Pharmacokinetics

Elimination

by the end of this lecture you should be able to

- use your knowledge of drug elimination to formulate a treatment plan to ensure that sufficient drug is present in the target tissue for an adequate time

Bivatop® 200 – the proven *true* long-acting oxytetracycline

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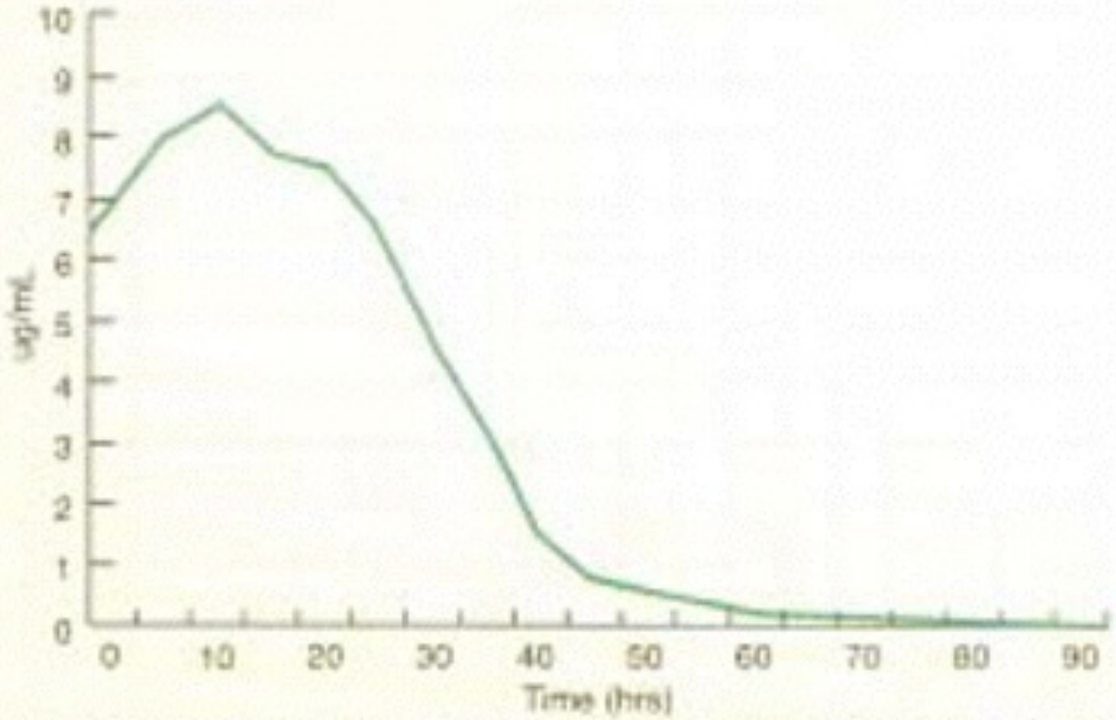
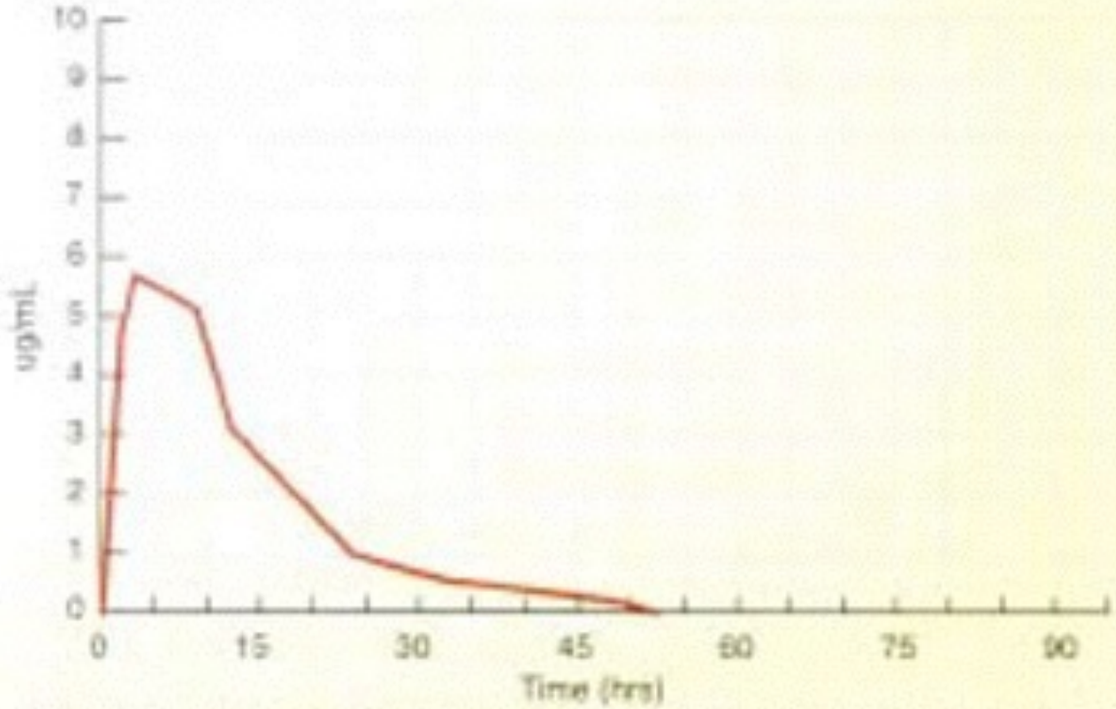
When you need longer-term maintenance of oxytetracycline levels as part of treatment, Bivatop®200 clearly offers a *true* long-acting answer. Even at double-dosing, short-acting competitors are left standing. The higher AUC concentrations and longer activity provided by Bivatop®200, ensure *true* long-acting antibiotic cover, for a *true* long-acting treatment.



Serum oxytetracycline levels following S.C. administration of Bivatop®200 at 20mg/kg[1]



Serum oxytetracycline levels following I.M. administration of 10% Oxytetracycline/PVP at a dose of 20mg/kg[2]

Bivatop® 200 – Gain without Pain

1. Boehringer Ingelheim data on file.
2. Engamycin® promotional material (Chemavet Div. Pharmaco NZ Ltd).

Pain Response in Calves following injection of different oxytetracycline preparations

Due to its unique polyethylene glycol base, Bivatop®200 is the only long-acting oxytetracycline that can be administered to all

