Overview

1. PK : Basic principles and processes
2. Important PK Parameters
3. Modulating PK Parameters
4. PK : Drugs vs. contrast agents

Part 1
PK: Principles & Processes

How do drugs work?

Pharmacodynamics:
- a discipline within pharmacology that studies the biochemical and physiological effects of drugs and their mechanisms of action
- processes involved: receptor-ligand interactions, enzyme-binding, post-receptor signaling, dose-response effects and drug-drug interactions

Pharmacokinetics:
- a discipline within pharmacology that uses mathematical models to describe and predict the time-course of drug concentrations in the body
- processes involved: absorption, distribution, metabolism and elimination

What does the body do to a drug?
Pharmacokinetics

'what the body does to the drug' => 4 essential processes => ADME

<table>
<thead>
<tr>
<th>A</th>
<th>absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>distribution</td>
</tr>
<tr>
<td>M</td>
<td>metabolism</td>
</tr>
<tr>
<td>E</td>
<td>elimination</td>
</tr>
</tbody>
</table>

Drug effect phase

All four processes are important for controlling drug levels and tissue exposure, and they are therefore critical for determining the performance and the activity of a drug.

1st Phase: Absorption

=> the uptake of agents into the blood stream
=> for orally applied agents: from the GI-tract
=> for i.v. applied agents: absorption = 100%

Drug absorption is governed by:
- anatomy of the organ
- dosage form / formulation
- physicochemical properties of the drug

Important terms:
- Pharmaceutical availability (Fₐ) => fraction released from dosage form
- Bioavailability (Fₜ) => fraction reaching systemic circulation

Stomach: limited absorption

Absorption is limited by:
- protective mucosa
- muscle layer
- low perfusion
- low surface area
- lack of carriers

Small intestine is the preferred site for drug absorption

Drug absorption is promoted by:
- large surface area: Many (micro-)villi
- without villi: 0.5 m² => with: 200 m²
- efficient perfusion of villi
- very short distance between epithelial surface and blood vessels
- multiple transporters on villi

Distribution of drugs (in-) to tissues depends on:
- perfusion of tissues (blood flow)
- biological barriers
- uptake of drugs into tissues
- protein binding
- albumin-binding (longer t½; lower Vₜ)

2nd phase: Distribution

=> the process by which the drug spreads out over the body

Distribution of drugs (in-) to tissues depends on:
- perfusion of tissues (blood flow)
- biological barriers
- uptake of drugs into tissues
- protein binding
- albumin-binding (longer t½; lower Vₜ)

Mathematical modeling of distribution: 1-compartment model

Assumptions:
- Most simple model: Whole body = 1 compartment
- Instantaneous distribution over blood and organs
- Constant elimination process

Easy model
Simple PK analyses
Not very realistic...
One vs. multiple compartments

- 1-compartment model: instantaneous distribution over both blood and organs
- 2-compartment model: first blood ($V_1$, distr-vol), then organs ($V_2$, periph-vol)

Real-life situation is much more complicated

- The human body consists of many different compartments:
  - blood, different organs/tissues, extracellular fluids, cells, organelles, ...
  - 1- and 2-compartment models are used to simplify PK studies.
  - Computers and algorithms are needed to describe real-life PK

3rd Phase: Metabolism

- The chemical modification of drugs to enable/enhance their elimination
  - The liver is the main metabolizing organ
  - CYP450 (CYP3A4) enzymes in the liver metabolize drugs via:
    - Phase I-reactions: oxidation, reduction, hydrolysis
    - Phase II-reactions: conjugation with hydrophilic sulfate, glucuronic acid, or glutathione groups
  - Metabolites generally are much more water-soluble than the parental drug, and therefore can be eliminated more efficiently via the kidney / urine

PK: it all starts with the route of administration

- Enteral: oral, rectal
- Parenteral: intravenous, intramuscular, intraperitoneal
- Respiratory: inhalation, intratracheal, intranasal
- Topical: skin, mucosal

The route of administration strongly affects the PK of a drug
**PK : Blood concentration vs. time curves**

- Upon different routes of administration

**Routes of administration**

- **Drugs**: mainly orally administered
- **Contrast agents**: mainly i.v. administered

**PK profiles upon i.v. and oral administration**

- Blood concentrations vs. time curves

**Important PK parameters**

- $c_0$: the concentration at t = 0: the concentration of the drug in blood at the time point of administration. For orally applied agents and i.v. infusions, $c_0 = 0$. For agents applied via an i.v. bolus injection, $c_0 = c_{max}$
- $c_{max}$: the maximal concentration: the highest concentration achieved by a drug in the bloodstream (i.e. in systemic circulation)
- $t_{max}$: the time of maximal concentration: the time point at which the highest concentration of a drug in systemic circulation is achieved
- $t_{1/2}$: the half-life time: the time needed to reduce the concentration of the drug in systemic circulation by 50%

**Pharmacokinetic profiles of a drug upon intravenous and oral administration**

- Blood concentrations vs. time curves

**Important PK parameters**

- $k_a$: the fraction of orally applied drug that is absorbed (i.e. entering the circulation) per unit time is determined by the absorption constant
- $k_e$: the fraction of drug that is eliminated (i.e. leaving the circulation) per unit time is determined by the elimination constant

