5. DESIGNING DOSE REGIMENS

•Dose regimen: The schedule of doses of a therapeutic agent per unit of time, including the time between doses (e.g. every 6 hours) or the time when the dose(s) have to be given (e.g. at 8 a.m. and 4 p.m. daily), and the amount of medicine (e.g. number of capsules) to be given at each specific time.

•Need to know the pharmacokinetics parameters

5.1. Determination of the PK parameters of a drug

1. *Single dose studies* : The critical pharmacokinetic parameters are clearance, volume of distribution and half-life (or elimination rate constant).

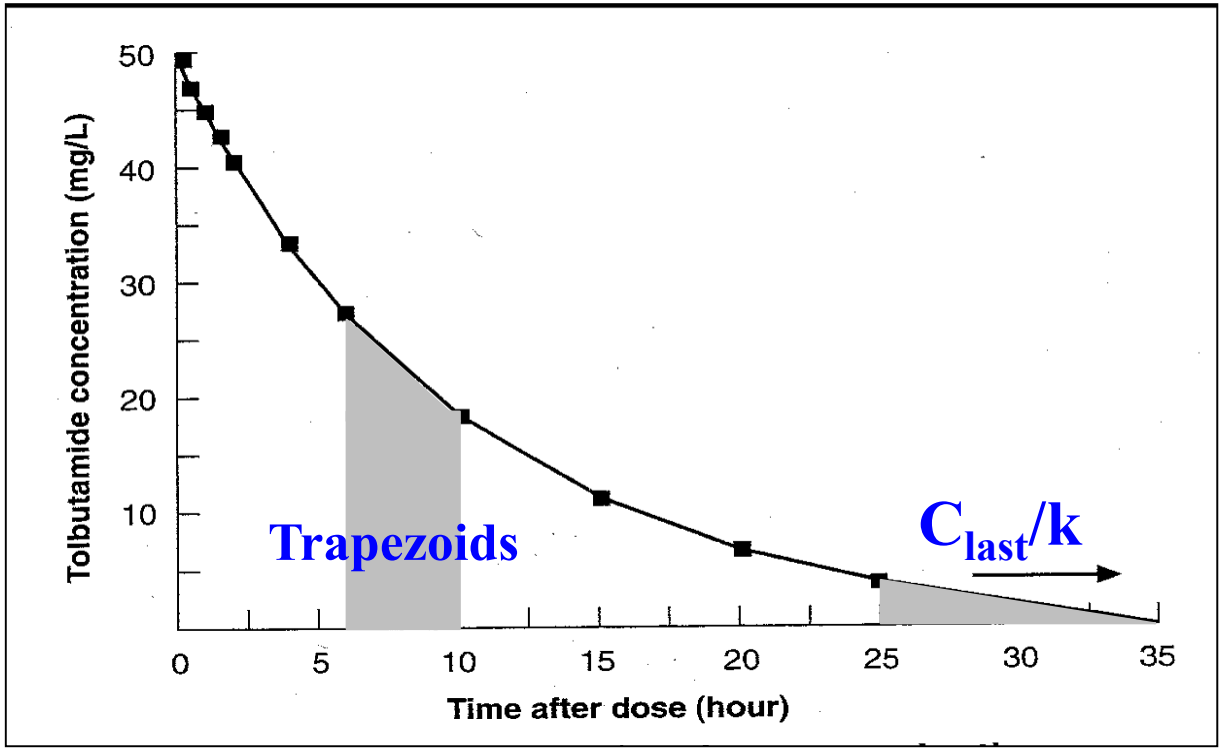
$$CL = \frac{dose}{AUC}$$

$$t_{1/2} = \frac{0.693}{k_e}$$

$$V = \frac{CL}{k_e}$$

- After a single intravenous dose of a drug :
- **Clearance (CL)** is calculated from the area under the plasma concentration time curve from zero to infinite time
- **Elimination rate constant (k_e)** and **half-life ($t_{1/2}$)** are calculated from the slope of the ln concentration versus time plot.
- **Volume of distribution (V)** is calculated from the clearance and elimination rate constant

Example: Tolbutamide



$$CL = \frac{dose}{AUC}$$

$$t_{1/2} = \frac{0.693}{k_e}$$

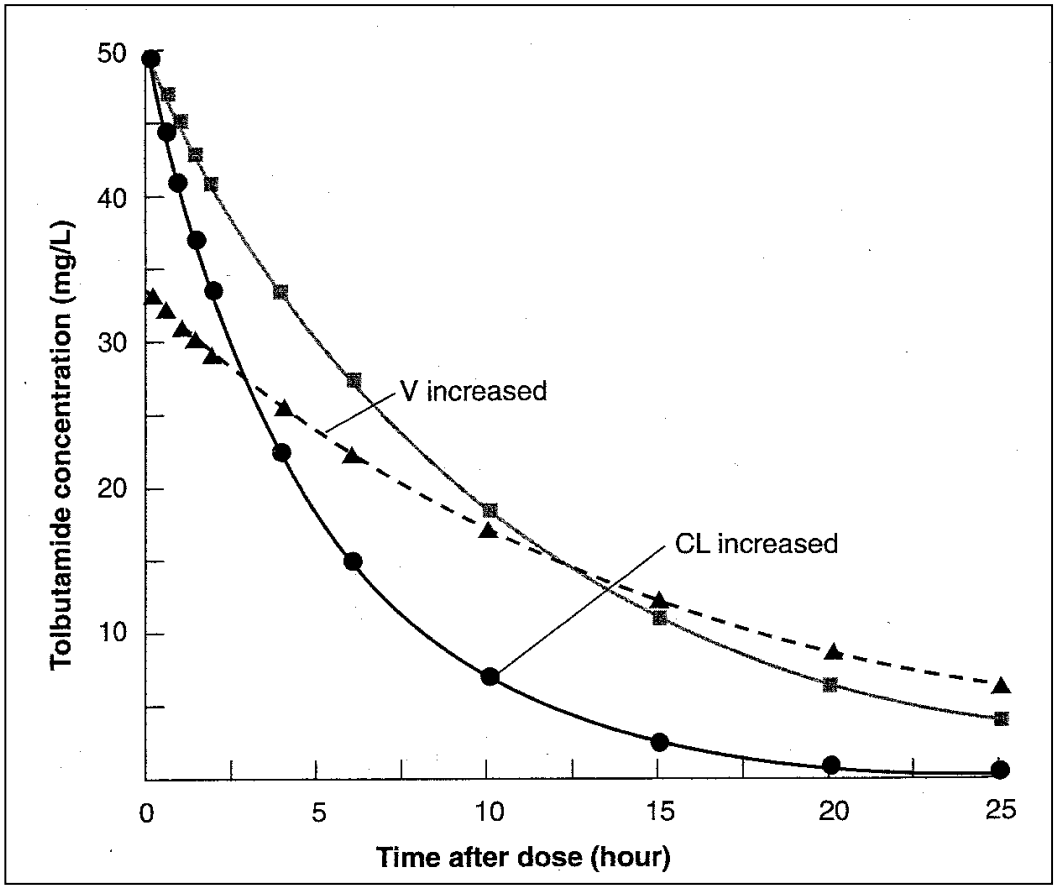
$$V = \frac{CL}{k_e}$$

$$\mathbf{AUC_{0\text{-}\infty} = AUC_{0\text{-}t} + AUC_{t\text{-}\infty}}$$

$$AUC_{0\ t} = \sum_{i=1}^{n} \frac{C_i + C_{i+1}}{2} \times (t_{i+1} - t_i) \qquad AUC_t = \frac{C_n}{0{,}693 / t_{1/2}} = \frac{C_n}{k_{el}}$$

