Pharmacokinetics (From clinical or mathematical aspect)

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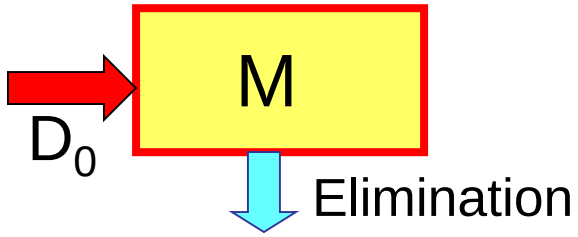
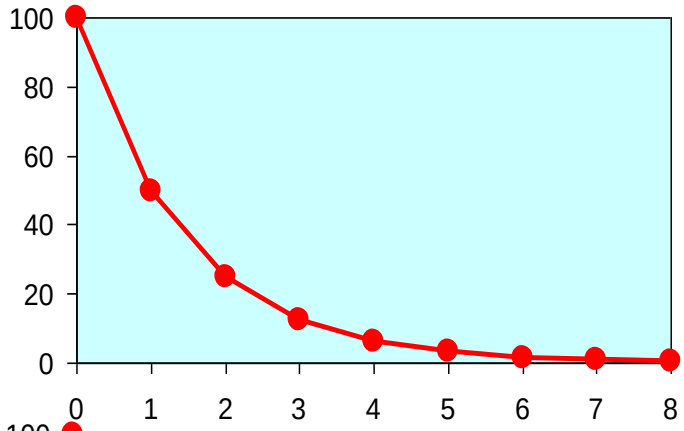
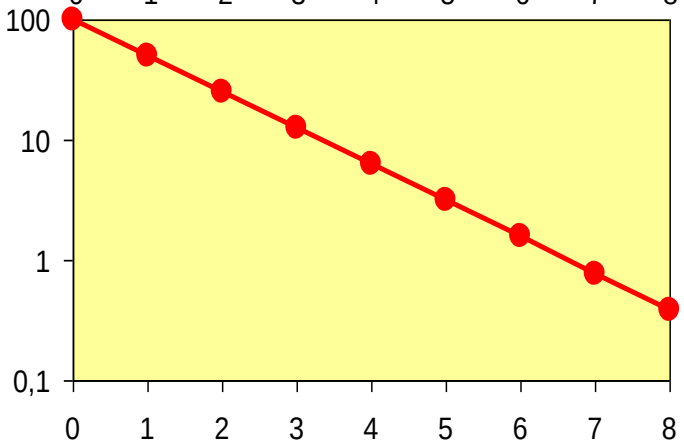
One compartment open model – 1st order kinetics

- Pharmacokinetics in clinical practice
  - Investigates the relations of blood or plasma concentration of the drug and time
  - The elimination velocity of the drugs is directly proportional to the blood or plasma (1st order of the) concentration
  - Elimination coefficient: $k_{el} = CL/V_d$ Shows the partiell drop of concentration per time unit (0.1 → 10% drop)
  - $\Delta c = -k_{el} \times c(t) \times \Delta t = -CL/V_d \times c(t) \times \Delta t$
  - The result of this differential equation
  - $c = c_0 \times e^{-CL/V_d \times t}$
  - The curve is a negative exponential form in the most simple case after iv. application. (it is linear in semilogarithmic scale = called linear kinetics)
  - Concentration increases with the dose linear







Appearent Volume of distribution V_d

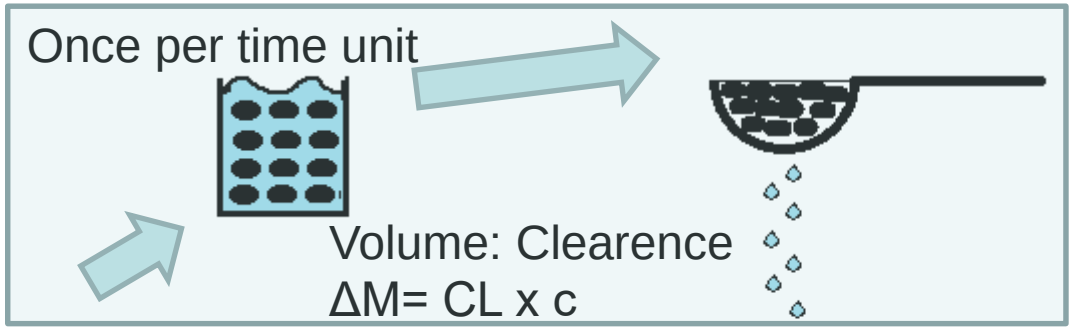
- Volume of distribution is volume of a virtual homogenous fluid compartment, where the concentration appears the same as it is measured in the blood or plasma.
- $V_d = M / c_{plasma}$ (where M is the amount of the drug)
- Mainly it is expressed for kg body weight
  - **Plasma volume: 0.04 x l/kg, blood volume: 0.08 x l/kg**
  - **Extracellular water volume: 0.2 x l/kg**
  - **Total body water volume: 0.6 x l/kg**
- For drugs accumulating in the tissues V_d >> 0.6 x l/kg. The distribution is determined by the strength of binding of the drugs to the plasma and tissue proteins, respectively

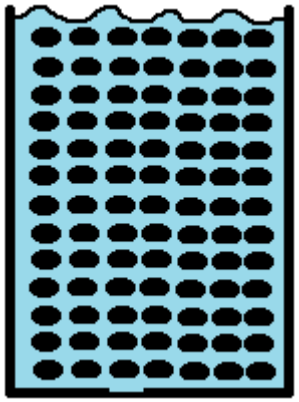
Drug	V_d (l / kg)
Heparin	0,06
Insulin	0,08
Tolbutamid	0,1
Gentamicin	0,28
Ampicillin	0,3
Theophyllin	0,4
Isoniazid	0,6
Phenytoin	0,6
Ethanol	0,65
Paracetamol	1,0
Pentobarbital	1,8
Procainamid	2,0
Morphin	2,0
Chinidin	2,3
Propranolol	3,0
Lidocain	3,0
Pethidin	3,5
Digoxin	7,0
Imipramin	15,0
Chlorpromazin	20,0

