One Compartment Modeling

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Pharmacokinetics

Definition: Pharmacokinetics is the study of drug and/or metabolite **kinetics** in the body. It deals with a mathematical description of the rates of drug movement into, within and exit from the body. It also includes the study of drug metabolism or biotransformation rates. The body is a very complex system and a drug undergoes many steps as it is being **absorbed**, **distributed** through the body, **metabolized** or **excreted** (ADME).

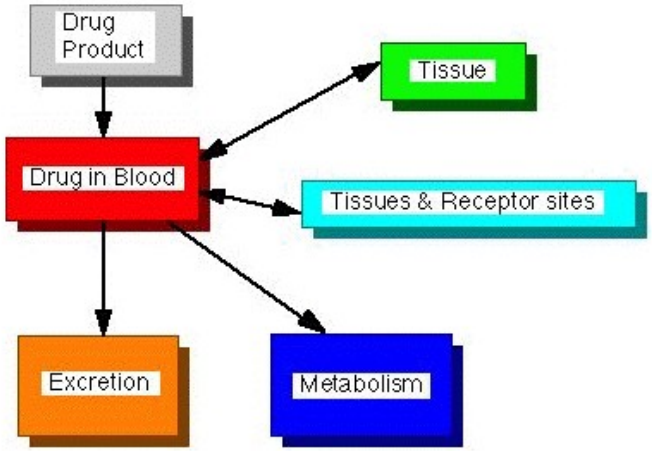


Figure 5.1.1 Drug Disposition

The drug also interacts with receptors and causes therapeutic and/or toxic responses. Although the details of drug kinetics are complicated it is fortunate that we can often approximate drug kinetic processes using "simple" mathematical models.

Pharmacokinetics: Mechanisms

- Absorption
- Distribution
- Metabolism
- **Excretion (main topic for project)**

Pharmacokinetics
Online Content for Student
https://sepia2.unil.ch/pharmacology/mechanisms/

- Focus on clearance of drug

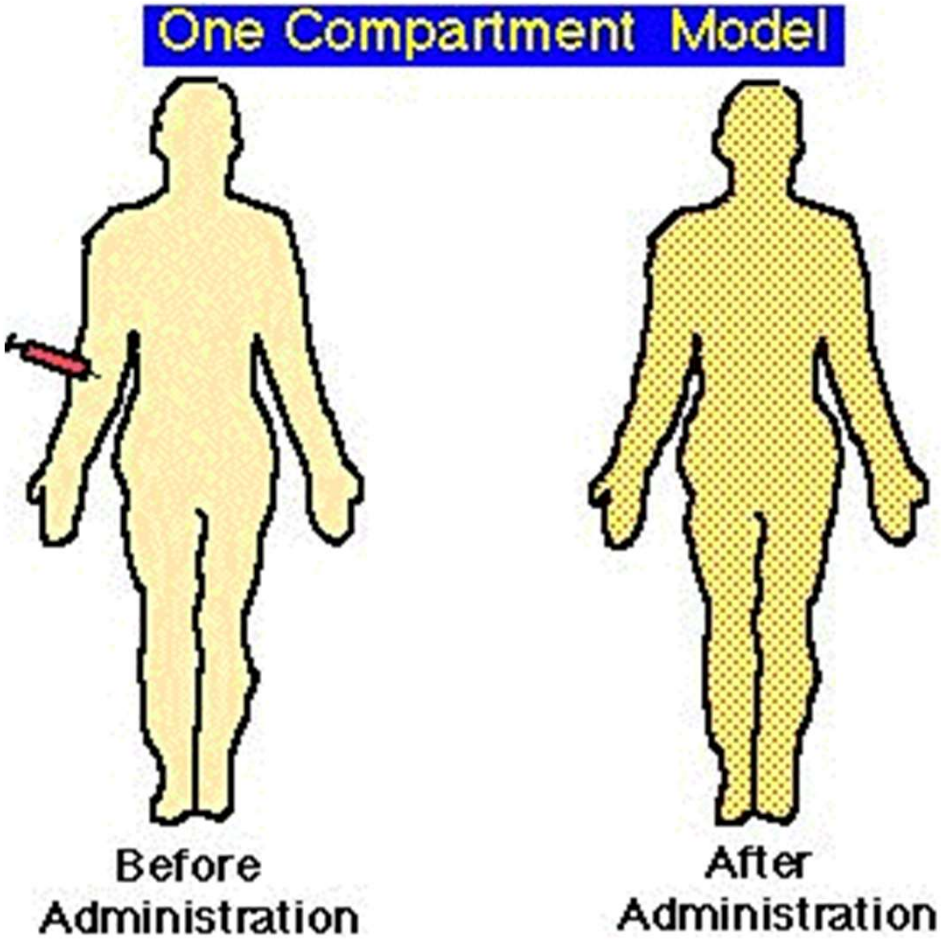
https://sepia2.unil.ch/pharmacology/parameters/clearance/

