Introduction to pharmacokinetics

Michael Meyer

Outline

• Introduction
  importance of pharmacokinetics

• Basic aspects of pharmacokinetics
  pharmacokinetic parameters, compartment models, statistical models, single and multiple dosing

• Bioavailability
  analysis, physicochemical basis

• ADME processes
  absorption, distribution, metabolism, excretion
Pharmacokinetics

- Definition

  description of the time dependent processes acting on a drug in an organism

  liberation
  absorption
  distribution
  metabolism
  excretion

- Toxicokinetics

  kinetics applied to toxicology

Pharmacokinetics II

- Relevance

  characterisation of ADME properties of a drug or a metabolite as a function of time

  determination of the optimal therapeutic scheme
    type and frequency of administration, dose

  therapeutically relevant drug concentration at the place of action

  comparison of different formulations of the same drug

  drug interactions (pharmacokinetic interactions)
Basic aspects of pharmacokinetics

Linear and non-linear pharmacokinetics

- Linear pharmacokinetics
  
  linear relation between dose and plasma concentration

  in a given interval always the same drug fraction is eliminated

- Non-linear pharmacokinetics

  no linear relation between dose and plasma concentration

  reasons for non-linearity:
  saturation of enzymatic processes,
  enzyme induction,
  active transport processes, ...
**Area under the plasma concentration curve**

- Area under the curve (AUC)

\[ AUC = \int_{0}^{\infty} C(t) dt \]

**Area under the curve II**

- The integral can be calculated using the trapezoidal rule for numerical integration

\[ AUC_{0,1} = \frac{(c_0 + c_1)}{2} (t_1 - t_0) \]

\[ AUC_{1,2} = \frac{(c_1 + c_2)}{2} (t_2 - t_1) \]

\[ AUC = \sum_{i=1}^{n-1} AUC_i \]

if necessary extrapolation \( t \rightarrow \infty \)
Clearance

Many drugs are eliminated in a first order process, i.e. the amount of drug eliminated is proportional to the amount of drug in the plasma.

- Clearance CL

  volume of plasma purified from drug per time interval

  the clearance is constant and independent of the drug concentration in a first order process

  relation between clearance, intravenous dose and area under the curve

  \[ CL = \frac{D_{iv}}{AUC} \]

Volume of distribution

- The volume of distribution \( V_d \) is the amount of drug in the body divided by the plasma concentration

  \[ V_d = \frac{X}{C} \]

  it is the apparent volume of a solution required to obtain the observed plasma concentration
**Half life**

- Time interval required to eliminate half of the drug quantity (refers frequently to the terminal elimination phase).

- Example
  - the half life $t_{1/2}$ of a drug is 2 h
  - What is the percentage eliminated after 4 h?
    
    - 2 h: 50% eliminated, 50% remaining
    - 4 h: 50% + 25% = 75% eliminated, 25% remaining

- Relation to primary variables
  
  $t_{1/2} = 0.693 \frac{V_d}{CL}$

**Compartment models**

- Linear kinetics for iv injection

  $\text{bolus iv} \rightarrow \text{compartment 1} \rightarrow$ 

  first order differential equation

  $\frac{dc}{dt} = -k_e c$

  c: plasma concentration
  $k_e$: elimination constant
  t: time

  integration

  $c = c_0 e^{-k_e t}$

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Compartment models II

- Half life for first order kinetics

\[ c = c_0 e^{-k_e t} \]
\[ \ln c = \ln c_0 - k_e t \cdot \ln e \]
\[ \ln c = \ln c_0 - k_e t \]
\[ \ln \frac{c_0}{2} = \ln c_0 - k_e t_{1/2} \]
\[ \ln c_0 - \ln 2 = \ln c_0 - k_e t_{1/2} \]
\[ \ln 2 = k_e t_{1/2} \]
\[ t_{1/2} = \ln 2 / k_e \]
\[ t_{1/2} = 0.693 / k_e \]

Compartment models III

- Zero order kinetics

elimination independent of drug concentration

\[ \frac{dc}{dt} = -k_e \]

integration

\[ c = c_0 - k_e t \quad \text{linear decrease of plasma concentration} \]

- Example

ethanol is approximately eliminated in a process of order zero (limited elimination capacity of alcohol dehydrogenase, \( \approx 0.1 \text{ g h}^{-1} \text{ kg}^{-1} \text{ body weight} \))

First order eliminations are much more important than zero order
Compartment models IV

- One compartment model for intravenous administration and multiple routes of elimination

[Diagram showing one compartment model with compartments 1 and 2, elimination via metabolism, urine, biliary excretion, ...]