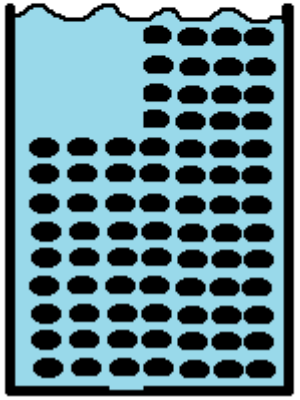
Clearence (CL)

- The clearence (CL) of a drug is defined as the volume of blood cleared of drug by metabolism or excretion per time unit
- From the original differential equation (multiplied with Vd):
  - $\Delta M = - CL \times c(t) \times \Delta t$
  - Elimination rate = $\Delta M / \Delta t = - CL \times c(t)$ So clearence is the constant velocity factor of the elimination
- Total body clearence = metabolic clearence + renal clearence + any other clearence

Clearence(CL)





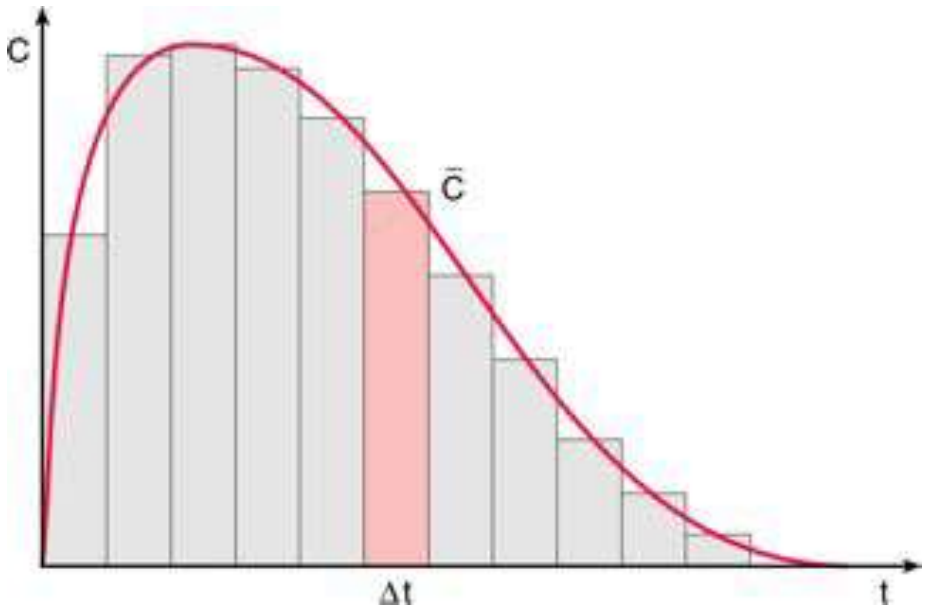


Volume: Volume of distribution
c= M / Vd

M'= M-ΔM = c x Vd – c x CL (x t)
c' = M' / Vd = c – c x CL/Vd (x t)

AUC (Area Under Curve)

- AUC is the integral of the concentration time curve
- It is calculable as the quotient of administered amount and clearence
- In the practice clearance is calculated from dose and measuring AUC (checking blood concentration in different time point)



Surface of a column

↓

$\Delta M = \overline{c} \times \Delta t \times CL \longrightarrow$ *The amount eliminated in the time period*