Example: Tolbutamide

Effect of CL and V on AUC



$$CL = \frac{dose}{AUC}$$

$$t_{1/2} = \frac{0.693}{k_e}$$

$$V = \frac{CL}{k_e}$$

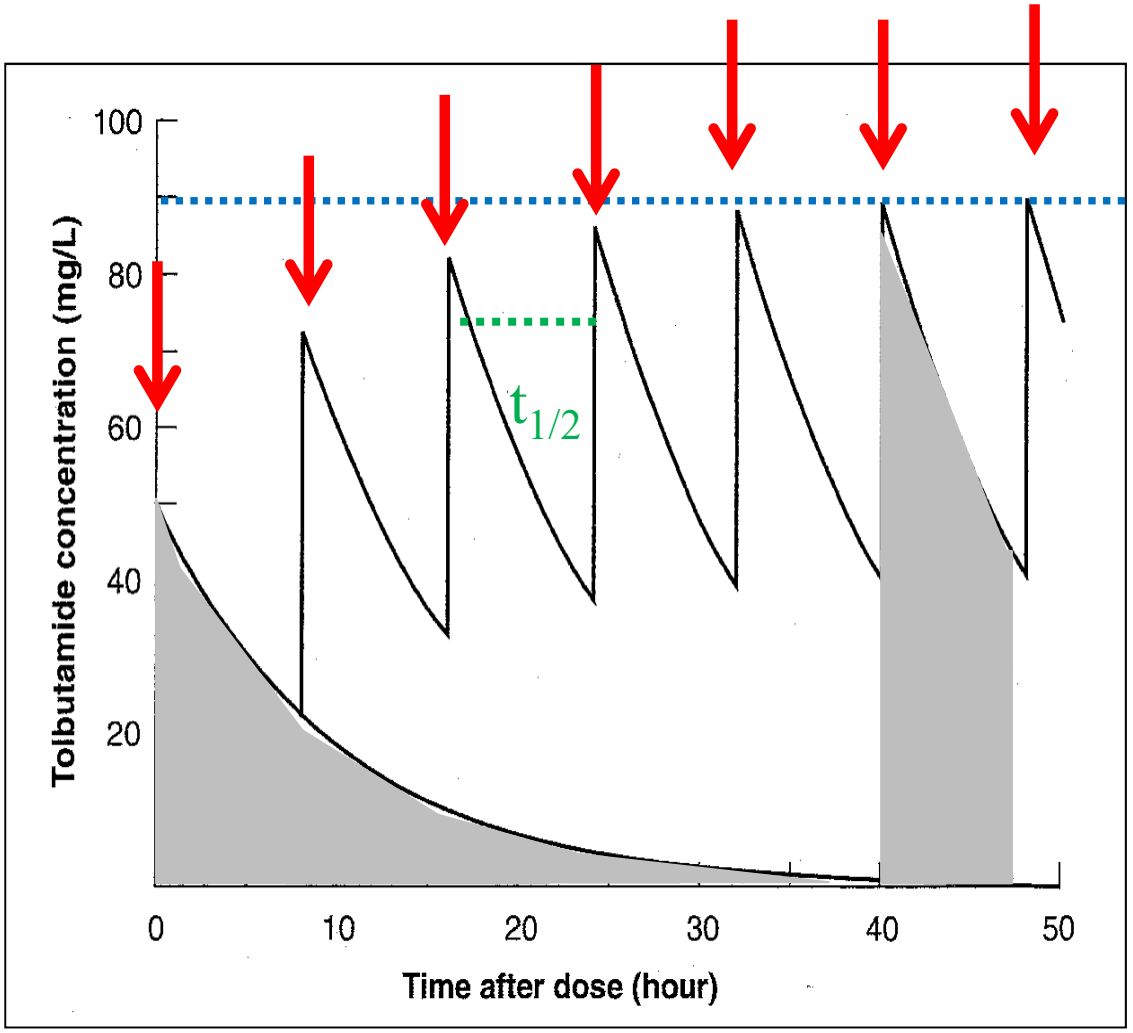
Single dose of 500 mg

Determining AUC during multiple dosing

2. *Multiple dose studies* : At steady state during multiple dosing, **by definition one dose of the drug is eliminated over one dosage interval**. The AUC to infinite time after a single dose (one dose eliminated) must therefore be the same as the AUC under a dosage interval at steady state (one dose eliminated over the dosage interval) provided that the CL has not changed.

- Dosage interval is given by $t_{1/2}$.
- **When this relationship does not hold, it indicates that CL has changed due to non-linear or time dependent PK behaviour of the drug**.

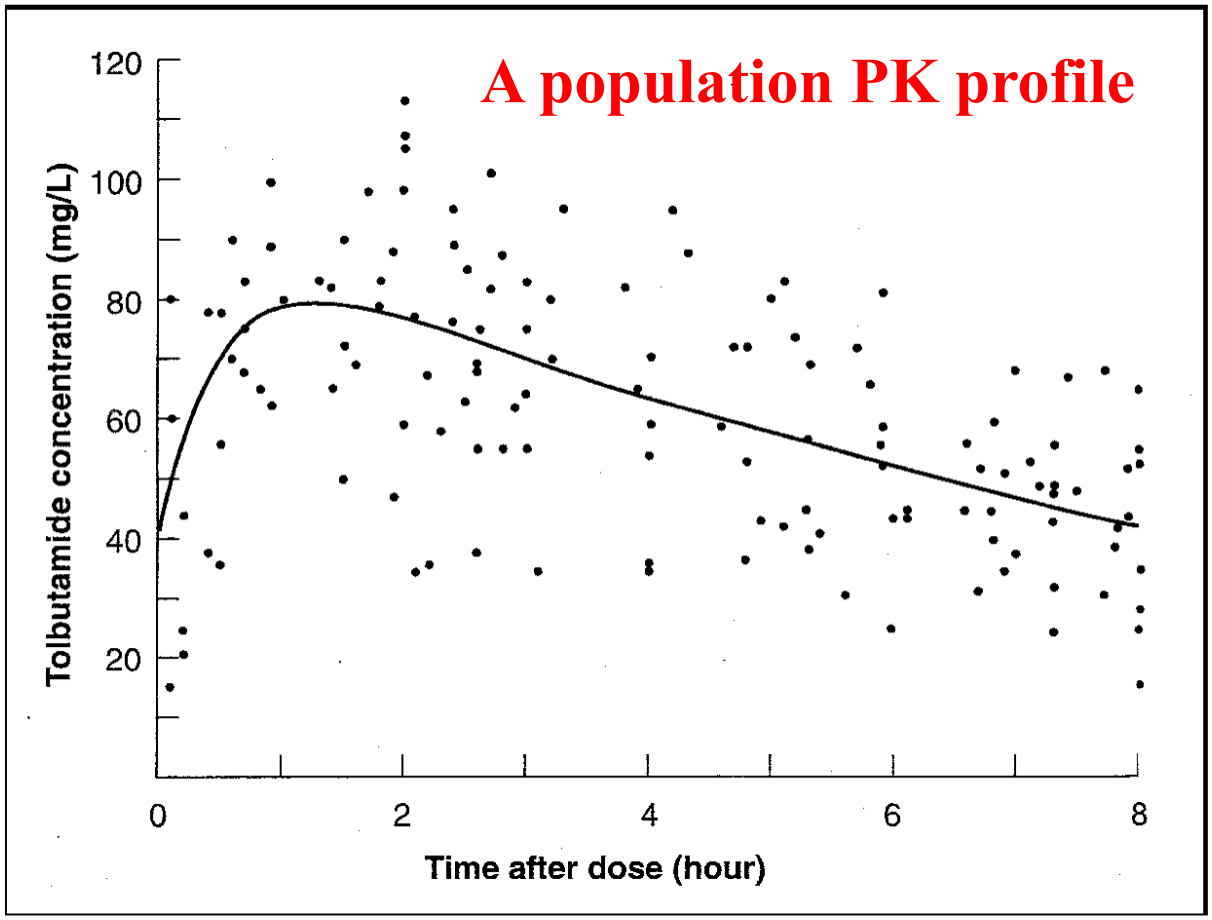
Example: Tolbutamide



The $AUC_{0-\infty}$ after a single dose is the same as the AUC over a dosage interval at steady state unless there are non-linear or time dependent kinetics.

Multiple dosing of 500 mg 8 hourly

Determining the PK parameters of a drug directly in the patient population – population pharmacokinetics



One dosage of the multiple steady-state situation

Multiple dosing of 500 mg 8 hourly

Determining the PK parameters of a drug directly in the patient population – population pharmacokinetics

- The **Standard Two-Stage (STS) Approach** involves intensive sampling to determine individual pharmacokinetic parameters (First Stage), and then using statistical methods to make inferences about the population (Second Stage).

⇒ very cost-intensive

- The **Population Pharmacokinetic Approach** treats the population as the unit of analysis and uses sparse sampling methods to determine the pharmacokinetic parameters. The basic pharmacokinetic parameters, and demographic and physiological and pathophysiological variables that affect them, are determined in a one-stage analysis using Non-Linear Mixed Effects Modelling (**NONMEM**).

The NONMEM Approach

Programs available, which are using a 'mixed-effects' model describes the data in terms of two types effects:

The **fixed effect parameters** include :

- population average values of PK parameters (CL, V, k_e).
- parameters that may cause variation in the PK parameters (age, weight, gender, renal or hepatic disease, smoking, alcohol intake, and other drug therapy)

The **random effect parameters** include :

- residual intersubject variability due to parameters not included
- residual intrasubject and other variability including random fluctuations in an individual's parameter values from time to time, measurement error and all sources of error not accounted for.

The NONMEM Approach

Example of vancomycin in neonates (Seal *et al*., 1994) :

$$CL(L/hour) = 0.0626 \quad WT \quad 0.455^{Z1} \quad 0.656^{Z2}$$

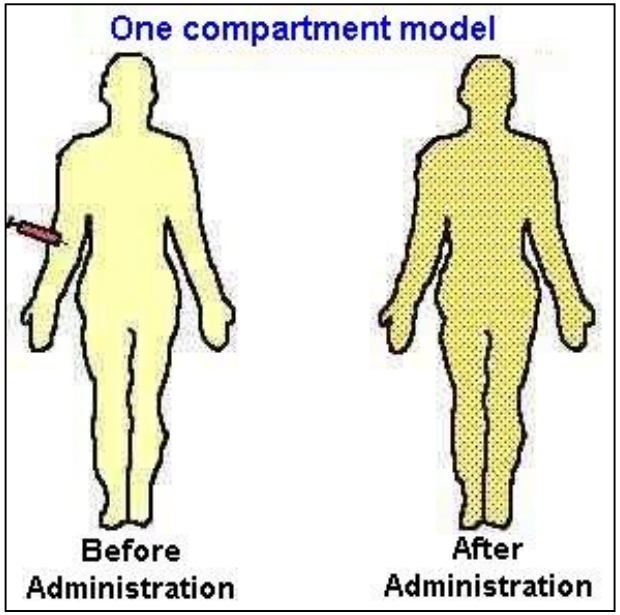
$$V(L) = 0.496 \quad WT$$

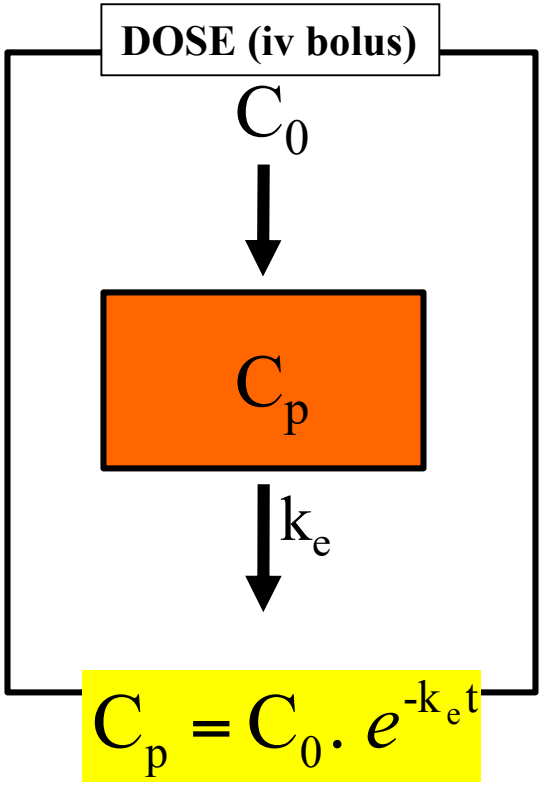
WT is body weight in kg
Z1 = 1 if exposed to dopamine, else Z1 = 0
Z2 = 1 if gestational age < 32 weeks, else Z2 = 0