pharmacokinetics

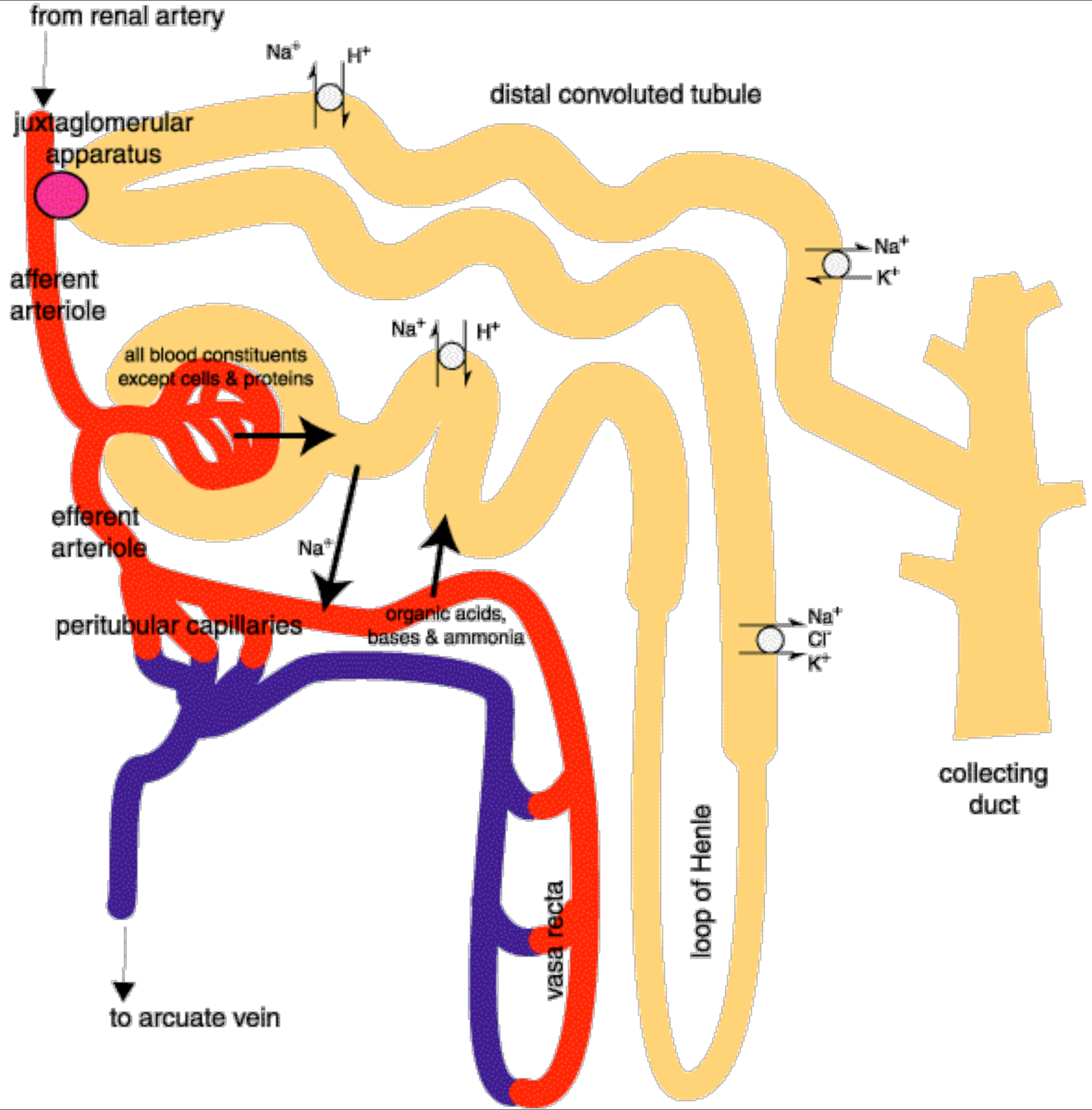
- absorption
- distribution
- metabolism
- elimination

elimination

- mainly metabolites
  - urine
  - bile
  - lungs
  - secretions

renal excretion

- depends on
  - glomerular filtration
  - active excretion
  - reabsorption


from renal artery
juxtaglomerular apparatus
afferent arteriole
efferent arteriole
peritubular capillaries
to arcuate vein
vasa recta
distal convoluted tubule
all blood constituents except cells & proteins
organic acids, bases & ammonia
loop of Henle
collecting duct
Na+
H+
K+
Cl-

glomerular filtration

- 20% of kidney blood flow
- most drugs filtered except
  - large molecules (proteins)
  - protein bound drugs

active transport

- carriers in proximal tubule for
  - organic acids
  - organic bases
- requires energy
- saturable
- drugs may compete for sites
  - eg penicillin & probenecid

passive reabsorption

- lipid soluble drugs absorbed easily
- urine pH important
  - basic drugs trapped and excreted in acidic urine
  - acidic drugs trapped and excreted in alkaline urine

clearance

- the volume of plasma cleared of drug per unit time

clearance

- renal clearance Clr
- metabolic clearance Clmet
- plasma clearance = Clr + Clmet
- total body clearance Clt

biliary excretion

- important for some drugs
  - opioids
- usually glucuronides
- may cause enterohepatic recirculation

enterohepatic recirculation

- conjugated drug excreted in bile
- gut bacteria lop off conjugate
- drug reabsorbed
- prolonged effects / animal recovers then effects reappear

secretions

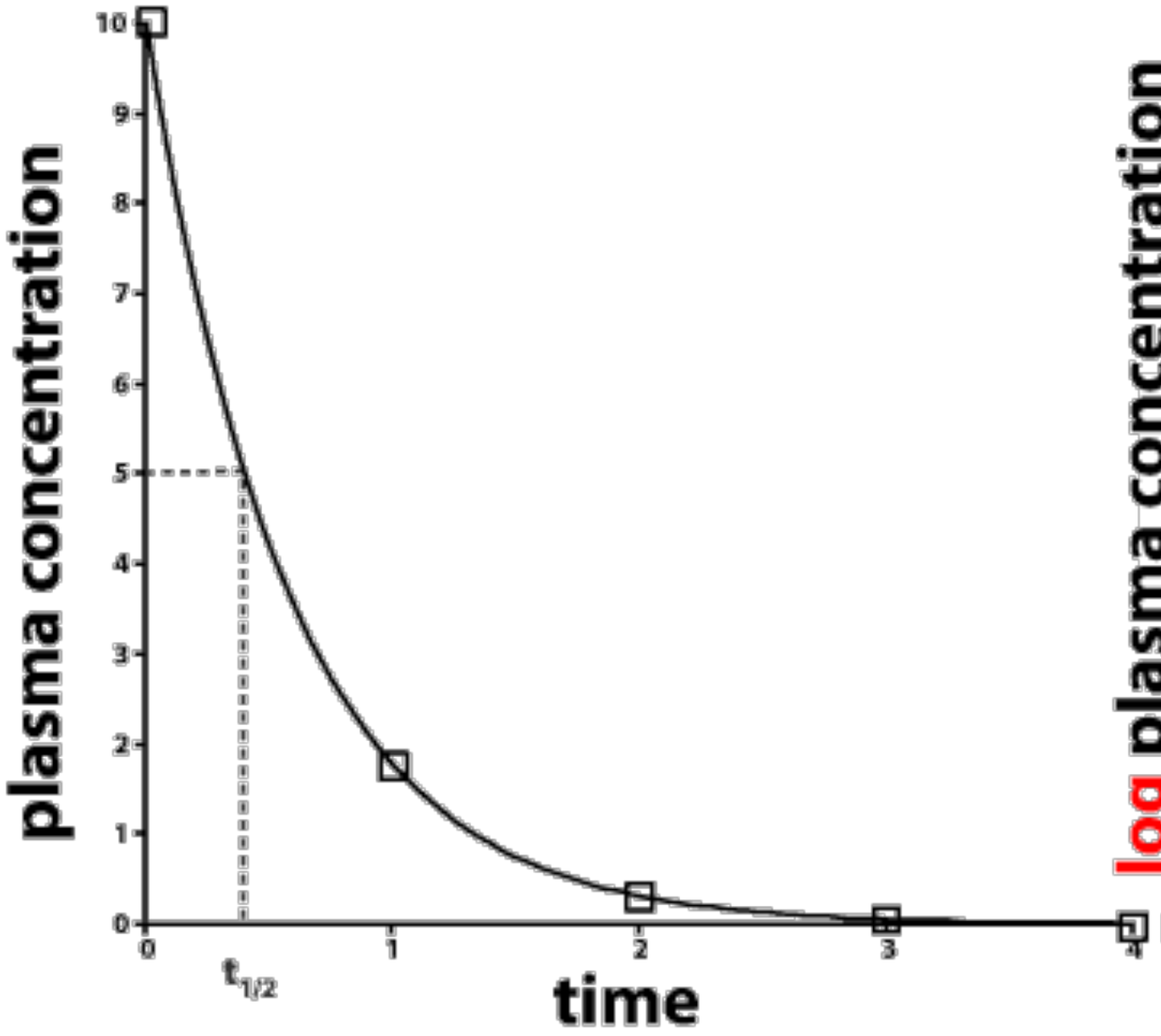
- milk
  - most lipid soluble drugs
  - most not in high enough concentration to harm the young animal
  - but high enough concentration to worry Fonterra / NZFSA
    - How do you deal with this?

