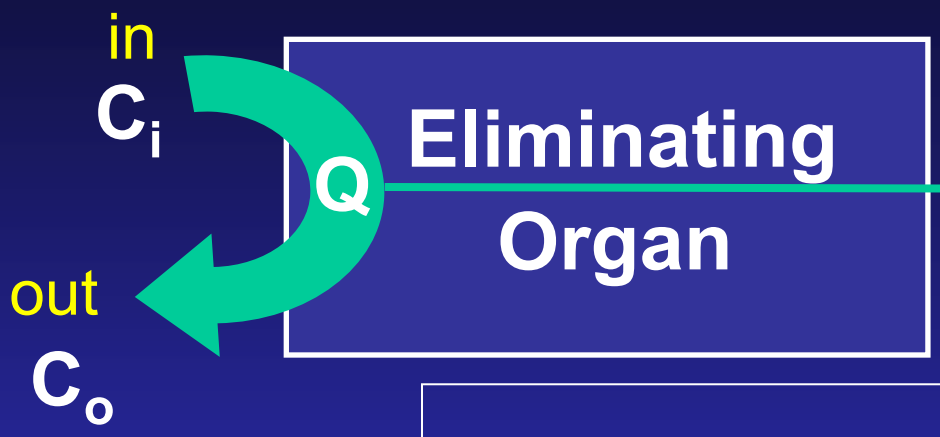
- Clearance (Cl)
- Volume of distribution (V_d)
- Half-life ($t_{1/2}$)
- Bioavailability
- Area under the curve (AUC)
- Protein Binding



Clearance (Cl)

- quantifies **ELIMINATION**
- is the volume of body fluid cleared per time unit (L/h, mL/min)
- is usually constant in a given physiopathological situation
- is a primary parameter

Clearance (Cl)



Quantity eliminated per unit of time

➔ $C_o < C_i$

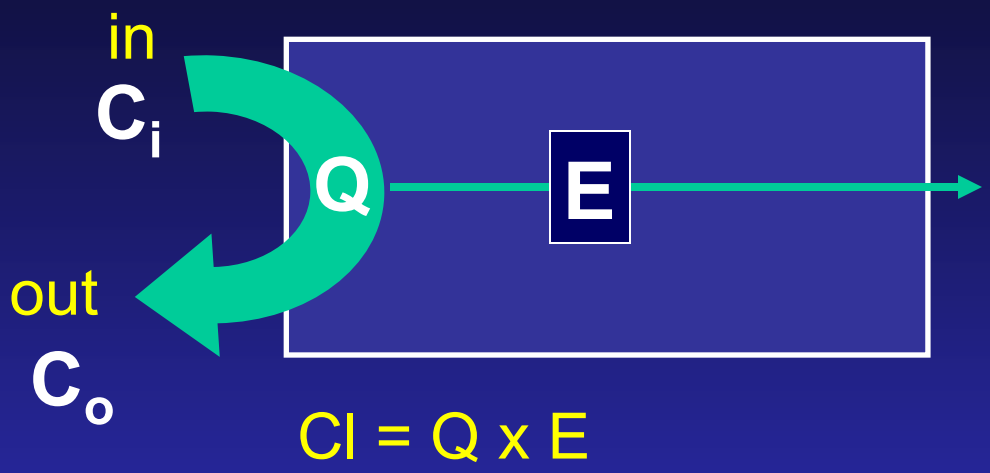
extraction $E = \frac{C_i - C_o}{C_o}$

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)

Which parameters influence the clearance ?



- blood flow
- intrinsic clearance
- drug availability for the clearance mechanism

$Cl = Q \times E$

- high extraction drugs : $E \sim 1$

➔ $Cl \sim Q$

- low extraction drug ($E << 1$)
  - protein binding (reduces free drug)
  - no transport by the eliminating organ

➔ $Cl << Q$

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 with a slow clearance may be bound to proteins and unavailable
  (see later …)
- If clearance falls during treatment (or is abnormally low at the beginning of treatment), patient will be overdosed !!

How do we determine the clearance ?

- Directly from the measurement of the excretion rate
  - easy if only one eliminating organ (kidney, e.g.)
  - but drugs may be cleared by many organs (total clearance = sum of individual clearances)
- Indirectly from the ratio of the dose administered and the AUC (see later)

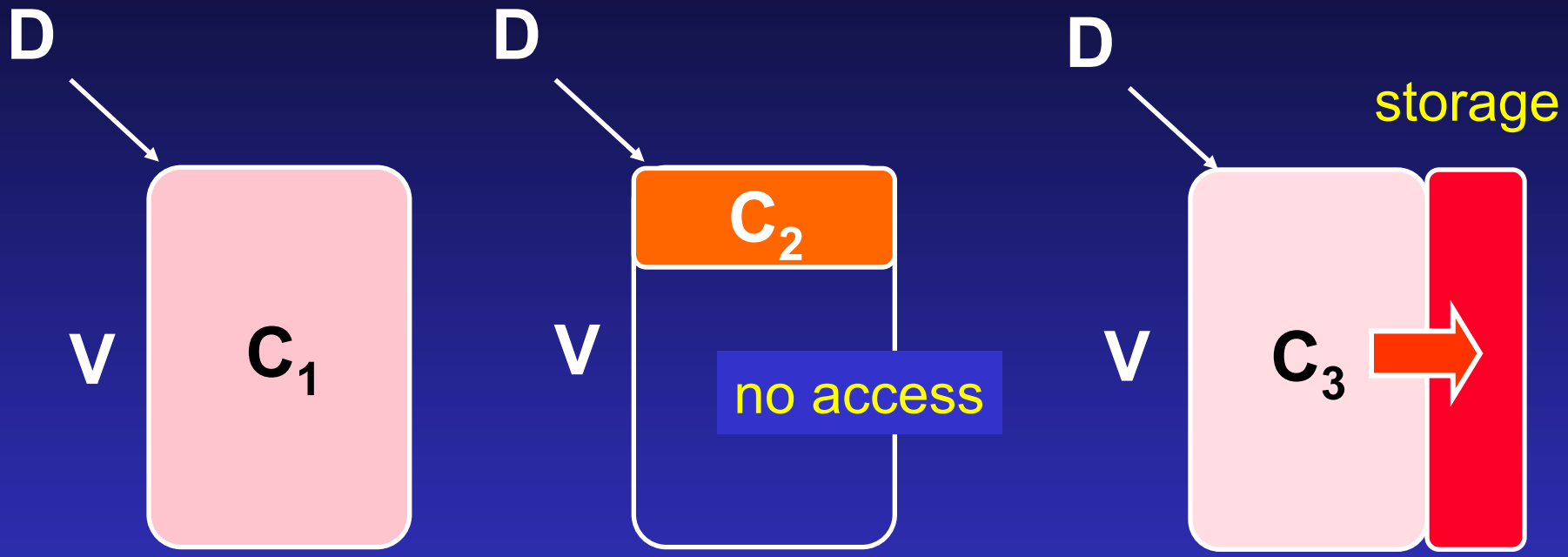
Volume of distribution (V_d)

- Quantifies the **DISTRIBUTION** (i.e. 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)

Vd = Dose / Concentration in blood

- is also a primary parameter
- but may be an apparent volume ...