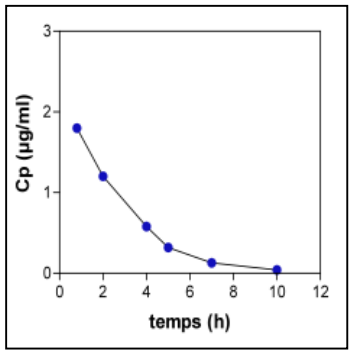
TP Exercise 1 : Administration i.v. bolus

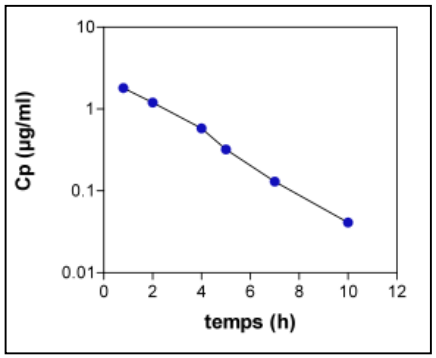
Question : With a dose of 37.5 mg (and a fraction excreted unchanged of 0.85), what is the half-life, the total clearance, the renal and non-renal clearance and the volume of distribution ?

Time (h)	Cp (µg/ml)
0	---
0.8	1.80
2.0	1.20
4.0	0.58
5.0	0.32
7.0	0.13
10.0	0.041





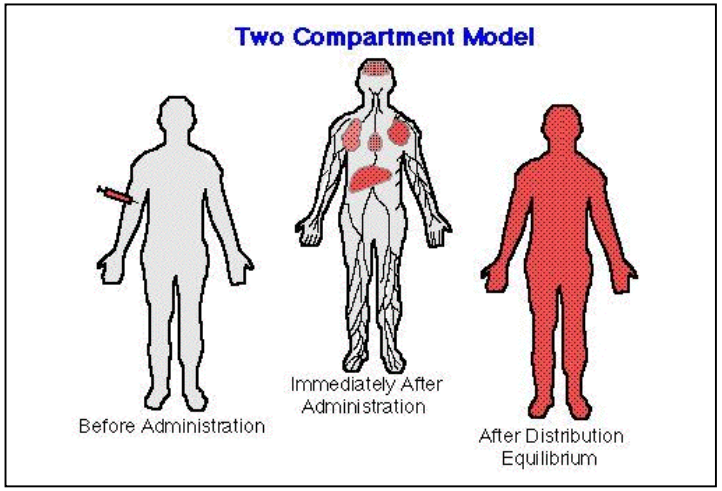


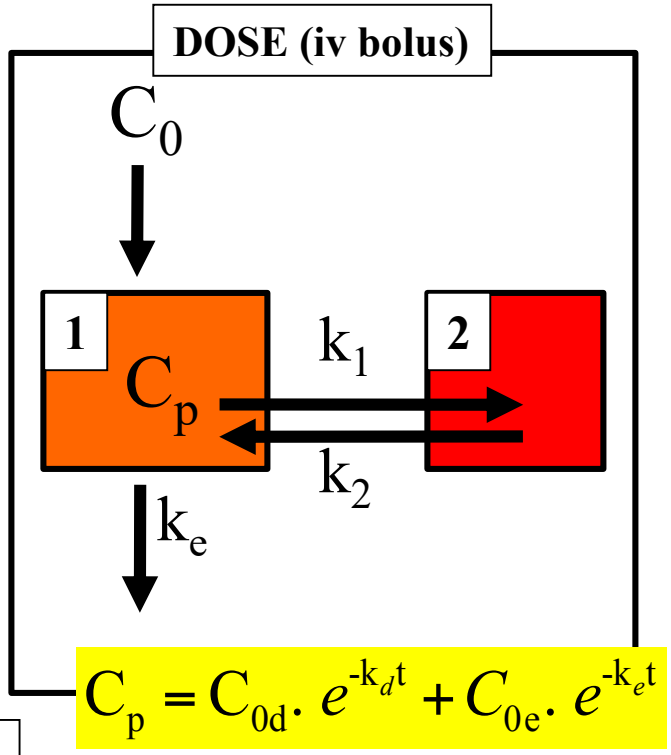


TP Exercise 2 : Administration i.v. 2 phases

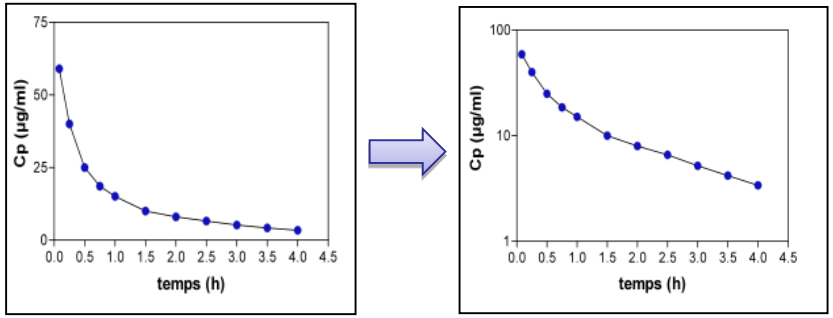
Question : With a dose of 500 mg, what is the half-life, the total clearance, and the volume of distribution ?

Time (h)	Cp (µg/ml)
0	---
0.083	59.0
0.25	40.0
0.50	25.0
0.75	18.6
1.0	15.1
1.5	10.0
2.0	8.0
2.5	6.6
3.0	5.2
3.5	4.2
4.0	3.4





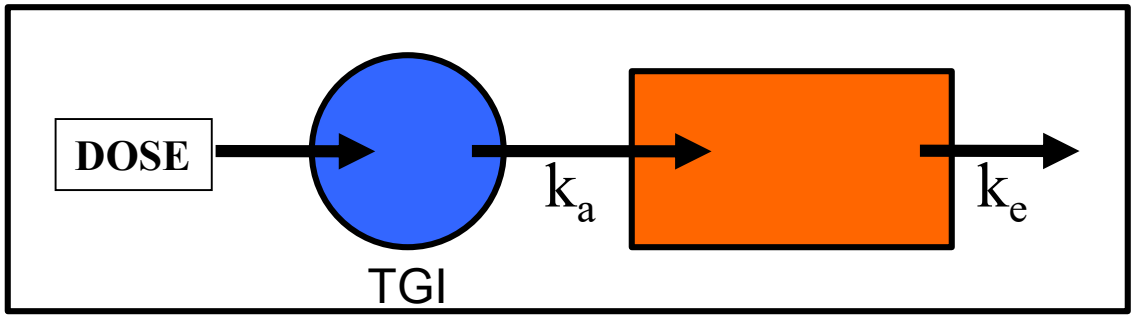
$$C_p = C_{0d} \cdot e^{-k_d t} + C_{0e} \cdot e^{-k_e t}$$



TP Exercise 3 : oral dose 2 phases

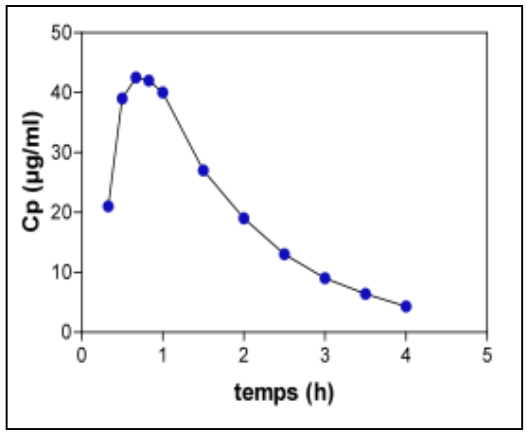
Question : With a dose of 500 mg and a bioavailability of 0.9, what is the half-life, the total clearance, and the volume of distribution ?