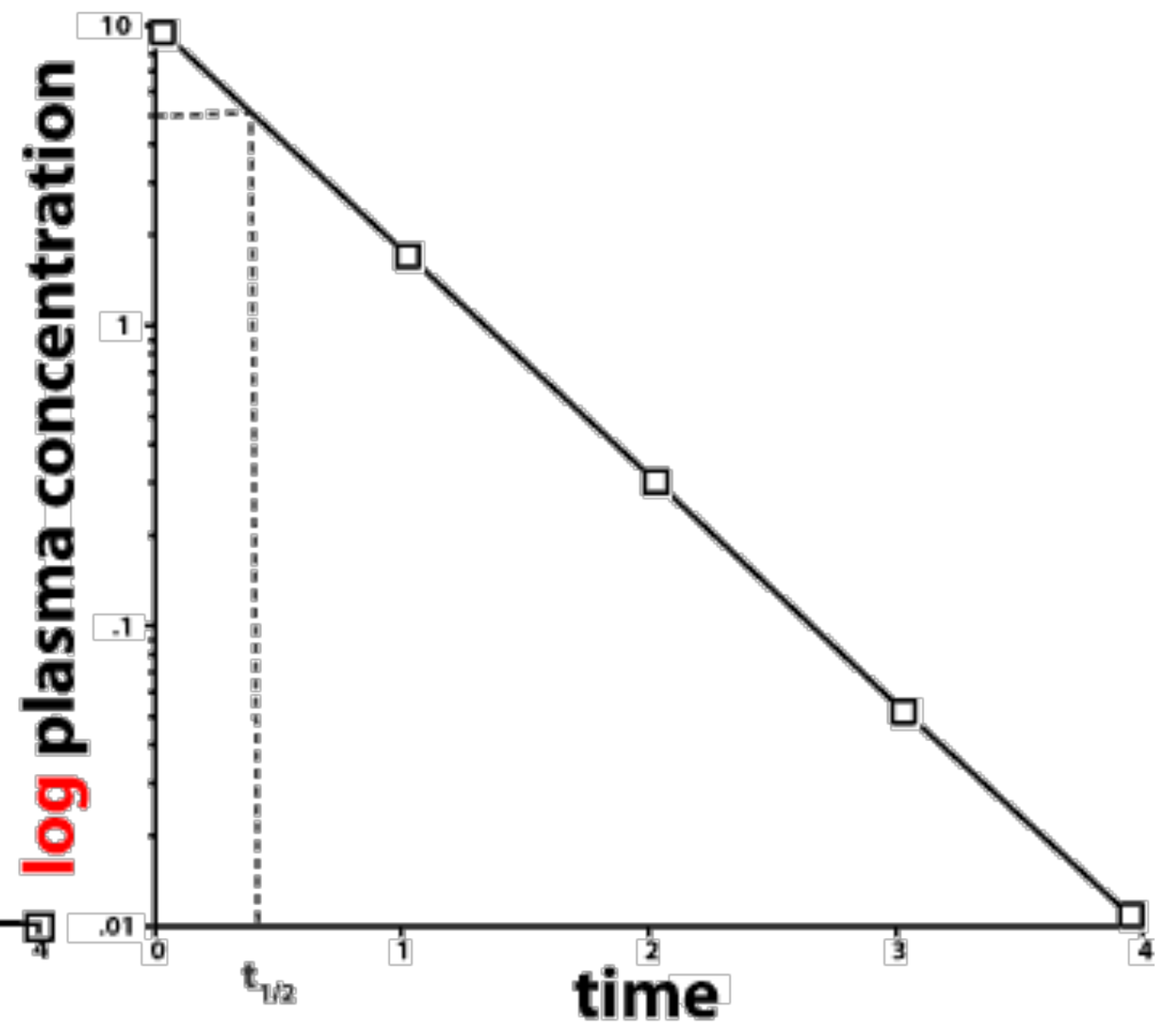
mathematical models to describe elimination of drugs

single compartment open model

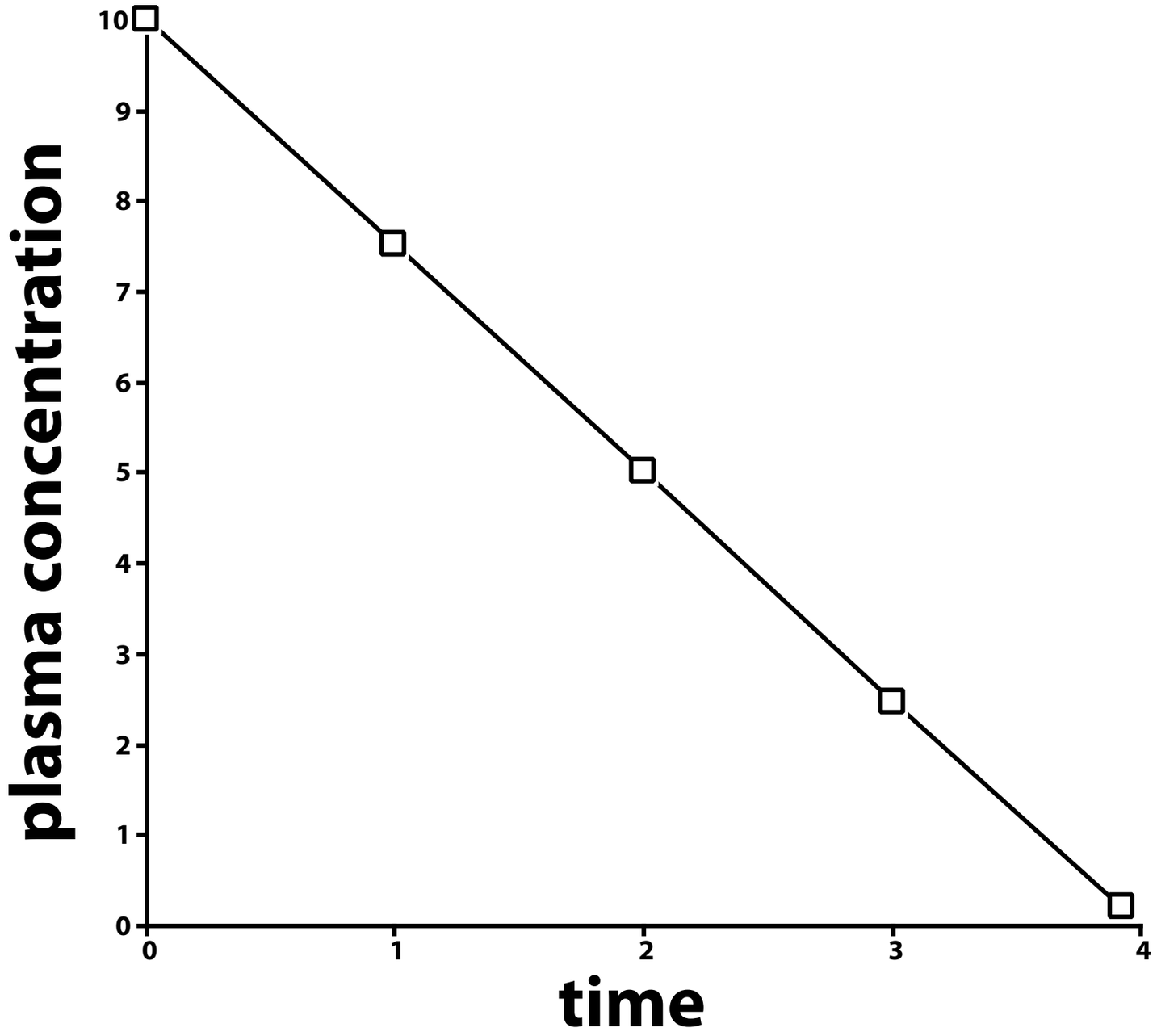
- drug distributes evenly in one compartment
- volume of compartment is Vd
- plasma concentration falls as drug is cleared

