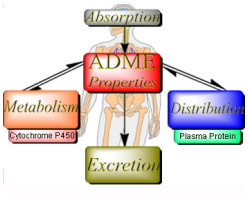
Pharmacokinetics : Basic Principles



Twan Lammers

Dept. of Experimental Molecular Imaging, RWTH Aachen
Dept. of Targeted Therapeutics, University of Twente
Dept. of Pharmaceutics, Utrecht University

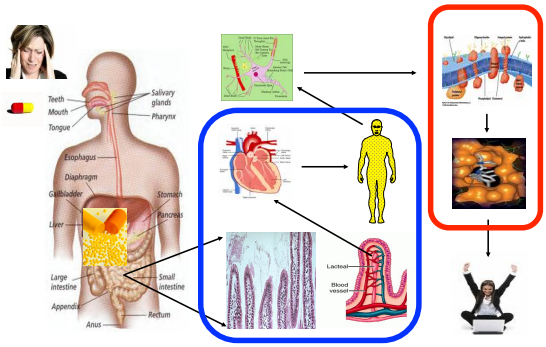
Overview

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?

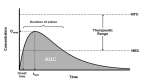


PK vs. PD

Pharmacodynamics:

- a discipline within pharmacology that studies the biochemical and the 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

=> "what the drug does to the body"

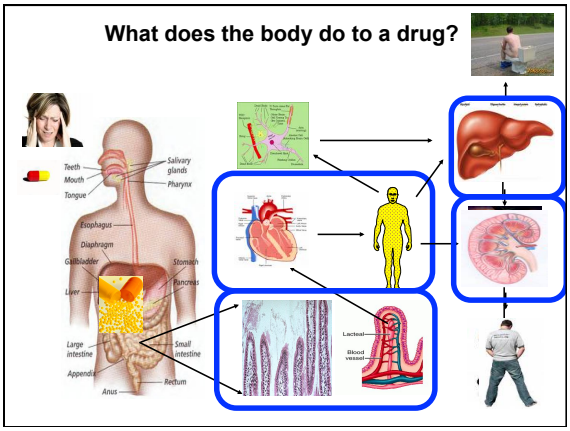


Pharmacokinetics:

- 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 the body does to the drug"

What does the body do to a drug?



Pharmacokinetics

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

A	absorption
D	distribution
M	metabolism
E	elimination

Drug effect phase

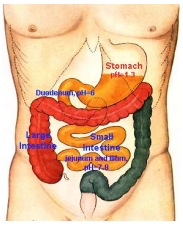
All four processes are important for controlling drug levels and tissue exposure, and they are therefore critical for determining the performance and the activity of a drug

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%

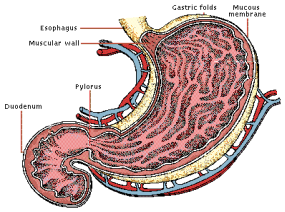
Drug absorption is governed by:
- anatomy of the organ
- dosage form / formulation
- physicochemical properties of the drug

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



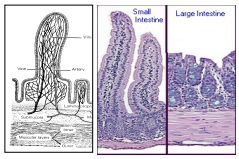
Stomach: limited absorption

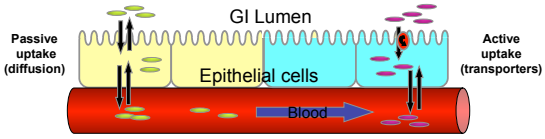
Absorption is limited by:
- protective mucosa
- muscle layer
- low perfusion
- low surface area
- lack of carriers



Small intestine is the preferred site for drug absorption

Drug absorption is promoted by:
- large surface area: Many (micro-) villi
- without villi: 0.5 m^2 => with: 200 m^2
- efficient perfusion of villi
- very short distance between epithelial surface and blood vessels
- multiple transporters on villi