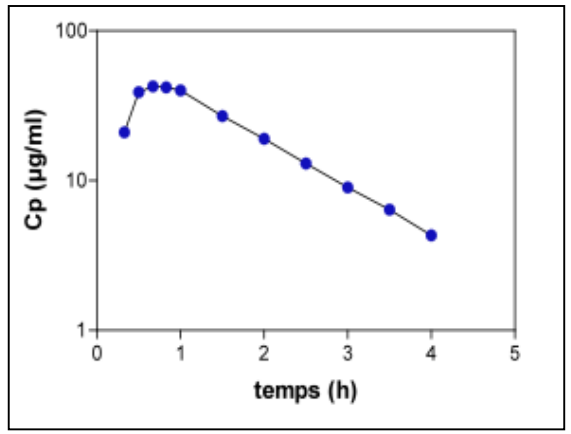
temps (h)	Cp (µg/ml)
0	0
0.25	ND
0.33	21.0
0.50	39.0
0.67	42.5
0.83	42.0
1.0	40.0
1.5	27.0
2.0	19.0
2.5	13.0
3.0	9.0
3.5	6.4
4.0	4.3



$$C_p = A \times \left(e^{-k_e t} - e^{-k_a t} \right)$$

$$A = \frac{k_a \cdot F \cdot DOSE}{V\left(k_a - k_e\right)}$$

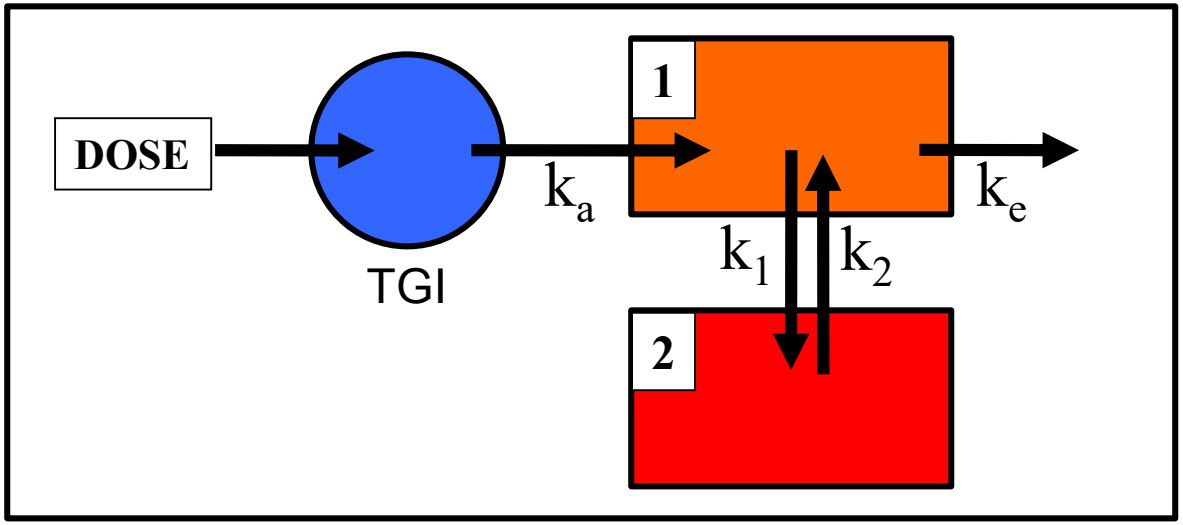


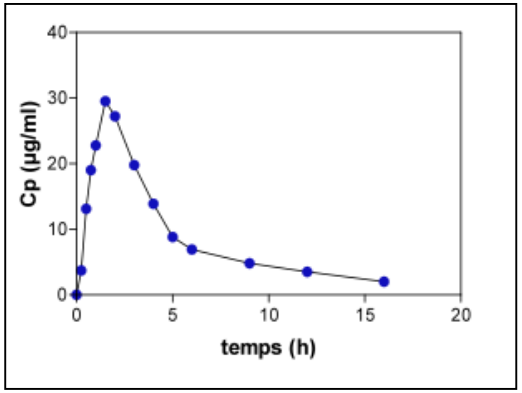


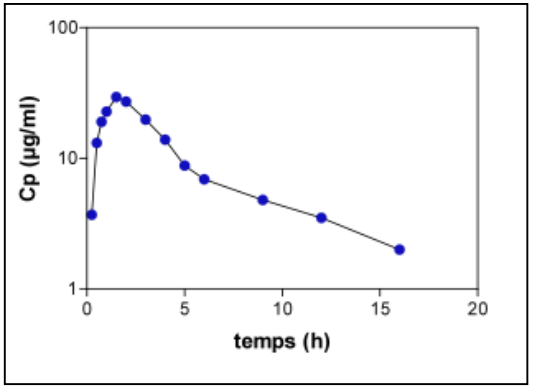
TP Exercise 4 : oral dose 3 phases

Question : With a dose of 100 mg, what is the half-life, the total clearance, and the volume of distribution ?

Time (h)	Cp (µg/ml)
0	0
0.25	3.7
0.50	13.1
0.75	19.0
1.0	22.8
1.5	29.5
2.0	27.2
3.0	19.8
4.0	13.9
5.0	8.8
6.0	6.9
9.0	4.8
12.0	3.5
16.0	2.0



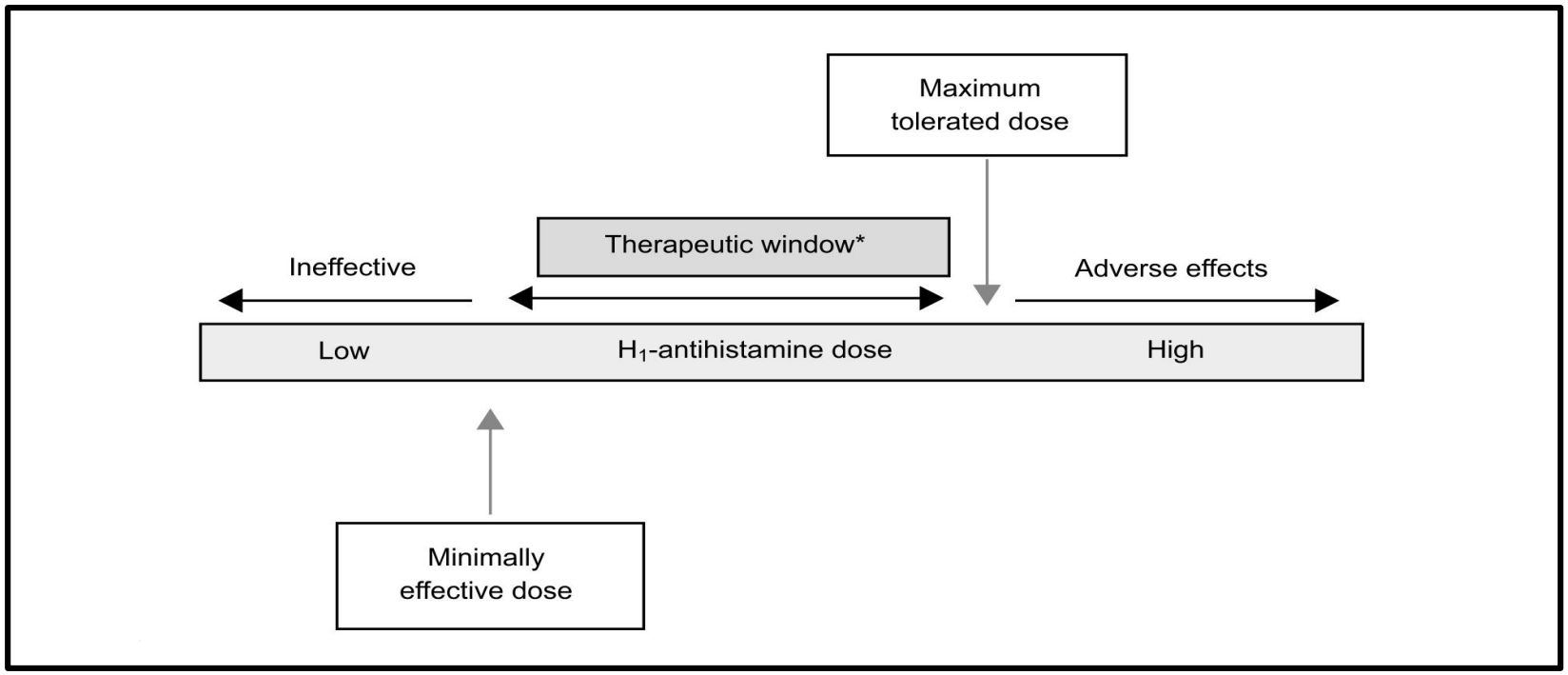




5.2. Designing dose regimens

The therapeutic window

Le comportement pharmacocinétique du PA avec son activité pharmacodynamique/toxique vont déterminer la dose qui doit être administrée pour obtenir un effet thérapeutique.



