Basic Concepts of Pharmacokinetics

Achiel Van Peer, Ph.D.
Clinical Pharmacology
Some introductory Examples
15 mg of Drug X in a slow release OROS capsule administered in fasting and fed conditions in comparison to 15 mg in solution fasting.
Prediction of drug plasma concentrations before the first dose in a human

First dose 5 mg
Fabs 100%
Fabs 50%
Fabs 20%

NOAEL in female rat
NOAEL in female dog
NOAEL in male dog
NOAEL in male rat
Allometric Scaling

![Graph showing allometric scaling with log clearance (ml/hr) vs. log body weight (kg) for Rat, Monkey, and Dog.](image)
Pharmacokinetics:
Time Profile of Drug Amounts

Rowland and Tozer, Clinical Pharmacokinetics: Concepts and Applications, 3rd Ed. 1995
Definition of Pharmacokinetics?

Pharmacokinetics is the science describing drug

- absorption from the administration site
- distribution to
  - tissues,
  - target sites of desired and/or undesired activity
- metabolism
- excretion

PK = ADME
We will cover

- Some introductory Examples
- Model-independent Approach
- Compartmental Approaches
- Drug Distribution and Elimination
- Multiple-Dose Pharmacokinetics
- Drug Absorption and Oral Bioavailability
- Role of Pharmacokinetics
The simplest approach
... observational pharmacokinetics
The Model-independent Approach

\[ C_{\text{max}}: \text{maximum observed concentration} \]
\[ T_{\text{max}}: \text{time of } C_{\text{max}} \]
\[ \text{AUC}: \text{area under the curve} \]
**C\textsubscript{max}, T\textsubscript{max} and AUC in Bioavailability and Bioequivalence Studies**

**Absolute bioavailability (F\textsubscript{abs})**

- compares the amount in the systemic circulation after intravenous (reference) and extravascular (usually oral) dosing

\[ F\textsubscript{abs} = \frac{\text{AUC}_{po}}{\text{AUC}_{iv}} \text{ for the same dose} \]

- between 0 and 100% (occasionally >100%)

**Relative bioavailability (F\textsubscript{rel})**

- compares one drug product (e.g. tablet) relative to another drug product (solution)

**Bioequivalence (BE): a particular F\textsubscript{rel}**

Two drug products with the same absorption rate (C\textsubscript{max}, T\textsubscript{max}) and the same extent (AUC) of absorption

(90% confidence intervals for F\textsubscript{rel} between 80-125%)
Absolute oral bioavailability
flunarizine, J&J data on file

Other example: nebivolol:
10% in extensive metabolisers; 100% in poor metabolisers
Area under the curve

Trapezoidal rule: divide the plasma concentration-time profile to several trapezoids, and add the AUCs of these trapezoids

\[ \text{AUC}_{t_1}^{t_2} = \left( \frac{C_1 + C_2}{2} \right) \cdot (t_2 - t_1) \]

Units, e.g. ng.h/mL

\[ \text{AUC}_{\text{extrapolated}} = \frac{C_{\text{last}}}{\lambda z} \]
Elimination half-life?

**Half-life (t1/2):** time the drug concentration needs to decrease by 50%
Elimination half-life?
visual inspection
Elimination half-life?
visual inspection or alternatives?

Half-life (t1/2): time to decrease by 50%

T1/2 = 6 hrs
Derived from a semilog plot

T1/2 = 0.693/λz
From *Whole-Body Physiologically based Pharmacokinetics to Compartamental Models*

Poggesi et al., Nerviano Medical Science

\[
\frac{dC_T}{dt} = \frac{Q_T \cdot C_{\text{input}}}{V_T} - \frac{C_T \cdot Q_T}{P_{tp} \cdot V_T} - \frac{E_T \cdot C_{\text{input}}}{V_T}
\]

- \( C_T \): Drug concentration for tissue T
- \( C_{\text{input}} \): Drug concentration in input
- \( Q_T \): Blood flow
- \( V_T \): Tissue volume
- \( P_{tp} \): Tissue-plasma partition coefficient
- \( B:P \): Blood to plasma ratio
- \( E_T \): Extraction ratio (\( E_T = 0 \) in non-eliminating tissues)
Compartmental Approach

- drug distributes very rapidly to all tissues via the systemic circulation
- an equilibrium is rapidly established between the blood and the tissues, the body behaves like one (lumped) compartment
- does not mean that the concentrations in the different tissues are the same