$M = CL \times AUC = CL \times \int c \times dt$

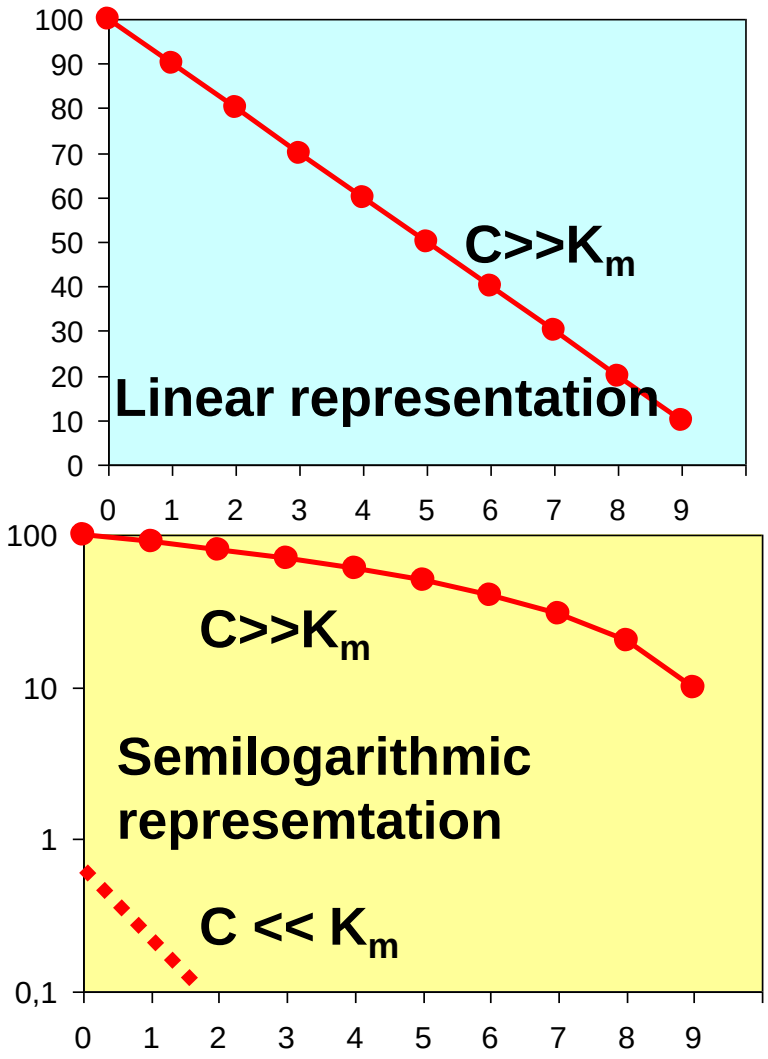
$CL = M / AUC$

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

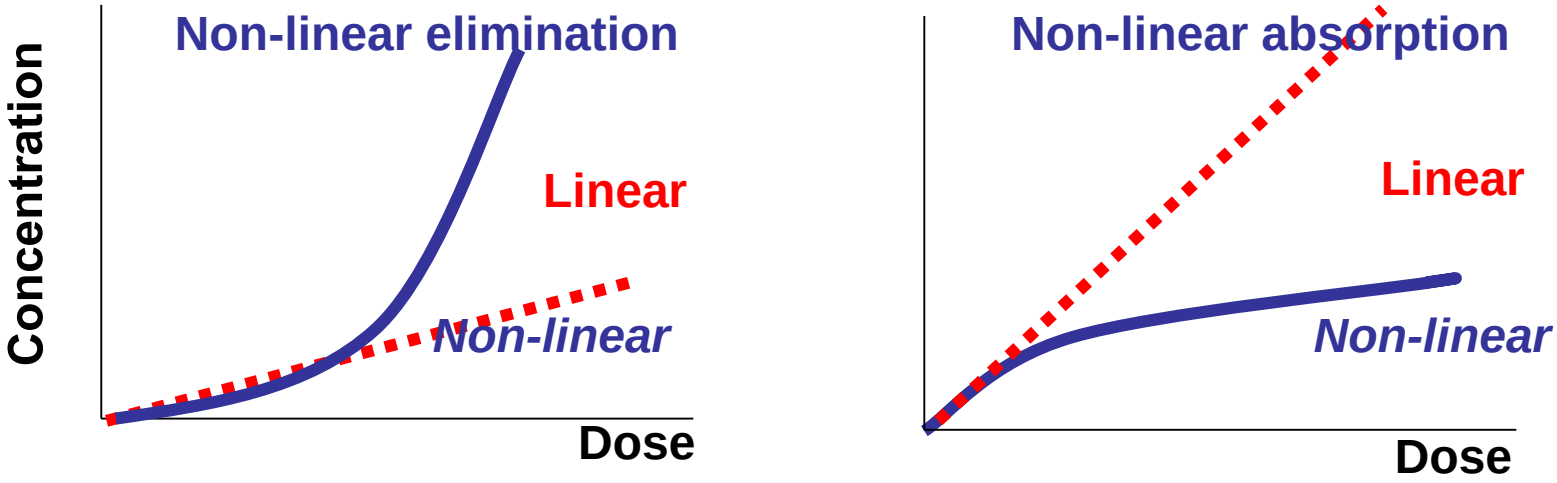
- The property of an exponential curve that it changes with fixed ratio in fixed intervals (in the case of a negative curve it means decrease – k_{el} for a time unit)
- Half life is the interval during which the curve decreases by 50% (1 to 0.5, 0.5 to 0.25 etc.)
- $T_{1/2} = \ln 2 / k_{el} = V_d / CL \times \ln 2$ (0.693)
  - [$c_0/2 = c_0 \times e^{-CL/V_d \times t}$; $e^{-CL/V_d \times t} = 0.5$]
- So it directly proportional with volume of distribution and reciprocally with clearence and elimination coefficient

Zero order kinetics

- The rate of elimination is independent from the concentration ($c^0 = 1$)
- Background: The elimination process is saturated in the whole (eg. ethanol) or in the higher concentration range (then 1st order kinetics in lower and 0 order in the higher range) Plasma concentration is higher than the saturating concentration (Km) of the elimination process (eg. phenytoin). Max. elimination velocity: Km x CL
- It is called as non linear kinetics (because on semilogarithmic scale it is non linear)
- Plasma concentration is non linearly increases with the dose
- Half-life can not be determinated
- Elimination is slower than it would be expected in the case of 1st order kinetics



Linear vs. Non-linear kinetics



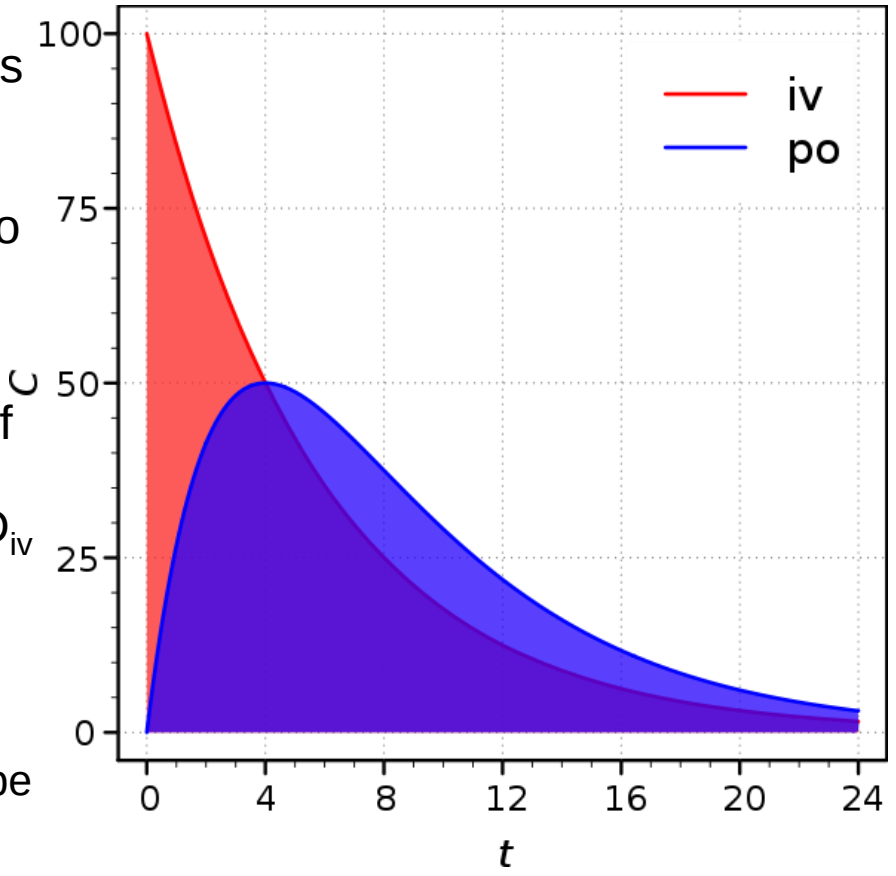
Characteristics of the drugs following first-order kinetics

- The clearence and the apparent volume of distribution are independent of the dose
- The AUC increases linearly with the dose
- Following multiple administration the plateau plasma level is in direct proportion to the dose and reciprocal to the clearence

- In case of non-linear elimination at a low dose level the plasma concentration increases first linearly, then, after reaching the threshold level, exponentially, which results in an unexpected increase of the drug effect
- In case of non-linear absorption after reaching the threshold level, the increase of the plasma level is smaller than the calculated value (eg: Methotrexate – because saturation of folic acid transporter)