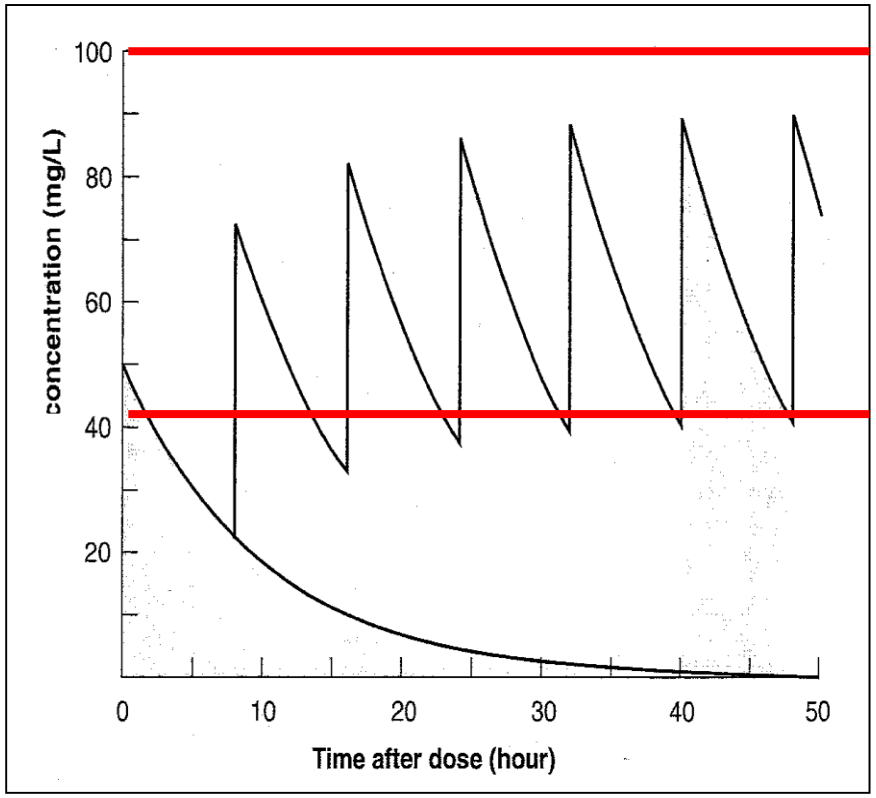
The therapeutic window : examples

Drug	Disease	Therapeutic Window (mg/liter)	Therapeutic Window (micromolar)
Acetazolamide	Glaucoma	10–30	50–150
Amikacin	Gram-negative infection	12–25[a]	—
Digitoxin	Cardiac dysfunction	0.01–0.02	0.013–0.026
Digoxin	Cardiac dysfunction	0.0006–0.002	0.0008–0.003
Ethosuximide	Epilepsy	25–75	180–540
Gentamicin	Gram-negative infection	4–12[a]	7–21
Kanamycin	Gram-negative infection	12–25[a]	25–50
Lidocaine	Ventricular arrhythmias	1–6	4–25
Lithium	Manic and recurrent depression	—	0.4–1.4[b]
Nortriptyline	Endogenous depression	0.05–0.15	0.2–0.6
Phenobarbital	Epilepsy	10–30	40–120
Phenytoin	Epilepsy	10–20	30–60
	Ventricular arrhythmias	10–20	30–60
Procainamide	Ventricular arrhythmias	4–8	17–34
Propranolol	Angina	0.02–0.2	0.08–0.8
Salicylic Acid	Aches and pains	20–100	150–750
	Rheumatoid arthritis	100–300	750–2200
	Rheumatic fever	250–400	1800–3000
Theophylline	Asthma and chronic obstructive airway diseases	6–20	33–100
Tobramycin	Gram-negative infection	4–12[a]	35–120
Warfarin	Thromboembolic diseases	1–4	3–13
Vancomycin	Penicillin-resistant infection	5–15[c]	3.3–10

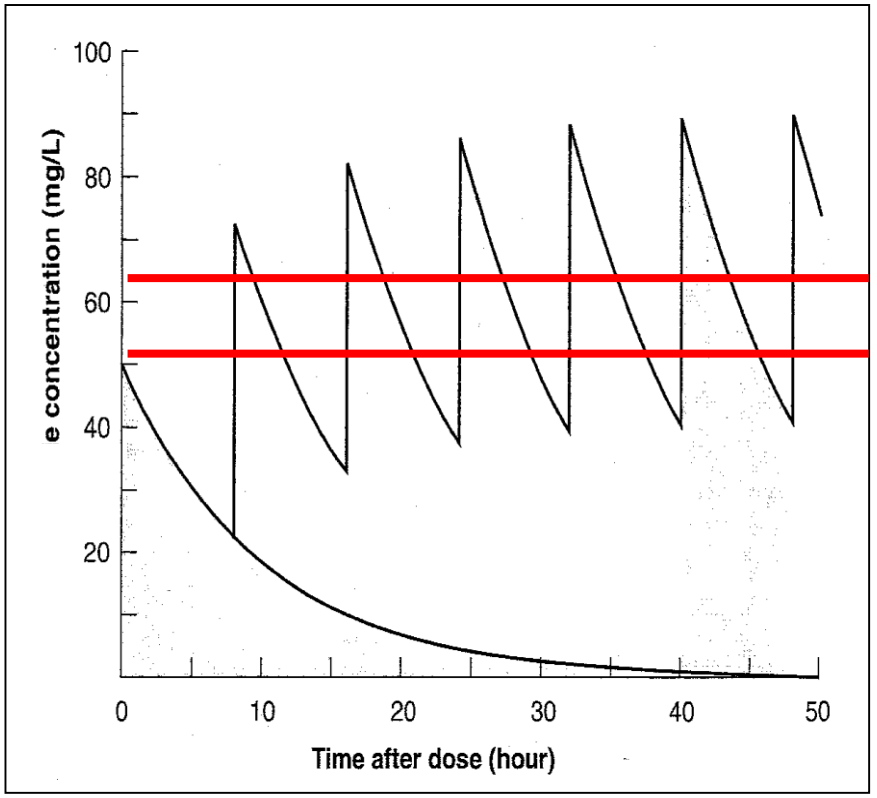
[a]Thirty minutes after a 30-minute infusion.
[b]Milliequivalents/liter.
[c]Sample obtained just before next dose.

The therapeutic window: Importance

Broad window

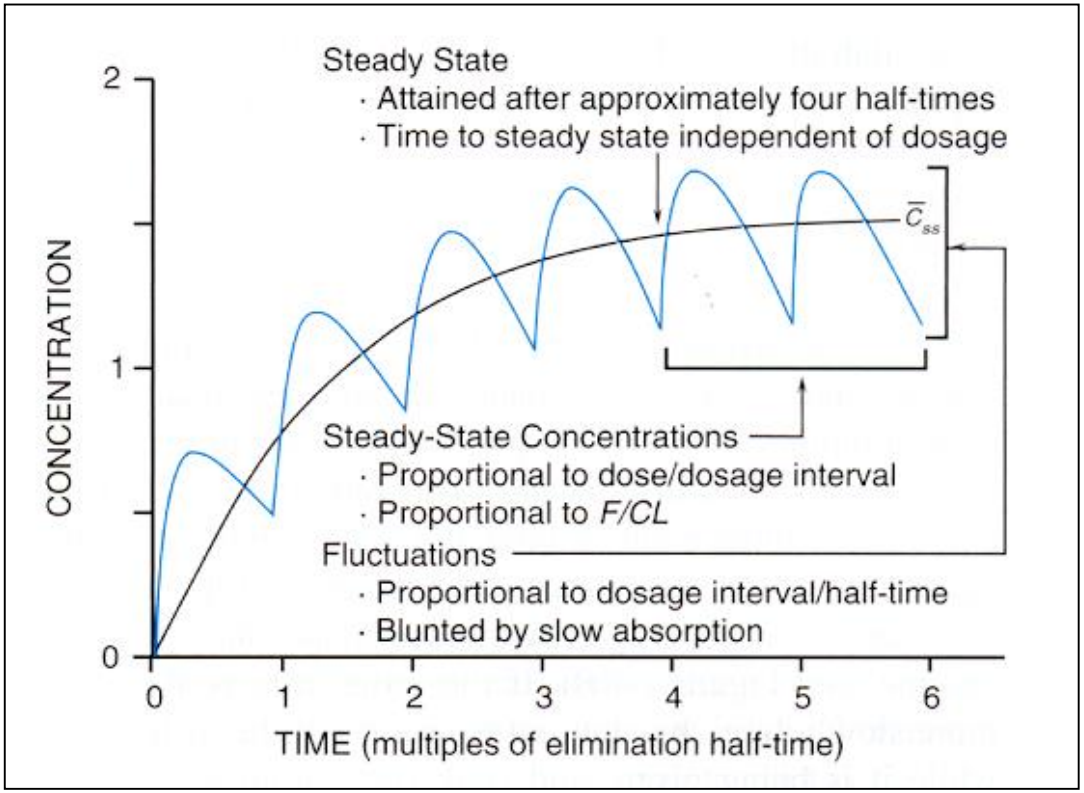


Narrow window



Multiple dosing of 500 mg 8 hourly

The therapeutic window : Steady state



input rate = elimination rate

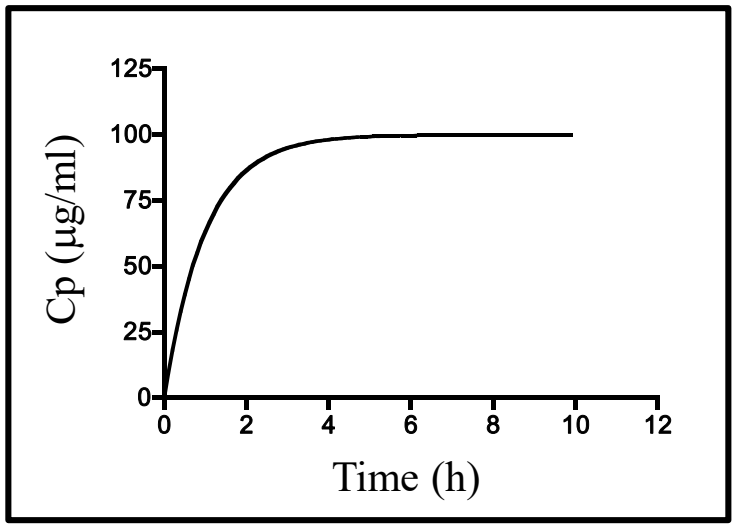
TIME (in half-lives)	percent of plateau
0.5	29
1	50
2	75
3	88
3.3	90
4	94
5	97
6	98
7	99

- The time to reach steady state is determined by the half-life (3-5 half-lives).
- After a change in dose rate it takes 3-5 half-lives to reach the new steady state.

