# Basic Concepts of Pharmacokinetics

## Issues to be discussed

- Pharmacokinetics/Pharmacodynamics
- Plasma levels
- Pharmacokinetic models
- 1. order, 0. order, MM order kinetics
- Pharmacokinetic parameters ($Cl_P$, $V_D$, $t_{1/2}$, $k_a$, F)
- Population pharmacokinetic modelling of radioiodine turnover in patients with Graves disease

# Competence-based learning objectives of the chapter

- Students are able to design a pharmacokinetic trial
- Students are able to conduct basic pharmacokinetic analysis of plasma levels
- Students are able to interpret the role of pharmacokinetic parameters
- Students are able to differentiate between linear and nonlinear pharmacokinetics
- Students are able to build a simple pharmacokinetic model
- Students are able to conduct a pharmacokinetic trial with radiopharmaceuticals

# Pharmacokinetics/Pharmacodynamics

- **Pharmacokinetics:**
  **Translolaction of drug molecules around the body by**
  1. **Convectional transfer**
  2. **Diffusional transfer**
- **Biophase (Targets)**
- **Pharmacodynamics:**
  **Interactions of drug molecules with the targets**
  1. **Receptors**
  2. **Enzymes**
  3. **Ion channels**
  4. **Carriers**

## Modeling of Pharmacokinetic/Pharmacodynamic (PK/PD) Relationships

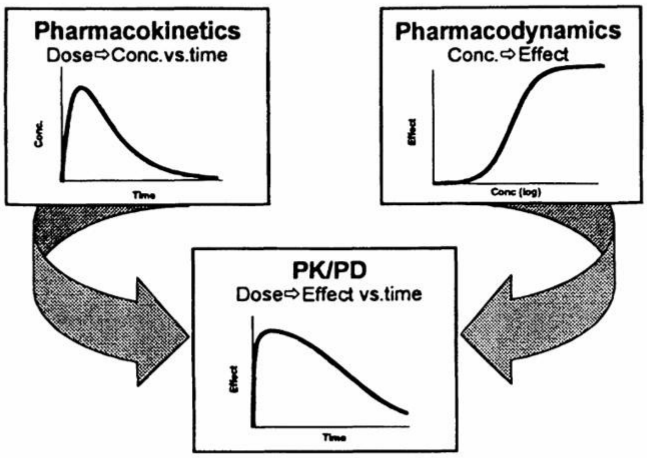



**Fig. 1.** Pharmacokinetic/pharmacodynamic (PK/PD) modeling as combination of the classic pharmacological disciplines pharmacokinetics and pharmacodynamics (modified from (15), reproduced with permission).

**Pharmacokinetic measurements of plasma and urine levels of**

- **the drug and/or**
- **metabolite(s)**

are obtained by an **analytical method** with defined specificity, accuracy, repeatability, sensitivity, linearity, limit of detection, limit of quantification

**Pharmacodynamic measurements of effects such as**

- **haemodynamic**
- **electrocardiogramic**
- **electroencephalogramic**
- **hormones suppression**
- **muscle relaxation**
- **pain rating**
- **natriuresis**

are obtained by different methods which should meet the criteria: objectivity, sensitivity, repeatability, continuity

## Pharmacodynamic (PD) behaviour of a drug is altered by:

- **Pharmacokinetic (PK) processes**

  Systemic: distribution, metabolism, elimination

  Nonsystemic: release, absorption

  Cp-t profile of a parent drug.

  Cp-t profile of active metabolite

- **Biophase distribution**

  The extent and rate depend on the anatomical location of the target tissue, its perfusion rate and its permeability to the drug (metabolite) to reach the receptor

  Kinetics of biophase distribution determinates E-t profile

  Cp-t profile good predictor for E-t profile if distribution is fast

  Cp-t profile poor predictor for E-t profile if redistribution is slow

- **Drug-receptor interaction**

  Sigmoid $E_{max}$ model

- **Transduction processes**

  **Include all biological events following drug-receptor binding**

  **Binding to extracellular receptors**

  **Binding to intracelluar receptors**

  *(i.e., glucocorticoids have to transfer the cell membrane and interact with soluble receptors; the drug-receptor complex then translocates into the nucleus and interferes with the transcription of nuclear DNA or the translation mechanism)*

  **Transduction kinetics can be faster or slower than biophase distribution kinetics**

- **Secondary postreceptor events**

  **Primary, drug induced biological responses occur at the cellular level**

  **Most PD effects are measured (observed) at the level of the organism, i. e. animals, humans**

  *(i.e. a vasoconstrictor agent may shorten the length of a series of cells in arterial muscular level, thereby reducing the vessel diameter and increasing the resistance of the local vascular bed and then increasing systemic vascular resistance; the observed PD effect is elevation in arterial blood pressure)*

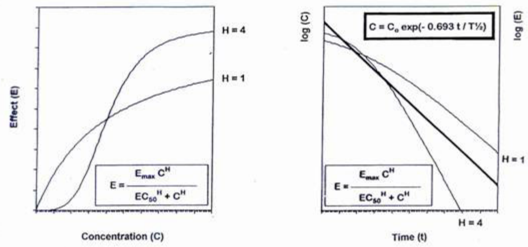



*Fig. 1* Effect-concentration correlation and effect-time correlation. Left: the dependence of effect (E) on concentrations (C) is described by the sigmoid $E_{max}$ model. The higher the Hill coefficient, the more sigmoid is the curve. Right: in the most simple case, the logarithm of concentrations (log C) linearly decreases with time. The logarithm of the effect (log E) will decline with time either slower, in parallel or even faster than logarithms of concentrations depending on the $EC_{50}$ value and Hill coefficient.

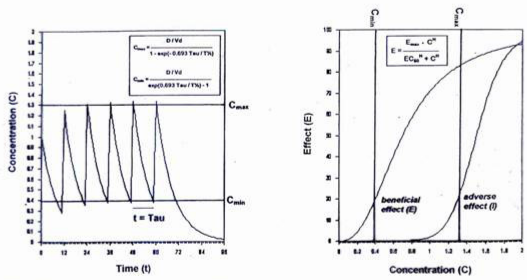
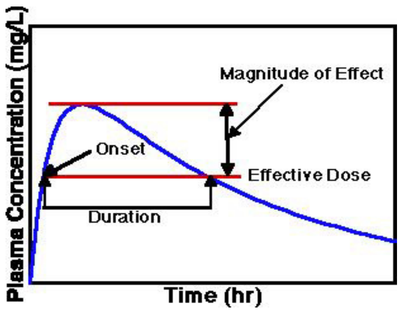
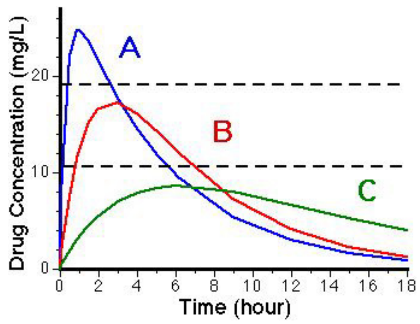



*Fig. 2* Pharmacokinetics and pharmacodynamics. Left: following accumulation kinetics, repetitive dosing leads to peak ($C_{max}$) and trough ($C_{min}$) levels. Right: according to empirical drug use, dosage is adjusted in such a way that the beneficial effect will just occur at troughs ($C_{min}$), but the adverse effect will not yet occur at peaks ($C_{max}$).