One-compartment PK model

- Drug Absorption
- Body compartment
- Drug Elimination
One compartment behaviour more often observed after oral drug intake
Intravenous dose of 0.2 mg Levocabastine
(J&J data on file)
Depending on rate of equilibration with the systemic circulation, lumping tissues together, and simplification is possible

- Multi-Tissue or Multi-Compartment Whole Body Pharmacokinetic model
- Tri-compartment model
- Two-compartment model
- One-compartment model
Zero-order rate drug administration and first-order rate drug elimination

Infusion rate
mg/ min

dDose/ dt = Ko = mg/ min

Amount A in blood, plasma

Rate of elimination is proportional to the Amount in blood/ plasma

dA/ dt = -k.A

[Often K=Kel=K10]
First-order rate of drug disappearance

Intravenous bolus

Amount A [or Concentration C] in blood, plasma

Rate of elimination is proportional to the Amount or Concentration in blood, plasma

\[ \frac{dA}{dt} = -kA = -kVdC \]

If A = Amount in plasma, then V = Plasma volume
If A = Remaining amount in the body, then Vd = Total volume of distribution
A single iv dose of 5 mg for a drug with immediate equilibration (one compartment behaviour)

\[ \frac{dA}{dt} = -k_{10}.A = -k_{10}.V.C \]

\[ \frac{dA}{dt} = -k_{10}.A = -CL.C \]

\[ \frac{dC}{dt} = -k_{10}.C \]

\[ C = C_0 \cdot e^{-k_{10}.t} \]
A single iv dose of 5 mg

\[ C = C_0 e^{-k_{10} t} \]

\[ \ln C = \ln C_0 - k_{10} t \]

Remark for log_{10} scale:
\[ \text{slope} = k_{10}/2.303 \]
A single iv dose of 5 mg

\[ \ln C = \ln C_0 - k_{10} \cdot t \]

\[ k_{10} = \frac{\ln C_1 - \ln C_2}{t_2 - t_1} = \frac{0.693}{t_2 - t_1} \]

\[ \text{Half-life} = \frac{0.693}{k_{10}} \]

C2 = half of C1

Slope = k_{10} = the elimination rate constant

Predicted
A single iv dose of 5 mg

\[ V_d = \frac{dose}{C_{po}} = \frac{5000000 \text{ng}}{162 \text{ng/mL}} = 30.9 \text{L} \]

\[ V_d = \text{volume of distribution, relates the drug concentration to the drug amount in the body} \]
One-Compartment model after intravenous administration

\[ V_d = \text{volume of distribution}, \]
relates the drug concentration at a particular time
to the drug amount in the body at that time

\[ k_{10} = \text{(first-order) elimination rate constant} \]

\[ \text{Clearance (CL)} = V_d \cdot k_{10} \]
The volume of drug in the body cleared per unit time

\[ \text{Half-life} = 0.693 \cdot \frac{V_d}{\text{CL}} \]
Compartmental Approach after intravenous dosing

- Rapidly equilibrating tissues: plasma, red blood cells, liver, kidney, ...
- Slower equilibrating: adipose tissues, muscle, ...
  - Usually peripheral compartment
  - Slowly redistribution reason for long terminal half-life
Intravenous dose of 0.2 mg levocabastine

- $V_1 = 44 \text{ L}$
- $V_2 = 35 \text{ L}$
- $K_{12} = 0.84 \text{ h}^{-1}$
- $K_{21} = 1.05 \text{ h}^{-1}$
- $K_{10} = 0.4 \text{ h}^{-1}$
Intravenous dose of 0.2 mg levocabastine

\[ \text{Cld}= k_{12} \cdot V_1 = 36.7 \text{ L/h} \]

\[ \text{V1} = 44 \text{ L} \quad \text{V2} = 35 \text{ L} \]

\[ \text{Cld}= k_{21} \cdot V_2 = 36.7 \text{ L/h} \]

\[ \text{Cl}=K_{10} \cdot V_1=\text{Dose/ AUC}= 1.77 \text{ L/h}=30 \text{ mL/min} \]

\[ \text{Vdss} = V_1 + V_2 \]
Rates of drug exchange

\[ \text{DAp/dt} = -K_{10}.V_c.C_P - K_{12}.V_c.C_P + K_{21}.V_t.C_t \]

\[ \text{DAT/dt} = K_{12}.V_c.C_P - k_{12}.V_t.C_t \]