Pharmacokinetics: Clearance

Clearance

"Rate of drug elimination divided by plasma concentration, giving a volume of plasma from which drug is completely removed per unit of time"

- https://sepia2.unil.ch/pharmacology/parameters/clearance/



A whole human body as one compartment

One Compartment Model

SINGLE-COMPARTMENT MODEL

Definition : "Model describing drug absorption, distribution and elimination from a unique compartment in the body."

Description

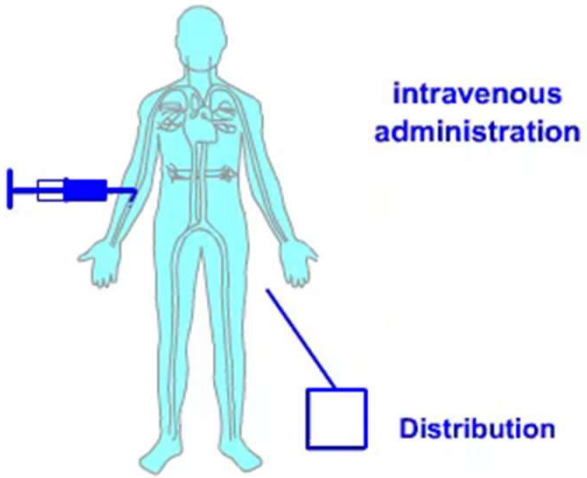
In single-compartment modeling, the drug is considered to be distributed instantaneously into a unique compartment in the body. This compartment is characterized by a distribution volume. The drug input into this volume depends on the dosage regimen. The drug output from this volume is characterized by an elimination constant rate. Several dosage regimens are considered here:

1. An intravenous bolus injection: the input is equal to the dose at the time point 0 and becomes equal to 0 thereafter. The concentration at time 0, C(0), corresponds to the dose divided by the volume. Subsequently, the concentration decreases in an exponential manner.
2. Intravenous infusion: the drug input is constant and equal to the rate of infusion of the drug. Therefore, the amount of drug in the volume progressively increases until equilibrium is reached when the drug input rate equals the output rate. In other words, equilibrium is reached when the rate of elimination (which increases with the amount of drug in the volume) compensates for the rate of infusion.
3. Extravascular dose: we only consider the case when the input rate follows linear kinetics: the rate of absorption may be characterized by an absorption rate constant and is proportional to the amount of drug available for absorption. The concentration at any time point results from the drug input into the volume minus the output which both vary with time depending on the amount of drug available for absorption and for elimination.

Intravenous Bolus Injection

Intravenous Bolus Injection

"Drug administration through the intravenous route over a negligible period of time"

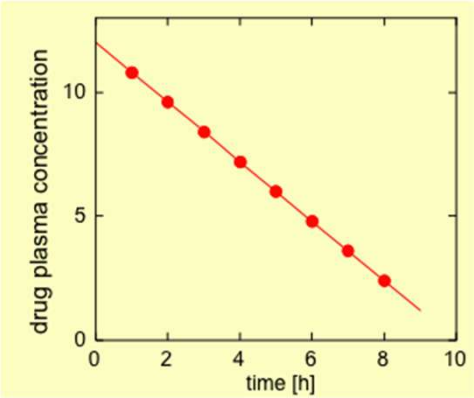


https://sepia2.unil.ch/pharmacology/profiles/intravenous-bolus/

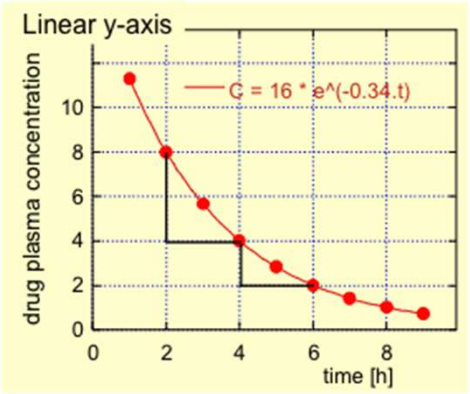
Elimination Kinetics

Elimination Kinetics

- Zero-order elimination kinetics : "Elimination of a constant quantity per time unit of the drug quantity present in the organism."