Effect as a function of time. From a graph such as this we can see the relationship between drug concentration and drug effect. If a drug has to reach an effective concentration at a target site this will be reflected as a required blood concentration.




Plasma concentration time curves for three theoretical formulations with different $k_a$ values. The plasma concentrations achieved can be controlled by the rate of drug absorption. As shown product A would be toxic. A smaller dose, or a slower formulation should be considered. Formulation B appears to be effective in the dose and formulation used. The dosage form C appears to be too slow and thereby ineffective. If it is a drug requiring a sustained effect this formulation may be more useful at a higher dose or after repeated doses.

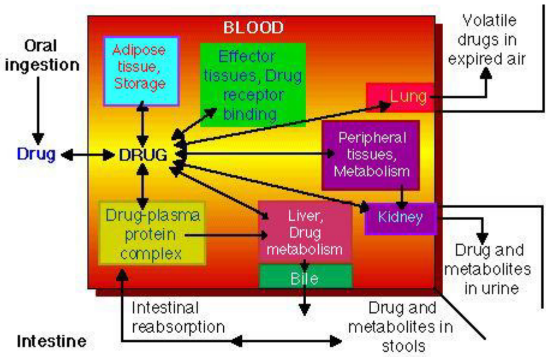
## Pharmacokinetics?

**A young child given an intramuscular injection might ask "How will that 'ouch' get from there to my sore throat"?**

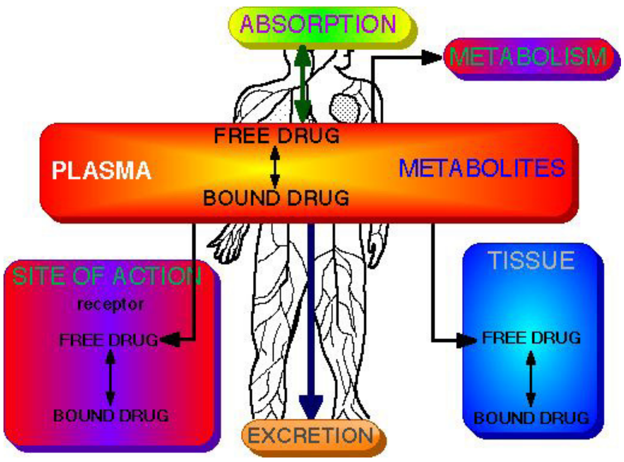
**The answer to this question is the basis of pharmacokinetics.**

**That is, how drugs move around the body, how quickly drugs come to, how long they stay in biophase and how quickly drugs leave the body.**

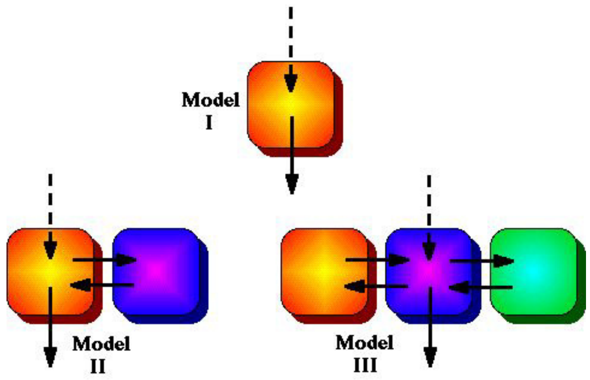
**Many of the technologic and biologic parameters which control the dissolution, absorption, distribution, metabolism, and excretion of drugs will be discussed.**



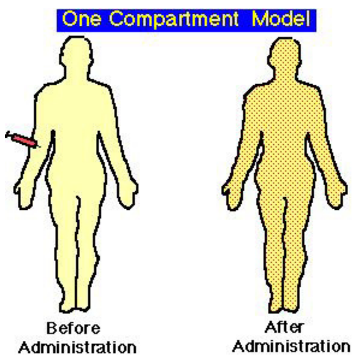

Complex picture of drug interactions in the body. It gives an idea of the complexity of drug disposition. Shown in this picture are many of the steps to getting drug from one site in the body to another. Many of these processes are enzyme induced. However, the overall picture is often much simpler. Many of these processes may be fast or not significant for any given drug.



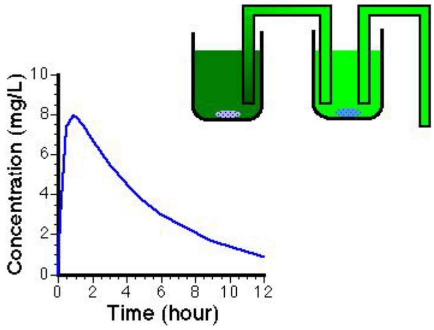

Processes involved in drug transport. Here the major processes are represented in a less physiological fashion. The headings (**A**bsorption, **D**istribution, **M**etabolism, and **E**xcretion**)** are important.



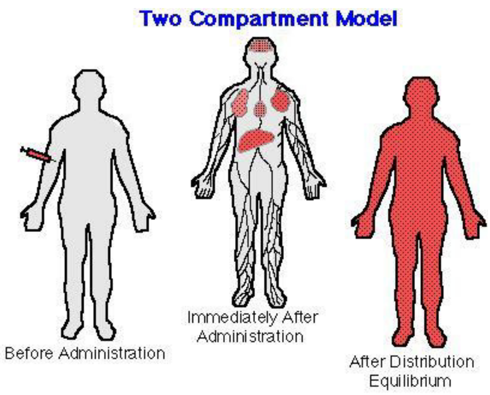

One, two, and three compartment pharmacokinetic models. Fortunately many of the processes involved in drug movement around the body are not saturated at normal therapeutic dose levels. The body may even be represented as a single compartment or container for some drugs. For other drugs a two or three compartment model is found to be necessary.



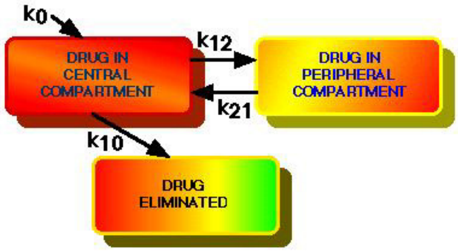

Body before and after a rapid intravenous injection, considering the body to behave as a single compartment. In order to simplify the mathematics it is often possible to assume that a drug given by rapid intravenous injection, a bolus, is rapidly mixed. This slide represents the uniformly mixed drug very shortly after administration.



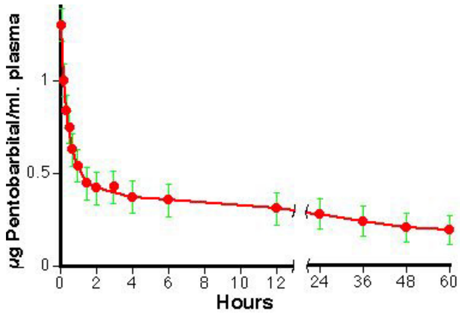

Oral curve and beakers. We can picture oral administration as water flowing from one bucket (representing the GI tract) into a second beaker (representing the body). At first drug flows into the 'body' beaker and the level rises, as drug concentration rises, then after peaking the levels start to fall as elimination overtakes absorption.