Initially very fast decay due to distribution to tissues and elimination ("distribution phase") until equilibrium is reached (influx into and efflux from tissue is equal)

After a pseudo-equilibrium is reached, there is only loss of drug from the body ("elimination phase"), but is in fact combination of redistribution from tissues and elimination

Rate of redistribution may differ significantly across drugs; long terminal half-life is compounds sticks somewhere
Intravenous dose of 0.2 mg levocabastine

\[ C_p = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \]

\[ C_p = 2.1 \cdot e^{-1.91 t} + 2.5 \cdot e^{-0.0224 t} \]

\[ t_{\frac{1}{2}, \text{term}} = t_{\frac{1}{2}, \beta} = \frac{0.693}{\beta} = \frac{0.693}{0.0224 h - 1} = 31 h \]

\[ V_d \beta = \frac{\text{CL}}{\beta} = \frac{\text{Dose}}{(\text{AUC. } \beta)} = V_d \text{area} \]
Two-compartmental model

Central Compartment

$V_c$

K10

K12

K21

Peripheral Compartment

$V_t$

K10, K12, K21 are first order rate constants

hybrid first-order rate constants $\alpha$ and $\beta$ for the so-called distribution phase and elimination phases, $T_{1/2\alpha}$ and $T_{1/2\beta}$

$V_c$, $V_{dss}$, $V_{d\beta}$ or $V_{darea}$ are $V_d$ of central compartment, at steady-state, during elimination phase
Compartmental approach after intravenous dosing

Compartments serve as reservoirs with different drug amounts (concentrations), different volumes, and different rates of exchange of drug with the central compartment.

The shape of the plasma concentration-time profile empirically defines the number of compartments.
Intravenous Sufentanil

Gepts et al., Anesthesiology, 83:1194-1204, 1995
Three compartmental model
Sufentanil Pharmacokinetics

<table>
<thead>
<tr>
<th>Volume of distribution (L)</th>
<th>Mixed-effects Population PK analysis (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population Average</td>
</tr>
<tr>
<td>Central (V1)</td>
<td>14.6</td>
</tr>
<tr>
<td>Rapidly equilibrating (V2)</td>
<td>66</td>
</tr>
<tr>
<td>Slowly equilibrating (V3)</td>
<td>608</td>
</tr>
<tr>
<td>At steady-state</td>
<td>689</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clearance (L/min)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic (CL or CL1)</td>
<td>0.88</td>
</tr>
<tr>
<td>Rapid distribution (CL2)</td>
<td>1.7</td>
</tr>
<tr>
<td>Slow distribution (CL3)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Gepts et al., Anesthesiology, 83:1194-1204, 1995
## Three compartmental model

### Sufentanil Pharmacokinetics

<table>
<thead>
<tr>
<th>Fractional Coefficients</th>
<th>Rate constants (min⁻¹)</th>
<th>Rate constants (min⁻¹)</th>
<th>Rate constants (min⁻¹)</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>0.94</td>
<td>K10</td>
<td>0.06</td>
</tr>
<tr>
<td>B</td>
<td>0.058</td>
<td>K12</td>
<td>0.11</td>
</tr>
<tr>
<td>C</td>
<td>0.0048</td>
<td>K13</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>K21</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td></td>
<td>K31</td>
<td>0.0011</td>
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<tr>
<td><strong>Exponents (min⁻¹)</strong></td>
<td><strong>Half-lives (min)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α</td>
<td>0.24</td>
<td>t1/2 α</td>
<td>2.9</td>
</tr>
<tr>
<td>β</td>
<td>0.012</td>
<td>t1/2 β</td>
<td>59</td>
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<tr>
<td>γ</td>
<td>0.0006</td>
<td>t1/2 γ</td>
<td>1129</td>
</tr>
</tbody>
</table>

Gepts et al., Anesthesiology, 83:1194-1204, 1995
Compartmental approach after intravenous dosing

- Central compartment
- Shallow Peripheral compartment
- Deep Peripheral compartment
- Peripheral compartment
- Effect site
Time profile of opioid concentrations in plasma and the predicted concentrations at the effect site based upon an effect compartment PK-PD model (expressed as percentage of the initial plasma concentration)