Bioavailability

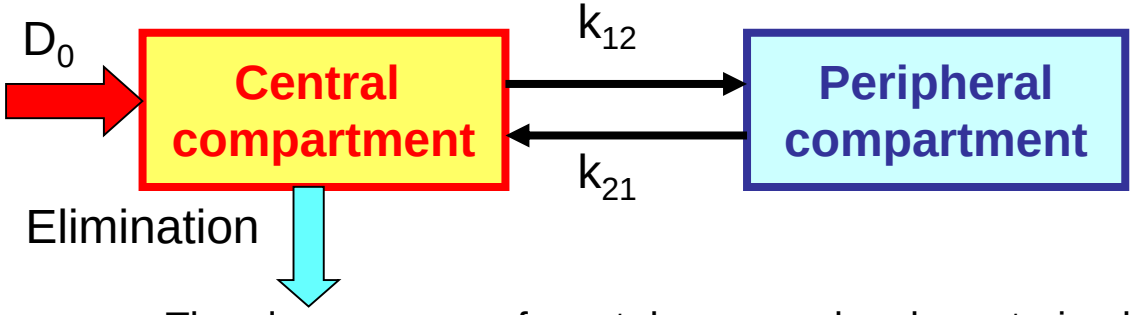
- After non iv. application the excretion phase is preceded by the absorption phase (it is mainly exponential – the uptake of the drugs depends on its concentration)
- C_{max} is not at time point 0
- Because the drug is not injected directly into the systemic circulation, a part of the dose could lost before reaching the blood (incomplete absorption, first pass)
- AUC directly proportional to total amount of drug reaching blood. (AUC = M / CL)
- Bioavailability: f= AUC_{other} / $AUC_{iv.}$ (where D_{iv} = D_{other})
  - Iv. bioavailability is ever total
  - We can determine sc., im., po. availability
  - Often expressed in percentage form
  - Doses for other route of administration can be calculated by dividing iv. dose with the availability D_{other} = D_{iv} / f

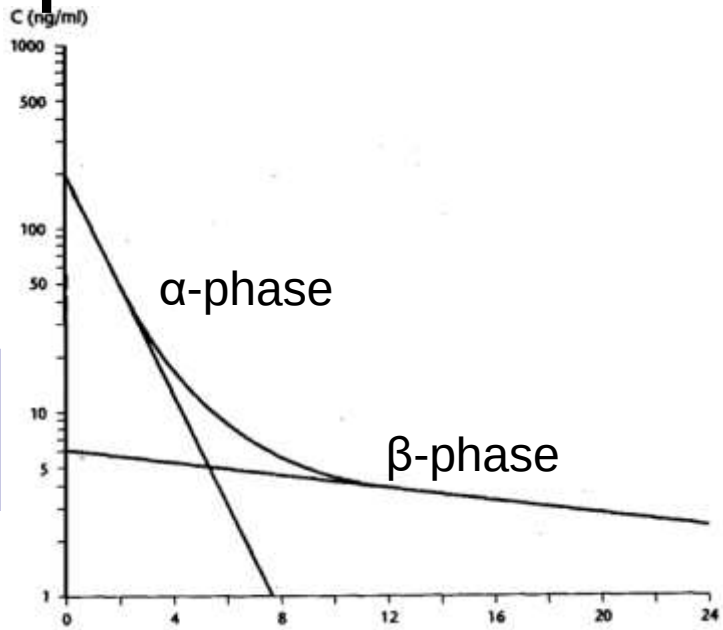


Two-compartment open model

$$C_1 = Ae^{-\alpha t} + Be^{-\beta t}$$

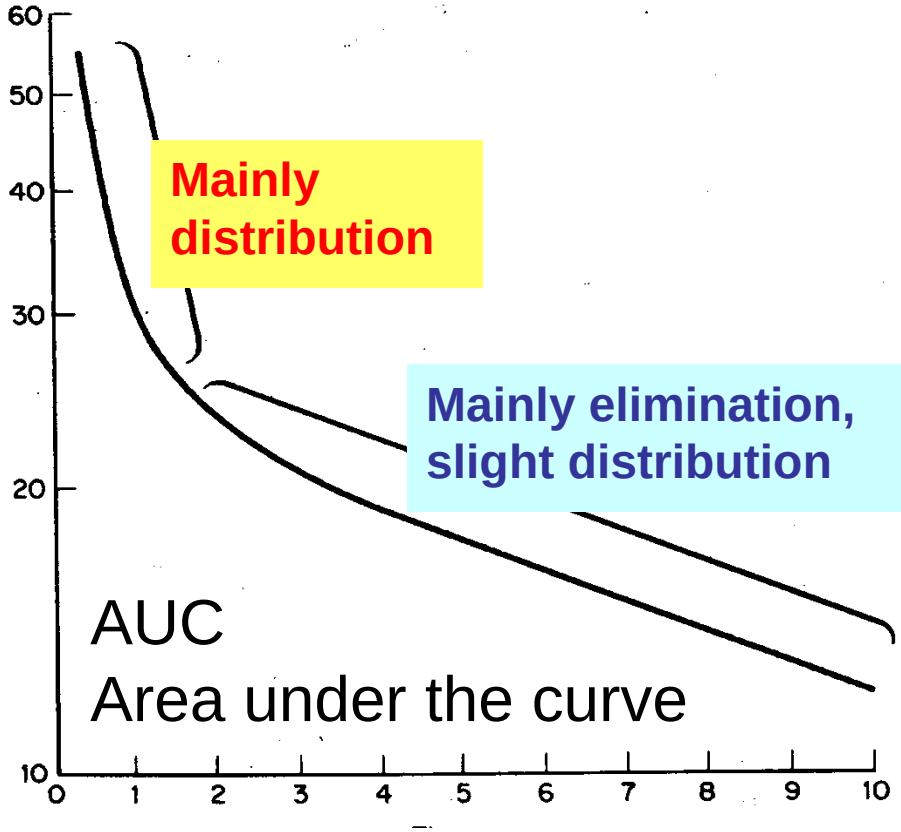
C_1 =concentration in the central compartment