- One compartment model for extravascular administration

[Diagram showing extravascular administration with compartments 1 and 2, and first-order processes]

Compartment models V

- Two compartment model for intravenous injection

[Diagram showing two compartment model with compartments 1 and 2, first-order processes]
Extravascular dosing

- First order absorption and excretion

\[ \text{dose} \rightarrow (R) \rightarrow \text{compartment 1} \rightarrow (k_a) \rightarrow k_e \]

Bateman function

\[ c = c_0 \left( e^{-k_a t} - e^{-k_e t} \right) \]

\[ c_0 = f \cdot \frac{D}{V} \cdot \frac{k_a}{k_e - k_a} \]

- Influence of individual parameters on plasma concentration

\[ c_0 = 40 \text{ ng/ml}, \quad k_a = 0.1 \text{ h}^{-1}, \quad k_e = 0.05 \text{ h}^{-1} \]

\[ c_0 = 20 \text{ ng/ml}, \quad k_a = 0.1 \text{ h}^{-1}, \quad k_e = 0.05 \text{ h}^{-1} \]

\[ c_0 = 40 \text{ ng/ml}, \quad k_a = 0.1 \text{ h}^{-1}, \quad k_e = 0.01 \text{ h}^{-1} \]
**Extravascular dosing III**

- Influence of individual parameters on plasma concentration

  maximum plasma concentration $c_{\text{max}}$ increases if

  $c_0$ increases (i.e. dose $D$ or bioavailability $f$ increases)

  $k_e$ decreases or $k_a$ increases

  time $t_{\text{max}}$ increases if $k_a$ decreases

  plasma concentration $c = 0$ if $k_a \leq k_e$

  $\text{AUC}_{\text{iv}} = \text{AUC}_{\text{ev}}$ for bioavailability $f = 1$

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**Kinetics for multiple dosing**

- Kinetics for multiple bolus iv dosing
  
  plasma concentration oscillates between minimum and maximum plasma concentration at steady state

- Example
  
  multiple iv doses with 12 h time difference, half life $t_{1/2} = 6\text{h}$, initial concentration 100 ng/ml

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**multiple dosing II**

- Pharmacokinetic parameters for multiple dosing

  τ  dose interval

  \( AUC_{\tau,ss} \)  area under the curve in dosing interval \( \tau \) at steady state

  \( c_{min,ss}, c_{max,ss} \)  minimum- and maximum concentration

  \( c_{trough} \)  concentration at the end of a dosing interval immediately before next dose

  \( c_{av,ss} \)  mean concentration \( c_{av,ss} = \frac{AUC_{\tau,ss}}{\tau} \)

  \( T_{\text{Cave}} \)  time range with concentrations exceeding \( c_{av,ss} \)

  \( \text{PTF\%} \)  peak-trough fluctuation \( \text{PTF\%} = 100 \cdot \frac{(c_{max,ss} - c_{min,ss})}{c_{av,ss}} \)

  \( R \)  accumulation ratio estimated from single dose

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**Urine excretion**

- Urine excretion after single iv-bolus

  \[ \begin{array}{c}
  \text{bolus iv} \\
  \rightarrow \text{compartment 1} \\
  \rightarrow k_e
  \end{array} \]

  first order differential equation

  \[ \frac{du}{dt} = k_e x \]

  u  amount of drug in urine

  x  amount of drug in plasma

  \( k_e \)  rate constant of elimination

  t  time

  integration

  \[ u_t = u_{\infty} \left(1 - e^{-k_e t}\right) \]  amount of drug excreted into urine up to time \( t \)
Urine excretion II

- Urine excretion after single iv-bolus

\[ U_t = U_\infty (1 - e^{-k_t t}) \]

the amount of drug in the body is the difference between iv-dose and amount of drug in urine provided that the urine excretion is the only route of elimination.