Intravenous bolus injection with a two compartment model. Often a one compartment model is not sufficient to represent the pharmacokinetics of a drug. A two compartment model has wider application. Here we consider the body is a central compartment with rapid mixing and a peripheral compartment with slower distribution. The central compartment is uniformly mixed very shortly after drug administration, whereas it takes some time for the peripheral compartment to reach a pseudo equilibrium.




A diagram of a two compartment model showing the parameters to be measured. The processes of distribution and excretion can be represented by the rate constants k12, k21, and k10. The rate constant k0 represents an infusion or absorption process. The drug appears to be dissolved in the body volume. This volume is the 'apparent' volume of distribution.




Pentobarbital plasma concentration versus time illustrating the multiphasic distribution pattern (redrawn from Smith, R.B., Dittert, L.W., Griffen, W.O., and Doluisio, J.T. 1973 *J. Pharmacokin. Biopharm.*, **1**, 5). From a plasma concentration time curve it may appear that this drug is rapidly eliminated from the body. Actually little of the drug is eliminated with much of it being distributed in various tissues of the body. Here distribution is a major factor affecting the overall kinetics of this drug. By looking further we can see the real picture.

## ADME PROCESSES

**A**bsorption
**D**istribution
**M**etabolism
**E**xcretion

The four pharmacokinetic processes. We will briefly consider each of these processes in turn. **A**(bsorption) **D**(istribution) **M**(etabolism) **E**(xcretion).

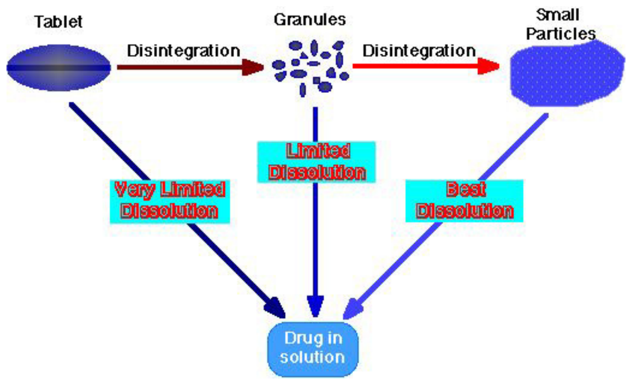
## Absorption

Intramuscular
Subcutaneous
Intravenous
Intrasynovial
Intracardiac
Intrathecal

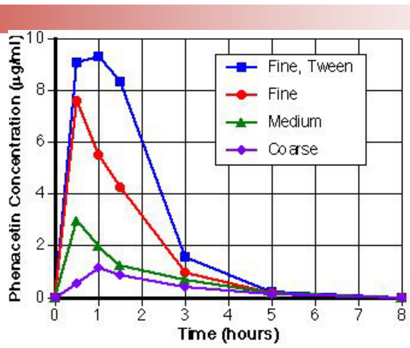
Eye
Nasal
Ear
Oral
Sublingual
Buccal

Rectal
Vaginal
Urethral
Topical

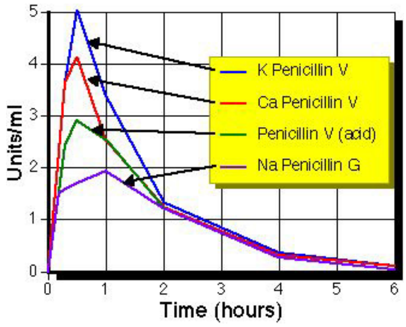
A model with the various routes of administration. For example absorption through the lining of the mouth, buccal absorption, often results in rapid absorption without the drug passing through the liver where it can be broken down. However, only low dose drugs can be accommodated by this route of administration. Orally absorbed drugs are absorbed in the stomach or intestines and enter the portal blood supply and go to the liver before getting into the central blood supply. This can result in extensive metabolism of the drug before it can take any action. For this reason some drugs are very inefficient when given orally.



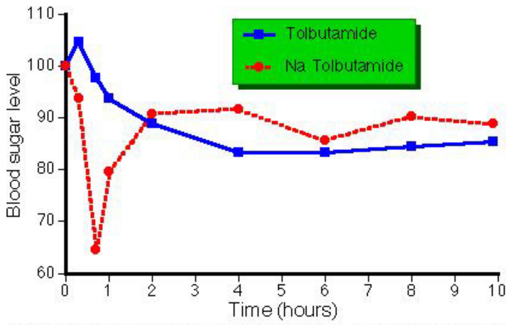

The processes involved in the dissolution of a tablet before absorption. A drug cannot be absorbed across the intestinal wall as a solid. It must first dissolve in the fluid of the G-I tract. Tablets are carefully formulated, designed, to stay together in the bottle during transport but break up quickly once they are in an aqueous environment. This can be an easy or difficult job depending on the drug and the dose required. There are therefore dissolution tests specified to ensure that tablet formulations work. Also it may be appropriate to conduct experiments with human volunteers to ensure that the tablet does release the drug as it should.




Plasma phenactin versus time curve after various suspensions (redrawn from Prescott, L.F., Steel, R.F., and Ferrier, W.R. 1970 *Pharmacol. Ther.*, **11**, 496-504). The effect of particle size on drug absorption is shown in this slide. Generally speaking the smaller the particle size the quicker the absorption. By increasing the particle surface area it is possible to increase the dissolution rate. However very small particle can clump together. Therefore a wetting agent such as Tween 80 can have a beneficial effect on the overall absorption. The intestinal fluids usually contain some materials which can act as wetting agents, however drug dissolution testing *in vitro* may neglect this effect.



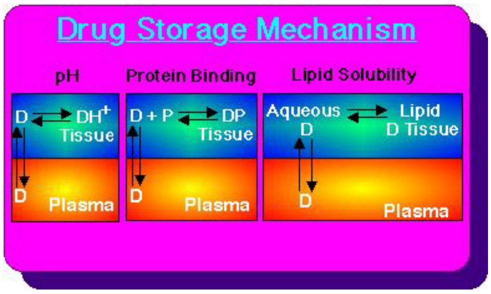

Plasma penicillin concentration versus time curve after oral administration of various salts (redrawn from Juncher, H. and Raaschou, F. 1957 The solubility of oral preparations of penicillin V, *Antibiot. Med. Clin. Therap.*, **4**, 497). The rate at which a drug dissolves is dependent on the solubility of the drug. A common occurrence is that different salts will have quite different solubility characteristics, and again somewhat different to the free acid (or base) form. In the case of penicillin V it appears that only drug which is dissolved quickly can be absorbed.




**The effect of dissolution rate on the absorption and biological response of tolbutamide (1.0 g) and sodium tolbutamide (1.0 g equivalent) when formulated in compressed tablets.**

Blood sugar levels after tolbutamide acid and salt (redrawn from Wagner, J.G. 1961 Biopharmaceutics: absorption aspects, *J. Pharm. Sci.*, **50**, 359). Rapid dissolution and absorption is not always the objective. Sometimes a slower release is required. In the case of tolbutamide, used to lower blood sugar concentrations, a more sustained release is better causing a more gradual reduction in blood sugar.