What is V_d ?



$V_d = D / C_1$

$V_d = 1$ L/kg

if D in g/g

$C_2 >> C_1$

$Vd = D / C_2$

Vd < 1 L/kg

if D in g/g

$C_3 << C_1$

$Vd = D / C_3$

Vd > 1 L/kg

if D in g/g

Typical volumes of distribution of drugs

if found in	L/kg
• serum only ➔ dicloxacillin	0.1
• serum plus extracell. fluids ➔ gentamicin	0.25
• total body fluids ➔ antipyrine	0.60
• in fluids plus moder. accumul. in tissues ➔ ciprofloxacin	1.8
• in fluids plus marked accum. in tissues ➔ azithromycin	31

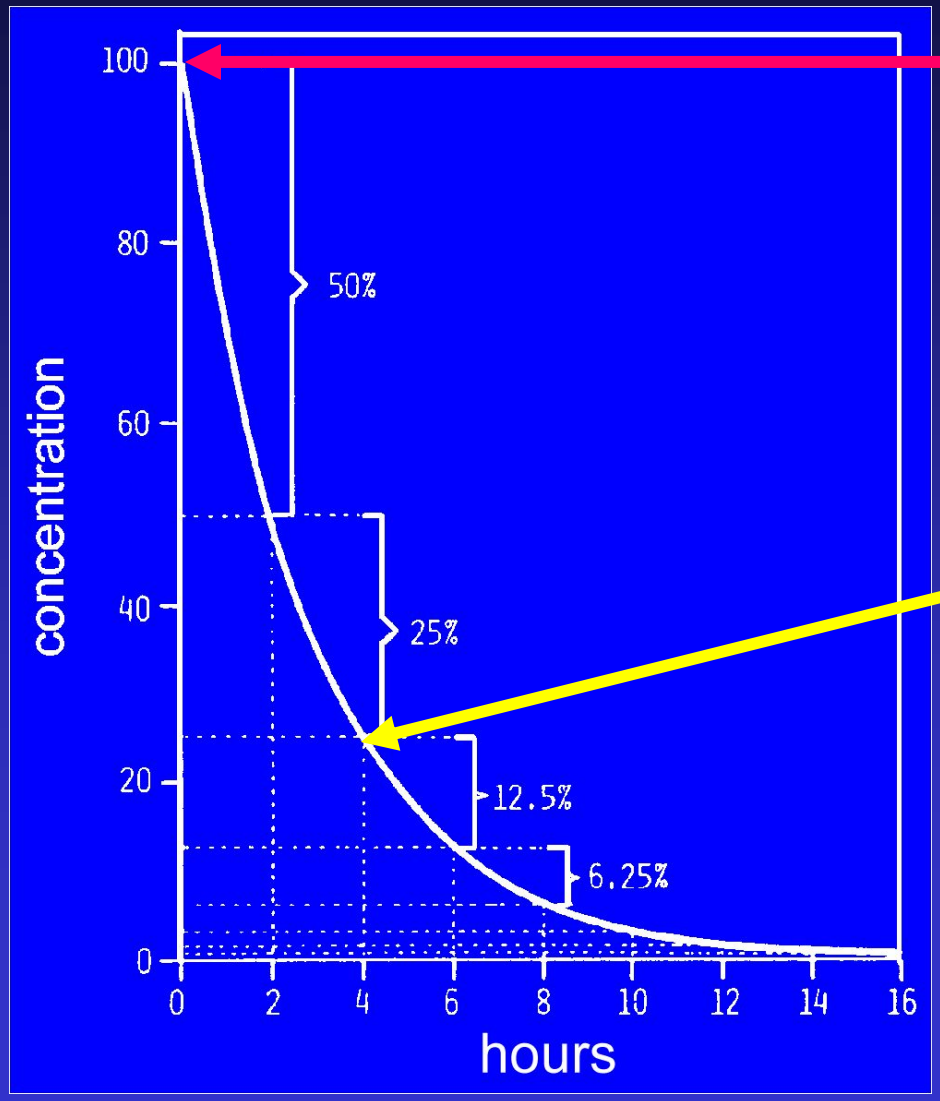
What is the significance of the Vd ?

- A drug with a small V_d will have high initial blood levels ...
- A large Vd will cause low initial blood levels …
  - if it is patient related, you need to give more of the drug (e.g., burn patients)
  - if it is drug-related, the drug cannot be too concentration-dependent …and 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 clearance and volume of distribution

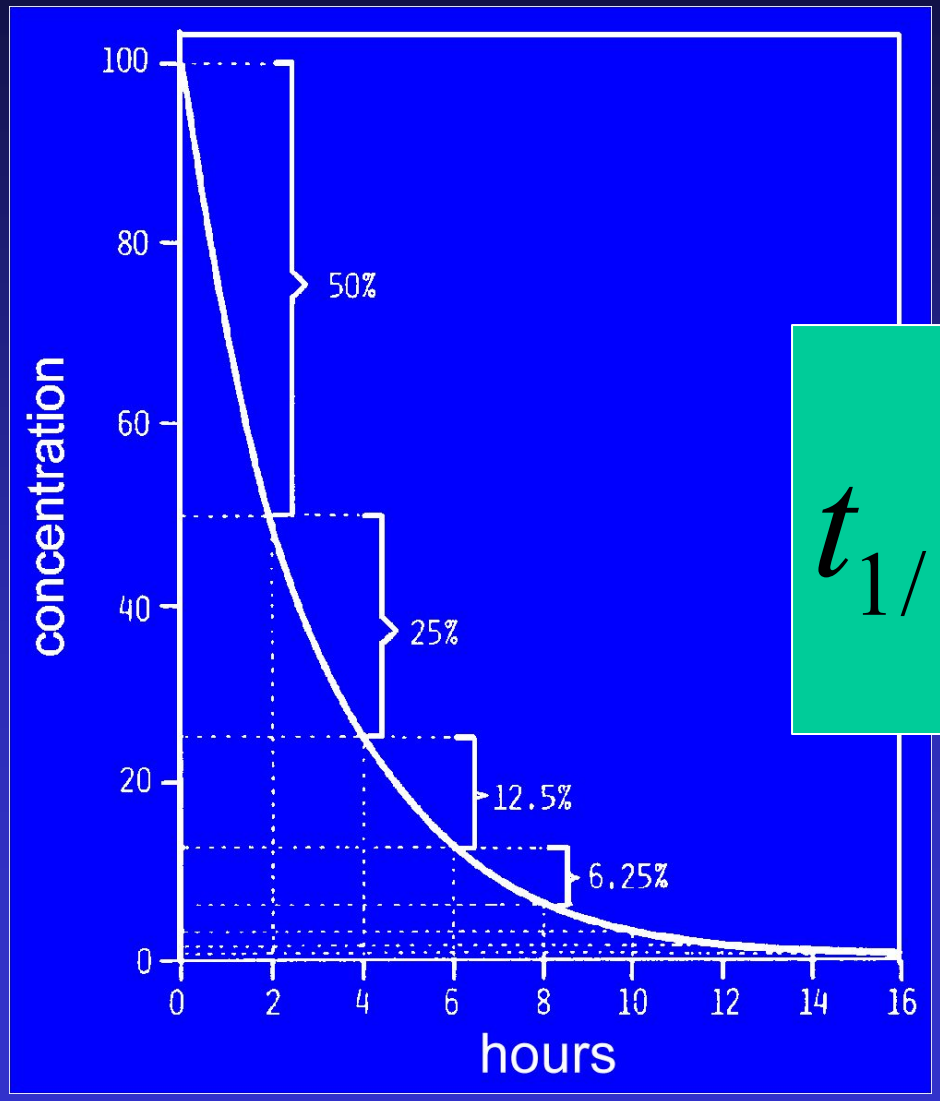
Why is half half-life a secondary parameter



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

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 ?