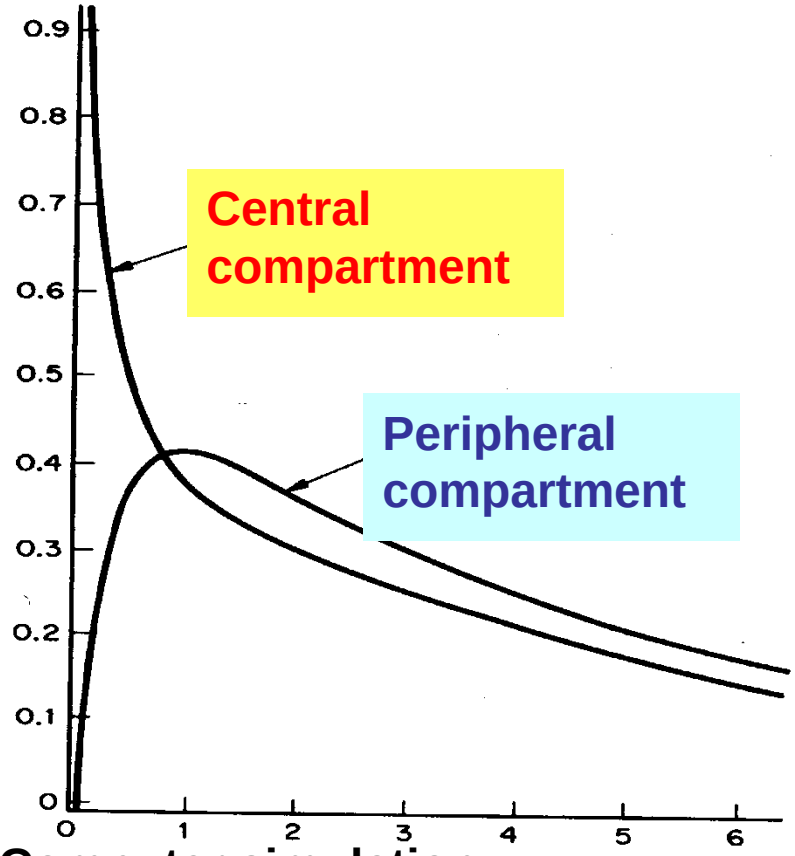


- The plasma curve of most drugs may be characterized well by two exponential members which describe the phases of distribution and elimination, respectively
- The first, α phase is characterized by the rapid inflow of the drug into the peripheral compartment, the rate of the second, β phase is determined by the rate of elimination (the flow of the drug from the periphery into the plasma is mainly faster) ($\alpha=CL_\alpha/V_{d\alpha}$, $\beta=CL_\beta/V_{d\beta)}$
- Rarely a further, γ phase may also be encountered. It has a practical significance when the area under the 3rd phase is larger than 10% of AUC. This phase refers to a „deep" compartment.
- In case of multiple administration the cumulation is determined mainly by the half-life of the terminal phase
- Dominant half-life: it refers to the phase with the largest AUC part, it is mainly the terminal phase

Two-compartment open model



Plasma curve
Two exponential members with elimination rate constants
α and β



Computer simulation
Distribution of the drug in the peripheral and central compartments

Pharmacokinetics of continuous and intermittent administrations

- A steady-state drug concentration in the tissues is achieved by a zero-order, constant rate of infusion
- When the steady state is reached, the rate of infusion will equal to the rate of elimination, then plasmaconcentration remains stabile
- *When the plateau level is reached, Dosing rate = Rate of elimination*

$$R_0 = D / t = Cl \times C_{ss}$$

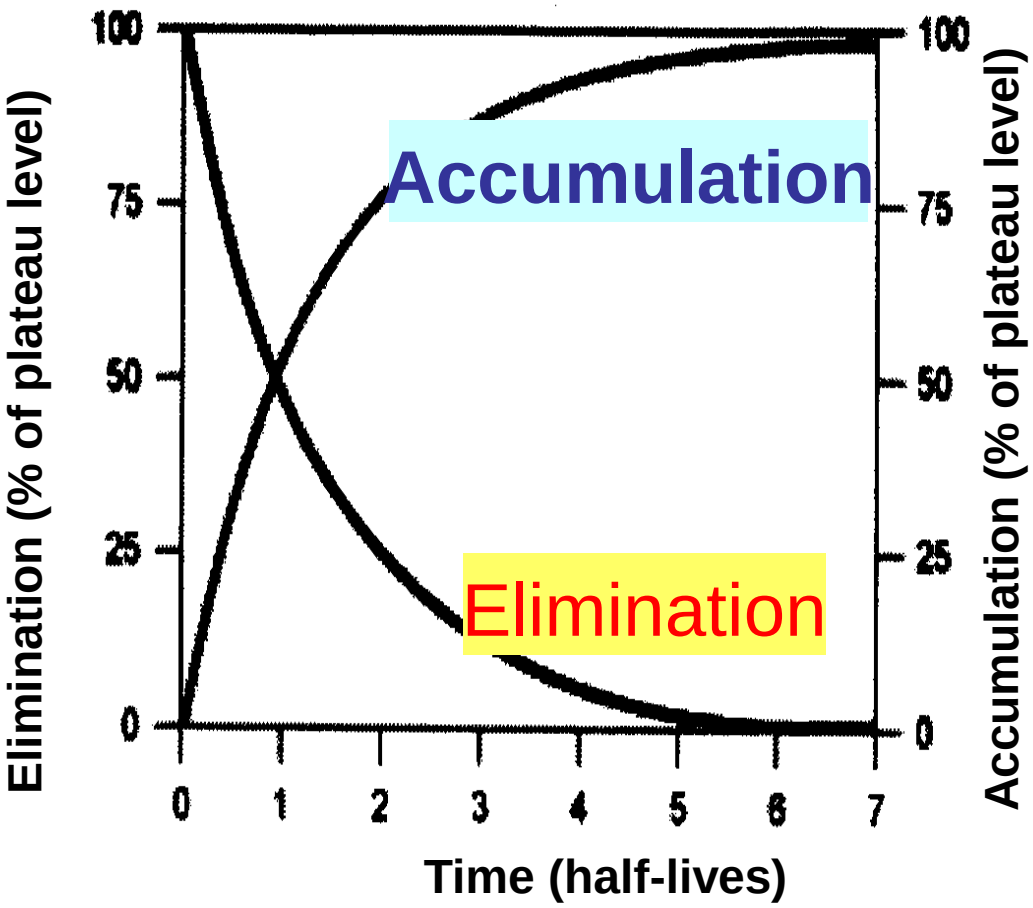
- The plateau concentration C_{ss} is dependent solely on the rate of infusion (R_0): Dose / time unit (eg. mg/min)

$$C_{ss} = (D / t) / CL$$

- The steady-state plasma level following intermittent administration, similarly to that at infusion, is in a direct proportion to the dosing rate, I.e. to the amount of the dose and the frequency of the administration (eg. 100 mg each 4 h = 25 mg/h)
- The time to reach the plateau level depends solely on the elimination constant of the drug. This time is in inverse proportion to the elimination constant, i.e. in direct proportion to the half-life