Effect site concentration profile reflect difference in onset time of analgesia

Shafer and Varvel, Anesthesiology 74:53-63, 1991
Rate of Drug Distribution

*perfusion-limited* tissue distribution

- immediate equilibrium of drug in blood and in tissue
- only limited by blood flow
- highly perfused: liver, kidneys, lung, brain
- poorly perfused: skin, fat, bone, muscle

**Permeability rate limitations or membrane barriers**

- blood-brain barrier (BBB)
- blood-testis barrier (BTB)
- placenta
Unbound Fraction and Drug Disposition

Plasma

Cell membrane

Tissue

Protein-bound drug → Free drug (non-ionized)

Free drug (non-ionized) → Protein-bound drug

Pka-pH, affinity for plasma and tissue proteins, permeability, …

Ionized drug (free)
# Physicochemistry, PK and EEG PD of narcotic analgesics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Alfentanil</th>
<th>Fentanyl</th>
<th>Sufentanil</th>
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<tbody>
<tr>
<td>pKa</td>
<td>6.5</td>
<td>8.43</td>
<td>8.01</td>
</tr>
<tr>
<td>% unionized at pH 7.4</td>
<td>89</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>P oct/water</td>
<td>130</td>
<td>810</td>
<td>1750</td>
</tr>
<tr>
<td>% unbound in plasma</td>
<td>8</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Vdss (L)</td>
<td>23</td>
<td>358</td>
<td>541</td>
</tr>
<tr>
<td>Cl (L/min)</td>
<td>0.20</td>
<td>0.62</td>
<td>1.2</td>
</tr>
<tr>
<td>t1/2 keo EEG (min)</td>
<td>1.1</td>
<td>6.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Ce50, EEG (ng/ml)</td>
<td>520</td>
<td>8.1</td>
<td>0.68</td>
</tr>
<tr>
<td>Ce50, unb (ng/ml)</td>
<td>41</td>
<td>1.2</td>
<td>0.051</td>
</tr>
<tr>
<td>Ki (ng/ml)</td>
<td>7.9</td>
<td>0.54</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Localisation and Role of Drug Transporters
Zhang et al., FDA web site and Mol. Pharmaceutics 3, 62-69, 2006

Liver Sinusoidal
Hepatic Uptake:
OCT1, OATP-C, OATP-B, OATP8, NTCP, OAT2
Secretion: MRP1, MRP3

Brain Transporters: P-gp
(MDR1), OAT3, OATP-A,
MRP1, MRP3

Liver Canicular
Biliary Excretion:
P-gp, MRP2, BCRP, MDR3

Intestinal Luminal
Absorption: PEPT1
Secretary: P-gp,
OATP3

Kidney Basolateral:
OCT1, OCT2, OAT1,
OAT2, OAT3, MRP1

Kidney Apical
Renal Secretion: P-gp,
OAT4
Reabsorption: PEPT2
Apparent Volume of Distribution

- **Vd** = Amount of drug in body/concentration in plasma
- Minimum Vd for any drug is ~3L, the plasma volume in an adult, for ethanol: equal to body water
- For most basic drugs very high due to sequestering in specific organs (liver, muscle, fat, etc.)

---

Vd (L/kg) after iv dosing in rat and human (J&J data)
Multiple Dosing Concepts
Dosing to Steady-state

On continued drug administration, the amount in the body will initially increase but attain a steady-state, when the rate of elimination (drug loss per unit time) equals the amount administered per unit time.

- **Amount A in body**
  - $C_{\text{plasma}} \cdot V_{\text{dss}}$

- **mg/day**

- **Fractional loss of A or Cp**
  - First-order rate
    - $-K \cdot A$; $-CL \cdot C_p$

1. **Initial increase when** $k_o > -K_{10} \cdot A_{\text{body}}$

2. **Steady state when** $k_o = K \cdot A_{\text{body}} = CL \cdot C_p$

3. $A_{ss}$ or $C_{ss}$ constant as long $k_o$ constant and CL constant
Time to steady-state
Half-life of 24 hr and dosing interval of 24 hrs

Steady-state when drug loss per day equals drug intake per day
Time to steady-state
Half-life of 24 hr and dosing interval of 24 hrs

\[ C_{max} = \frac{AUC_{ss}}{\tau} \]

\[ C_{avg,ss} = \frac{AUC_{ss}}{\tau} \]

\[ C_{min} = \frac{AUC_{ss}}{\tau} \]

\[ AUC_{ss} = AUC_{\infty} \text{ single dose} \]

\[ \frac{AUC_{ss}}{AUC_{\tau \text{ first dose}}} = \text{Accumulation Index} \]
**Steady-state**