first order kinetics





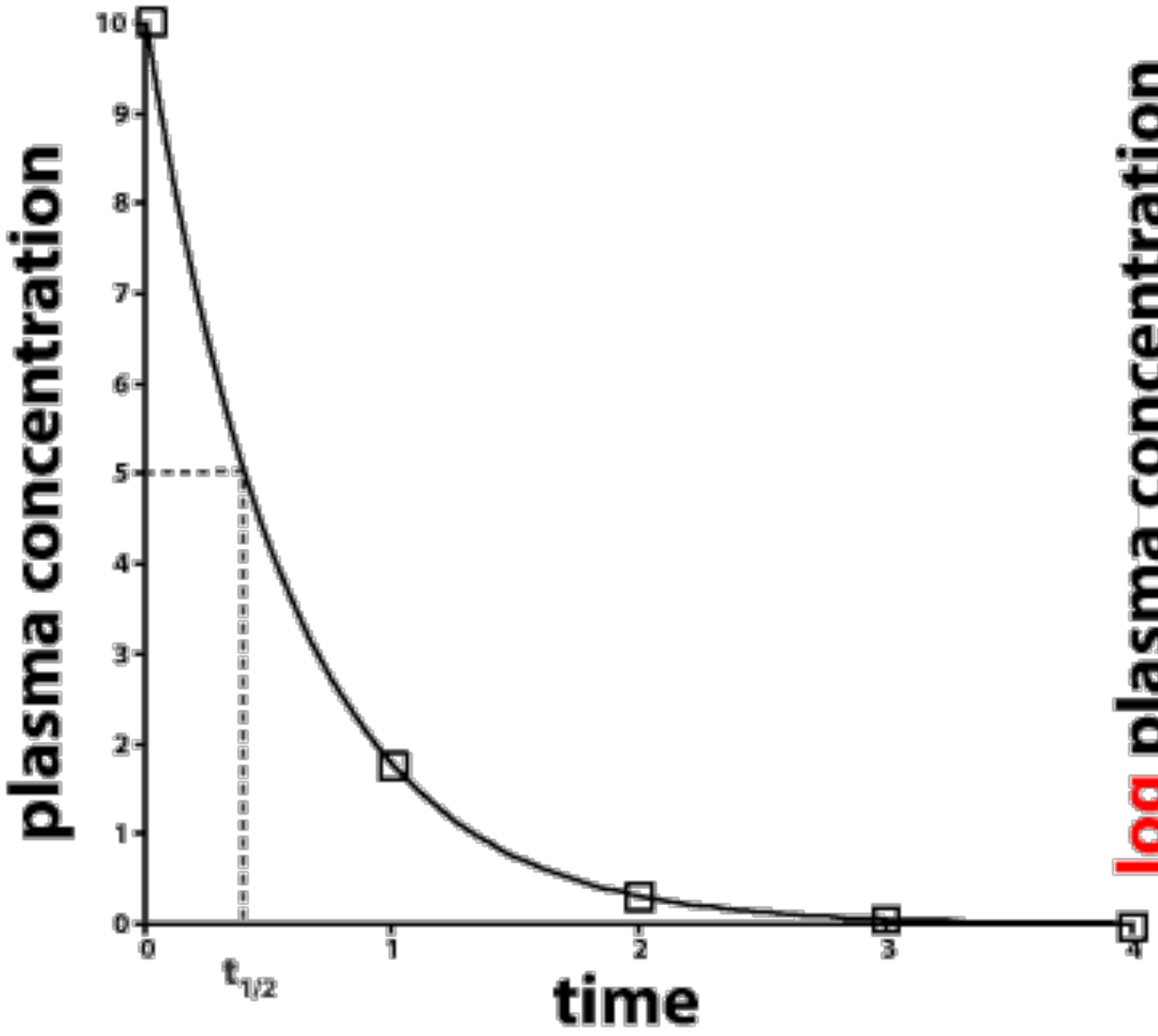
zero order kinetics

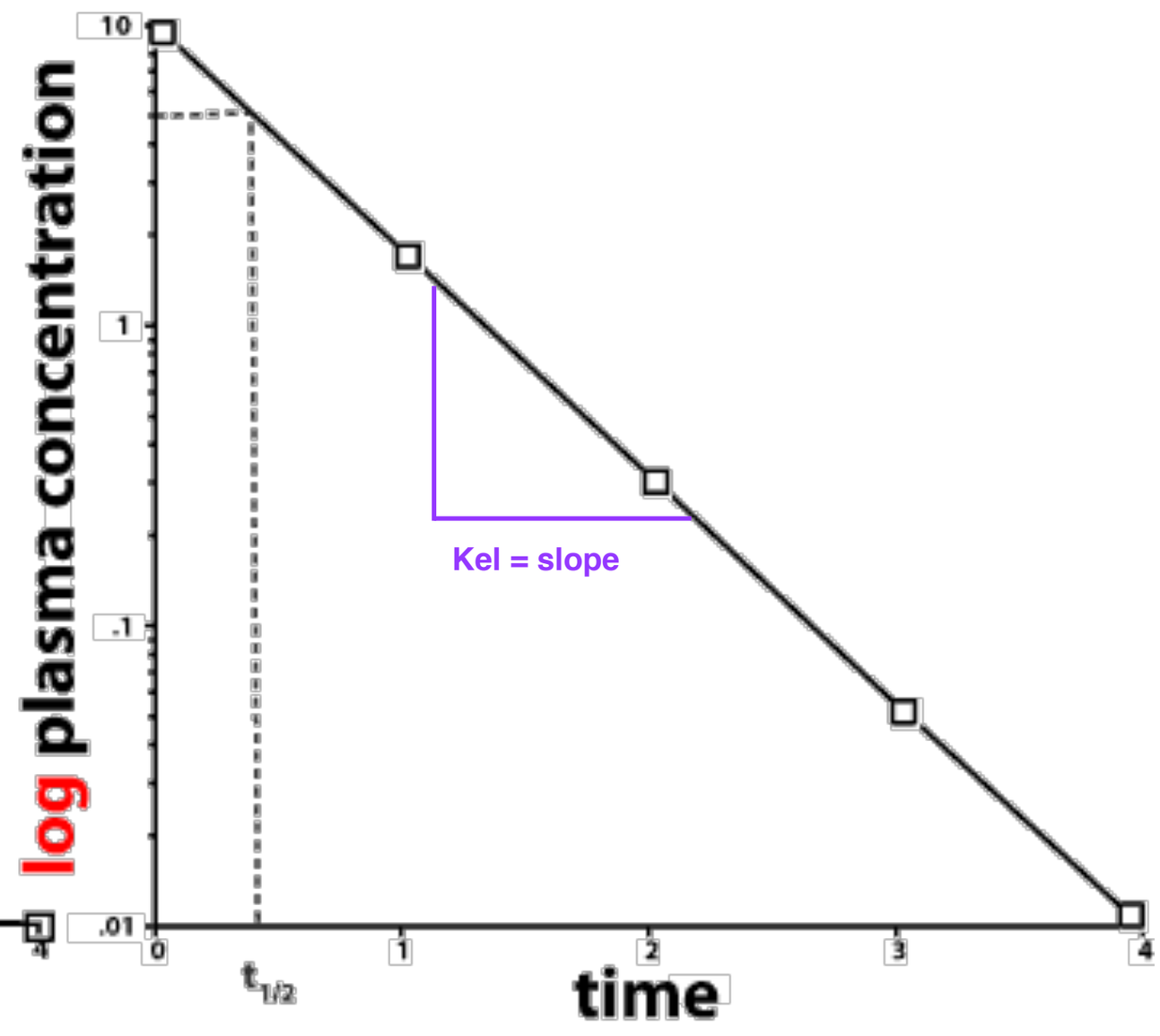


half life

- the time taken for the drug concentration to fall to / by half

half life & elimination rate constant





elimination rate constant

- the fraction of drug that would be eliminated per unit time
  - eg kel = 0.05 minutes-1
  - 5% of drug eliminated / min