## Distribution



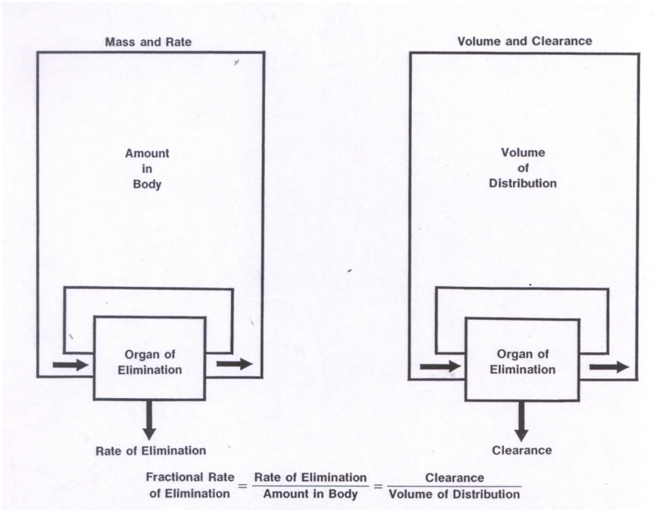

Distribution mechanisms. Methods by which drug is kept in the body for extended action. pH, protein binding and fat storage are three major processes by which drug may be kept within the body. These are mechanisms by which drugs can be distributed throughout the body, protected from elimination, and cause a more prolonged activity.

## Metabolism Excretion

THE "TASK" OF DRUG ELIMINATION

Conjugation
Hydrolysis
Oxidation
Reduction
Excretion

Methods of drug elimination: metabolism and excretion. Drugs are eliminated by a number of processes. Polar drugs are easily filtered from the blood in the kidneys and removed into urine. However non polar material is generally reabsorbed from the kidney or distributed into fat tissue. The liver however is capable of metabolizing many drugs, generally producing compounds which are more polar and more easily excreted. Enzymes in the liver are able to form conjugates with drugs or hydrolyze and oxidize drugs. Drug kinetics can be markedly altered by changes in metabolism or excretion of drugs. These processes together result in the elimination of a drug.




*The fractional rate of elimination of a drug can be thought of either as the fraction of the total amount in the body that is eliminated per unit time (left), or as the fraction of the total volume from which the drug is cleared per unit time (right).*

# Drug elimination

Expressed by:

- Elimination rate and amount of drug in the body,
  $k_e = dX/dt/U$ (kinetic view)
- Clearance and volume of distribution,
  $k_e = Cl/V$ (physiologic view)

- $k_e$ is a proportional factor called first-order elimination rate constant with units ($h^{-1}$)

# Drug elimination

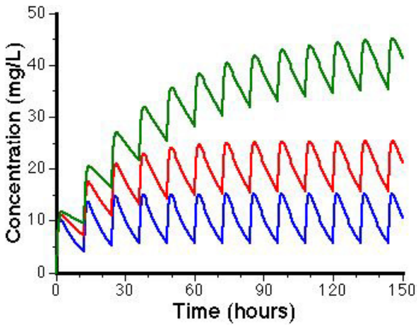
- **$dX/dt = k_e U$**
- **$dX/dt = Cl\ C$**

$k_e$ is a proportional factor called elimination rate constant (1/h)

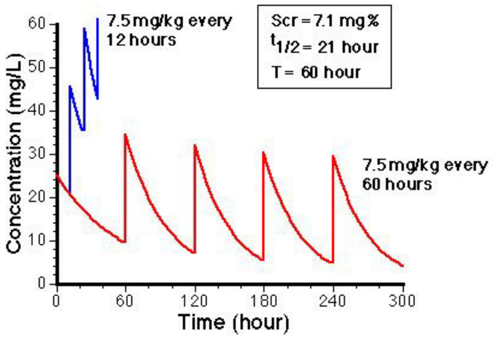
Cl is a proportional factor called clearance (L/h)

U – drug amount in the body (plasma)

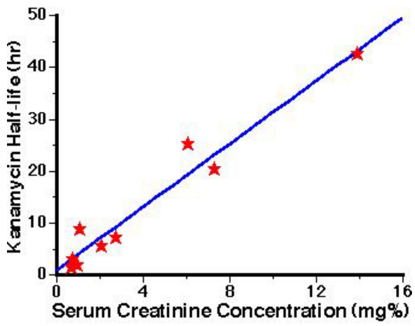
C – drug concentration in the body (plasma)




Multiple dose curves with slow, medium, and fast elimination. Alteration of drug elimination is particularly important when drugs are given repeatedly. If it is assumed that the drug is eliminated normally when in fact it is slowly eliminated, drug accumulation may occur with toxic concentrations reached. Alternately faster elimination than expected may cause sub therapeutic concentrations to be reached.

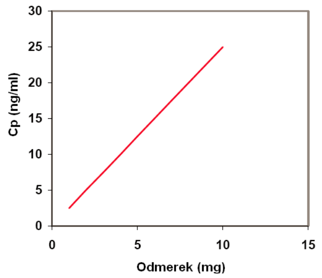



A clinical example with kanamycin, showing theoretical curve after multiple dose and a better curve after dose adjustment. Kanamycin is a useful drug but it can cause some serious side effects. By controlling the blood concentration of this drug it is possible to use it effectively. In the case of patients with impaired renal, or kidney function it is possible to determine the kidney function ahead of time and adjust the kanamycin dosing schedule accordingly.

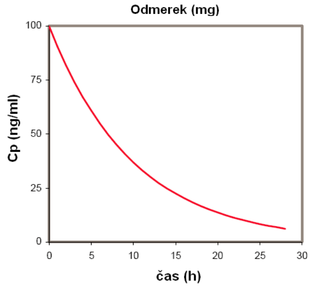



Relationship between kanamycin half-life and serum creatinine level. As kidney function is reduced the serum creatinine level increases and the also the kanamycin takes longer to be eliminated from the body.

# Linear Pharmacokinetics

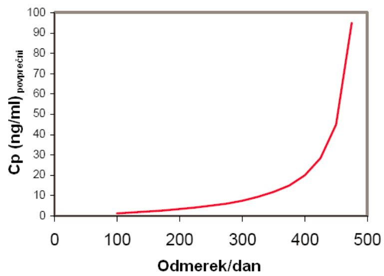



- Plasma concentrations PROPORTIONAL to dose

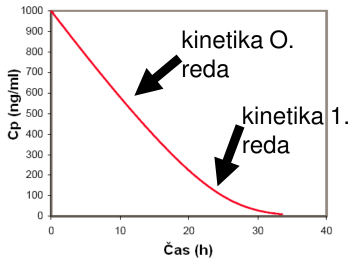



- Elimination rate PROPORTIONAL to concentration ⇨ first order kinetics

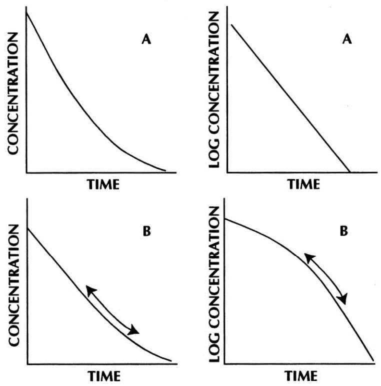
# Nonlinear pharmacokinetics



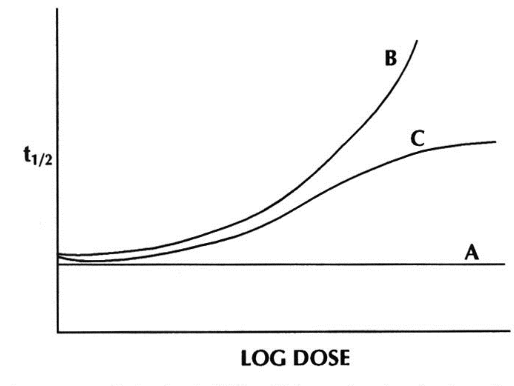

- Plasma concentration NOT PROPORTIONAL to dose




- Elimination rate NOT PROPORTIONAL to concentration ⇨ Michaelis-Menten enzyme kinetics