Pharmacokinetics of continuous and intermittent administrations

- During one half-life the half of the plateau concentration may be reached, 4-6 half-lives must elapse before the final steady-state concentration is approached
- The equation of the accumulation:
  $c = c_{ss} \times (1 - e^{-(CL/Vd) \times t})$
- C at n half-lives: $c_{ss} \times (1- 0.5^{n})$
- The time required for the elimination of the drug from the body after the end of the infusion is the same as the time necessary for reaching the plateau level
- c after 5 half-lives is
  $c_{ss} \times 0.5^{5} = c_{ss} / 32$

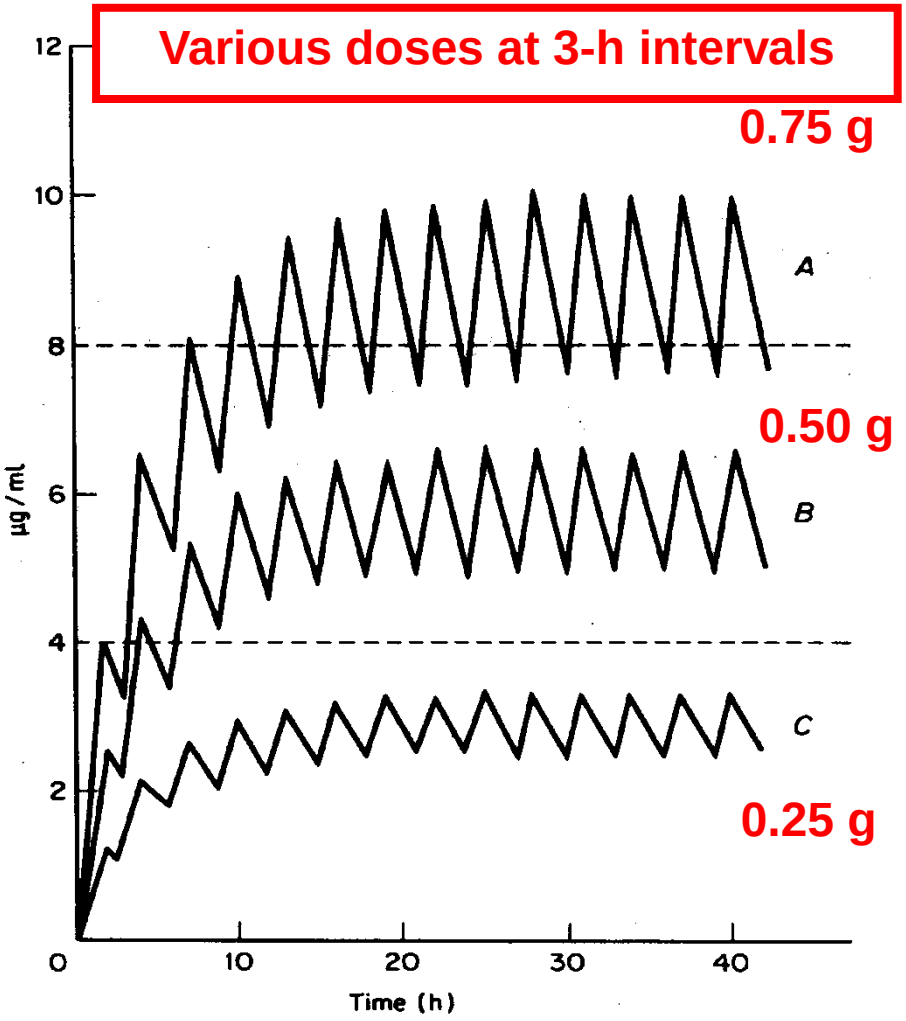


Pharmacokinetics of intermittent administration

Rogers et al.: Textbook of Clinical Pharmacology

- Half-life of the drug: 3.5 h
- Therapeutic range : 4-8 µg/ml
- Dosing at intervals of 3h
- As higher the dose (fix intervals), then higher the dosing rate and then higher the steady-state plasma level
- A curve 0.75g / 3h = 0.25g/h
  B curve 0.5g / 3h = 0.17g/h
  C curve 0.25g / 3h = 0.083g/h
- The steady state is reached after 4-6 half-lives, ie. 14-21 h
- The fluctuation between the maximum and minimum concentrations is single dose-dependent
- $c_{max} - c_{min} = D / V_d$

Maintainer dose =
Dosing rate x dosing interval
$D = \underline{c_{ss} \times CL \times T (/ f)} = R \times T (/ f)$