elimination rate constant

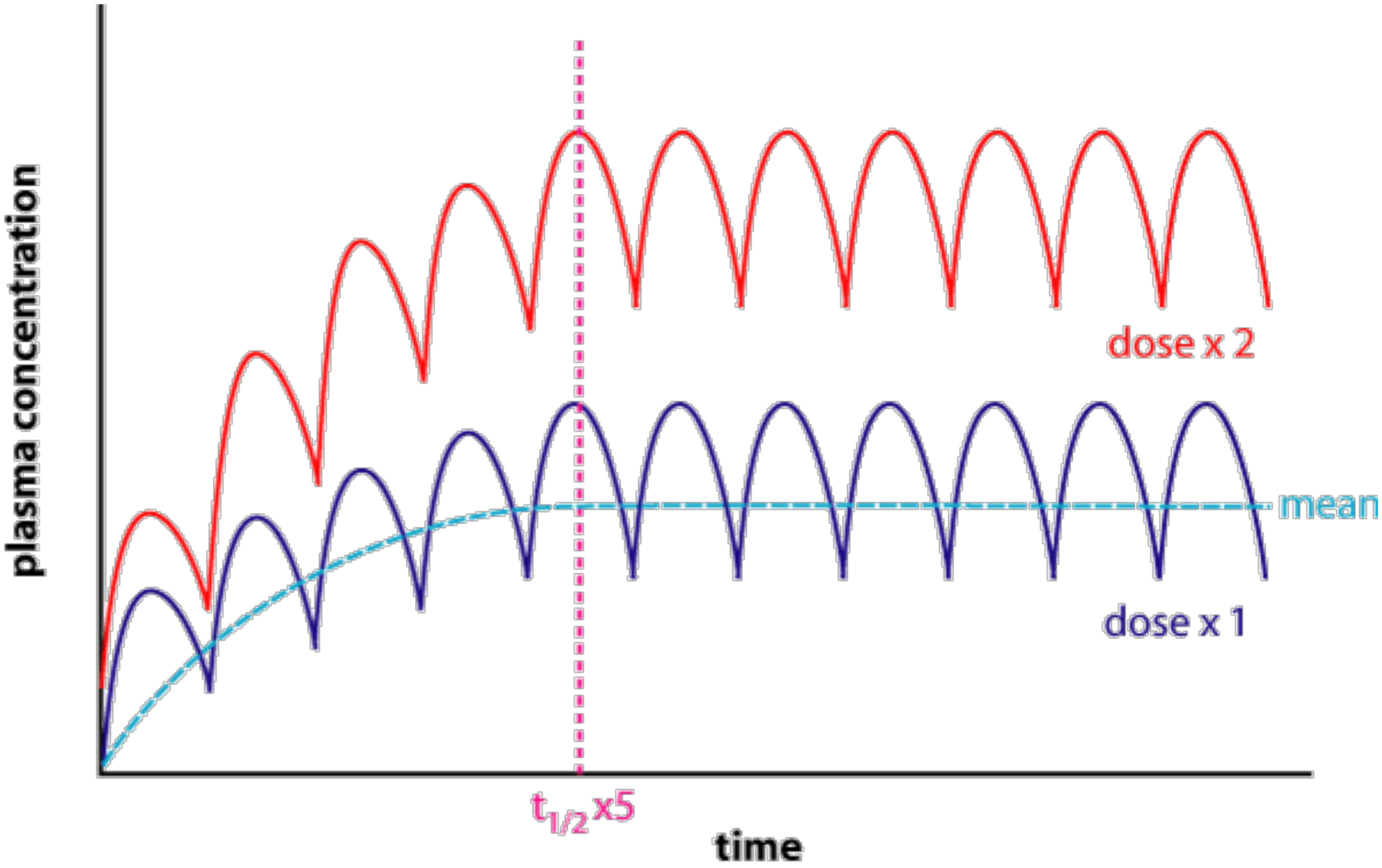
$$t_{1/2} = \frac{\ln 2}{k_{el}}$$

$$t_{1/2} = \frac{0.693}{k_{el}}$$

half life

- after 1 half life 50% of drug has gone
- after 2 half lives 75% of drug has gone
- after 3.3 half lives 90% of drug has gone
- after 5 half lives 97% of drug has gone and it is unlikely to have any more effect
- does not apply to drug residues!!!

repeated dosing



repeated dosing

- steady state (Cp ss) effectively reached after 5 half lives

dosage

- steady state reached when
  - drug in (dose) = drug out (clearance)