Urine excretion III

- Pharmacokinetic parameters for urine excretion

- \( U_{t_1,t_2} \) amount of unchanged drug in urine in time interval from \( t_1 \) to \( t_2 \)
- \( c_{ur} \) urine concentration
- \( V_{ur} \) urine volume
- \( f_e \) fraction of unchanged drug in urine

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**Statistical moments**

**Moments of the concentration time curve**

- Intravenous application

The mean residence time of a drug can be obtained from the quotient of the first (AUMC) and zero order moment (AUC) of the plasma concentration time curve.
Mean residence time

- Mean residence time of a drug in the body

\[ MRT = \frac{AUMC}{AUC} \]

\[ AUMC = \int_0^\infty tC(t)dt \]

\[ AUC = \int_0^\infty C(t)dt \]

Based on theory of statistical moments, not on compartment models, can be used for any type of administration.

Relation to half life for intravenous bolus injection

\[ t_{1/2} = 0.693 \cdot MRT_{iv} \]

Mean residence time II

- Numerical calculation

\[ MRT = \frac{AUMC}{AUC} \]

\[ AUC = \int_0^\infty c(t)dt \]

\[ AUMC = \int_0^\infty tc(t)dt \]

\[ AUC_i = \frac{C_i(t_{i+1}) - C_i(t_i)}{2} (t_{i+1} - t_i) \]

\[ AUMC_i = \frac{C_i(t_{i+1} + t_{i+1})}{2} (t_{i+1} - t_i) \]

\[ AUC = \sum_{i=1}^{n-1} AUC_i \]

\[ AUMC = \sum_{i=1}^{n-1} AUMC_i \]
Mean absorption time

- Mean residence and absorption times

mean absorption time MAT

$$\text{MAT} = \text{MRT}_{\text{iv}} - \text{MRT}_{\text{iv}}$$

difference between mean residence times after non-intravenous and intravenous administration of a drug solution

mean dissolution time MDT

$$\text{MDT} = \text{MAT}_{\text{tabl.}} - \text{MAT}_{\text{sol.}}$$

difference between the mean absorption times after oral administration of a drug in a tablet and in solution

Bioavailability and bioequivalence
Bioavailability

- The absolute bioavailability $F$ is the percentage of the dose reaching the global circulation

$$F = \frac{D_{iv} \cdot AUC_{nv}}{D_{nv} \cdot AUC_{iv}} \cdot 100$$

$D =$ dose

(n)iv = (no)intravenous e.g. oral

- Relative bioavailability refers to non-iv administrations

- Bioavailability is a property of the dosage form and not a property of the drug

Bioavailability II

- Factors involved

  physicochemical factors
  solubility, pK, lipophilicity, permeability

  pharmaceutical factors
  particle size, solubilizer, density of tablet

  delivery method

  local factors
  ingestion of food, vomiting, gastric emptying disorders

  first pass effect
  metabolism of drugs taken orally in the liver prior to reaching systemic circulation
**Lipinski-rule of oral bioavailability (rule of 5)**

Oral absorption is unlikely if two or more of the parameters are outside of the range given below

<table>
<thead>
<tr>
<th>descriptor</th>
<th>potential problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>MW ≤ 500</td>
<td>poor diffusion</td>
</tr>
<tr>
<td>logP ≤ 5</td>
<td>too much lipophilicity</td>
</tr>
<tr>
<td>hydrogen bond donor atoms ≤ 5</td>
<td>too many H-bonds with membrane</td>
</tr>
<tr>
<td>hydrogen bond acceptor atoms ≤ 10</td>
<td></td>
</tr>
</tbody>
</table>


**Octanol-water distribution coefficient**

distribution of a compound in n-octanol / water

\[ P_{ow} = \frac{c_{Oct}}{c_{aq}} \]

\[ \log P_{ow} = \log \left( \frac{c_{Oct}}{c_{aq}} \right) \]

<table>
<thead>
<tr>
<th>compound</th>
<th>log ( P_{ow} )</th>
<th>( P_{ow} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetamide</td>
<td>-1.155</td>
<td>0.833</td>
</tr>
<tr>
<td>methanol</td>
<td>-0.824</td>
<td>3.370</td>
</tr>
<tr>
<td>formic acid</td>
<td>-0.413</td>
<td>6.410</td>
</tr>
</tbody>
</table>

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**Distribution coefficient II**

regression model for log P calculation derived from a training set

\[ \log P_{\text{OW}} = \sum n_i a_i \]