The amount in the body at steady-state ($A_{ss}$)

$$A_{ss} = \frac{K_0}{K_e}$$

The plasma concentration at steady-state ($C_{ss}, C_{avgss}$)

$$C_{pss} = \frac{K_0}{K_e.V_{dss}} = \frac{K_0}{C_l}$$

$C_{ss}$ is proportional to the dosing rate (zero-order input) and inversely proportional to the first-order elimination rate or clearance.
Time to steady-state
Half-life of 24 hr and dosing interval of 24 hrs

\[ C = C_{ss}(1 - e^{-k \cdot t}) \]

5-6 half-lives to reach steady-state
An effective half-life reflects drug accumulation

Drug A: A=20 ng/mL; B=80 ng/mL; $T_{1/2\alpha} = 3$ h; $T_{1/2\beta} = 24$ h

Drug B: A=80 ng/mL; B=20 ng/mL; $T_{1/2\alpha} = 3$ h; $T_{1/2\beta} = 24$ h
An effective half-life reflects drug accumulation

Accumulation ratio = \frac{AUC_{ss, \tau}}{AUC_0 - \tau} = \frac{1}{1 - \exp(-K_{eff} \cdot \tau)}

Drug A: \text{T}_{1/2_{eff}} = 20 \text{ h}
Drug B: \text{T}_{1/2_{eff}} = 10 \text{ h}

\text{Boxenbaum, J Clin Pharmcol 35:763-766, 1995}
Mean residence time = MRT

MRT is the time the drug, on average, resides in the body.

MRT = Vdss/Cl
Loading and Maintenance Dose

- **Maintenance Dose**
  \[ = \text{desired } \text{Css} \times \text{CL} \]

- **Loading Dose**
  \[ = \text{desired } \text{Css} \times \text{Vd} \]

Loading dose can be high for drugs with large Vd, then LD divided over various administrations

*(J&J data on file)*
Total body clearance (CL)

A measure of the efficiency of all eliminating organs to **metabolize** or **excrete** the drug

Volume of plasma/blood cleared from drug per unit time

\[
CL = k_{10} \cdot Vc = \lambda_z \cdot Vd_z = MRT \cdot Vd_{ss}
\]

\[
CL = \text{Dose} / AUC_{\text{plasma}}
\]
Physiological approach to Clearance

Amount A
or Concentration C
in blood

Rate in
Q.Cpa

Rate out
Q.Cpv

Clearance = $\frac{Q(Cpa - Cpv)}{Cpa} = Q \cdot \frac{fu.Clint}{Q + fu.Clint}$

Low hepatic clearance
if extraction ratio $E << 1$
eg. Risperidone (Fabs 85%)

High hepatic clearance
if $E \approx 1$
eg. Nebivolol (Fabs 10%)
Bioavailability F

After oral administration, not all drug may reach the systemic circulation.

The fraction of the administered dose that reaches the systemic circulation is called the bioavailability F.
Oral drug absorption, Influx and Efflux Transporters, Drug Loss by First-pass

\[ F = F_{\text{absorbed}} \cdot (1 - E_{\text{gut}}) \cdot (1 - E_{\text{liver}}) \]
Grapefruit inhibits gut-wall metabolism (J&J data on file)

Gent, 24 August 2007/avpeer 60
Total body clearance (CL)

**Intravenous clearance**

\[ \text{Cl} = k_{10} \cdot Vc = \lambda_z \cdot Vd_z = \text{MRT} \cdot Vdss \]

\[ \text{CL} = \text{Dose} / \text{AUC}_{iv} \]

**Apparent oral clearance**

Oral clearance \( \text{CL/F} = \text{Dose} / \text{AUC}_{oral} \)
Biopharmaceutical Classification


Class 1
High Solubility
High Permeability
Rapid Dissolution

Class 2
Low Solubility
High Permeability

Class 3
High Solubility
Low Permeability

Class 4
Low Solubility
Low Permeability
Predicting Drug Disposition via BCS

Wu and Benet, Pharm Res 22:11-23, 2005

High Solubility

Class 1
Transporter effects minimal

Class 3
Absorptive transporter effects predominate

Low Solubility

Class 2
Efflux transporter effects predominate

Class 4
Absorptive and efflux transporter effects could be important
Predicting Drug Disposition via BCS
Wu and Benet, Pharm Res 22:11-23, 2005