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

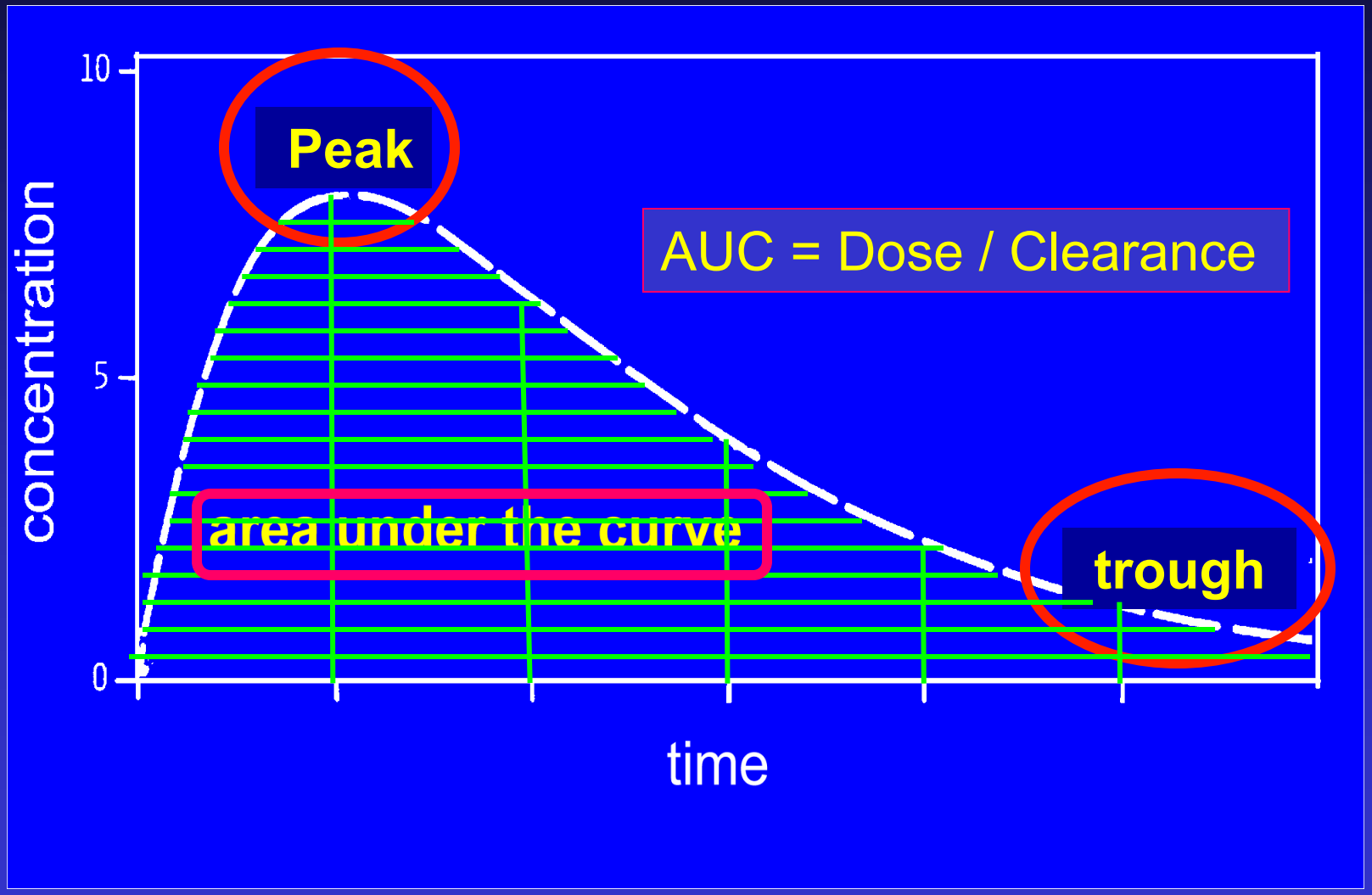
What is useful in half-life ?

- 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, e.g. but you CANNOT compare β-lactams and azithromycin, e.g.

Area under the Curve (AUC)



Area under the Curve (AUC)

- Useful to assess the total drug exposure
- but profoundly influenced by
  - the Vd (height of the curve)
  - the clearance (rate of elimination)
- advantage: it combines the two primary parameters so that the final value is relatively stable and independent of the mode of administration ...

Interrelations between secondary PK parameters

Parameter	influenced by		
C_{max} :	+ dose *	– clearance	– Vd
half-life:		– clearance	+ Vd
AUC:	+ dose **	– clearance	