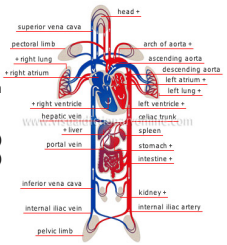


2nd phase: Distribution

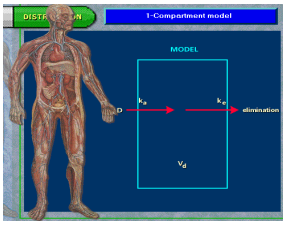
=> the process by which the drug spreads out over the body

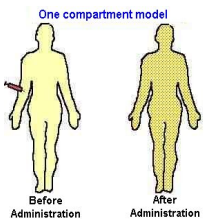
Distribution of drugs (in-) to tissues depends on:

- perfusion of tissues (blood flow)
- biological barriers
  => membranes or cell layers to be crossed
  => drug lipid solubility and degree of ionization
- uptake of drugs into tissues
  => passive transport (across lipid membranes)
  => active transport (via receptors/transporters)
- protein binding
  => albumin-binding (longer $t_{1/2}$; lower V_d)



Mathematical modeling of distribution: 1-compartment model

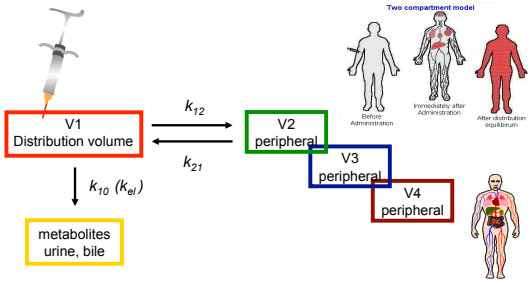




Assumptions:
- Most simple model: Whole body = 1 compartment
- Instantaneous distribution over blood and organs
- Constant elimination process

} Easy model
Simple PK analyses
Not very realistic…

One vs. multiple compartments



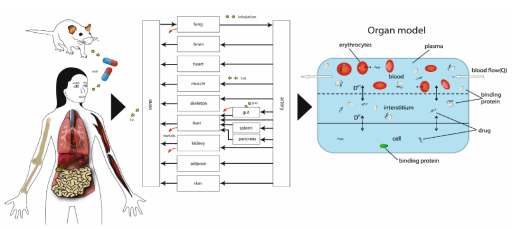
=> 1-compartment model : instantaneous distribution over both blood and organs

=> 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 consist 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



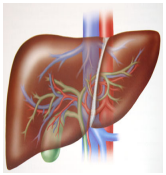
3rd Phase: Metabolism

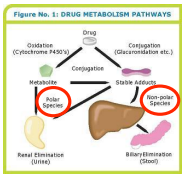
=> The chemical modification of drugs to enable / enhance their elimination

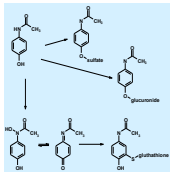
- The liver is the main metabolizing organ

- Cytochrome P450 (CYP450) enzymes in the liver metabolize drugs via:
  => Phase I-reactions : oxidation, reduction and hydrolysis
  => Phase II-reactions : conjugation with hydrophilic sulfate, glucuronic acid or gluthathione groups

- Metabolites generally are much more water-soluble than the parental drug, and they can therefore be eliminated more effieciently via the kidney / urine







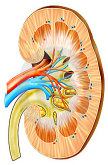
4th Phase: Elimination

=> The excretion of the drug and its metabolites from the body

- Elimination can be effectuated via various routes:
  - elimination via urine (hydrophilic compounds)
  - excretion via bile or stool (lipophilic compounds)
  - expiration of gasses (CO_2) and volatile substances (e.g. garlic)
  - transpiration

- The kidney is the main organ responsible for elimination

- Elimination by the kidney takes place via:
  - glomerular filtration (passive)
  - tubular secretion (active)



Part 2

PK Parameters

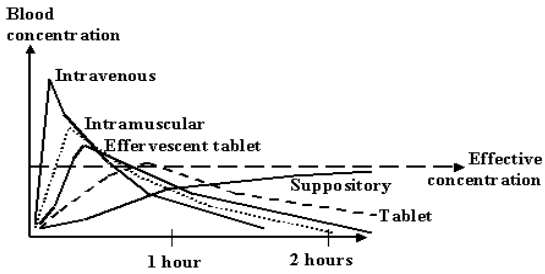
PK: it all starts with the route of administration