High Solubility

Class 1
Metabolism

Class 3
Renal & Biliary Elimination of Unchanged Drug

Low Solubility

Class 2
Metabolism

Class 4
Renal & Biliary Elimination of Unchanged Drug

High Permeability

Low Permeability
Biliary Excretion: Enterohepatic Recycling

- The drug in the GI tract is depleted.
- Biliary excreted drug is reabsorbed.
- Drug in blood
- Metabolism
- Drug in intestine
- Enzymatic breakdown of glucuronide
- Conjugate in bile
- Dumped from gall bladder
- Conjugate in intestine
- Excretion in feces
- Excretion in urine
- Re-absorption
- Biliary excreted drug is reabsorbed
- The drug in the GI tract is depleted.
**Highly variable drugs and drug products**

- **Drugs with high within-subject variability in Cmax and AUC (≥ 30% coefficient of variation)** are called “highly-variable drugs”

- **Highly-variable drug products are pharmaceutical products in which the drug is not highly variable, but the product is of poor pharmaceutical quality**
From PK to relevant information for the patient

**Compound X®**

**Tablets and oral solution**

......

**Pharmacokinetics:** The estimated mean ± SD half-life at steady-state of compound X after intravenous infusion was 35.4 ± 29.4 hours.

**Renal impairment:** The oral bioavailability of compound X may be lower in patients with renal insufficiency. A dose adjustment may be considered.

**Other medicines:** Do not combine compound X with certain medicines called azoles that are given for fungal infections. Examples of azoles are ketoconazole, itraconazole, miconazole and fluconazole.

You should not take compound X with grapefruit juice.

......
Useful Material

Handbooks

- Pharmacokinetics, 2nd Ed., by Milo Gibaldi
- Clinical Pharmacokinetics, Concepts and Applications, 3rd Ed., by Malcolm Rowland and Thomas N. Tozer

WinNonLin software™, Pharsight®

- Noncompartmental and Compartmental analysis
- Pharmacokinetic-pharmacodynamic analysis
- Statistical Bioequivalence analysis
- In vitro-in vivo Correlation for drug products
Thank for your attention!
Rates and Orders of pharmacokinetic processes

The rate of a process is the speed at which it occurs

The rate of drug elimination represents the amount (A) of drug absorbed, distributed or eliminated per unit time

Zero-order process or rate: constant amount per unit time
Input rate of infusion: mg per h
- \( \frac{dA}{dt} = k_0 = \text{zero order rate constant} \)

First-order process or rate: rate is proportional to the amount of drug available for the process
- \( \frac{dA}{dt} = -k.A = -k.Volume.CC\)
Rates of drug exchange

Change of the drug amount in central compartment

\[
\frac{dA_{\text{plasma}}}{dt} = -K_{10}.A_{\text{plasma}} - K_{12}.A_{\text{plasma}} + K_{21}.A_{\text{peripheral}}
\]

\[
\frac{dA_{\text{plasma}}}{dt} = -K_{10}.V_{c}.C_{\text{plasma}} - K_{12}.V_{c}.C_{\text{plasma}} + K_{21}.V_{t}.C_{\text{peripheral}}
\]

\[
\frac{dA_{\text{plasma}}}{dt} = -C_{L}.C_{\text{plasma}} - C_{Ld}.C_{\text{plasma}} + C_{Ld}.C_{\text{peripheral}}
\]

\[
\frac{dC_{p}}{dt} = -K_{12}.C_{\text{plasma}} + K_{21}.C_{\text{peripheral}}
\]

Change of the drug amount in peripheral compartment

\[
\frac{dA_{\text{peripheral}}}{dt} = -K_{12}.V_{c}.C_{\text{plasma}} + K_{21}.V_{t}.C_{\text{peripheral}}
\]

\[
\frac{dA_{\text{peripheral}}}{dt} = -C_{Ld}.C_{\text{plasma}} + C_{Ld}.C_{\text{peripheral}}
\]

\[
\frac{dC_{\text{peripheral}}}{dt} = -K_{12}.C_{\text{plasma}} + K_{21}.C_{\text{peripheral}}
\]