- \( n_i \) number of atoms of type i
- \( a_i \) contribution of each atom i to \( \log P_{\text{OW}} \)

<table>
<thead>
<tr>
<th>atom type</th>
<th>contr. ( a_i )</th>
<th>atom type</th>
<th>contr. ( a_i )</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 aliphatic</td>
<td>0.1441</td>
<td>O2 alcohol</td>
<td>-0.2893</td>
</tr>
<tr>
<td>C8 aromatic</td>
<td>0.08452</td>
<td>H2 alcohol</td>
<td>-0.2677</td>
</tr>
<tr>
<td>H1 H bound to C</td>
<td>0.1230</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Lipinski rule**

- Example

paracetamol
N-(4-hydroxyphenyl)acetamide

![Structure of paracetamol]

donor atoms 2
acceptor atoms 3
molecular weight 151.1
\( \log P \) (XlogP3) 0.5
## Bioequivalence

- **Objective**
  equivalence of two preparations of a drug based on similarity of pharmacokinetic properties

- **Example**
  generic drug vs. original formulation
  modification of excipients

- **Parameters**
  AUC, in addition maximum plasma concentration and time to reach the maximum plasma concentration

- **Analysis**
  statistical analysis based on confidence intervals

### Study design

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**Design of PK-Studies**

- **Subjects**
  
  frequently healthy male volunteers  
  later volunteers from target populations  

- **Example of plasma sampling** ($t_{1/2}$ ca. 3-4 h for i. v. dosing)
  
  i.v. study  
  (pre-dose), 5, 10, 15, 20, 30, 45 min, 1, 1.5, 2, 4, 6, 8, 12, 24 h  

  s. c. study  
  (pre-Dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 20, 24, 30, 36, 48 h  

- **Example of urine sampling**
  
  (pre-Dose), 0 - 4, 4 - 8 h, 8 – 12 h, 12 - 24 h  

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**Design of bioequivalence studies**

- **Study design**
  
  randomised cross-over study  

  sequence | period 1 | wash out | period 2  
  1 | test | reference | test  
  2 | reference |  

  alternatively parallel study for drugs with long half life  

  at least 12 volunteers (> 18 years, normal lab values and health status, preferably non-smokers, no alcohol/drugs)  

  standardised food / beverage intake  

  often single dose sufficient
**ADME**

**Liberation**

- Physicochemical factors
  - polymorphism (different crystal forms)
  - solubility
  - local pH-value
  - particle size

- Pharmaceutical factors
  - property of dosage form, e.g. excipients
### Absorption

- **Drug application**
  - topical
    - local action at location of administration, absorption often undesirable
  - systemic
    - distribution via global circulation

- **Choice of application**
  - time, duration and location of drug action, absorption, route of administration, health status of patient

- **Route of administration**
  - skin / mucous membranes e.g. oral, nasal, sublingual, pulmonary, rectal, percutaneous
  - injections e.g. intravenous, subcutaneous, intramuscular

### Absorption II

- **Mechanisms**
  - passive diffusion, active transport (Influx)
    - paracellular – between cells
    - transcellular – through cells

- **pH - influence**
  - drugs with acidic or basic substituents are partially ionized or neutral (depending on pK<sub>a</sub>-value and local pH).
  - the ionic fraction is less lipophilic and has less ability of diffusion through membranes
**Distribution**

- Total body water

  body water
  males: ca. 60% of body weight, ca. 40 L
  females: ca. 50% of body weight, ca. 30 L

distribution
  ca. 30-40% intracellular water
  ca. 20% extracellular water
  ca. 15% interstitial water (15 L)
  ca. 5% plasma water (3 L)

**Distribution II**

- Plasma proteins
  - albumins (60%), globulins, acidic glycoprotein

- Consequences
  - bound drugs cannot interact with the target
  - bound drugs cannot be metabolized or excreted
  - drug interactions possible
**Distribution III**

- Fraction of bound and unbound drug

\[
[W] + [P] \rightleftharpoons [WP]
\]

\[
K = \frac{[WP]}{[W][P]}
\]

\[
f_b = \frac{[WP]}{[W]_{\text{tot}}} = \frac{[WP]}{[WP] + [W]}
\]

bound fraction

\[
f_u = 1 - f_b = 1 - \frac{[WP]}{[WP] + [W]} = \frac{1}{1 + K [P]}
\]

unbound fraction

\[f_u\] increases if the binding constant \(K\) decreases and the protein concentration \([P]\) decreases.