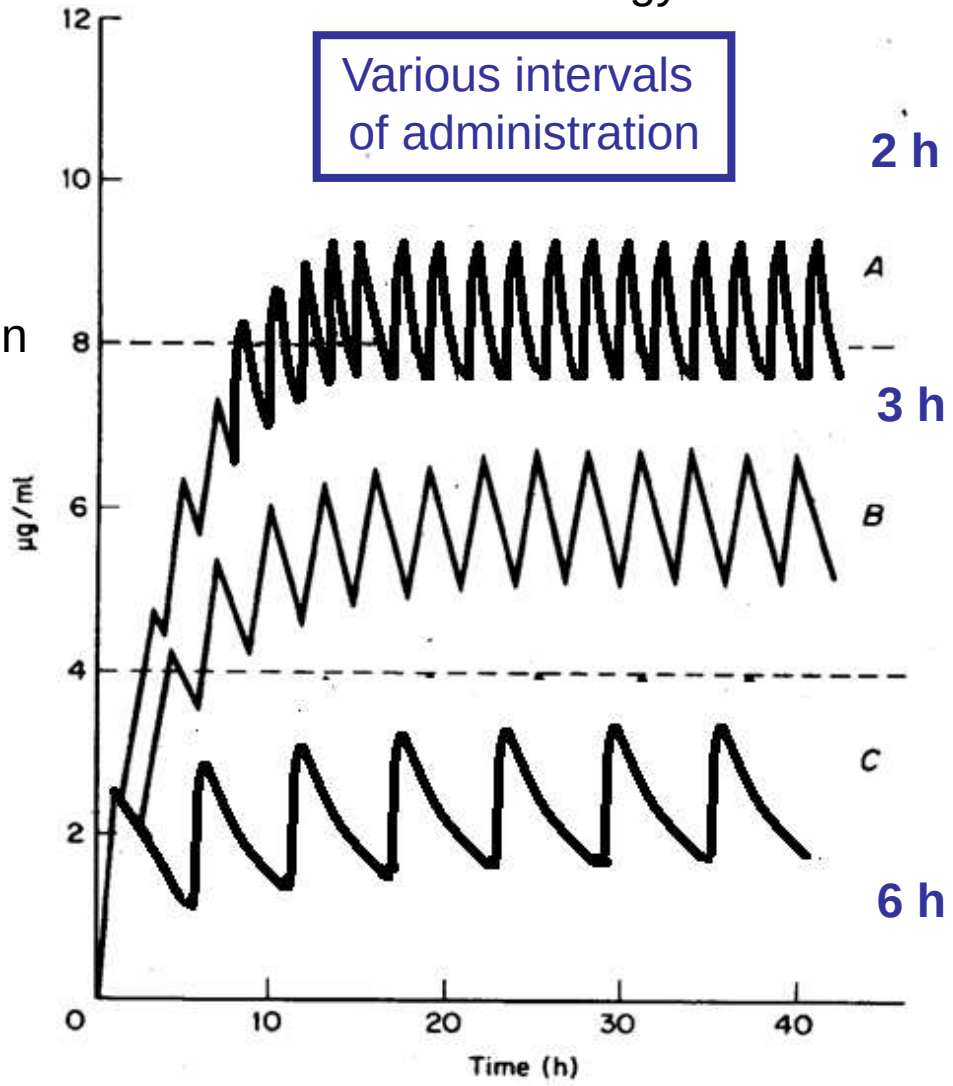


[f: Bioavailability]

Pharmacokinetics of intermittent administration

Rogers et al.: Textbook of Clinical Pharmacology

- Half-life of the drug: 3,5 h
- Therapeutic range : 4-8 µg/ml
- Dose: 0.5 g
- As shorter the interval (fix dose), then higher the dosing rate and then higher the plateau plasma level
- A curve 0.5g / 2h = 0.25g/h
  B curve 0.5g / 3h = 0.17g/h
  C curve 0.5g / 6h = 0.083g/h
- **c_{ss} = D / (CL x T)**
- The plateau level is reached after 4-6 half-lives, i.e. 14-21 h



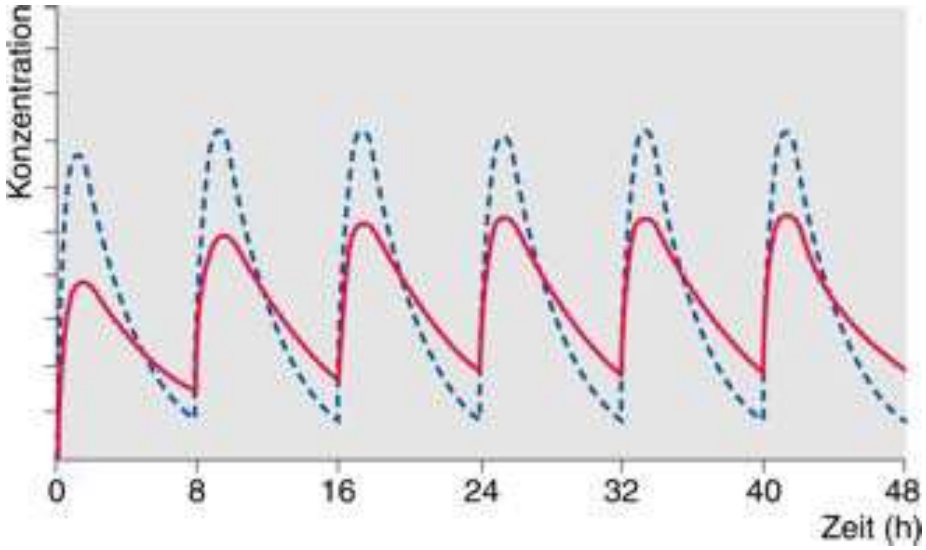
Volume of distribution and repeated administration

(Aktories et al. Allgemeine und spezielle Pharmakologie und Toxikologie)

- The dose for sustaining steady state concentration is independent of V_d
- Fluctuation of the plasma concentration at a fixed dosing rate and interval reciprocally proportional to volume of distribution
- $c_{max} – c_{min} = D / V_d$
- Example: Lipid soluble drugs can have larger concentration fluctuations in thin patients than in fat ones (if CL is the same)
- The single dose for saturating the drug can be calculated:

