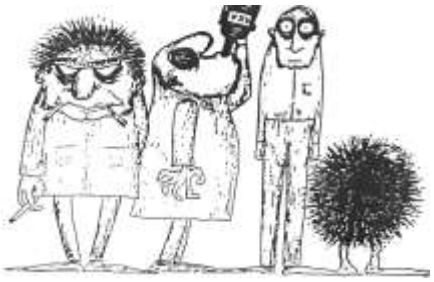
PH5 Individualised therapy
Managing the differences

Vienna, 17/18 March 2016

Introduction to TDM



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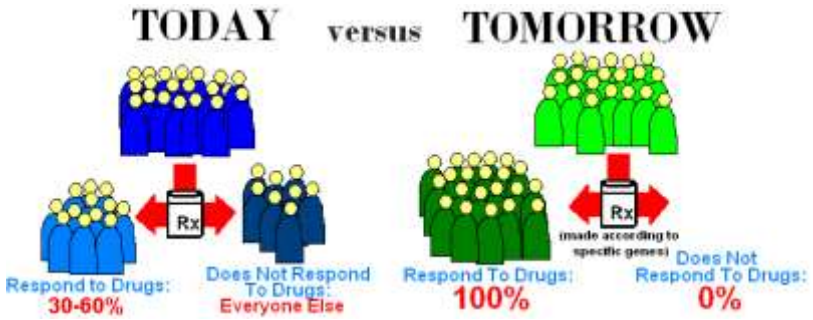
Conflicts of Interest

None

Questions

- What is superior:
  Pharmacokinetic or pharmacodynamic dose adaptation?
- Which is the most important pharmacokinetic parameter for adjusting the maintenance dose:
  Clearance or half-life?
- TDM should be applied for all drugs with narrow therapeutic range.
  True or false?

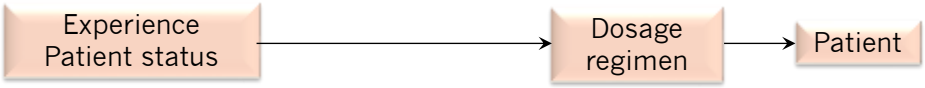
Individualised therapy is that easy...



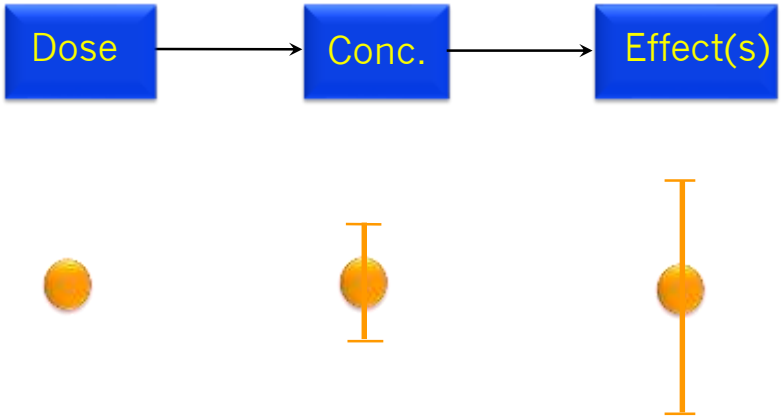
From pharmacogenomics.webs.com

Dosing Strategies (I)

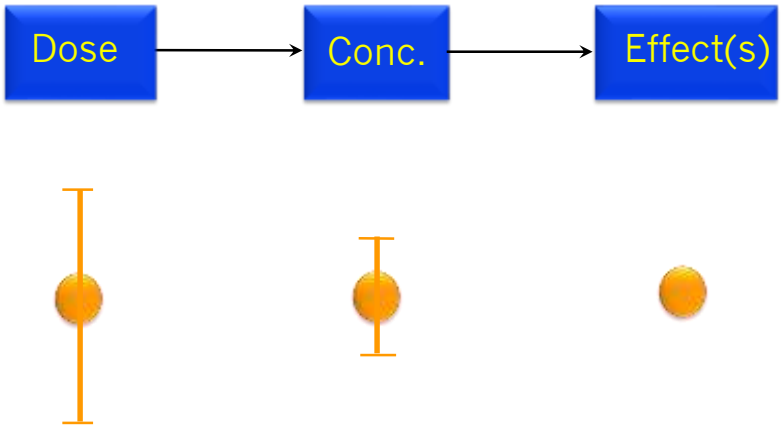
Empirical Dosing



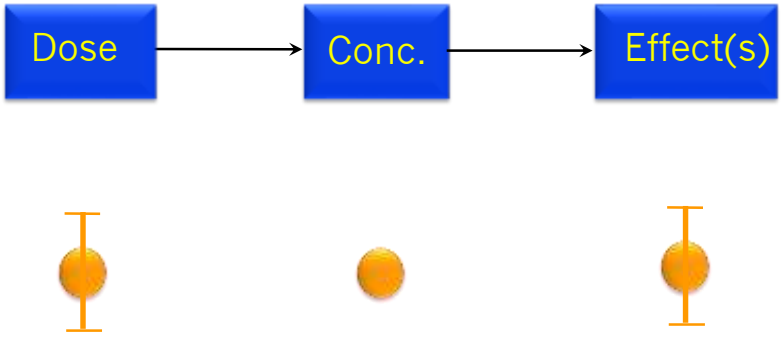
Empirical Dosing



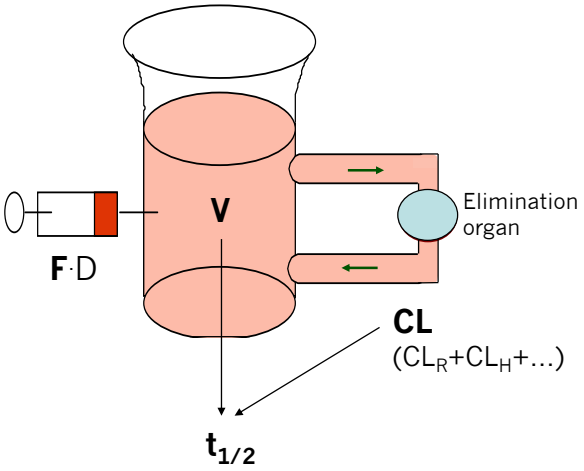
Pharmacodynamic Dose Adaptation



Pharmacokinetic Dose Adaptation



Relevant Pharmacokinetic Parameters



F Bioavailability (0 < F < 1)