- First order elimination kinetics : "Elimination of a constant fraction per time unit of the drug quantity present in the organism. The elimination is proportional to the drug concentration."



https://sepia2.unil.ch/pharmacology/parameters/elimination-kinetics/

Renal Clearance

Renal Clearance

- "Part of the total clearance due to renal excretion"

Total Clearance

https://sepia2.unil.ch/pharmacology/parameters/renalclearance/

One Compartment Model

Clinical implications

This model is an easy way of representing the drug outcome in the body when the drug is rapidly distributed within the volume of distribution. Such a representation allows predictions of plasma drug concentration profiles in different conditions and a more accurate estimation of the initial dosage regimen to be given to a patient.

Assessment

Single compartment representation

Differential equation describing this single compartmental model:

$$\frac{dA}{dt} = Input - (k10 * A)$$

Considering that :

$$CL = k10 * V$$

The following equation may apply to the model:

$$\frac{dC}{dt} = \frac{Input - (CL * C)}{V}$$

A = amount of drug

k10 = Transfer constant rate from the compartment (1) to the outside of the body (0)

V = volume of the compartment

CL = clearance

C = concentration in the volume

One Compartment Model

INTRAVENOUS BOLUS INJECTION

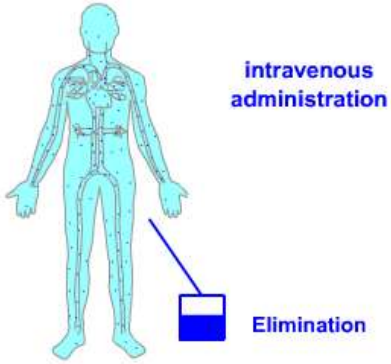
Definition : "Drug administration through the intravenous route over a negligible period of time."

Description

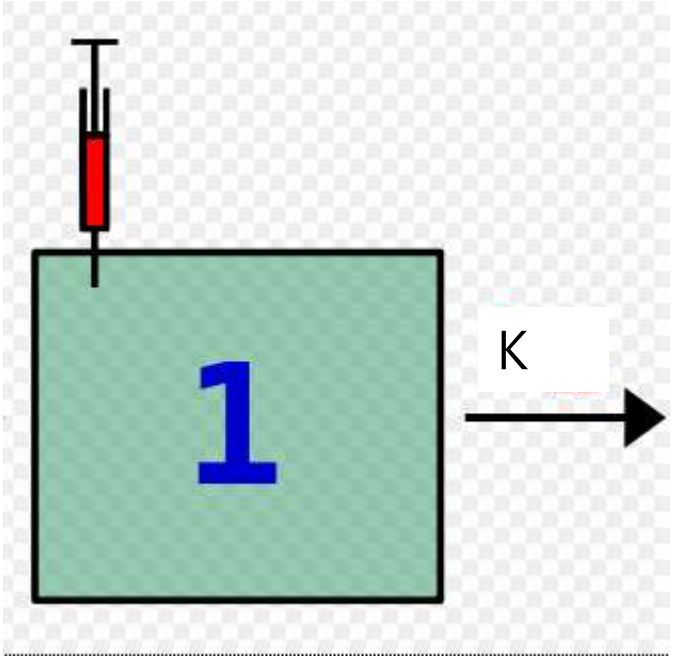
Administering a drug intravenously ensures that the entire dose enters the general circulation. Intravenous administration bypasses the absorption phase and the hepatic first-pass effect. Bioavailability is therefore complete. The drug is then distributed throughout the body and then eliminated by the liver and/or kidney.

Three parameters determine the drug concentration-time profile after administration of an iv bolus:

1. Dose: with higher doses, the initial drug concentration is also higher, but its relative rate of decline remains identical.
2. Volume of distribution: a larger Vd implies a lower initial drug plasma concentration, but also a longer half-life ($t_{1/2}$).
3. Clearance: greater clearance of the drug leads to a faster rate of decline in the drug plasma concentration, and a shorter half-life ($t_{1/2}$).