\+ directly propoportional

– indirectly proportional

* unit dosis

** total dose for the period considered (usually 24h)

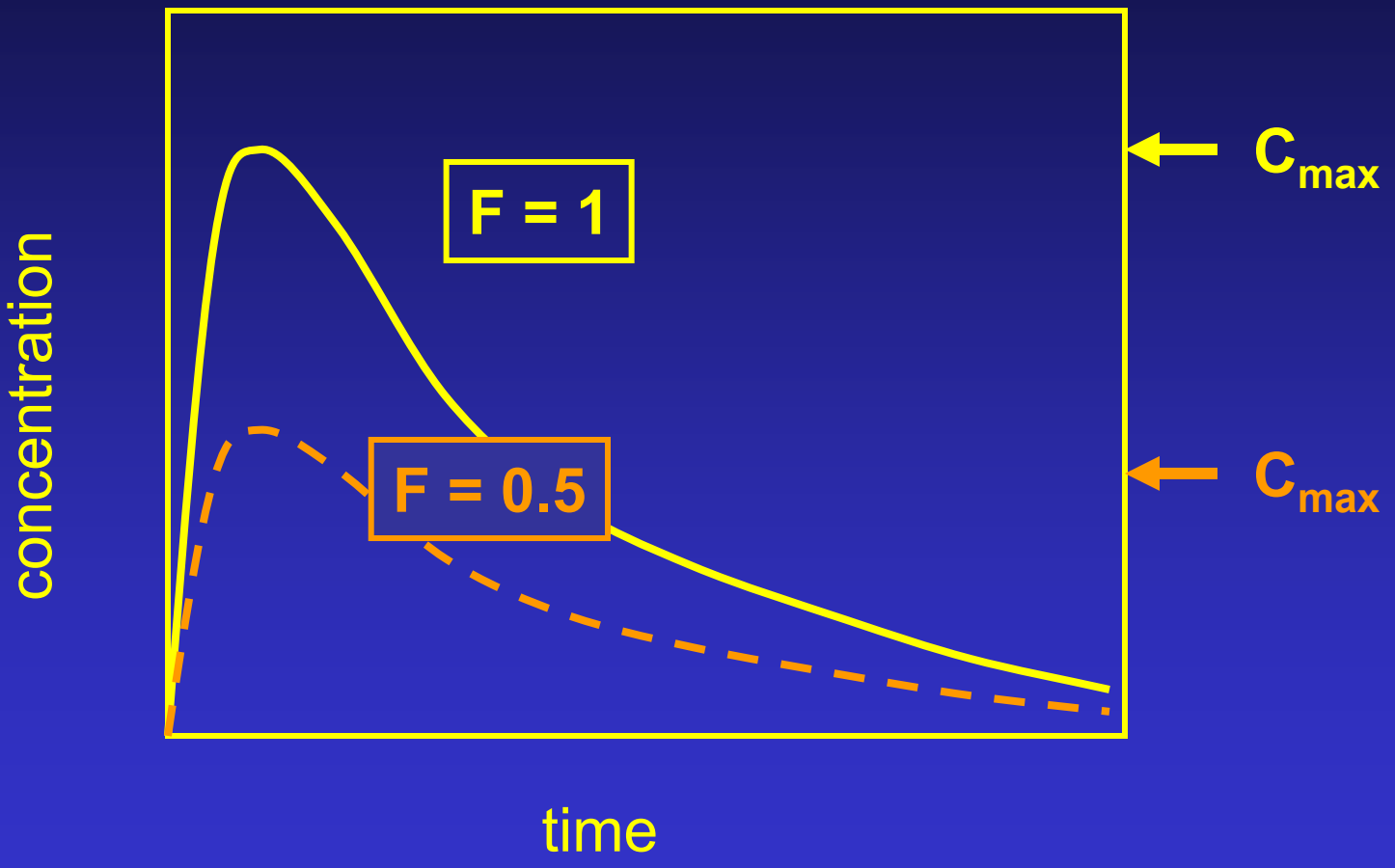
Bioavailability

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

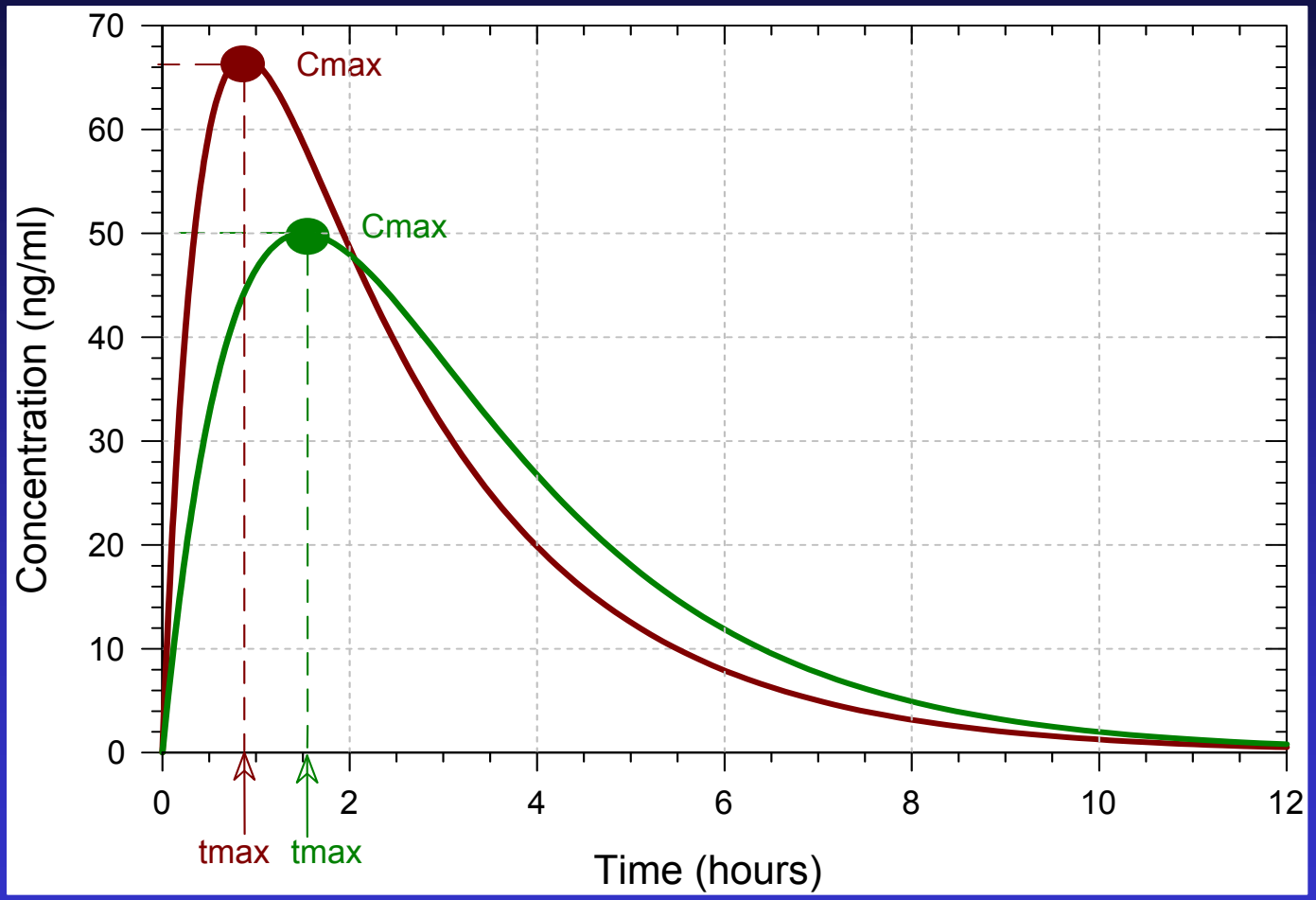
$$F = \frac{AUC_{po}}{AUC_{iv}}$$

- but the rate is also important ...