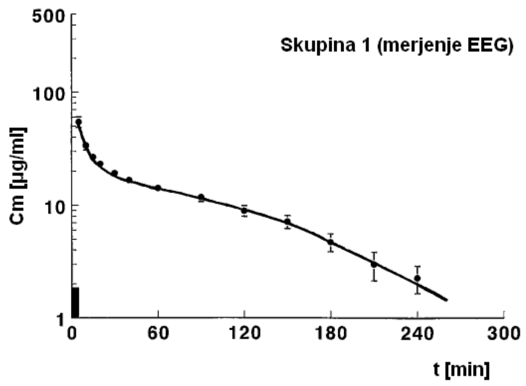


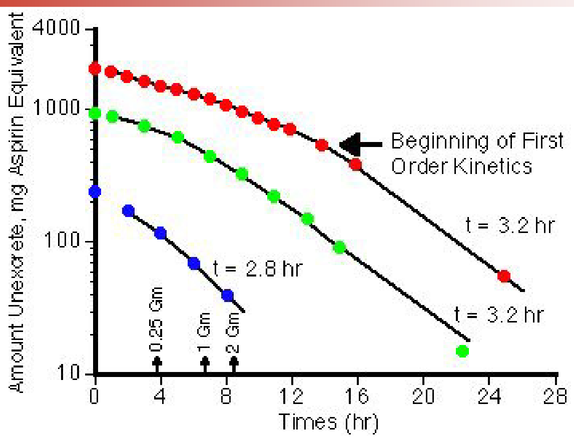

Blood concentration vs. time profiles of a drug that is eliminated by first-order kinetics (A), and by Michaelis–Menten kinetics (B). In (A), the profile is convex-curved when plotted on a linear scale and linear when plotted on a semilogarithmic scale (see Figure 13.1). In (B) the profile is initially linear at high drug concentrations, when elimination is essentially zero-order, and then curvilinear on a linear scale. On a semilogarithmic scale, the profile is initially convex-curved and then linear. The arrows indicate the transition concentration range between apparent zero-order and first-order elimination kinetics.



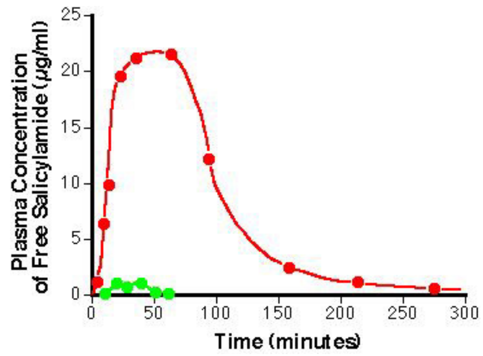

Changes in apparent elimination half-life with increasing dose for drugs that are cleared from the body by A, nonsaturable; B, saturable; and C, parallel saturable and nonsaturable pathways.

# Plasma concentrations of phenitoin




Aspirin plasma concentration as a function of time (redrawn from Levy, G. 1965 *J. Pharm. Sci.*, **54**, 959). At higher doses the metabolism of aspirin is reduced by saturation. The elimination rate constant (as represented by the slope) is reduced.




Extra absorption of salicylamide at higher doses (redrawn from Barr, W.H. *Drug Info. Bull.*, p27, 1969). Normally the amount of drug present in the body is no more than the enzymes can handle easily. Metabolism then proceeds in apparent first order fashion. However for some drugs the enzymes can not keep up. Illustrated here is one example, saturation of first pass metabolism allowing more or a higher fraction of drug to be absorbed.

# PK answers the following questions:

- **What is the influence of biological parameters (functionality of the organs, permeability, enzymatic activity, plasma/tissue protein binding) on drug plasma concentrations?**
- **How do dose, dosage form/mode of administration, and dosing interval affect drug plasma concentration?**

# Pharmacokinetic parameters

- Clearance ($Cl_P$)
- Volume of distribution ($V_d$)
- Biological half-life ($t_{1/2}$)
- Protein binding ($f_u$)
- Bioavailability ($k_a$, F)

# *Clearance (Cl)*

- A primary PK parameter.
- Describes the capability of drug elimination organs
- Reffers to the volume of plasma fluid that is cleared of drug per unit time (L/h).
- Usually a constant, although influenced by certain pathological status.
- Independent from dose, dosing interval, and drug application.
- Independent from volume of distribution, biological half-life, and bioavailability.

- $Cl=dU_E/dt/C_p=k_eV_d$

## Body fluids

**Rule of thirds**

Man (70 kg)

2/3 water (46.7 L)

1/3 dry substance (23.3 kg)

2/3 intracelular fluid (31.1 L)

1/3 extracelular fluid (15.6 L)

2/3 interstitial fluid (10.4 L)

1/3 blood (5.2 L), plasma: 1-Hct

## Volume of distribution ($V_D$)

- A primary PK parameter.
- Describes the extent of drug distribution in the body
- Reffers to the relationship between amount of the drug in the body and drug blood (plasma) concentration (apparent volumen of distribution, L)
- Usually a constant, although influenced by certain pathological status.
- Independent from dose, dosing interval, and drug application.
- Independent from volume of distribution, biological half-life, and bioavailability.

- $V_d = D/C_p$

## *Volume of distribution ($V_D$)*

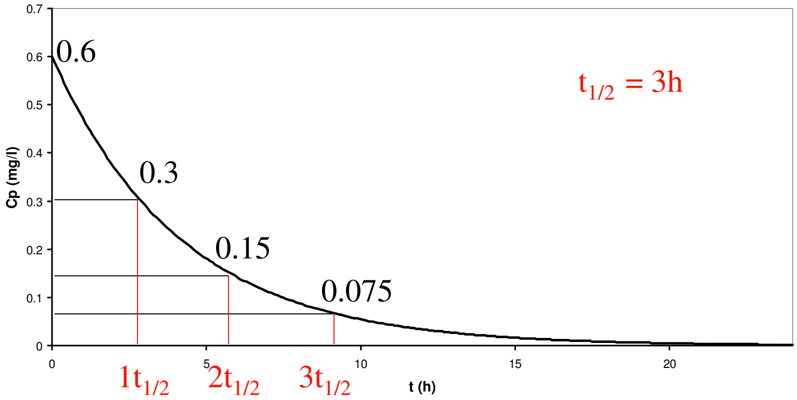
| | | |
|---|---|---|
| Gentamicin (ECF) | 0,25 L/kg | |
| Phenazon (TBW) | 0,6 L/kg | |
| Ciprofloxacin | 2,5 L/kg | (tissue accumulation!) |
| Azitromicin | 31,0 L/kg | (accumulation in phagocytes!) |

## *Elimination rate constant ($k_e$), biological half-life*

- Complex function of Cl and $V_d$
- Time for complete elimination of the drug: cca. 5 x $t_{1/2.}$
- Time to reach steady state: cca. 5 x $t_{1/2}$