Continuous i.v. infusion

infusion rate = elimination rate

$$k_0 = CL \times C_{ss} \quad \Rightarrow \quad C_{ss} = \frac{k_0}{CL}$$



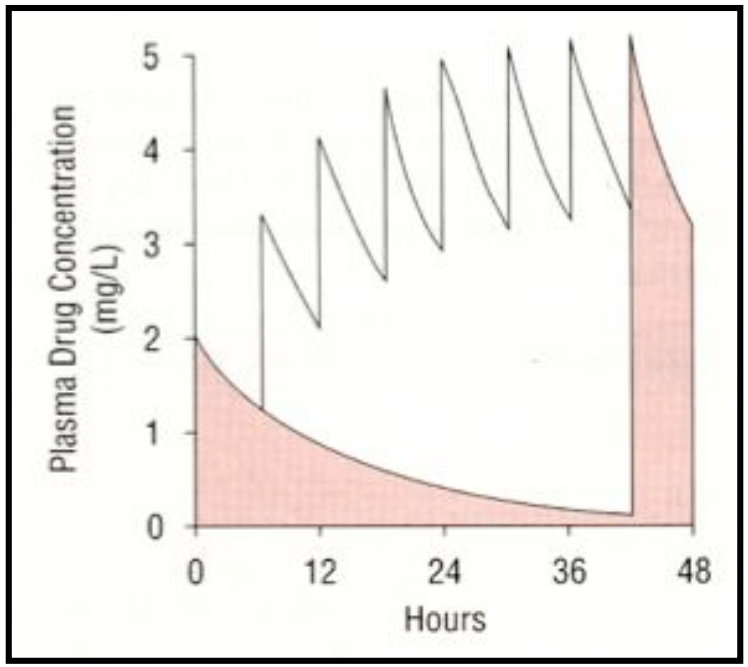
k_0: infusion rate
C_{ss}: steady-state concentration
CL: total clearance

- During constant dosing, the steady state drug concentration is determined only by dose rate and clearance.

Repeated i.v. bolus injections

administration rate = elimination rate

$$\frac{D_M^{iv}}{tau} = CL \times \overline{C_{ss}} \quad \Rightarrow \quad \overline{C_{ss}} = \frac{D_M^{iv}}{tau.CL}$$



D_M^{iv} : dose quantity

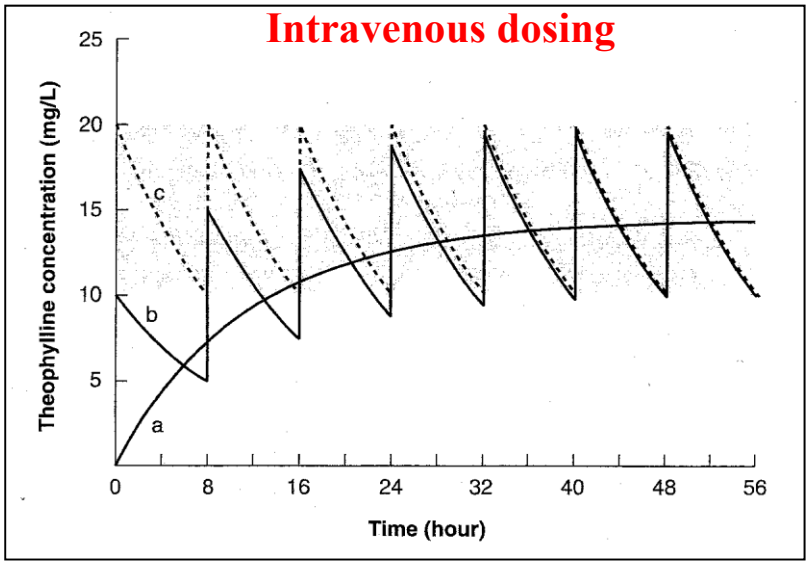
τ : dosage interval

$\overline{C_{ss}}$: time averaged steady-state concentration

CL: total clearance

Repeated i.v. bolus injections

$$\text{target concentration } (C_{SS}) = \frac{\text{maintenance dose rate}}{CL}$$



loading dose = V target plasma concentration

- With intermittent dosing, a dosing interval of the half-life of the drug produces about a two-fold fluctuation in drug concentration over the dosing interval.

The therapeutical index

•The therapeutical index or therapeutical ratio is a comparison of the drug amount needed for a therapeutic action to the amount causing toxicity

•In animal studies:

Therapeutic index = $\frac{LD_{50}}{ED_{50}}$,

LD_{50} dose at which 50 % of the treated animals dies (Lethal Dose)

ED_{50} dose at which 50 % of the animals are cured (Effective Dose)

•In human studies:

Therapeutic index = $\frac{TD_{50}}{ED_{50}}$,

TD_{50} dose at which 50 % of the humans show poison related symthomes (Toxic Dose)

ED_{50} dose at which 50 % of the humans are cured (Effective Dose)

• Toxicity limiting in human studies

Effects of varying the dose interval

(1) A **dosing interval of about a half-life** is appropriate for **drugs with half-lives of approximately 8-24 hours** allowing dosing once, twice, or three times daily.

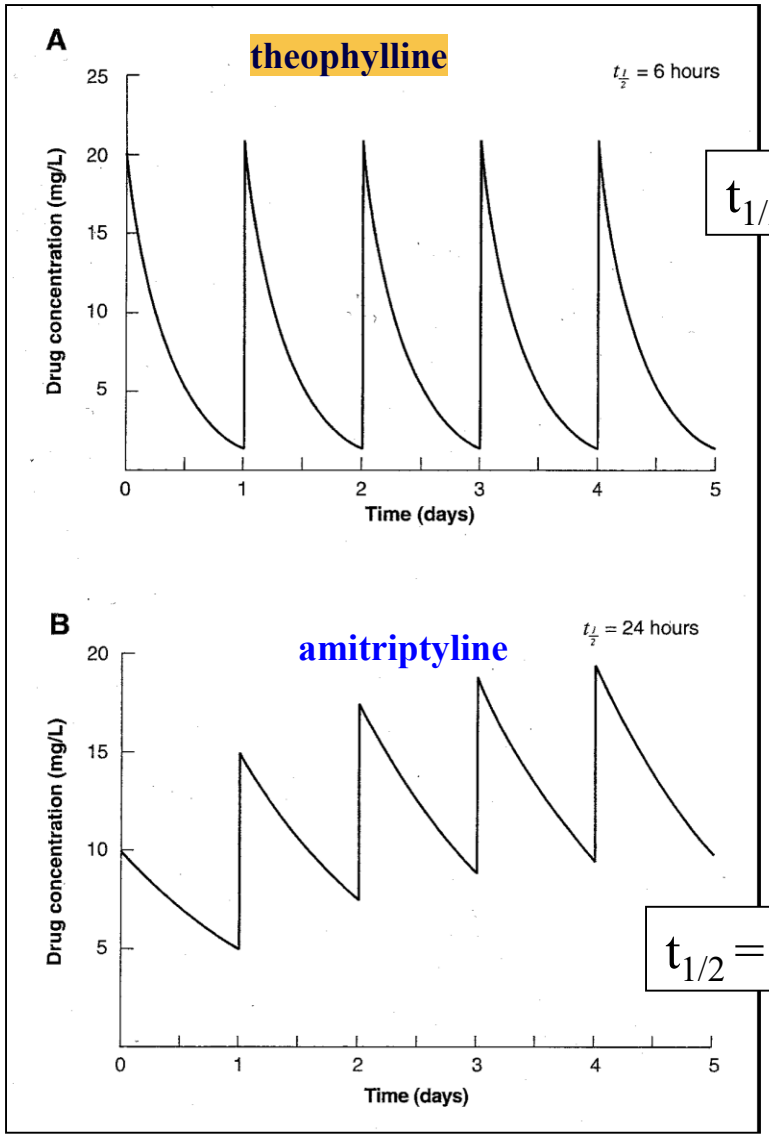
(2) It is usually **not practicable** to administer **drugs with shorter half-lives** more frequently as compliance with therapy becomes poor with dosing regimens involving complicated and frequent dosing.

(3) If a **drug with a short half-life** has a **high therapeutic index**, it can be given at **intervals longer than the half-life**.

(4) If a **drug with a short half-life** has a **low therapeutic index** (and low plasma concentrations), it needs to be maintained in a narrow therapeutic range, and the use of a **sustained release formulation** will be necessary.

(5) For **drugs with very long half-life**, **once daily administration** may still be appropriate and convenient. The fluctuation over the dosing interval will be small, but it should be remembered that it will still take 3-5 half-lives to reach steady state.

Effects of varying the dose interval

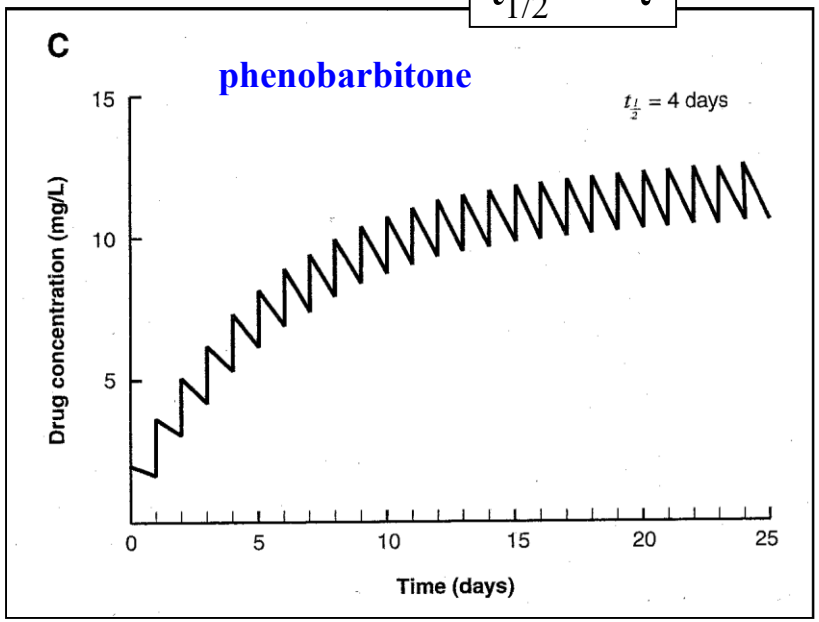


$t_{1/2} < \tau$

$t_{1/2} = \tau = 24h$

Effect of half-life on the fluctuation in plasma drug concentration over the dosing interval.