A low bioavailability reduces C_{max} and AUC



The rate of bioavailability may also influence C_{max} and T_{max}

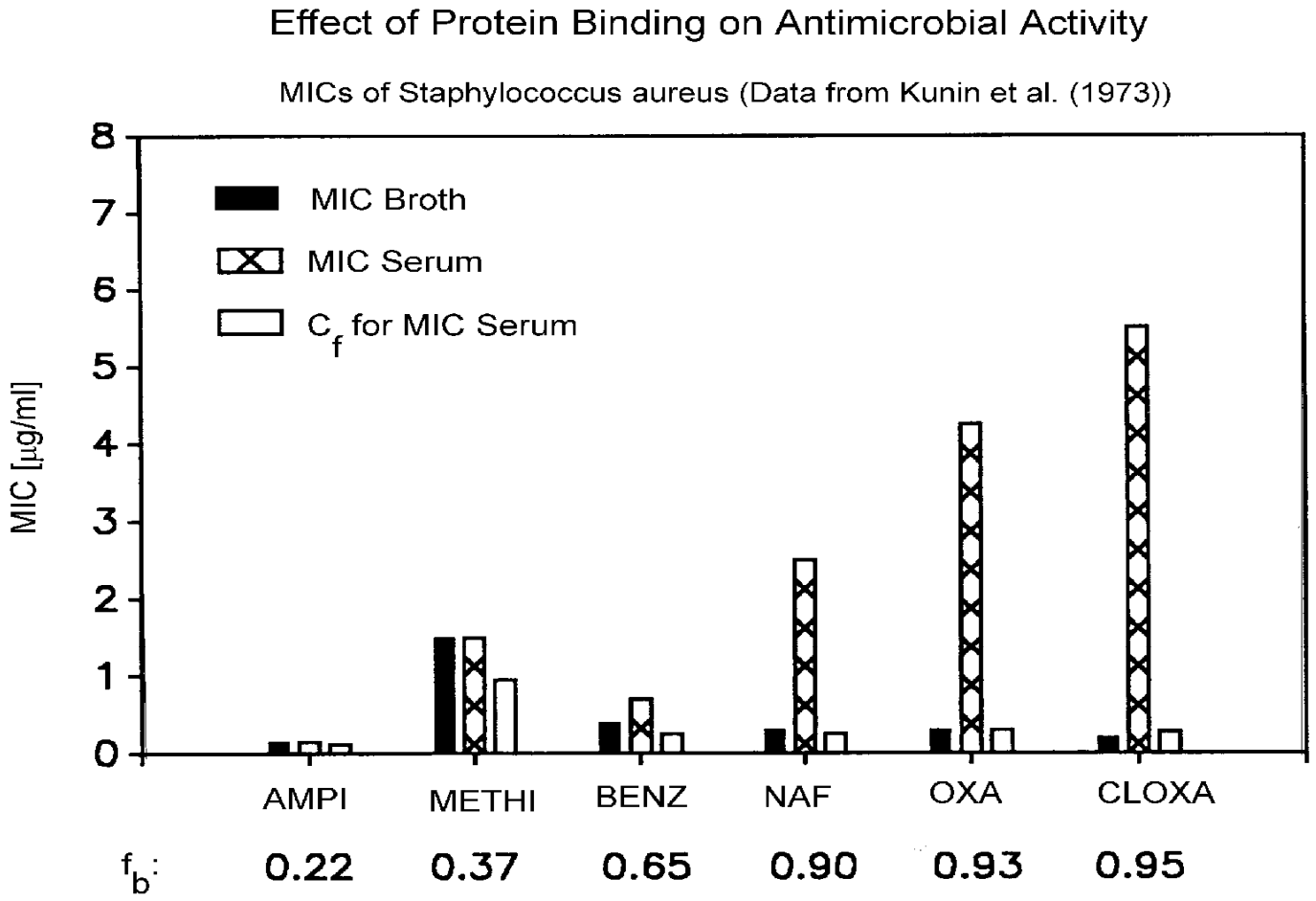


Protein Binding

- **reversible vs. irreversible**
- **linear vs. nonlinear**
- **rapid equilibrium**

The free (unbound) concentration of the drug at the receptor site should be used in PK/PD correlations to make prediction for pharmacological activity

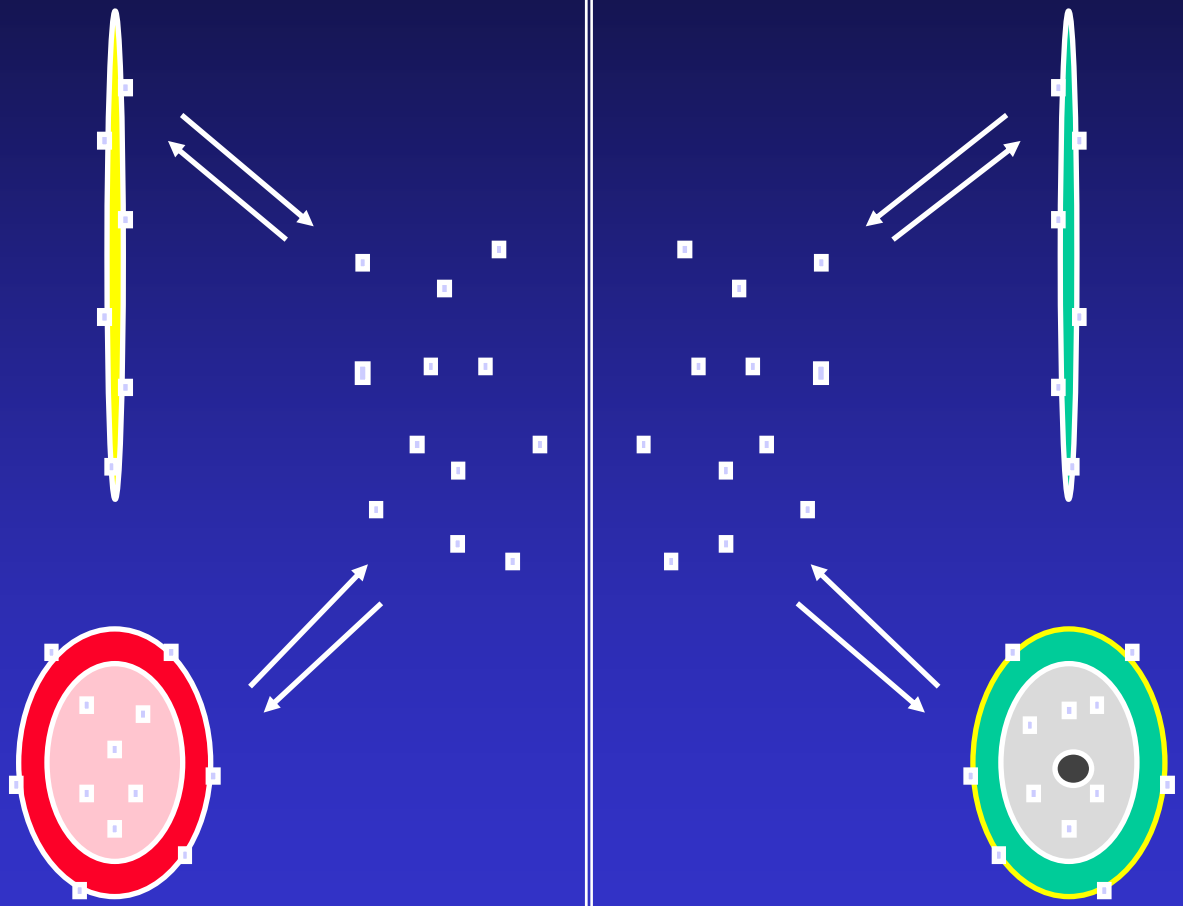
Protein binding decreases activity of antibiotics



It is the free drug that acts ...