$$dose = Cl_p \, C_{p\,ss}$$

$$Cl_p = V_d \, k_{el}$$

oral dosage

$$\frac{\text{dose} \times F}{\text{dose interval}} = Cl_p \, C_{p\,av}$$

2 compartment open model

drug in

central compartment

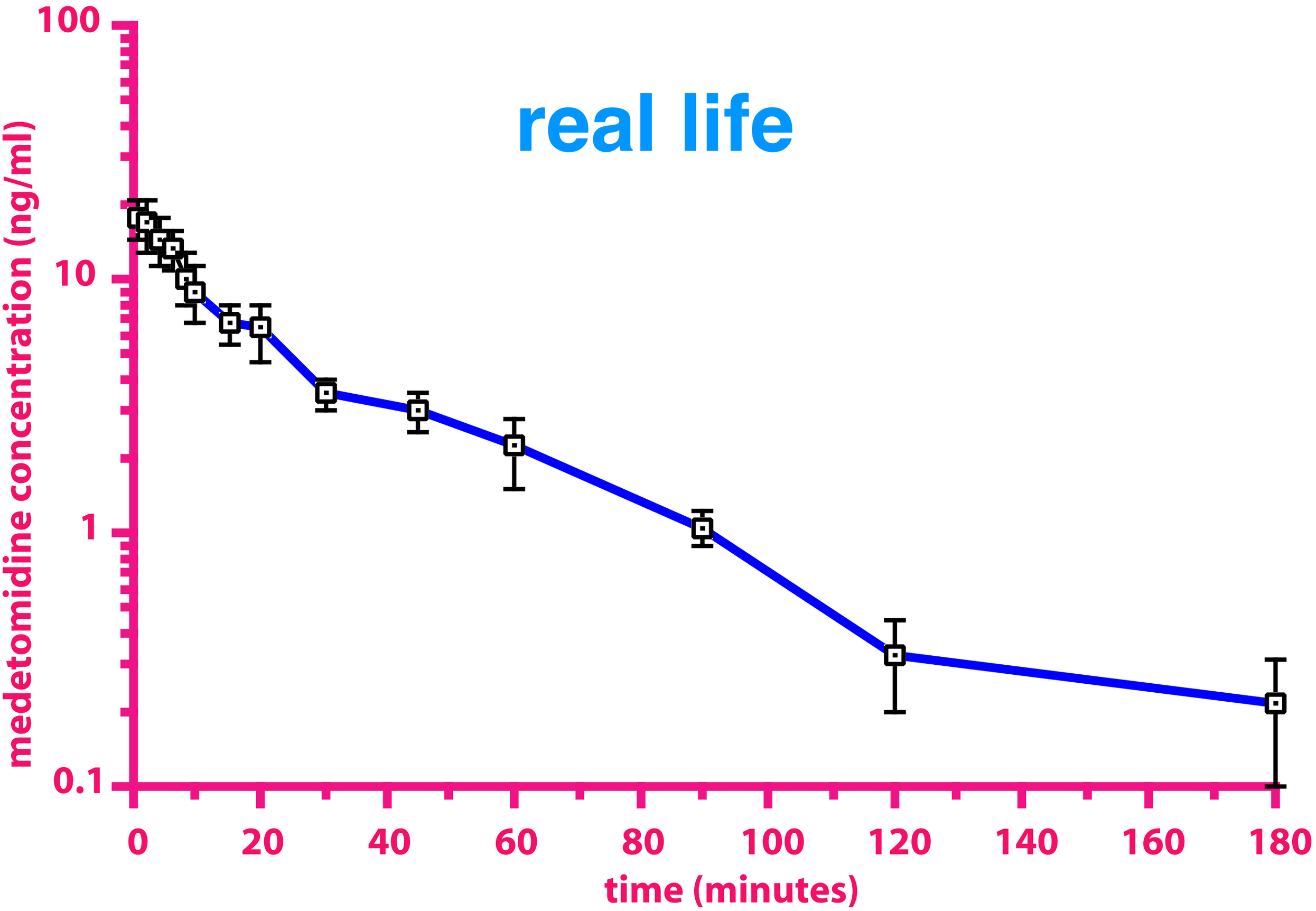
k_{12}

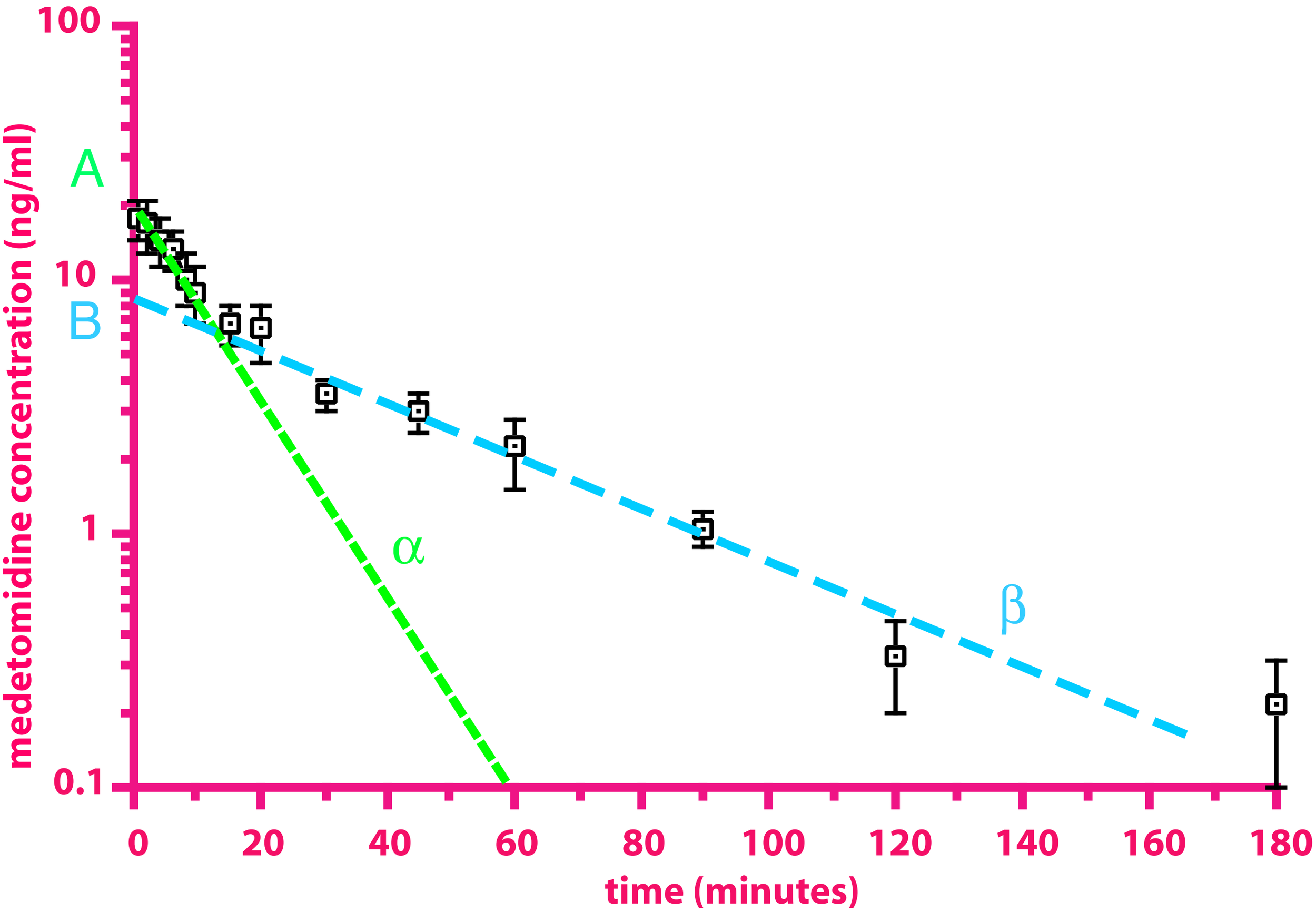
peripheral compartment

k_{21}

drug out

real life


100
10
1
0.1
medetomidine concentration (ng/ml)
0
20
40
60
80
100
120
140
160
180
time (minutes)


100
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A
B
α
β
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time (minutes)

therapeutic drug monitoring

- measurement of plasma levels of drug and adjusting dose to achieve target plasma levels

therapeutic drug monitoring

- why do it?

therapeutic drug monitoring

- when the drug has a low therapeutic index
- when the drug hasn't worked
- when the drug's effect is difficult to monitor
- when the drug's half life is likely to change
- when the pharmacokinetics cannot be predicted
- if you suspect that the owner hasn't given the drug correctly

Who would you believe?

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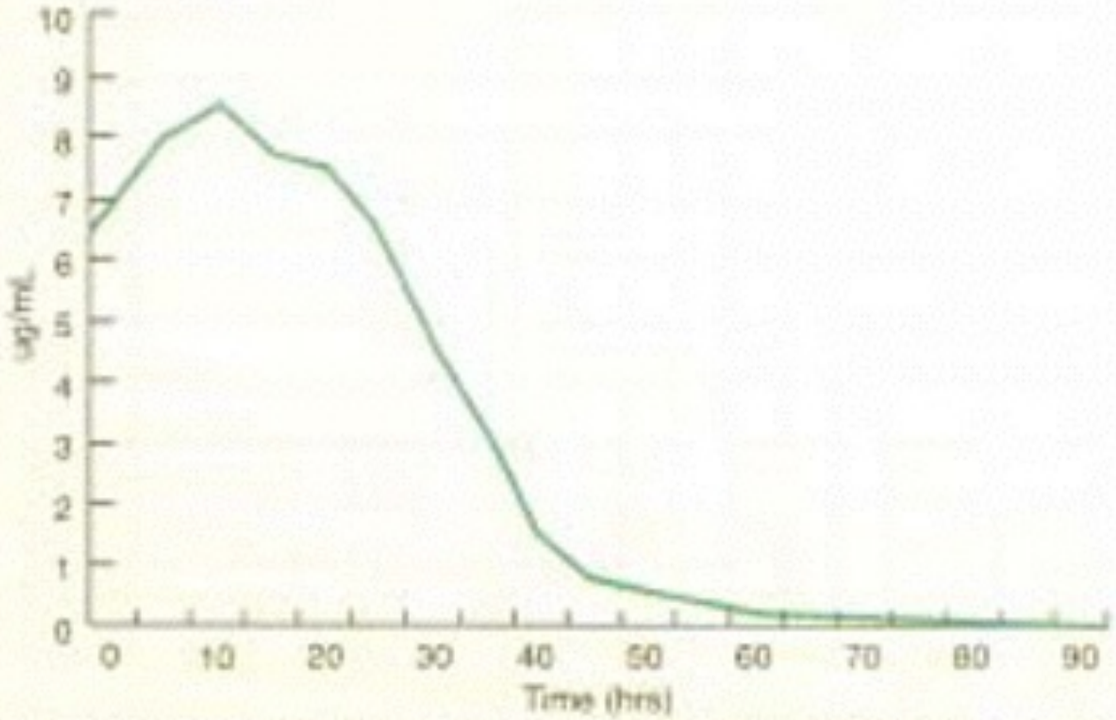