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**Distribution IV**

- Blood brain barrier

- stable medium
- transport of nutrients and waste
- protection of brain

reduced paracellular diffusion through tight junctions, enzymatic metabolism, active efflux-transport

transcellular diffusion of compounds with small polar surface area possible
**Distribution V**

- Placenta

  task
  transport of nutrients and waste elimination, otherwise transport barrier
  oxygen supply, production of hormones

  mechanisms
  transcellular diffusion, active transport, endocytosis, metabolism

  xenobiotics may possibly overcome the placenta barrier
  indirect treatment of fetus by treatment of mother

  factors involved
  gradient of concentrations, protein binding, molecular weight, lipophilicity

**Distribution VI**

- Enterohepatic circle
  circulation of (metabolised) drugs between liver and gut
  with re-absorption after excretion via bile

  consequences
  fluctuation of plasma levels, extension of residence time
  unexpected plasma levels after swallowing sublingual tablets
## Elimination

- **Processes**
  - metabolism – biochemical modification
  - excretion – elimination of drug or metabolites from organism

- **Routes of excretion**
  - renal - excretion via kidney to the urine
    - main route for MW < 300
  - biliary / intestinal – via bile / gut (re-absorption possible)
    - main route for MW > 500
  - lung – anesthetics
  - mother’s milk pH = 6.6, blood pH 7.4 => \( pK_a \)-dependent of distribution
  - respiration, saliva

## Metabolism

- **Relevance**
  - reduction of drug concentration, formation of metabolites with different efficacy / toxicity profile, activation of prodrugs
  - especially in the liver and intestinal mucosa, but also in lung and blood
  - first-pass effect after oral administration
    - metabolism of drug in liver or gut
    - reduction of systemic availability

- **Metabolic reactions**
  - Phase I – modification e. g. oxidation, reduction, hydrolysis
  - Phase II – conjugation e. g. glucuronidation, sulfonation, acetylation
Metabolism II

- Examples of metabolic reactions

**modification**

**oxidation of aromatic and aliphatic compounds**

\[
\text{Ph} \rightarrow \text{Ph}^\text{+}
\]

**reduction of aldehydes / ketones**

\[
\text{R}^\text{CH}=O \rightarrow \text{R}^\text{CH} \rightarrow \text{R}^\text{CH}_2\text{OH} \rightarrow \text{R}^\text{CH}_2\text{H} \rightarrow \text{R}^\text{H}
\]

**hydrolysis of esters and amides**

\[
\text{R}^\text{O}^\text{R} \overset{\text{H}_2\text{O}}{\longrightarrow} \text{R} ^\text{OH} \hspace{1cm} \text{R}^\text{N} \overset{\text{H}_2\text{O}}{\longrightarrow} \text{R}^\text{NH}_2 \hspace{1cm} \text{R}^\text{OH}
\]

Metabolism III

- Examples of enzymes catalysing modifications

**oxidoreductases**

- cytochrome P450 (CYP)
- flavin-dependent monooxygenases (FMO)
- monoamineoxidases (MAO)
- cyclooxigenases (COX)
- alcohol dehydrogenase (ADH)
- aldehyde dehydrogenase (ALDH)

**hydrolases**

- esterases
- amidases
**Metabolism IV**

- Cytochrome P450 (CYP)

monooxygenases catalysing the general reaction

\[ R-H + O_2 + NADPH + H^+ \rightarrow R-OH + H_2O + NADP^+ \]

**occurrence**

\( \approx 60 \) different cytochromes P450, especially in the liver

**relevance**

involved in the metabolism of many drugs

CYP3A4 (\( \approx 50\% \)), CYP2D6 (\( \approx 30\% \)), CYP2C9 und CYP2C19 (\( \approx 10\% \))

**consequences**

drugs may be substrates, inhibitors or inducers

possibility of drug interactions

variability of metabolism caused by genetic variability of cytochromes (e. g. CYP2D6,CYP2C19)

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**Metabolism V**

- Examples of metabolic reactions

**conjugation reactions**

- glucuronidation catalysed by glucuronyltransferases

- transfer of a sulfo-group by sulfotransferases \( R - O - SO_3^- \)

- acetylation by N-acetyltransferases

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## References