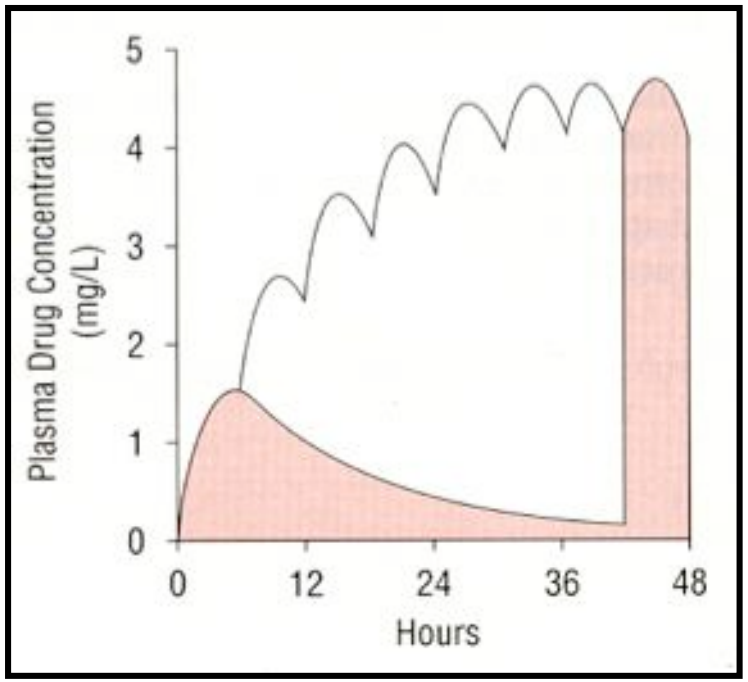
$t_{1/2} >> \tau$



Repeated oral administration

Administration rate = elimination rate

$$\frac{F \times D_M^{oral}}{tau} = \overline{C_{ss}} \times CL \quad \Rightarrow \quad \overline{C_{ss}} = \frac{F \times D_M^{oral}}{tau \times CL}$$



D_M^{oral} : dose quantity

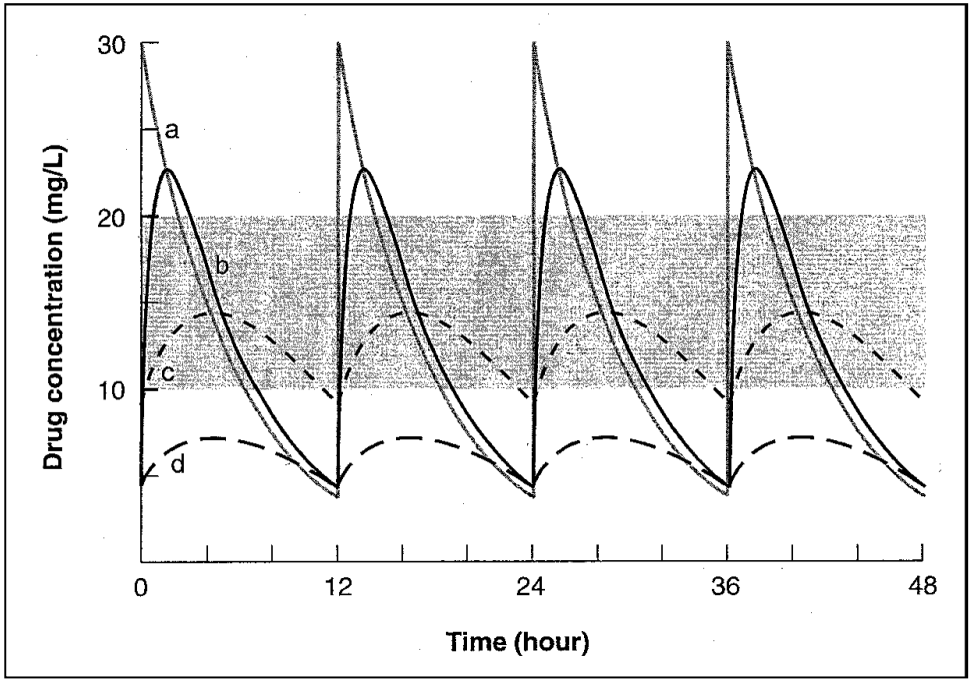
τ : dosage interval

$\overline{C_{ss}}$: time averaged steady-state concentration

CL : total clearance

F : Bioavailability

Oral dosing



Effect of absorption rate and bioavailability on the plasma drug concentration – time profile over the dose interval

- Oral sustained release formulations may be appropriate for drugs with short half-lives and narrow therapeutic indices.
- During oral dosing, the degree of plasma concentration fluctuation over the dosing interval is determined by the absorption rate and by the relationship of the dosing interval to the half-life.

Oral dosing

The principle applying to intermittent intravenous dosing also apply to oral dosing with **two difference** :

- The **slower absorption** of oral doses '**smooths' the plasma concentration** profile so that fluctuation over the dosing interval is less than with iv bolus dosing. This effect is **exaggerated with sustained release formulations**, **allowing less frequent administration for drugs with short half-lives**.
- The dose reaching the systemic circulation is affected by the **bioavailability** so that at steady state :

$$\text{target concentration } (C_{SS}) = \frac{F \quad \text{oral dose rate}}{CL}$$

$$\text{oral dose rate} = \frac{\text{intravenous dose rate}}{F}$$

F of theophylline is close to 1 => iv and oral dose rates are about the same.

F of morphine is 0.2 => oral dose rates are about 5 times iv dose rates.

TP: Determination of an oral loading dose

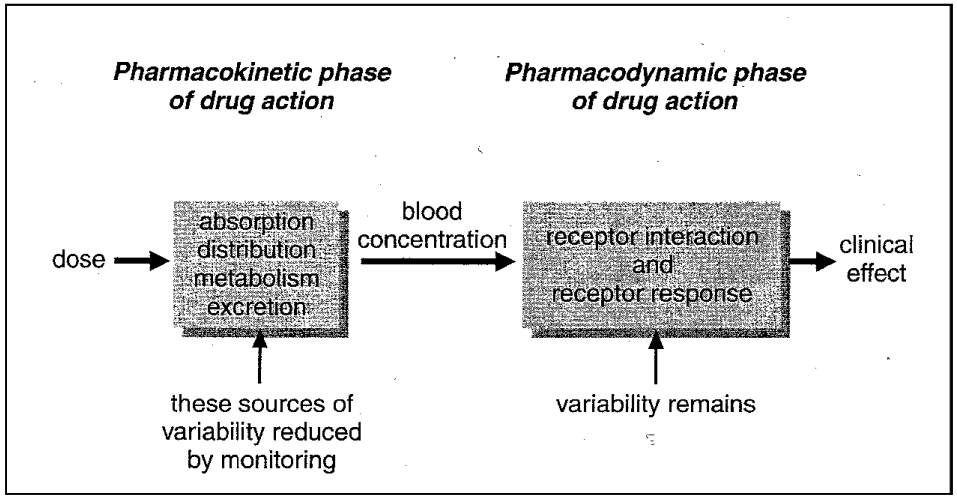
Phenobarbital, an anti-epileptic medication

time between the doses	T	24 h
Steady-state concentration	Css	10-30 mg/L
Fraction being absorbed	fa	1
Volume of distribution	V	0.54L/kg
Clearance	CL	0.062 ml/(min kg)
Weight of the patient		**70 kg**
Maintainance dose?		
Loading dose?		

5.3. Therapeutic drug monitoring

What is therapeutic drug monitoring ?

Therapeutic drug monitoring refers to the individualisation of dosage by maintaining plasma or blood drug concentrations within a target range.