  $D_{loading} = c_{ss} \times V_d (/ f)$

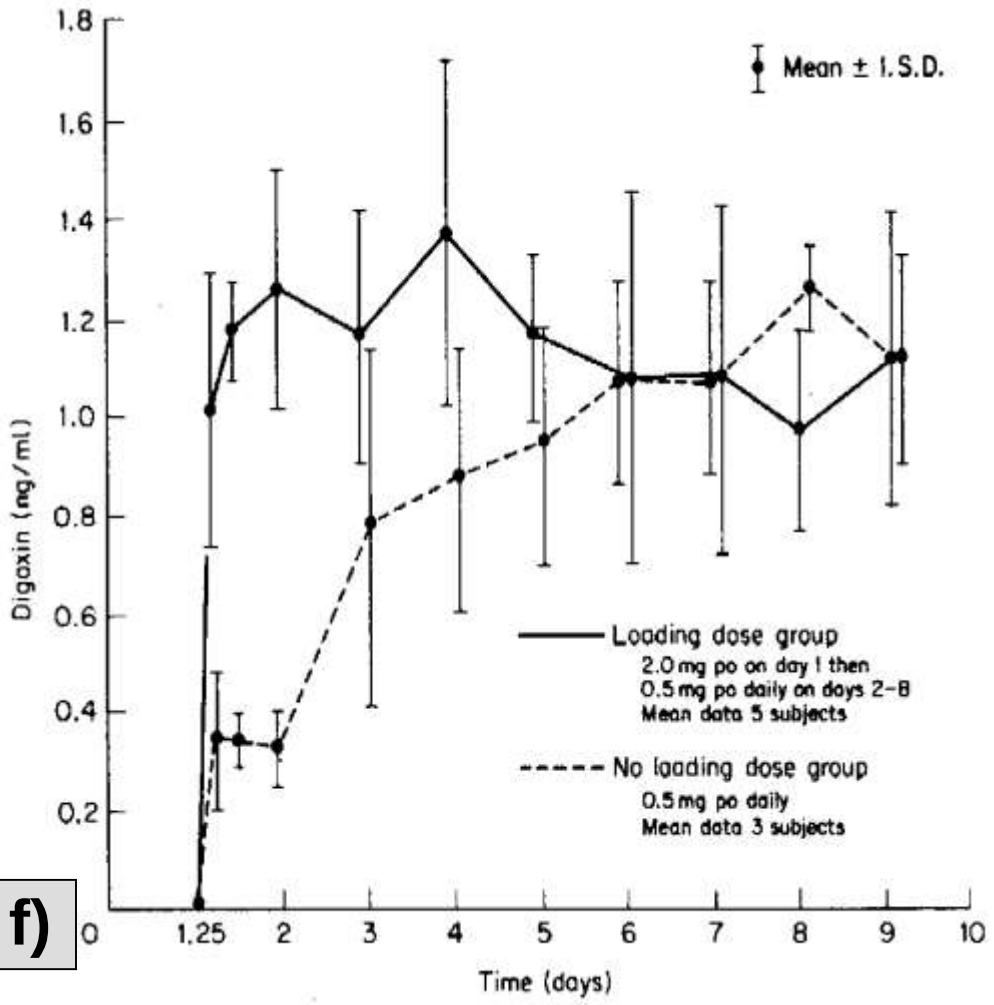
  [f: Bioavailability]



Digoxin administration ± loading dose

Marcus et al.: Circulation, 34: 865, 1966

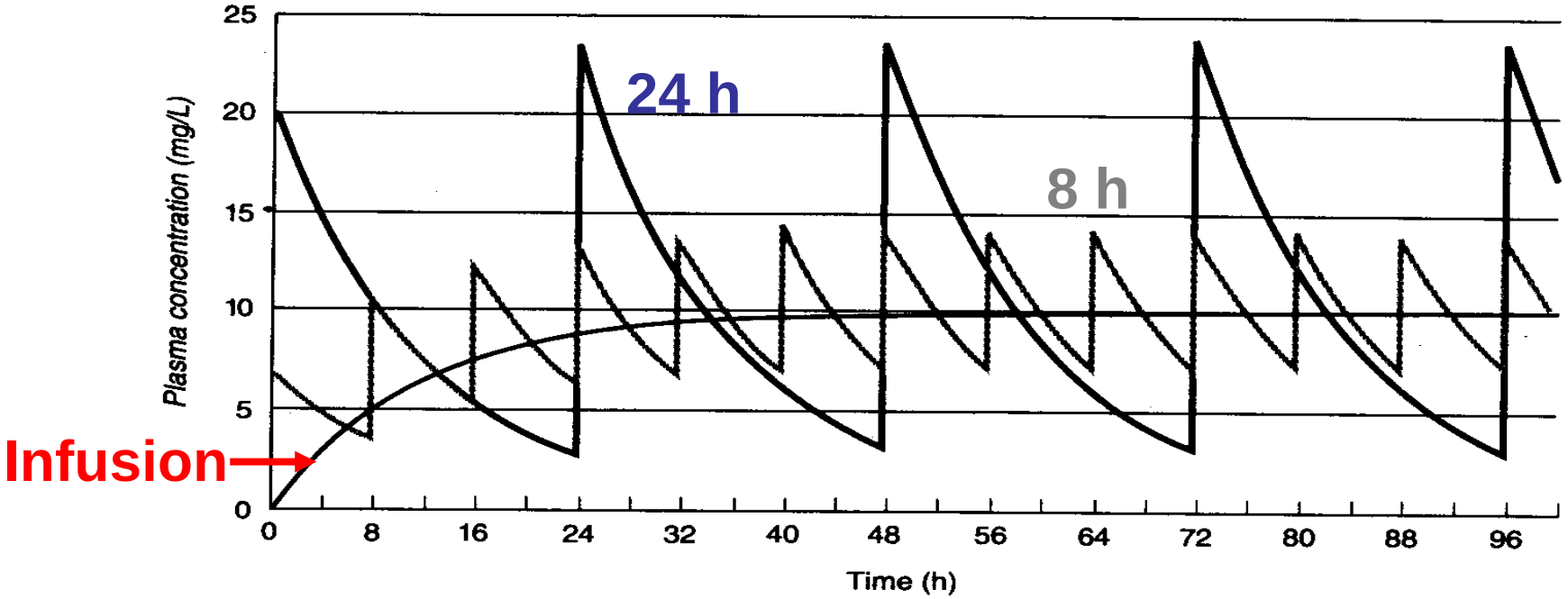
- Loading dose:
  - 2.0 mg po, 1st day
  - 0.5 mg/d, for 2-8 days
  - the required plasma level of 1 ng/ml was reached on the first day and could be maintained by a dose of 0.5 mg/d
- No loading dose:
  - 0.5 mg/d
  - The required plasma level of 1 ng/ml was reached in about 6 days
  - Digoxin $t_{1/2}$ = 1.5 days; the plateau level was reached in about 4 half-lives



Loading dose = V_d x C_{ss}(/ f)

Pharmacokinetics of intermittent administration

Katzung BC: Basic and Clinical Pharmacology



- If the clearance and the target concentration are known, the dosing rate may be calculated
  - Target plasma level: 10 mg/L; Cl = 2.8 L/h/70kg
  - Dosing rate: 10 mg/L x 2.8 L/h/70kg = 28 mg/h/70 kg infusion
- Maintainer dose = Dosing rate x Dosing interval
  - 28 mg/h x 8h / 0.96 = 224 mg; 24-hourly administration: 672 mg
  - (bioavailability 0.96)

Dosing rate$_{ss}$ = rate of elimination = Cl x C$_{ss}$