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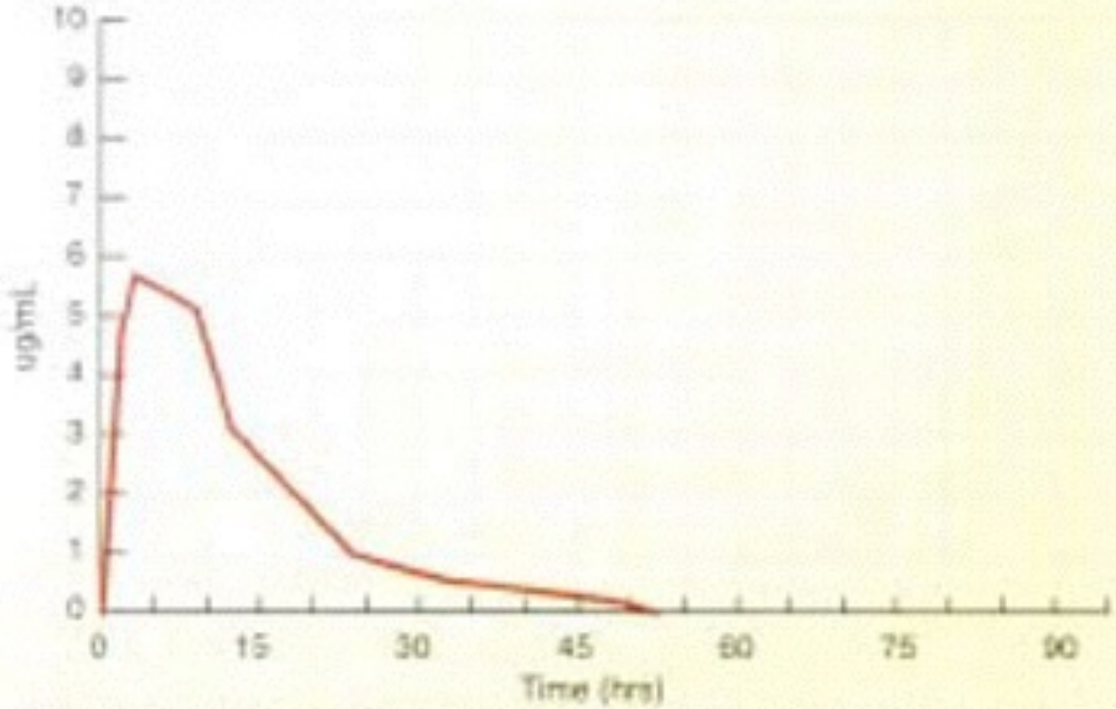

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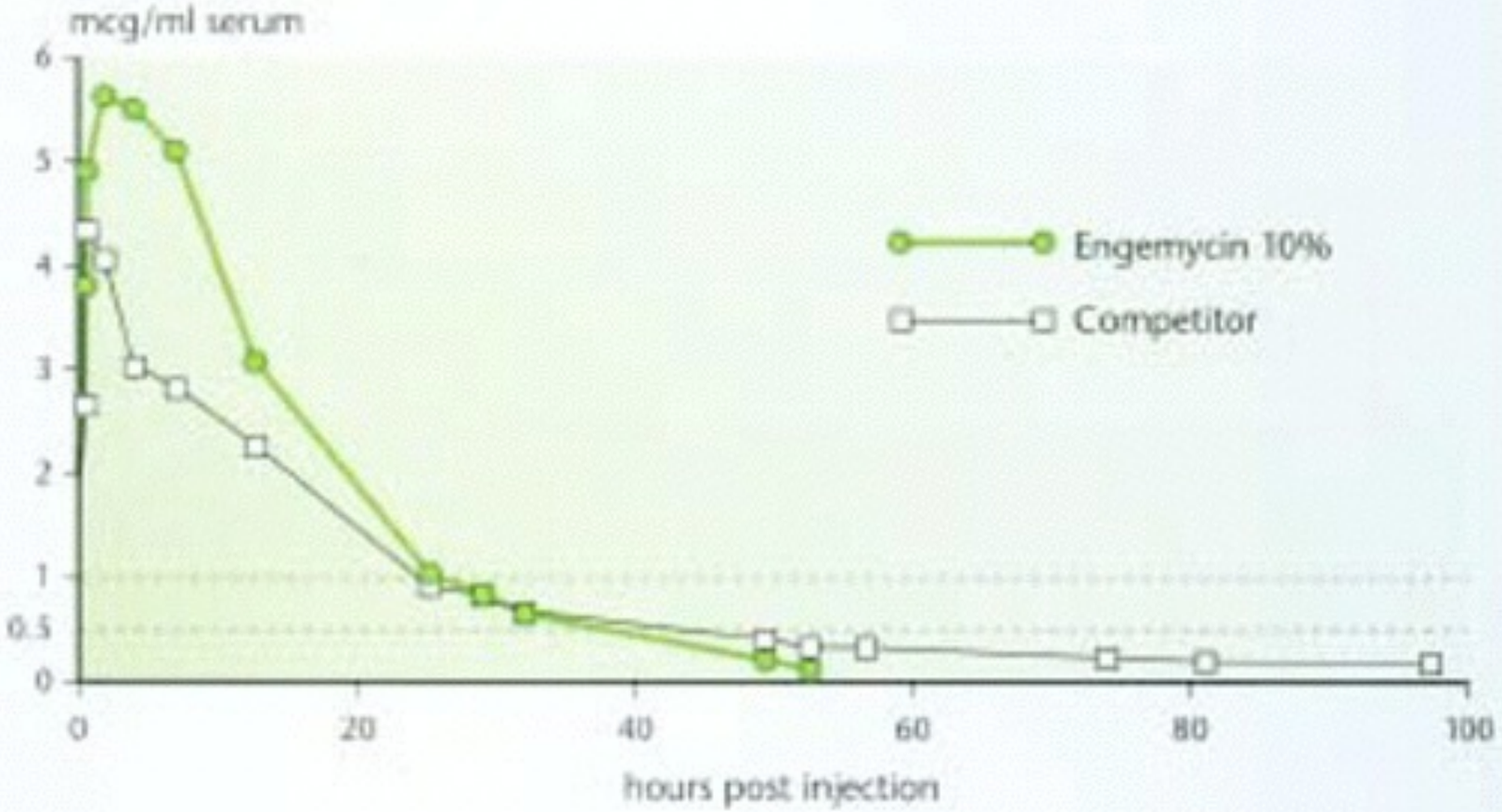
As a result of the PVP-OTC complex rapidly diffusing away from the injection site Engemycin® produces faster attainment of therapeutic plasma levels and an excellent bioavailability profile without the penalty/negative properties of an extended elimination phase.