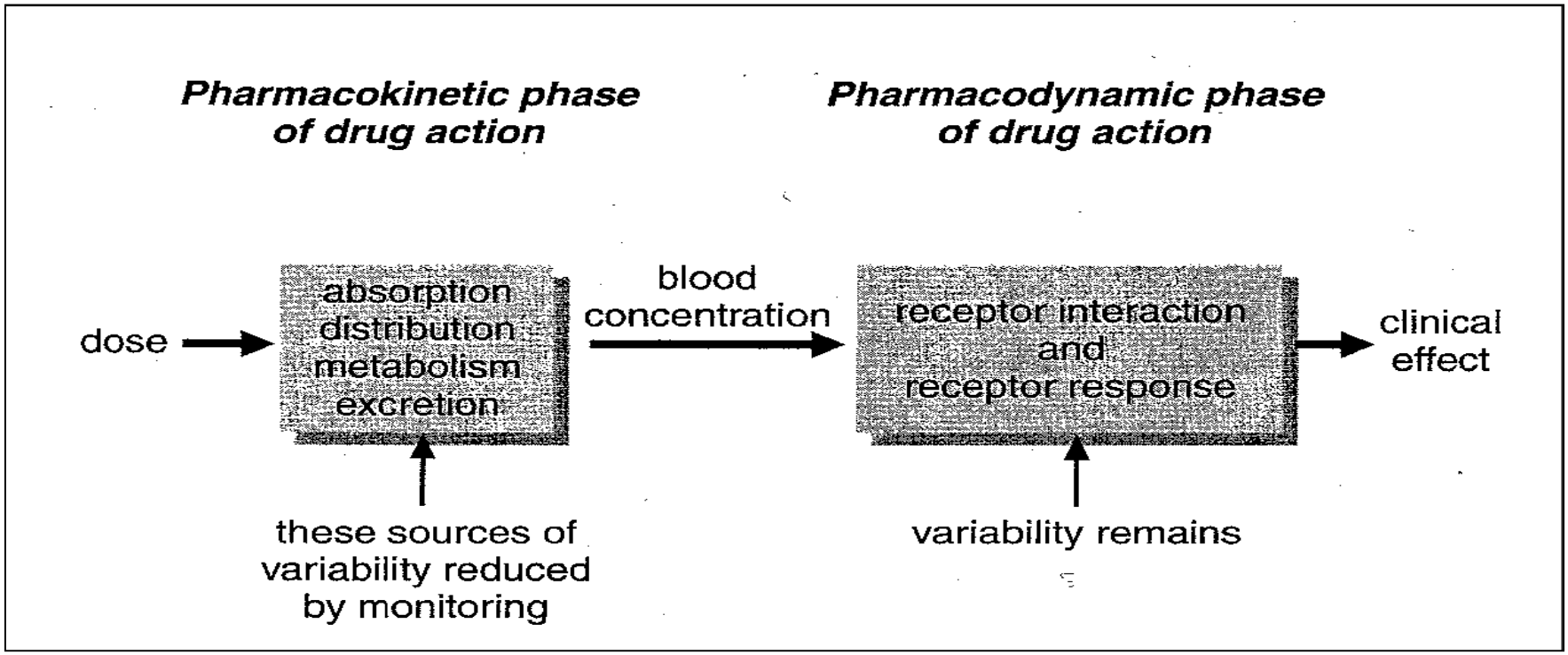
Major sources of PK variability

Compliance
Age — neonates, children, elderly
Physiology — gender, pregnancy
Disease — hepatic, renal, cardiovascular, respiratory
Drug interactions
Environmental influences on drug metabolism
Genetic polymorphisms of drug metabolism

What is therapeutic drug monitoring ?

- Therapeutic drug montiors the drug plasma concentration
- Adjusting dose to a target concentration range reduces variability in the pharmacokinetic phase of drug action.

⇒ optimizing the PK parameter



For which drug is monitoring helpful ?

The characteristics of drugs which make therapeutic drug monitoring useful are :

- marked PK variability
- therapeutic and adverse effects related to drug concentration
- narrow therapeutic index
- defined therapeutic (target) concentration range
- desired therapeutic effect difficult to monitor.

When is therapeutic drug monitoring used?

Therapeutic drug monitoring is used in 2 major situations :

- drugs used prophylactically to maintain the *absence* of a condition such as seizures, cardiac arrhythmias, depressive or manic episodes, asthma relapses or organ rejection
- to avoid serious toxicity as with the aminoglycoside antibiotics which, unlike most antibiotics, have a narrow therapeutic range.

Important in therapeutic drug monitoring:

1. Assay methods
2. Sample collection
3. Timing of samples

Sampling and drug analysis

1. *Assay methods*: **Drug assay methods should have adequate sensitivity**, **be specific for the drug** to be measured and have appropriate accuracy and precision (e.g. automated immunoassay, HPLC, GLC, etc.).
2. *Sample collection*: **Usually, plasma** or serum is used for drug assays. **However**, for example with cyclosporin there are large shifts of drug between red cells and plasma with storage and temperature change, so **whole blood is assayed**.
3. *Timing of samples*: **The correct time of sampling is important**. Drug concentrations vary over the dosing interval and with the duration of dosing in relation to achieving a steady state. This is unlike most physiological parameters, such as serum creatinine or serum sodium, which change relatively slowly.

What information is required for interpretation ?

Time of sample in relation to last dose
Duration of treatment with the current dose
Dosing schedule
Age, gender of patient
Other drug therapy
Relevant disease states particularly renal and hepatic
Reason for request — for example, lack of effect, routine monitoring, suspected toxicity

- Adequate information about the sample and the patient are required to interpret drug concentrations.

Difficult interpretation when :

- *Protein binding*
- *Active metabolites*

Drugs commonly monitored

Drug	*Therapeutic range (mg/L)*
Digoxin	0.5–2.0 (microgram/L)
Amiodarone	1.0–2.5
Lignocaine	2.0–5.0
Quinidine	2.0–5.0
Flecainide	0.2–0.9
Mexilitine	0.5–2.5
Salicylate	150–300
Perhexiline	0.15–0.6
Theophylline	10–20
Phenytoin	10–20
Carbamazepine	5–12
Sodium valproate	50–100
Phenobarbitone	15–40
Gentamicin, tobramycin, netilmicin	trough < 2; peak > 8[1]
Amikacin	trough < 8; peak > 32[1]
Vancomycin	trough 5–15; peak 25–40
Lithium	0.4–0.8 (mmol/L)

5.4. Pharmacokinetics of particular drugs

1. Paracetamol

- widely used against fever and pain
- Well absorbed in the GI tract
- Oral and rectal administration
- Dose-dependent oral bioavailability
- Homogenous distribution
- Effect due to small fraction entering the brain
- Binds up to 20 % to plasma protein
- Essentially metabolized (toxic metabolites?)
- Problems for hepatic failure patients

Oral bioavailability (F)	70%-90%
Rectal bioavailability	30%-70%
Clearance (CL)	20 L/h
Volume of distribution (Vd)	65 L
Half-life (t1/2)	2.5 h

2. Aspirin

Aspirin:

- Against mild to moderate pain, inflammation, and fever
- also an antiplatelet againt to prevent mycocardical infections or strokes
- Oral administration
- Fast absorption from stomach/intestin by passive diffusion
- Prodrug -> transformed into salicylate

Acetylsalicylate PK parameters

Oral bioavailability (F)	68%
Clearance (CL)	39 L/h
Volume of distribution (Vd)	10.5 L
Half-life (t1/2)	0.25 h

2. Aspirin

Aspirin:

- Prodrug -> transformed into salicylate
- Acetylsalicylate: antipatelet-aggregating effect
- Salicylate: anti-pain, anti-fever effect
- Acetylsalicyate: short half-life

Acetylsalicylate PK parameters

Oral bioavailability (F)	68%
Clearance (CL)	39 L/h
Volume of distribution (Vd)	10.5 L
Half-life (t1/2)	0.25 h

2. Aspirin

Salicylate:

- Rapid distribution
- Mainly metabolized by the liver (saturatable)
- Half-life depends on used clearance pathway
- 10 % Kidney elimination (all 3 processes)
- Urinary excretion is markedly pH-dependent

Salicylate PK parameters

Clearance (CL)	3.6 L/h (may decrease to 0.6 L/h depending on dose)
Volume of distribution (Vd)	11.9 L
Half-life (t1/2)	2h (may increase to 30h depending on dose)

2. Aspirin

Aspirin:

- short half-life -> adminstration every 4h
- Individual variability
- Drug interactions
- Hepatic failure patients

Acetylsalicylate PK parameters

Oral bioavailability (F)	68%
Clearance (CL)	39 L/h
Volume of distribution (Vd)	10.5 L
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Salicylate PK parameters

Clearance (CL)	3.6 L/h (may decrease to 0.6 L/h depending on dose)
Volume of distribution (Vd)	11.9 L
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3. Theophylline

Oral bioavailability (F)	96%
Clearance CL)	3 L/h
Volume of distribution (Vd)	35 L
Half-life (t1/2)	8 h

- reversible airway obstruction due to chronic asthma or chronic bronchitis
- Oral administration as rapid-release tablet or as liquid solution (well absorbed) or as controlled-release preparations (more variable absorption)
- Rapid distribution into fat-free tissues
- 40% bound to plasma proteins (albumin)
- Mainly hepatic elimination

3. Theophylline

- narrow therapeutic window
- Drug interactions/competitions
- Clearance dependent on many factors
- Intra- and inter-individual PK variability
- Drug monitoring

Clearance depends on
Age: neonats, elderly ↓ first life decade ↑
Cirrhosis ↓
Congestive heart failure ↓
Smoking ↓
Nutritional factors

Induction of theophylline metabolism by	Inhibition of theophylline metabolism by	
Phenobarbital	Cimetidine	Propanolol
Phenytoin	Ciprofloxacin	Erythomycin
Rifampicin	Disulfuram	Fluvoxamine
Hydrocarbons (smoke)	Oral contraceptives	

4. Digoxin

- used in several cardiac pathologies
- Well absorbed in the GI tract
- Metabolization in the GI in some patient
- No massive first pass effect
- High bioavailability
- Large volume of distribution
- Distinct distribution phase (2-Component model); lasts 6-8 h
- 20-30 % bound to plasma proteins

Oral bioavailability (F)	70%
Clearance (CL)	6 L/h
Volume of distribution (Vd)	400 L
Half-life (t1/2)	40 h

4. Digoxin

- mostly renal clearance (filtration, secretion)
- Clearance affected by renal diseases
- Long half-life
- 5-7 days until steady-state (with loading dose)
- Narrow therapeutic window

Oral bioavailability (F)	70%
Clearance (CL)	6 L/h
Volume of distribution (Vd)	400 L
Half-life (t1/2)	40 h