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

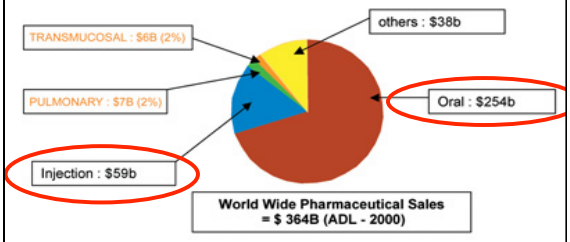
=> the route of administration strongly affects the PK of a drug

PK : Blood concentration vs. time curves

=> upon different routes of administration



Routes of administration

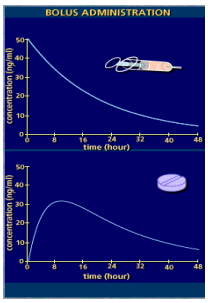


=> Drugs : mainly orally administered

=> 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%

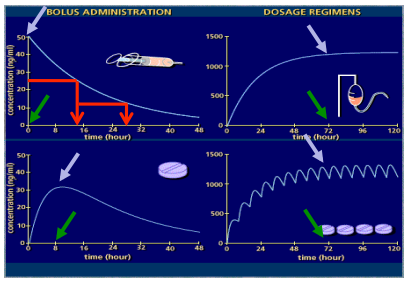
Pharmacokinetic profiles of a drug upon intravenous and oral administration

=> blood concentrations vs. time curves

c_{max}

t_{max}

$t_{1/2}$



Important PK parameters

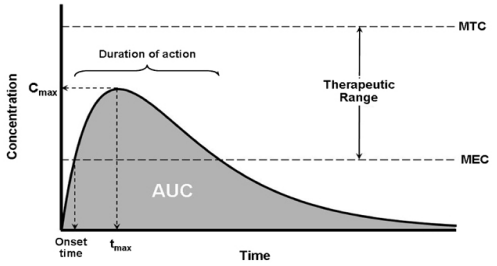
k_a : the fraction of orally applied drug that is absorbed (i.e. entering the circulation) per unit time is determined by the **absorption constant**

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_F), on the fraction absorbed (k_a) and on first-pass metabolism

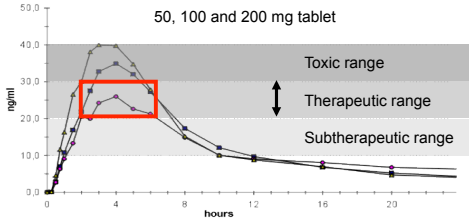
TR : The **Therapeutic Range** is the concentration range in which the levels of the drug in systemic circulation are optimal, i.e. leading to a good pharmacologic (therapeutic) response, and not causing any (toxic) side effects

AUC upon oral administration



MTC: Minimal Toxic Concentration
MEC: Minimal Effective Concentration

Oral administration: Blood concentration vs. time curve



c_{max} ≈ 40, 35 and 25 ng/ml (=> dose-dependent)
t_{max} ≈ 4 h (=> dose-independent ; formulation- and drug-dependent)

t_0 => t_{max} : absorption exceeds elimination
t_{max} => t_{end} : elimination exceeds absorption

Part 3

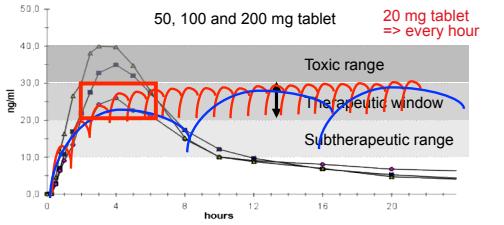
Modulating PK parameters

Modulating the PK of oral formulations

- limited time within the therapeutic window
- multiple doses are needed to ensure proper efficacy