V Volume of distribution

CL Total clearance

$t_{1/2}$ Half-life

Relevance of Pharmacokinetic Parameters for Dosing

Pharmacokinetic Parameter	Relevance for Dosing
CL	Maintenance dose (MD)
V	Loading dose (LD)
$t_{1/2}$	Dosage interval (τ)
F	Loading and Maintenance Dose

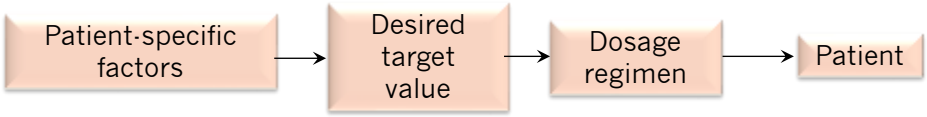
Target Criteria

Target	Examples
Therapeutic Range	Theophylline Phenytoin
Peak and trough concentrations	Aminoglycosides Vancomycin
Target AUC	Carboplatin Fluorouracil

Dosing Strategies (II)

Empirical Dosing

Adaptive dosing based on patient-specific factors



AUC-based dosing of carboplatin

Prediction of individual clearance

$$D_{ind} = \text{Target AUC} \cdot CL_{ind}$$

Calvert et al. (1989)

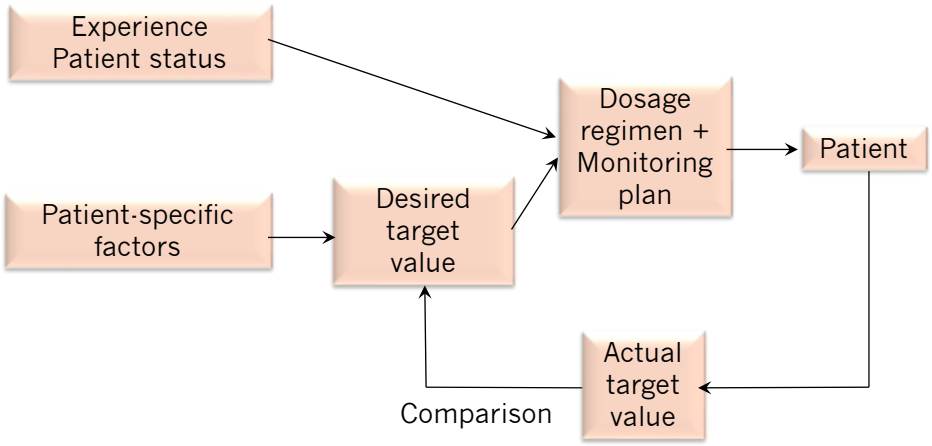
$$CL_{ind} = GFR + 25$$

Chatelut et al. (1995)

$$CL_{ind} = 0{,}134 \cdot \text{Weight} + \frac{218 \cdot \text{Weight} \cdot (1 - 0{,}00457 \cdot \text{Age})}{\text{Serum creatinine}} \cdot 0{,}686 \text{ (females)}$$

Dosing Strategies (III)

Adaptive dosing with feedback



Application of TDM

- Drugs with narrow therapeutic range
- Drugs with large interindividual variability of PK and PD
- No possibility of routine control of pharmacodynamic target parameters
- Correlation between PK and PD

Critical-Dose Drugs

ANTIBIOTICS
Aminoglycosides
Vancomycin

DIGITALIS GLYCOSIDES
Digoxin/Digitoxin

ANTICONVULSANT DRUGS
Carbamazepine
Phenytoin
Valproic acid

IMMUNOSUPPRESANT DRUGS
Cyclosporine
Tacrolimus
Mycophenolic acid

ANTIARRHYTHMICS
Procainamide
Amiodarone

ANTIDEPRESSANTS
Lithium
Tricyclic antidepressants

ANTICANCER DRUGS
Methotrexate
Fluorouracil

OTHER DRUGS
Theophylline
HIV protease inhibitors

Application of TDM

- Drugs with narrow therapeutic range
- Drugs with large interindividual variability of PK and PD
- No possibility of routine control of pharmacodynamic target parameters
- Correlation between PK und PD
- **High-risk patients**

High-risk patients

Example: Patients with severe burns

- Absorption
- Extracellular space
- Binding to albumin ↓
- Binding to α_1-acid glycoprotein
- Renal elimination:
  Acute phase ↓
  Hypermetabolic phase
- Metabolism ↓

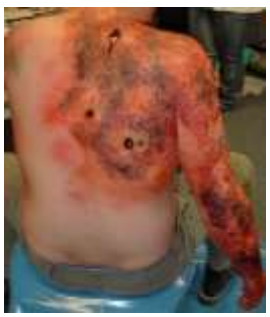


Photo: www.jrk-schoellnach.de

IMPORTANT:
- Severity of burn
- Time after burn

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