Drug Elimination
- Single Compartment Modeling-

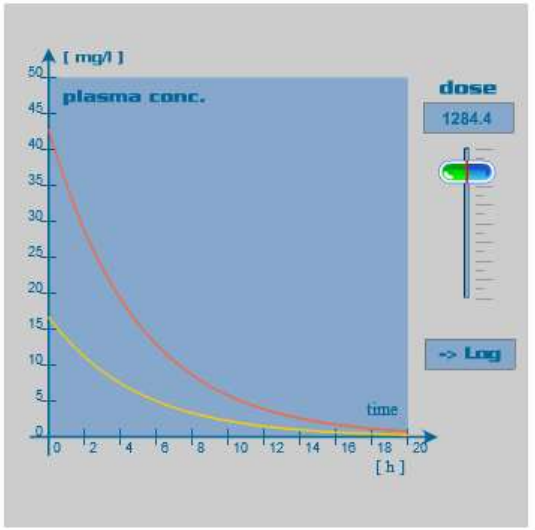


One Compartment Model

Clinical implications

An iv bolus injection ensures the rapid achievement of very high peak concentrations, as may be required for some drugs, but contra-indicated for others.

With an iv bolus administration the amount of drug delivery is precisely controlled.



Related terms

Distribution phase (early phase): After entering the systemic circulation, the drug is distributed throughout the body. Distribution can determine an early rapid decline in plasma concentration.

Elimination phase (late phase): Once the drug in the plasma and tissues has reached equilibrium, the decline of plasma concentration is driven by elimination of the drug from the body.

Assessment

Analysing the plasma concentration-time profile after an intravenous bolus injection is very useful to calculate the different parameters such as clearance (CL), half-life (t1/2) and volume of distribution (Vd) of a given drug.

The equation of the plasma concentration-time curve for a drug with a negligible distribution phase is:

$$C = C(0) * e^{-\lambda * t}$$

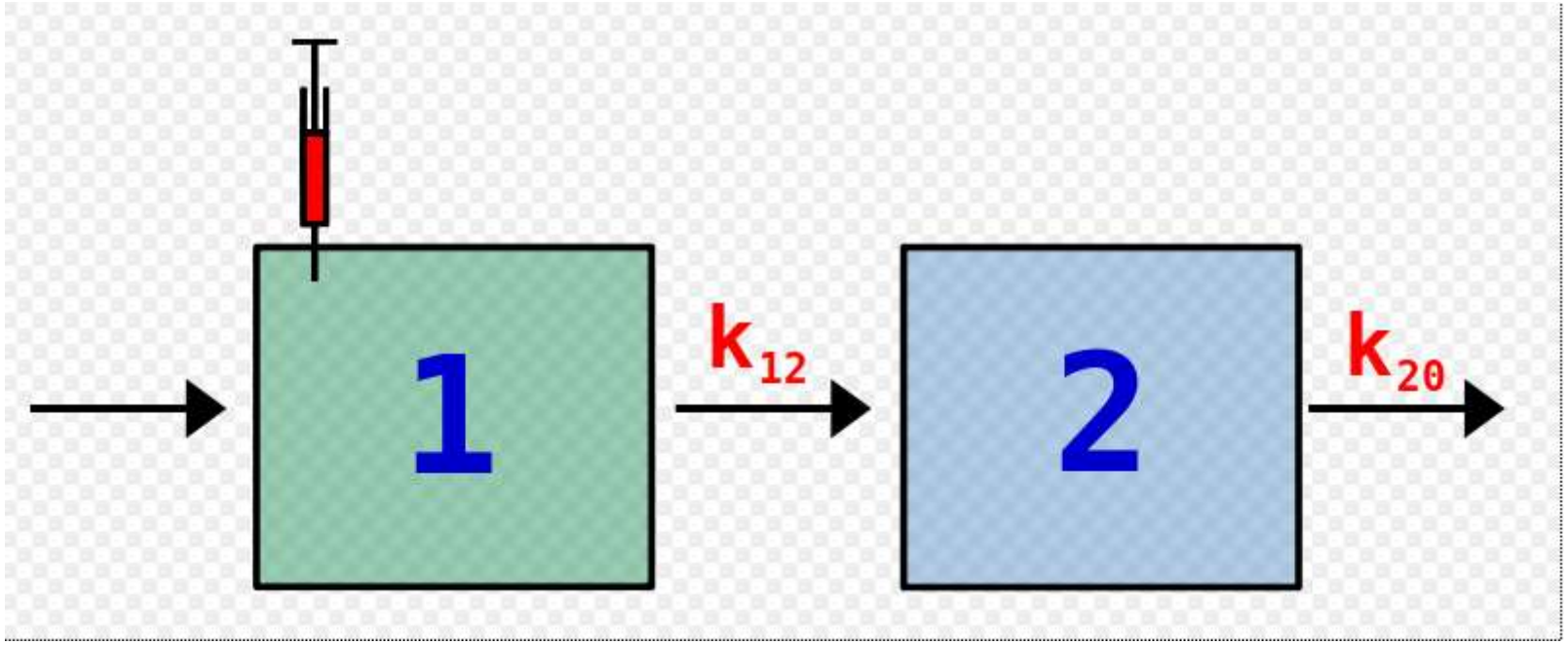
C(0) = plasma drug concentration at time 0