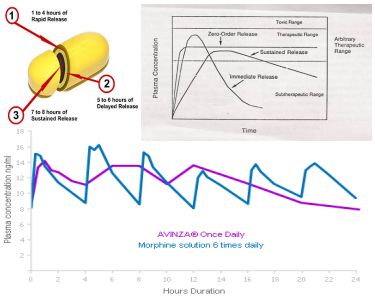
50 mg tablet
=> every 8 hours

20 mg tablet
=> every hour



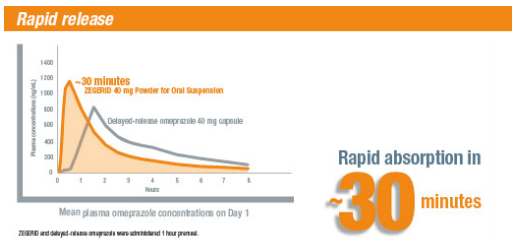
Slow release formulations for oral administration

- 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

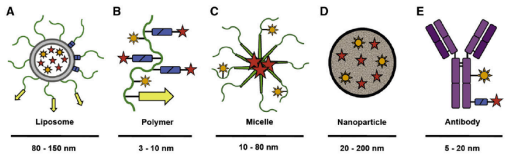
- certain symptoms call for rapid release formulations
- e.g. in case of gastric hyperacidity
- rapid and high peak concentration needed
- AUC less important



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 $t_{1/2}$ and low tumor concentrations
- and consequently with an improper efficacy-to-toxicity ratio (i.e. low therapeutic index)

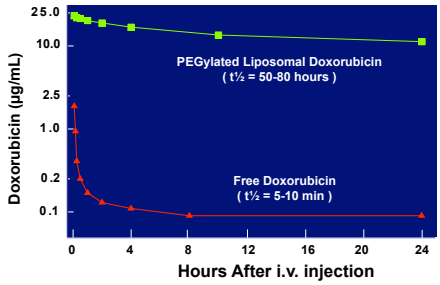
=> Drug Delivery Systems / Nanomedicines are much larger than standard CT drugs
=> they are therefore much less rapidly excreted by the kidney
=> and thereby increase the $t_{1/2}$ and the tumor concentrations of CT agents via EPR



Lammers et al., J Cont Rel 2012

Some examples

Long-circulating PEGylated liposomes

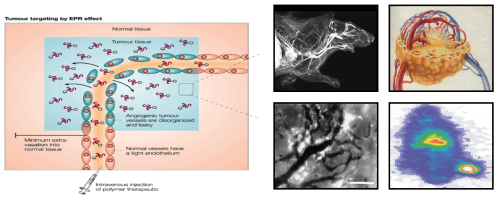


Gabizon et al., Cancer Res. 1994

EPR : Enhanced Permeability and Retention

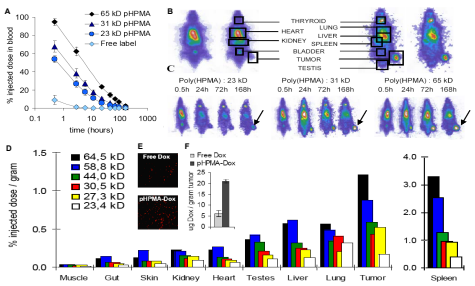
Long circulation time	+
High blood vessel density in tumors	+
Enhanced vascular permeability in tumors	+
Lack of functional lymphatic drainage	=> => =>

Effective and selective accumulation of DSS in tumors via EPR



Drug targeting to tumors using HPMA copolymers

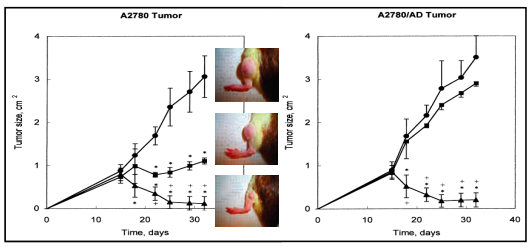
Polymeric drug carriers improve the PK parameters of low MW chemotherapeutic drugs