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

| | |
|---|---|
| Gentamicin | $t_{1/2}$ = 2 h, $k_e$ = 0,347 $h^{-1}$ |
| Ciprofloxacin | $t_{1/2}$ = 3 h, $k_e$ = 0,213 $h^{-1}$ |
| Azithromycin | $t_{1/2}$ = 70 h, $k_e$ = 0,010 $h^{-1}$ |



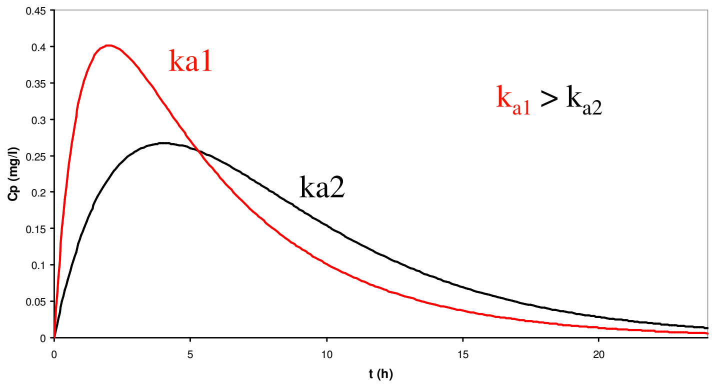

## *Plasma protein binding*

- Albumins
- $\alpha_1$-acid glycoproteins (basic drugs)
- Lipoproteins

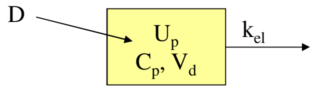
- Only drug in unbound (free) form is active. (antithrombotic drug warfarin, $f_u < 1\%$).

## *Bioavailability ($k_a$, F)*

- Rate of absorption ($k_a$)
- Extent of absorption (F)



# Single intravenous injection (bolus)



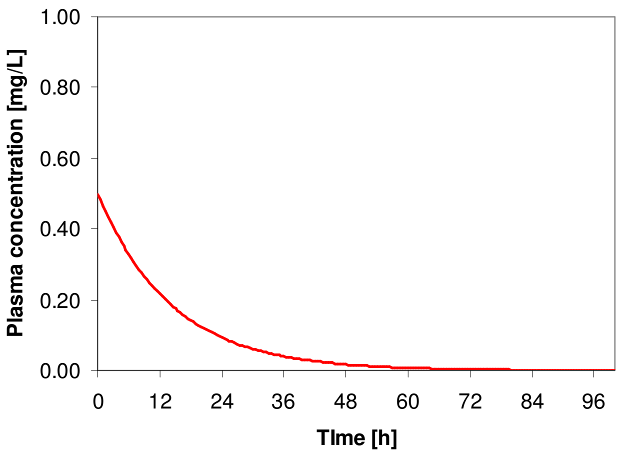

$$\frac{dU_p}{dt} = -k_{el} \cdot U_p$$

$$C_p = \frac{D}{V_d} \cdot e^{-kel \cdot t}$$

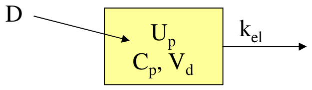
D… Dose
$k_{el}$…Elimination rate constant
$V_d$…Volumen of distribution
τ…. Dosing interval

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

| D (mg) | $V_D$ (L) | $k_{el}$ ($h^{-1}$) | $t_{1/2}$ (h) |
|---|---|---|---|
| 50 | 100 | 0.07 | 10 |



# Repetitive intravenous injection




$$\frac{dU_p}{dt} = -k_{el} \cdot U_p$$

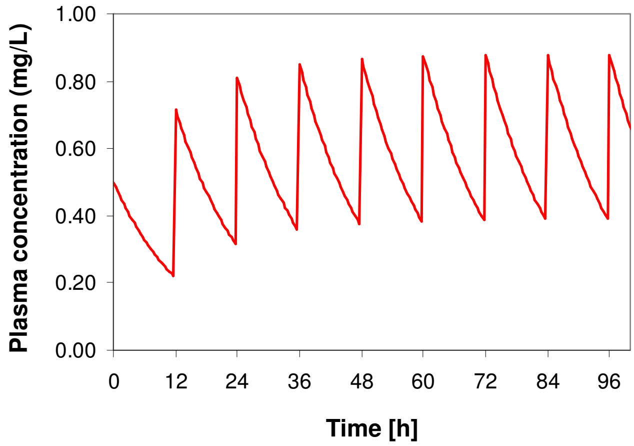
$$C_pss = \frac{D}{V_d} \cdot \frac{1}{1-e^{-kel \cdot \tau}} \cdot e^{-kel \cdot t}; 0 < t < \tau$$

$$C_pss^{\max} = \frac{D}{V_d} \cdot \frac{1}{1-e^{-kel \cdot \tau}}$$

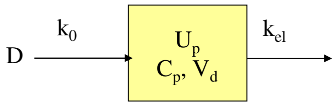
$$C_pss^{\min} = \frac{D}{V_d} \cdot \frac{1}{1-e^{-kel \cdot \tau}} \cdot e^{-kel \cdot \tau}$$

$$\overline{C_pss} = \frac{D}{V_d \cdot k_{el} \cdot \tau}$$

| D (mg) | $V_D$ (L) | $k_{el}$ ($h^{-1}$) | $t_{1/2}$ (h) | $\tau$ |
|---|---|---|---|---|
| 50 | 100 | 0.07 | 10 | 12 h |



# Intravenous infusion




$$\frac{dU_p}{dt} = k_0 - k_{el} \cdot U_p$$

$$k_0 = \frac{D}{T}$$

T… Infusion time

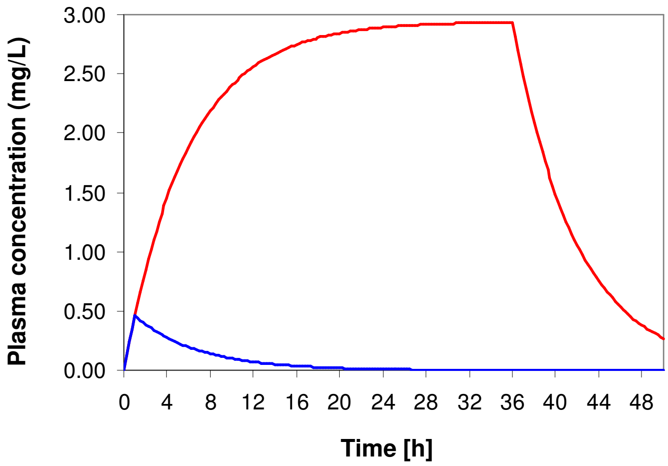
$$C_p = \frac{k_0}{V_d \cdot k_{el}} \cdot \left(1 - e^{-kel \cdot t}\right)$$

$$C_p ss = \frac{k_0}{V_d \cdot k_{el}}$$

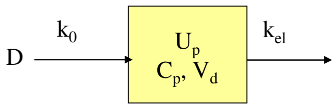
$$C_p{}^{post} = \frac{k_0}{V_d \cdot k_{el}} \cdot \left(1 - e^{-kel \cdot T}\right) \cdot e^{-kel \cdot (t - T)}$$

$$C_p ss^{post} = \frac{k_0}{V_d \cdot k_{el}} \cdot e^{-kel \cdot (t - T)}$$

| | $k_0$ (mg/h) | $V_D$ (L) | $k_{el}$ ($h^{-1}$) | T (h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| A | 50 | 100 | 0.18 | 24 | 4 |
| B | 50 | 100 | 0.18 | 1 | 4 |