vascular space

extravascular space



plasma protein binding

binding to extracellular biological material

blood cell binding,

diffusion into blood cells,

binding to intracellular biological material

tissue cell binding,

diffusion into tissue cells,

binding to intracellular biological material

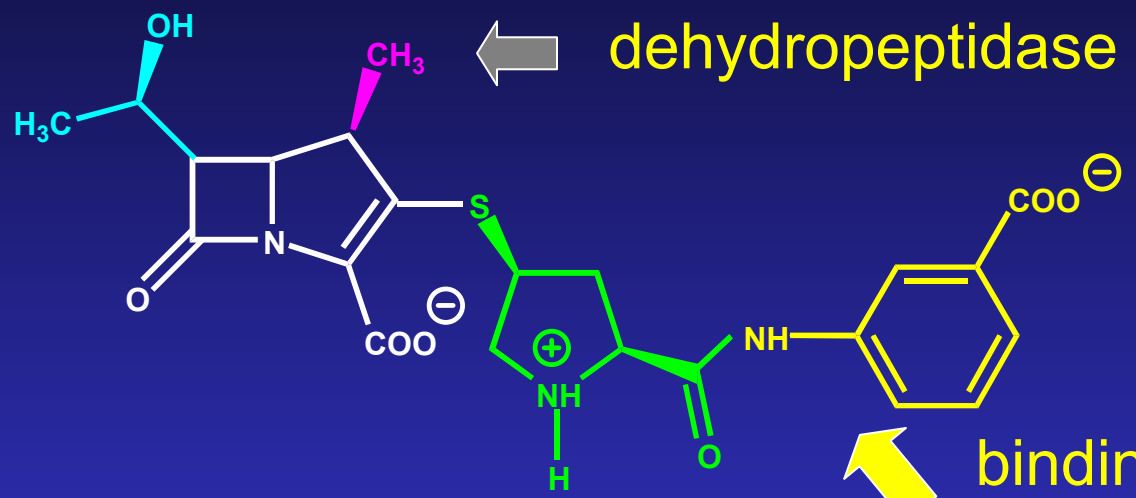
A couple of examples...

- Ertapenem, a long acting penem …
- Comparisons among fluoroquinolones
- Why has telithromycin been selected ?

imipenem → meropenem→ ERTAPENEM

stability to β-lactamases

resistance to dehydropeptidase



ERTAPENEM

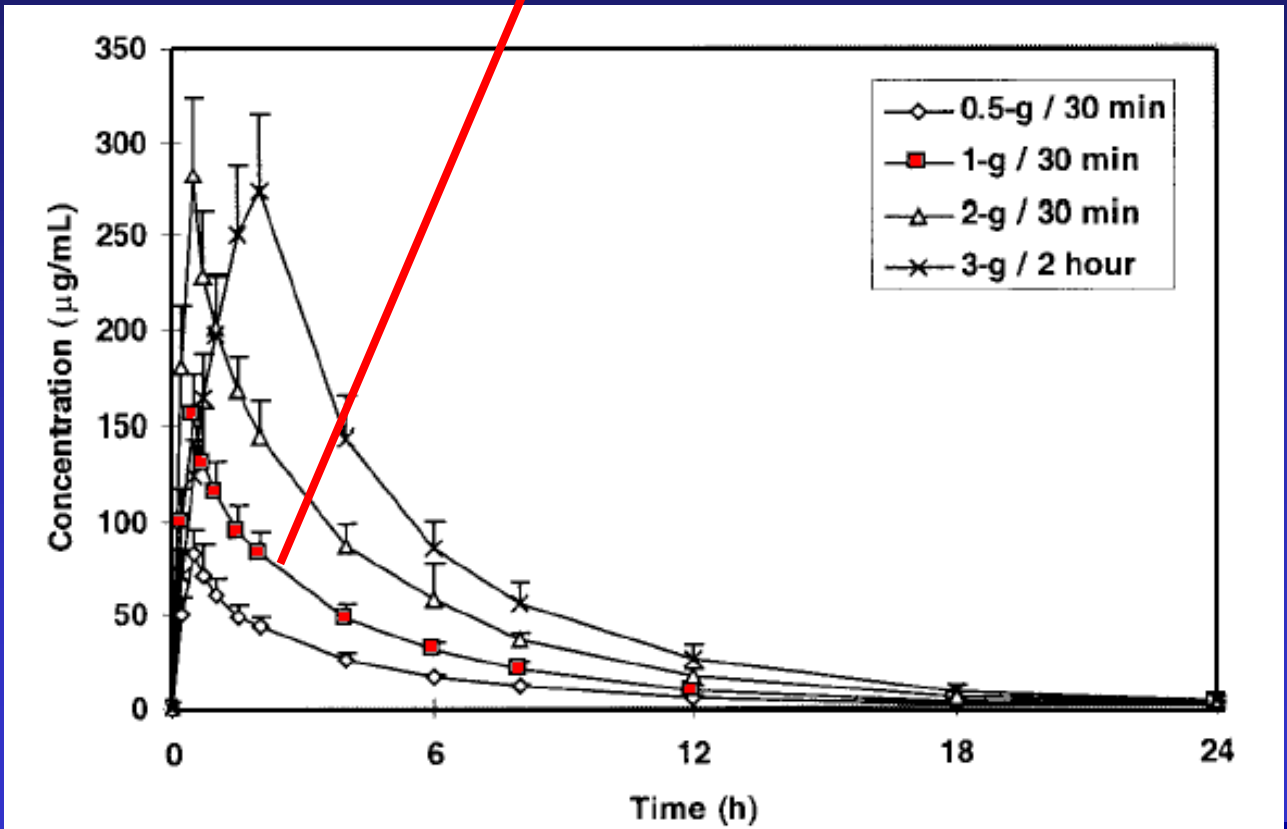
binding to proteins

change in spectrum

	Gram (-)	*P. aer.*	Gram (+)	anaer.	$t_{1/2}$ (h)	res. to renal hydrolysis
IMI	+	+++	+++	+++	1	-
MERO	++	+++	++	+++	1	+
ERTA	++	+	++	++	4	+