Lammers et al, J Contr Rel 2005, 2007
Lammers, Adv Drug Deliv Rev 2010

Drug targeting to tumors using HPMA copolymers

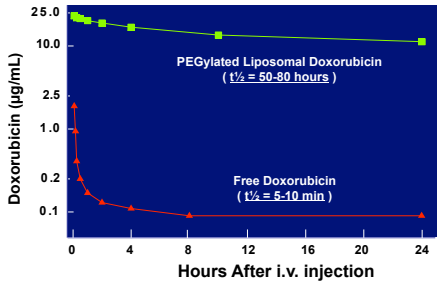
Polymeric drug carriers improve the antitumor efficacy of low MW chemotherapeutics



- Untreated control
- Free doxorubicin
- HPMA copolymer-bound doxorubicin

Minko et al, Int J Cancer 2001

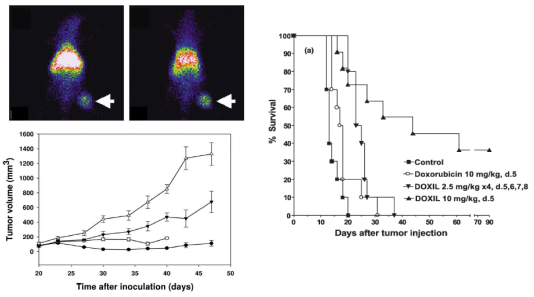
Drug targeting to tumors using liposomes



Gabizon et al., Cancer Res. 1994

Drug targeting to tumors using liposomes

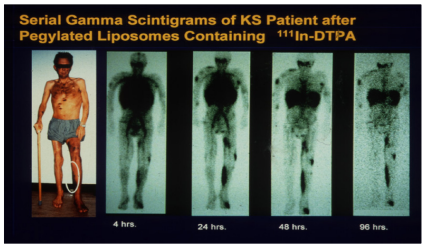
Efficient EPR-mediated passive drug targeting and tumor growth inhibition in rats and mice



Gabizon et al, J Drug Targeting 2002

Drug targeting to tumors using liposomes

Efficient EPR-mediated drug targeting in patients



Improved toxicity vs. free Dox => Less BMD, alopecia, nausea and vomiting

Substantially improved efficacy vs. ABV => 1 CR + 60/133 PR (46%) vs. 31/125 PR (25%)

Harrington et al, Clin Cancer Res 2000

Part 4

PK parameters : Drugs vs. CA

Drugs vs. contrast agents : Different PK requirements

Therapeutics

- Mainly orally administered => k_a is very important and should be high
- High concentration at the target site preferred => c_{max} should be high
- Rapid peak concentration not required => t_{max} not very important (disease-dependent)
- Long residence time in blood and at the target site preferred => AUC should be high
- Slow clearance preferred => k_e should be low
- No pre-defined elimination criteria

Diagnostics

- Mainly intravenously injected => k_a not important
- In case of oral administration => k_a should be low (GI imaging)
- High concentration at the target site preferred => c_{max} should be high
- Rapid peak concentration at the target site preferred => t_{max} should be low
- Short residence time in blood and at the target site preferred => AUC should be low
- Rapid clearance preferred => k_e should be high
- Stringent elimination criteria => for non-micro-dosed diagnostics: >90% @ 24 h; >99% @ 2 w

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

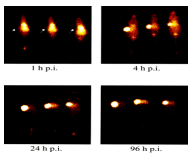
=> or they can only be used clinically at microdoses, e.g. radionuclide-labeled mAb for PET

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

Slow elimination

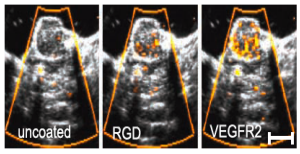
=> antibody-targeted PET agent
=> optimal enhancement after 96 h
=> microdosing clinically required



Boerman et al, UMCN Nijmegen

Rapid elimination

=> 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



Palmowski, Kiessling et al, Mol Cancer Ther 2008

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}, $t_{½}$, 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