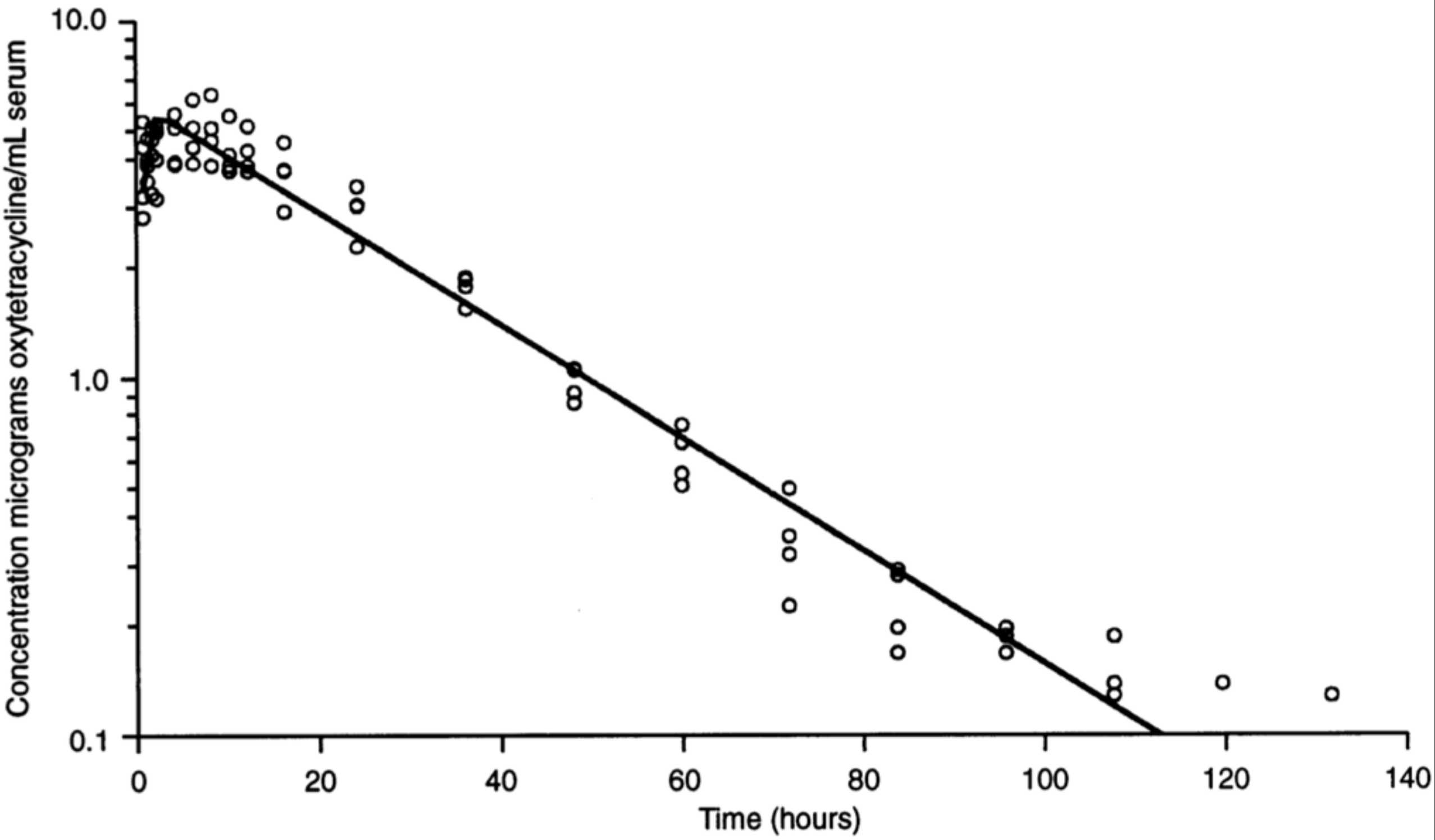
Traditional LA oxytetracyclines tend to produce a pharmacokinetic profile with lower serum concentrations and an extended tail that is offering little or no additional therapeutic benefit.

A comparative clinical trial carried out by the University of Ghent (Belgium) in calves with pneumonia showed that no significant differences were seen in the proportions of animals requiring 1, 2 or 3 injections for full recovery, with a final overall cure rate of >95% for both products.

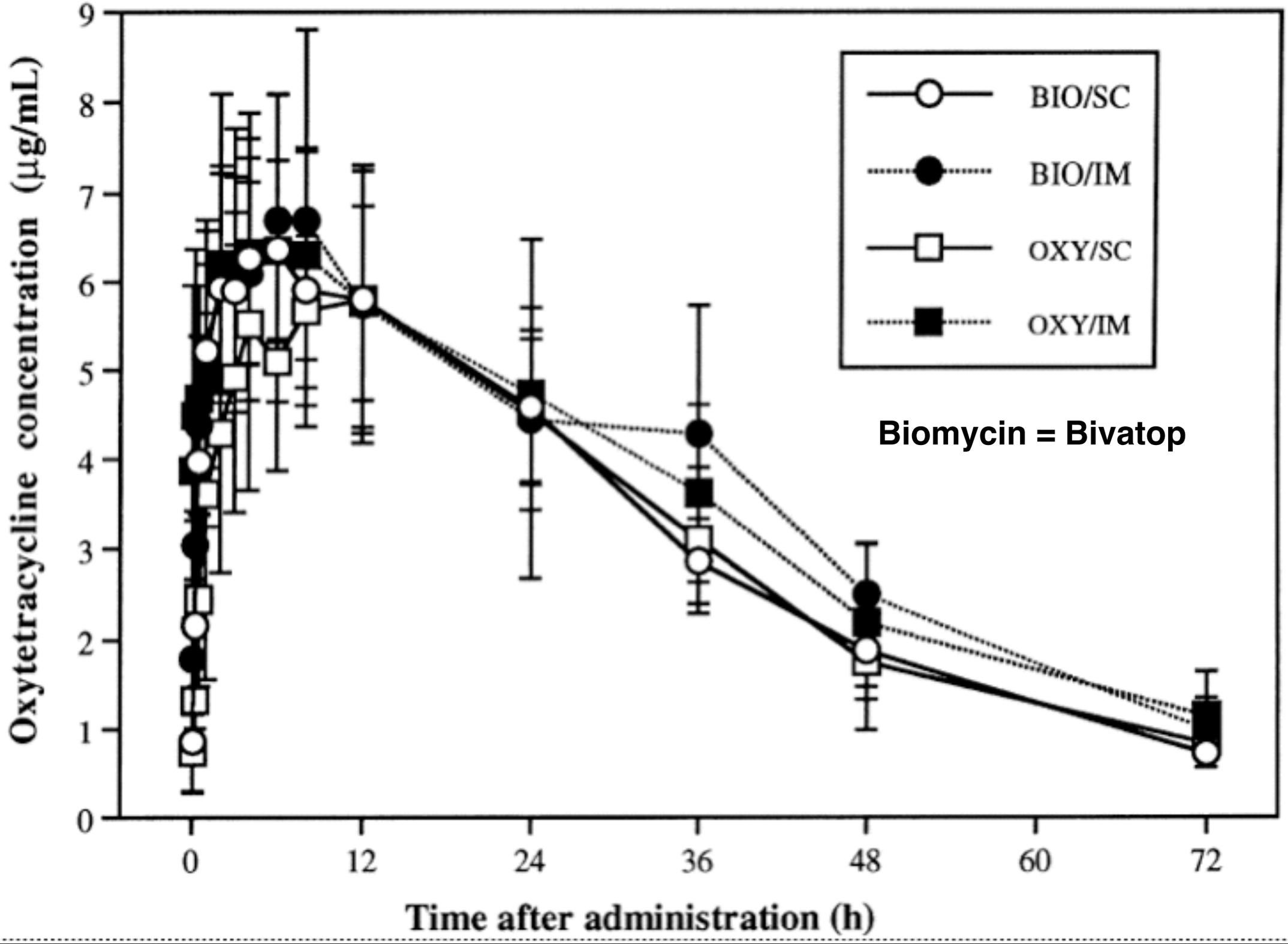
Blood serum concentrations after intramuscular administration of Engemycin10% and a competitive oxytetracycline preparation at a dosage of 20mg/kg body weight to calves approx. 190kg liveweight.



CRAIGMILL, A. L., HOLLAND, R. E., ROBINSON, D., WETZLICH, S. & ARNDT, T. Serum pharmacokinetics of oxytetracycline in sheep and calves and tissue residues in sheep following a single intramuscular injection of a long-acting preparation. *Journal of Veterinary Pharmacology & Therapeutics* 23 (6), 345-352, 2000.



Clarke C. R.; Wang Z.; Cudd L.; et al. Pharmacokinetics of two long-acting oxytetracycline products administered subcutaneously and intramuscularly. *Journal of Veterinary Pharmacology and Therapeutics* 22 (1): 65-67 1999



elimination

- the plasma concentration of most drugs falls exponentially
- half life is the time for drug concentration to fall by half
- the drug is effectively gone after 5 half lives
- with repeated doses a steady state is reached after 5 half lives
- some drugs show a biexponential fall corresponding to distribution and elimination