Ertapenem serum concentration in volunteers

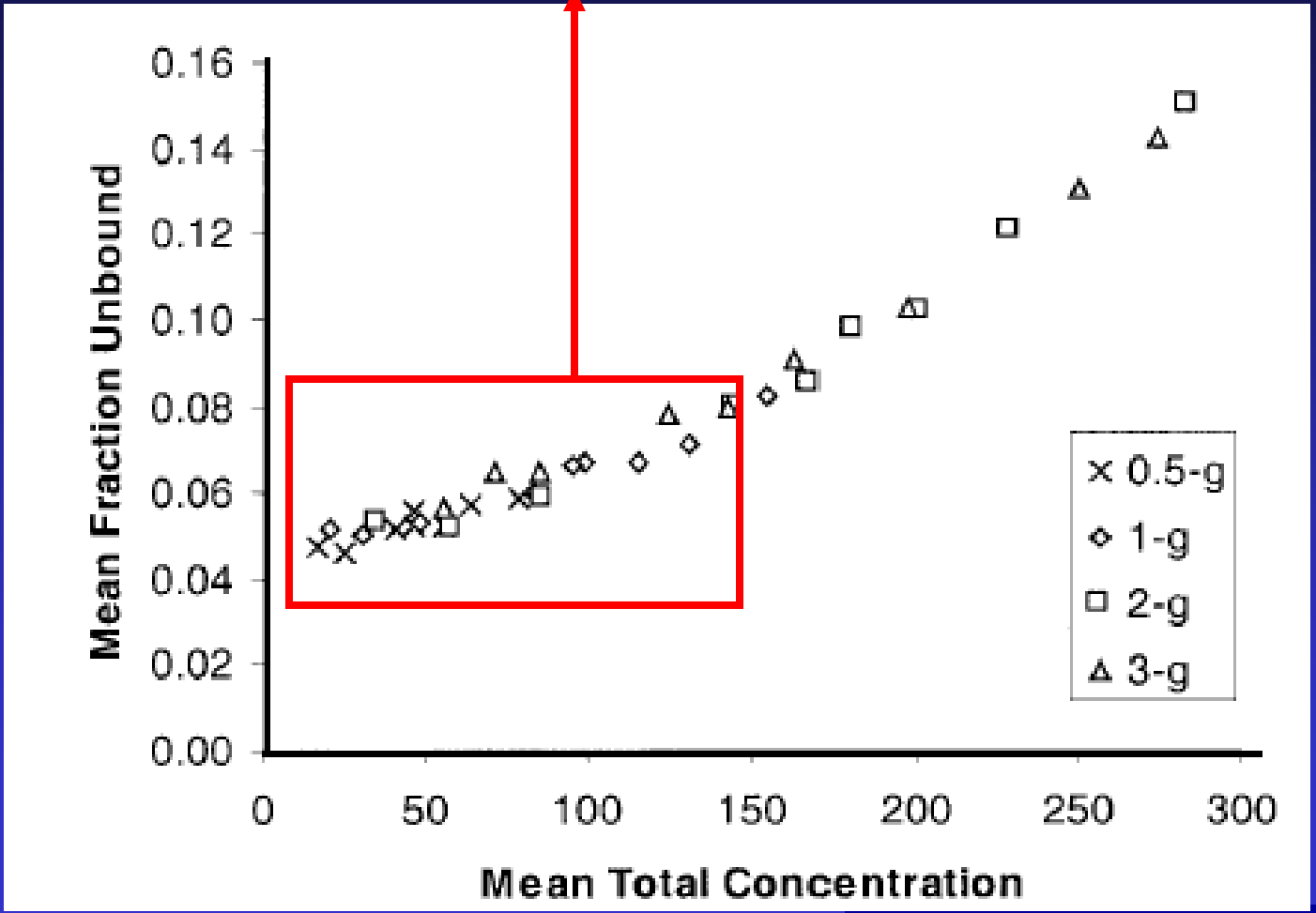
range of serum concentrations = 150 → 1 mg/L
for a daily dose of 1 g



Majumdar *et al*, AAC 2002, 46: 3506-3511

binding to serum proteins : to be linear or not ...

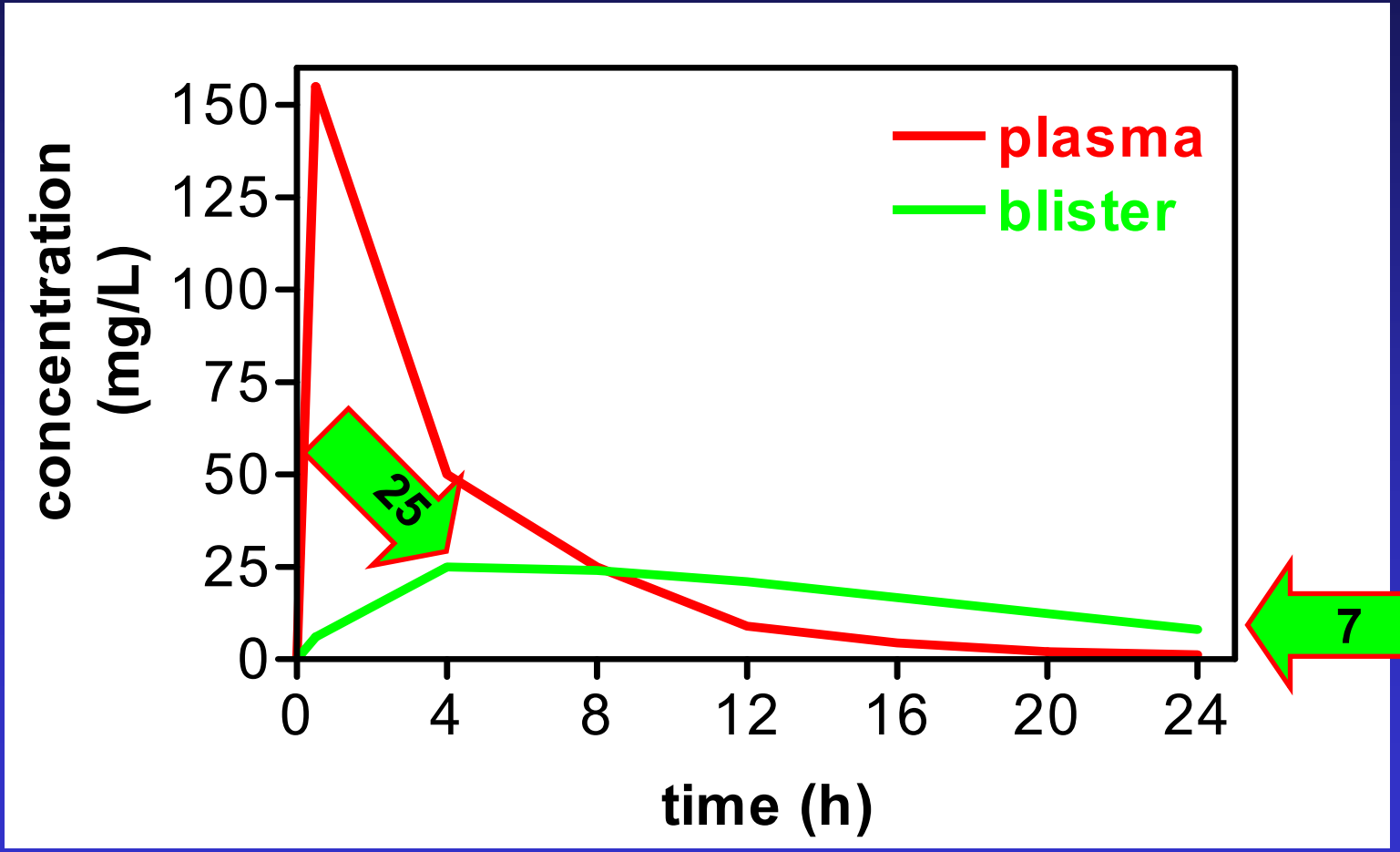
Free fraction = 5 - 10 % for a daily dose of 1 g



Majumdar *et al*, AAC 2002, 46: 3506-3511

Protein binding impairs tissue distribution...