# Repetitive intravenous infusion




$$\frac{dU_p}{dt} = k_0 - k_{el} \cdot U_p$$

$$k_0 = \frac{D}{T}$$

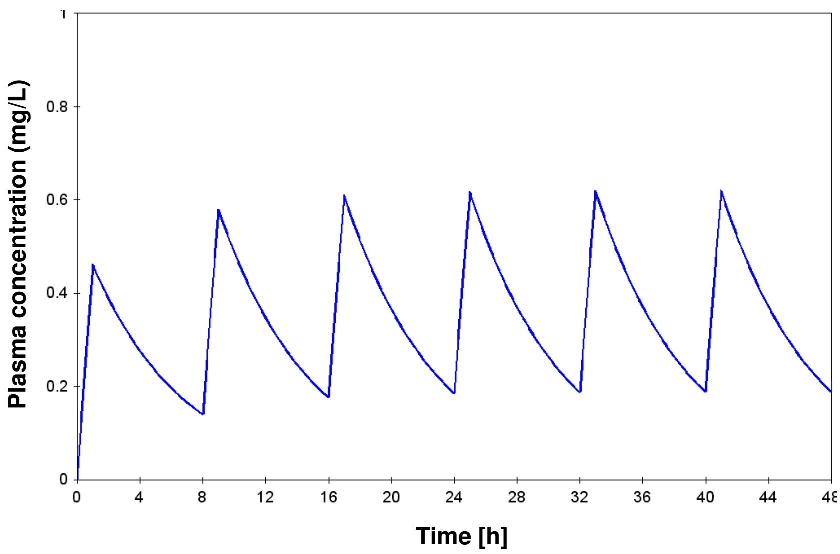
T… Infusion time

$$C_p ss = \frac{k_0}{V_d \cdot k_{el}} \cdot \left(1 - e^{-kel \cdot T}\right) \cdot \frac{1}{1 - e^{-kel \cdot \tau}} \cdot e^{-kel \cdot (t - T)}; \ T < t < \tau$$

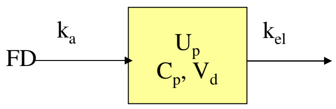
$$C_p ss^{\max} = \frac{k_0}{V_d \cdot k_{el}} \cdot \left(1 - e^{-kel \cdot T}\right) \cdot \frac{1}{1 - e^{-kel \cdot \tau}}$$

$$C_p ss^{\min} = \frac{k_0}{V_d \cdot k_{el}} \cdot \left(1 - e^{-kel \cdot T}\right) \cdot \frac{1}{1 - e^{-kel \cdot \tau}} \cdot e^{-kel \cdot (\tau - T)}$$

| $k_0$ (mg/h) | $V_D$ (L) | $k_{el}$ ($h^{-1}$) | T (h) | $t_{1/2}$ (h) | τ |
|---|---|---|---|---|---|
| 50 | 100 | 0.18 | 1 | 4 | 8 h |



# Single ekstravascular application
(oral, intramuscular)




$$\frac{dU_p}{dt} = F \cdot k_a \cdot U_{gi} - k_{el} \cdot U_p$$

$$C_p = \frac{F \cdot D}{V_d} \cdot \left( \frac{k_a}{k_a - k_{el}} \right) \cdot \left( e^{-k_{el} \cdot t} - e^{-k_a \cdot t} \right)$$

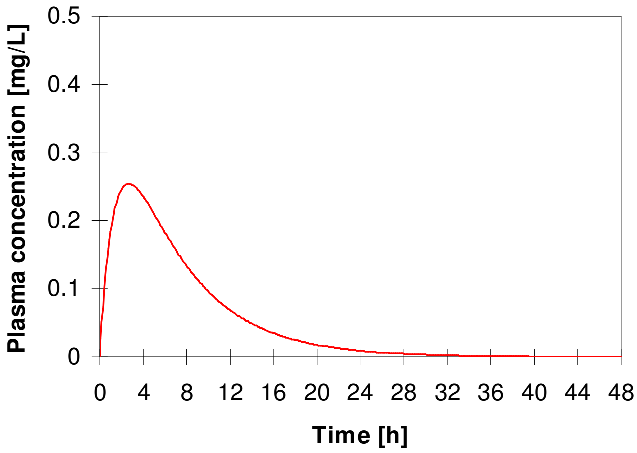
$$AUC_{0 \to \infty} = \frac{F \cdot D}{V_d \cdot k_{el}}$$

$$\overline{C_p ss} = \frac{F \cdot D}{V_d \cdot k_{el} \cdot \tau}$$

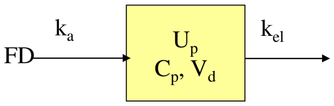
$$AUC_{0 \to \tau} = \frac{F \cdot D}{V_d \cdot k_{el}}$$

| D (mg) | F | Vd (L) | $k_a$ ($h^{-1}$) | $k_{el}$ ($h^{-1}$) |
|---|---|---|---|---|
| 50 | 0.8 | 100 | 0.72 | 0.18 |

| $T_{max}$ | $C_{max}$ | $t_{1/2\ ka}$ (h) | $t_{1/2\ kel}$ (h) |
|---|---|---|---|
| 2.7 | 0.25 | 1 | 4 |



# Repetitive ekstravascular applikacation




$$\frac{dU_p}{dt} = F \cdot k_a \cdot U_{gi} - k_{el} \cdot U_p$$

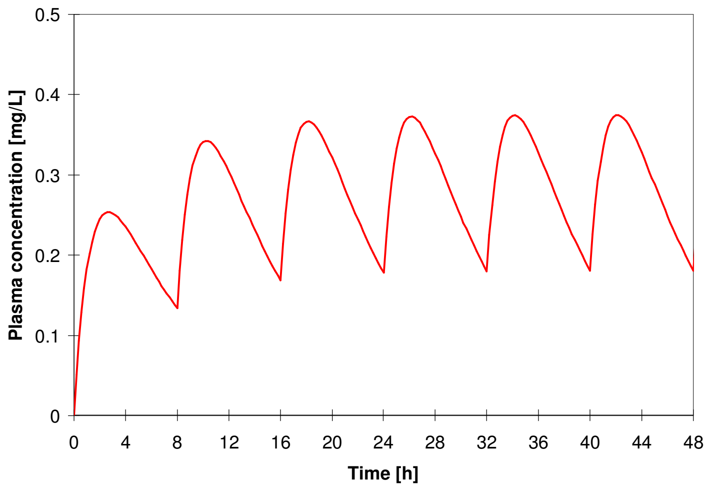
$$C_pss = \frac{F \cdot D}{V_d} \cdot \left(\frac{k_a}{k_a - k_{el}}\right) \cdot \left[\left(\frac{1}{1-e^{-kel\cdot\tau}}\right)\cdot e^{-kel\cdot t} - \left(\frac{1}{1-e^{-ka\cdot\tau}}\right)\cdot e^{-ka\cdot t}\right]$$