extrapolated value = D/Vd

D = dose

λ = elimination constant rate = CL/Vd

Two Compartment Model



Two Compartment Model

IV Bolus Two Compartment Model

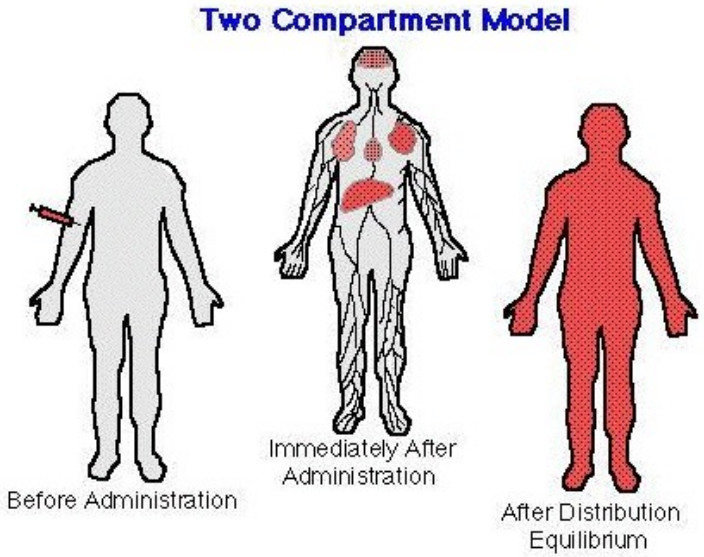
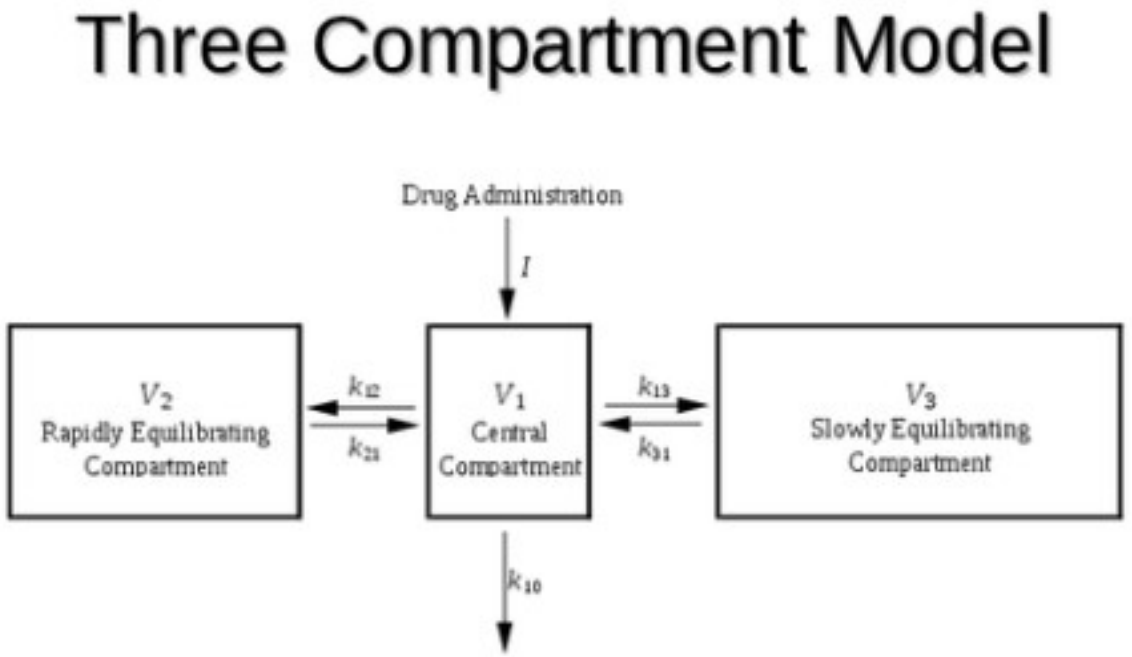
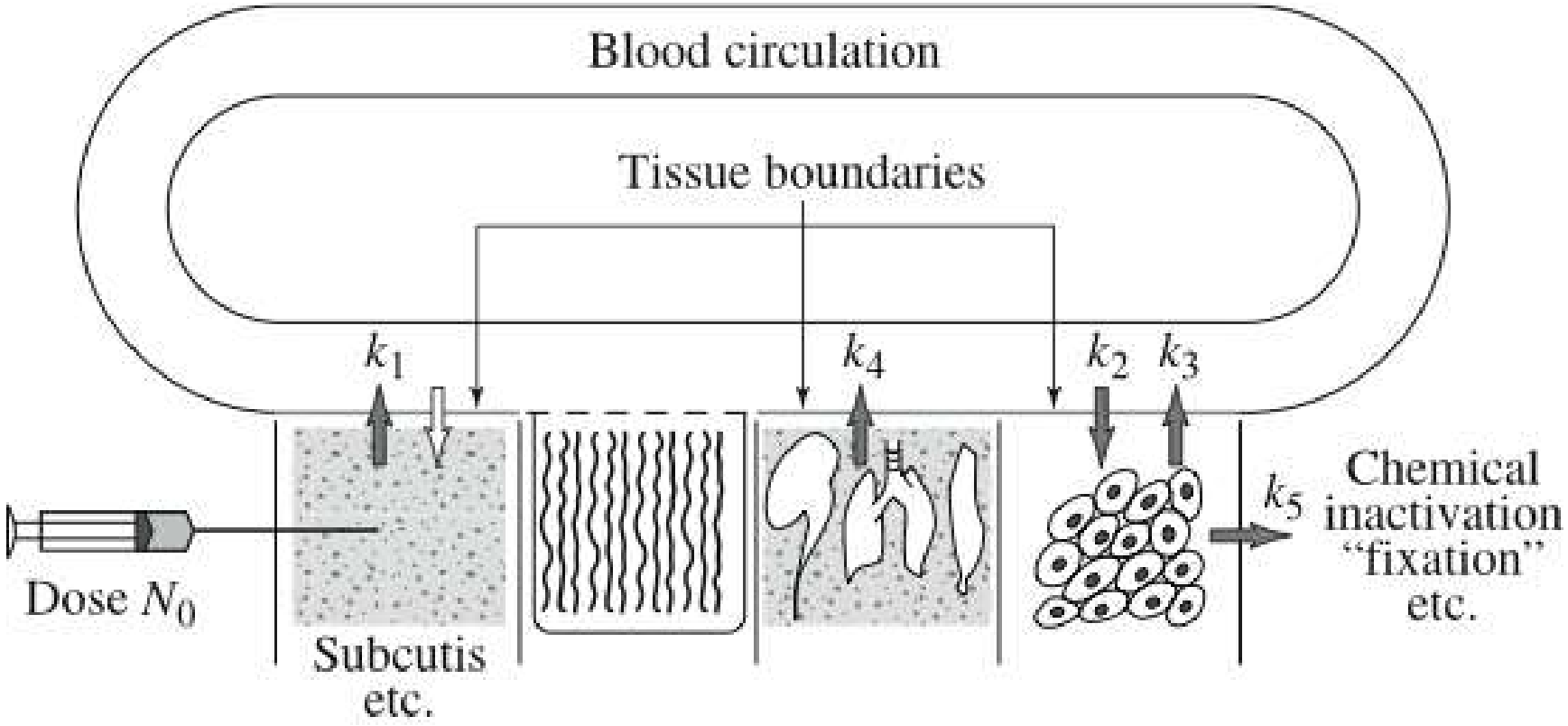


Fig 4.7.1 Slide of an intravenous bolus injection with a two compartment model. Often a one compartment model is not sufficient to represent the pharmacokinetics of a drug. A two compartment model often has wider application. Here we consider the body is a central compartment with rapid mixing and a 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.

Three Compartment Model



Many Compartment Model



Extra Info for Compartment Modeling

Extra Materials for Compartment Modeling

- http://virtualrat.org/introduction-compartmental-modeling
- Example 1: same as our project 1, a single compartment model

Extra Info for Compartment Modeling

Pharmacokinetic Modeling with Matlab

Create Pharmacokinetic Models with Matlab
https://kr.mathworks.com/help/simbio/ug/creating-pharmacokinetic-models.html

One compartment model (example)
https://kr.mathworks.com/help/simbio/gs/construct-a-simple-model.html