**AUC**: The Area Under the Curve (AUC; Bioavailability) is the fraction of the administered dose that reaches systemic circulation. The AUC is 100% for i.v. injections. For other routes of administrations, it varies, and e.g. depends on the fraction released from the formulation ($F_r$), on the fraction absorbed ($k_a$), and on first-pass metabolism

**TR**: The Therapeutic Range is the concentration range in which the levels of the drug in systemic circulation are optimal, i.e. leading to a good pharmacologic (therapeutic) response, and not causing any (toxic) side effects
Part 3
Modulating PK parameters

Slow release formulations for oral administration
- to enable less frequent dosing and more effective treatments
- different formulation => multilayered, sustained release tablets / capsules
- AUC => substantially increased vs. single-dose standard formulation

Rapid release formulations for oral administration
- certain symptoms call for rapid release formulations
  - e.g. in case of gastric hyperacidity
  - rapid and high peak concentration needed
  - AUC less important
Modulating the PK of i.v. formulations

- Chemotherapeutic (CT) agents are generally administered intravenously.
- As most other drugs, their size is well below 1000 Dalton (<1 nm).
- As most small i.v. applied agents, they are excreted rapidly by the kidney.
- They therefore tend to present with short $t_{\frac{1}{2}}$ and low tumor concentrations.
- Consequently, they result in an improper efficacy-to-toxicity ratio (i.e., low therapeutic index).

Drug Delivery Systems / Nanomedicines are much larger than standard CT drugs.
- They are therefore much less rapidly excreted by the kidney.
- And thereby increase the $t_{\frac{1}{2}}$ and the tumor concentrations of CT agents via EPR.

Some examples

Long-circulating PEGylated liposomes

<table>
<thead>
<tr>
<th>Hours After i.v. Injection</th>
<th>Free Doxorubicin</th>
<th>Pegylated Liposomal Doxorubicin ($t_{\frac{1}{2}} = 50-80$ hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.1</td>
<td>25.0</td>
</tr>
<tr>
<td>1</td>
<td>0.2</td>
<td>20.0</td>
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<tr>
<td>2</td>
<td>1.0</td>
<td>15.0</td>
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<tr>
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<tr>
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<td>2.5</td>
</tr>
<tr>
<td>24</td>
<td>25.0</td>
<td>0.2</td>
</tr>
</tbody>
</table>

EPR: Enhanced Permeability and Retention

- Long circulation time
- High blood vessel density in tumors
- Enhanced vascular permeability in tumors
- Lack of functional lymphatic drainage

Effective and selective accumulation of DSS in tumors via EPR

Drug targeting to tumors using HPMA copolymers

Polymeric drug carriers improve the PK parameters of low MW chemotherapeutics.

Some examples

Drug targeting to tumors using HPMA copolymers

Polymeric drug carriers improve the antitumor efficacy of low MW chemotherapeutics.

- Untreated control
- HPMA-copolymer-bound doxorubicin
Drug targeting to tumors using liposomes

Drug targeting to tumors using liposomes

Efficient EPR-mediated drug targeting and tumor growth inhibition in rats and mice

Gabizon et al., J Drug Targeting 2002

Part 4

PK parameters: Drugs vs. CA

Microdosing of therapeutic and diagnostic agents

Microdosing

For therapeutics:
- A technique for studying the behaviour of drugs in humans through the administration of doses so low they are unlikely to produce (systemic/whole-body) effects
- This enables assessment of the PK of a drug with almost no risk of side effects
- Microdosing is implemented in Phase 0 clinical trials (which are more and more conducted before starting Phase I), to assess whether a drug is suitable for the further evaluation

For diagnostics:
- For contrast agents, different criteria apply:
- Either diagnostics are rapidly eliminated (i.e. >90% within 24 h; >99% within 2 w).
- E.g. gadolinium-based MRI-agents, or iodine-based CT-agents
- Or they can only be used clinically at microdoses, e.g. radionuclide-labeled mAbs for PET
**Microdosing of contrast agents**

Rapid elimination of contrast agents is clinically generally preferred:
- as diagnosis can then be performed immediately after administration
- as diagnostic interventions can then be repeated more often and more rapidly

**Rapid elimination**
- antibody-targeted PET agent
- optimal enhancement after 56 h
- microdosing clinically required

**Slow elimination**
- antibody-targeted PET agent
- optimal enhancement after 96 h
- microdosing clinically required

- antibody-targeted US agent (microbubbles)
- optimal enhancement after < 10 min
- $t_{1/2} \approx 1$ min; no microdosing required
- additional advantage: destruction by US pulse

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**Summary**

- Important PK processes: Absorption, Distribution, Metabolism, Elimination
- Route of administration is very important for determining PK
- Important PK models: 1- and 2-compartment model
- Important PK parameters: $c_{max}$, $t_{max}$, $t_{1/2}$, $k_a$, $k_e$, AUC, TR
- PK are very important for determining therapeutic activity
- Modulating PK using (nano-)formulations improves drug efficacy
- PK requirements are very different for drugs vs. contrast agents
- Microdosing can facilitate the assessment of the PK of drugs and CA