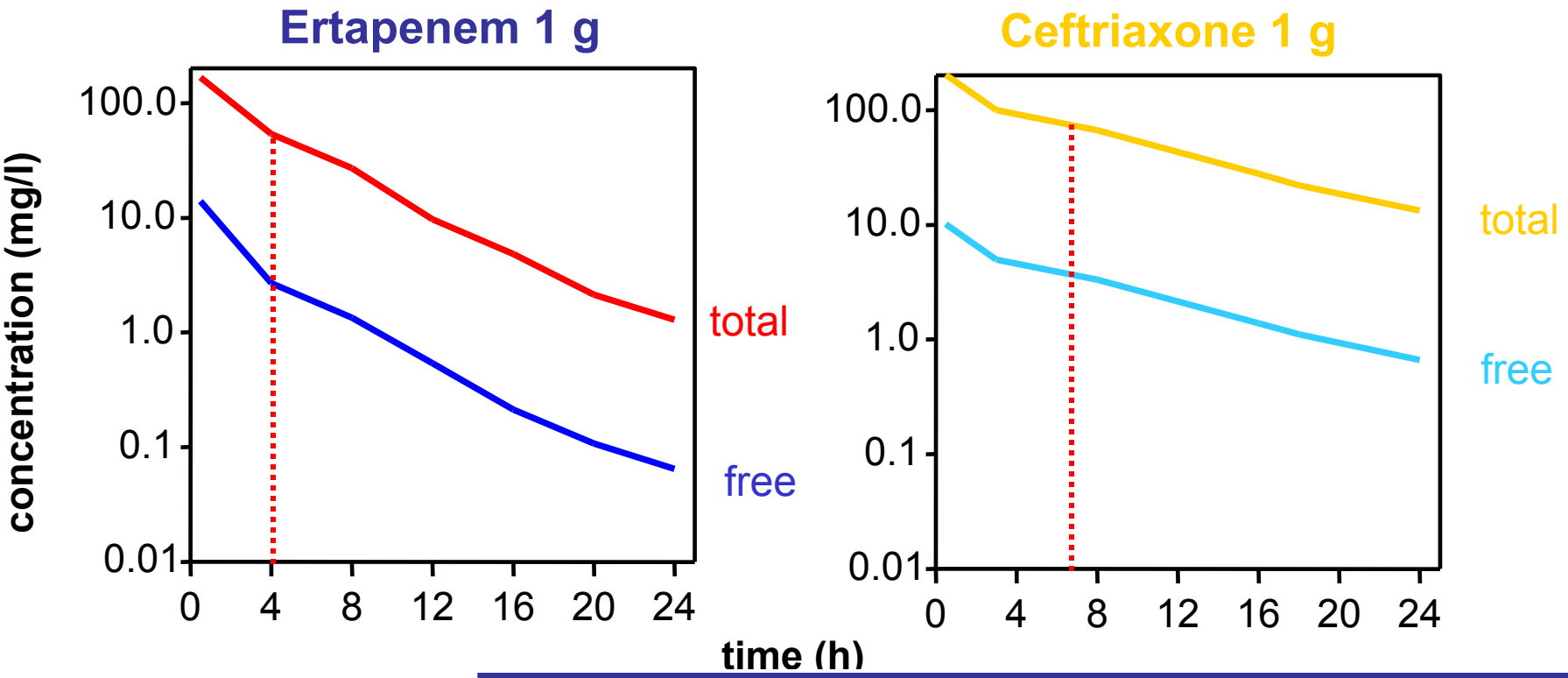
TOTAL drug concentration measured after 3 days



data submitted to the FDA for product registration

But protein binding does prolong half-lilfe

	Cmax (mg/l)	prot. binding (%)	$T_{1/2}$ (h)
ertapenem	160	90-95	4
ceftriaxone	180	83-96	7



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

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

This is better

But what about this ?

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

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

Drug (mg/24h)	Dosage (mg/L x h)	24h-AUC
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

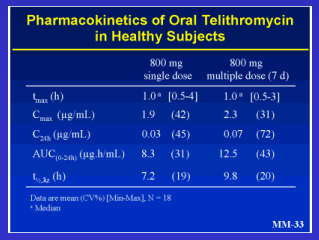
Pharmacokinetics of telithromycin

as submitted to the FDA (April 2001)

	800 mg (single dose)	800 mg (7 days)
C_{max} (mg/L)	1.9 (42)	2.3 (31)
C_{24h} (mg/L)	0.03 (45)	0.07 (72)
AUC_{24h} (mgxh/L)	8.3 (31)	12.5 (43)
$t_{1/2}$ (h)	7.2 (39)	9.8 (20)

Data is mean (% CV) for n=18

This was to be a once-a-day drug ...



Pharmacokinetics of Oral Telithromycin in Healthy Subjects

	800 mg single dose		800 mg multiple dose (7 d)	
t_{max} (h)	1.0[a]	[0.5-4]	1.0[a]	[0.5-3]
C_{max} (µg/mL)	1.9	(42)	2.3	(31)
C_{24h} (µg/mL)	0.03	(45)	0.07	(72)
$AUC_{0\text{-}24h}$ (µg.h/mL)	8.3	(31)	12.5	(43)
$t_{1/2,\beta z}$ (h)	7.2	(19)	9.8	(20)

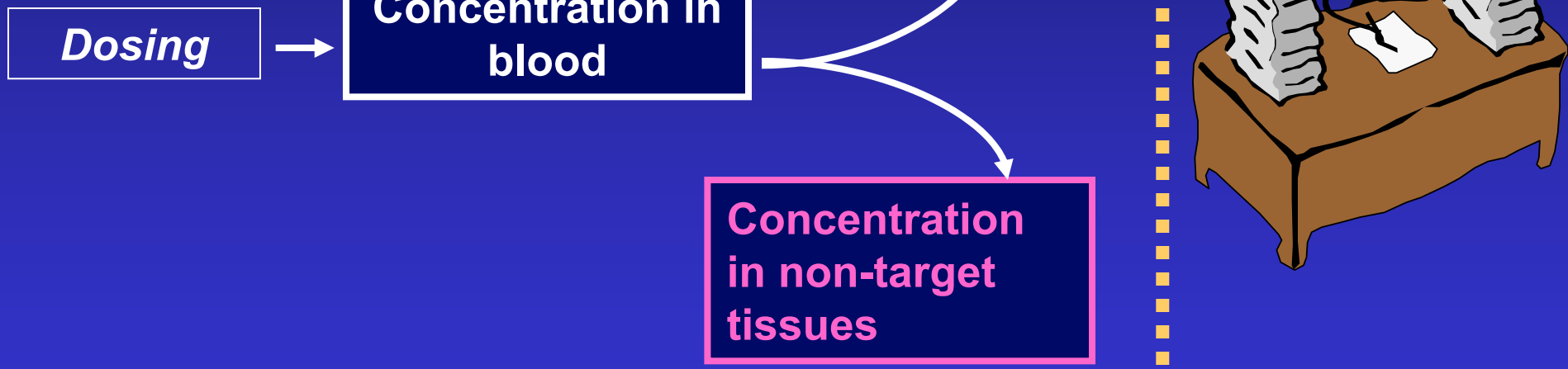
Data are mean (CV%) [Min-Max], N = 18
[a] Median

MM-33

http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_09_aventis/

This where we are ...

Pharmacokinetics



Got it ?