$$C_pss^{\max} = \frac{F \cdot D}{V_d} \cdot \left(\frac{1}{1-e^{-kel\cdot\tau}}\right) \cdot \left[\left(\frac{k_a \cdot \left(1-e^{-kel\cdot\tau}\right)}{k_{el} \cdot \left(1-e^{-ka\cdot\tau}\right)}\right)\right]^{-kel/(ka-kel)}$$

$$C_pss^{\min} = \frac{F \cdot D}{V_d} \cdot \left(\frac{k_a}{k_a - k_{el}}\right) \cdot \left[\left(\frac{e^{-kel\cdot\tau}}{1-e^{-kel\cdot\tau}}\right) - \left(\frac{e^{-ka\cdot\tau}}{1-e^{-ka\cdot\tau}}\right)\cdot e^{-ka\cdot t}\right]$$

$$tss^{\max} = \frac{1}{k_a - k_{el}} \cdot \ln\left[\frac{k_a \cdot \left(1-e^{-kel\cdot\tau}\right)}{k_{el} \cdot \left(1-e^{-ka\cdot\tau}\right)}\right]$$

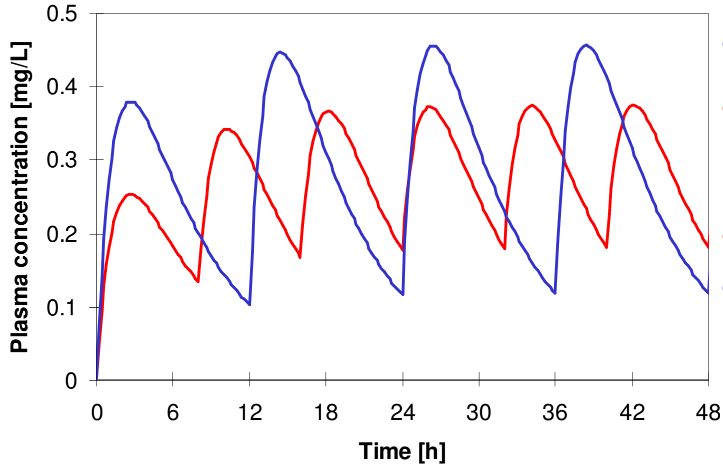
| D (mg) | F | Vd (L) | $k_a$ ($h^{-1}$) | $k_{el}$ ($h^{-1}$) | τ | $t_{1/2\ ka}$ (h) | $t_{1/2\ kel}$ (h) |
|---|---|---|---|---|---|---|---|
| 50 | 0.8 | 100 | 0.72 | 0.18 | 8 h | 1 | 4 |




$C_{SS}^{max}$ = 0.375 mg/L

$C_{SS}^{min}$ = 0.181 mg/L

| Application | D (mg) | τ | $k_a$ ($h^{-1}$) | $V_D$ (L) | $k_{el}$ ($h^{-1}$) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| 3 x per day | 3 x 50 | 8 h | 0.72 | 100 | 0.17 | 4 |
| 2 x per day | 2 x 75 | 12 h | 0.72 | 100 | 0.17 | 4 |



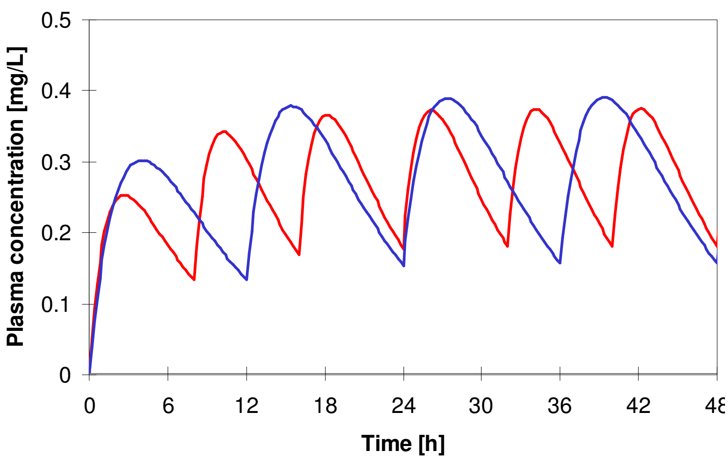

$C_{SS}^{max}$ = 0.475 mg/L

$C_{SS}^{max}$ = 0.375 mg/L

$C_{SS}^{min}$ = 0.181 mg/L

$C_{SS}^{min}$ = 0.119mg/L

| Application | D (mg) | τ | $k_a$ ($h^{-1}$) | $V_D$ (L) | $k_{el}$ ($h^{-1}$) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| 3 x per day | 3 x 50 | 8 h | 0.72 | 100 | 0.17 | 4 |
| 2 x per day | 2 x 75 | 12 h | 0.36 | 100 | 0.17 | 4 |



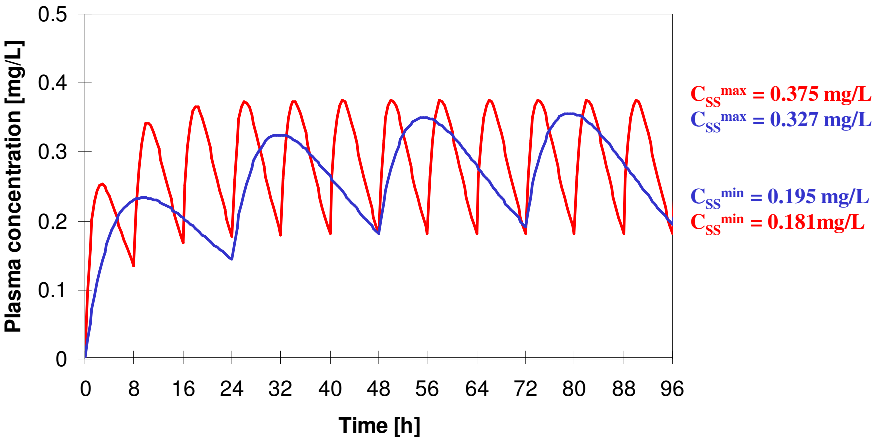

$C_{SS}^{max}$ = 0.391 mg/L

$C_{SS}^{max}$ = 0.375 mg/L

$C_{SS}^{min}$ = 0.181 mg/L

$C_{SS}^{min}$ = 0.157mg/L

| Application | D (mg) | τ | $k_a$ ($h^{-1}$) | $V_D$ (L) | $k_{el}$ ($h^{-1}$) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| 3 x per day | 3 x 50 | 8 h | 0.70 | 100 | 0.17 | 4 (el.) |
| 1 x per day | 1 x 150 | 24 h | 0.06 | 100 | 0.17 | 12 (abs.) |




# Primum nil nocere

- Therapeutic effect:
  ***Rx*** + ☹ = ☺
- Reduced or absence of the therapeutic effect:
  ***Rx*** + ☹ = ☹
- Adverse or toxic reaction:
  ***Rx*** + ☹ = ☠

# Take home messages

- pharmacokinetics rules plasma concentration profiles of drugs (radiopharmaceuticals)
- significant pharmacokinetic parameters are clearance, volume of distribution, biological half-life and bioavailability (rate and extent of absorption)
- plasma concentration profiles can be predicted by pharmacokinetic models
- drugs (radiopharmaceuticals) can be voided from the body either by linear or nonlinear kinetics